

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022472Orig1s000**

**MEDICAL REVIEW(S)**

**DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY**  
**PRODUCTS MEDICAL OFFICER CONSULTATION**

Date: June 26, 2014  
To: Lisa Yanoff, M.D., Acting Medical Team Leader, DMEP  
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Through: Banu Karimi-Shah, M.D., Medical Team Leader, DPARP  
Sally Seymour, M.D., Deputy Director for Safety, DPARP  
Subject: Pulmonary Safety of Afrezza (insulin monomer human [rDNA  
origin] Inhalation Powder)

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**General Information**

NDA/IND#: NDA 22-472  
Sponsor: MannKind Corporation  
Drug Product: Technosphere Insulin/Gen2 Inhaler - Afrezza  
Request From: Lisa Yanoff, M.D., Acting Medical Team Leader, DMEP;  
Jean-Marc Guettier, M.D., Division Director, DMEP  
Date of Request: October 15, 2013  
Date Received: October 15, 2013  
Materials Reviewed: Complete response submission dated October 15, 2013, DPARP  
Medical Officer Consultations dated December 2009, December  
2010, November 2011, and December 2011. Complete response  
letters dated March 12, 2010 and January 18, 2011.

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**I. Executive Summary**

This Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) medical officer review evaluates the pulmonary safety of Afrezza. MannKind Corporation has developed Afrezza, insulin monomer human [rDNA origin] Inhalation Powder (also referred to throughout this review as Technosphere® Insulin, or TI), as an ultra-rapid acting prandial insulin for the treatment of type 1 and type 2 diabetes mellitus (DM) in adults 18 years of age and older. TI Inhalation Powder is a dry powder formulation of recombinant human insulin and contains a novel proprietary excipient, fumaryl diketopiperazine (FDKP). Afrezza is a drug-device combination product, consisting of TI inhalation powder delivered via the Gen2 inhaler. The Division of Metabolism and Endocrinology Products (DMEP) has requested consultation from DPARP on multiple occasions (as listed above in the materials reviewed) to evaluate the pulmonary safety of Afrezza, given the inhaled route of delivery.

The inhaled route of administration for Afrezza and potential for chronic administration raise pulmonary safety concerns. There has been one previously approved inhaled insulin marketed for the treatment of type 1 and type 2 DM, Exubera Inhalation Powder. Review of the clinical

development program for Exubera demonstrated respiratory-related adverse events, a small decline in FEV1 (forced expiratory volume in 1 second) over time, and risk of bronchospasm in patients with asthma or chronic obstructive pulmonary disease (COPD). Lung cancer was also a concern based upon long-term safety data with Exubera. The pulmonary safety findings from the Exubera program will be summarized briefly in this review, as they are relevant to the current application.

With regards to the pulmonary safety of Afrezza, one of the main issues is the significant change in device during the development program. In the original submission, TI was delivered via the MedTone inhaler. Subsequently, the Applicant proposed a new device, the Gen2 Inhaler. For the original new drug application (NDA), the Applicant collected 2 years of pulmonary safety data with the MedTone Inhaler, as well as shorter-term data in patients with asthma and COPD. When the Applicant changed the device to the Gen2 inhaler, FDA had to consider what pulmonary safety data would be sufficient with the new Gen2 inhaler. As two additional trials were proposed to support the efficacy of Afrezza, FDA requested that the Applicant also collect pulmonary safety data with the new Gen2 inhaler, comparing it to the MedTone inhaler, with the intention to “bridge” the pulmonary safety data from the MedTone inhaler to the Gen2 inhaler.

Review of the pulmonary safety data that was submitted with the original NDA for Afrezza, identified several issues (e.g. decline in FEV1 over time, bronchospasm in patients with underlying lung disease, and cough). In the current submission, two clinical studies (MKC-TI-171 and MKC-TI-175) were submitted, both to address efficacy issues (as discussed in Dr. Yanoff’s review) and to compare pulmonary safety between devices. Study MKC-TI-171 provided a head-to-head comparison between the two devices in patients with type 1 DM. Study MKC-TI-175 compared the new device with and without active drug in patients with type 2 DM. The populations for both studies were similar to the studies included in the original submission. Pulmonary safety (FEV1 decline at 6 months and cough) was similar between the two devices and similar to the original submission when compared to an active control or placebo.

A brief summary of the pulmonary safety issues with Afrezza are outlined below and are discussed in more detail in the body of this consultative review.

### 1. Decline in FEV1 Over Time

A greater decline in FEV1 with Afrezza therapy versus comparator was noted during the first 3 months of therapy. In 2 year studies, Afrezza-treated patients experienced a small, (40 mL (95% CI: -80, -1)) but greater FEV1 decline than comparator-treated subjects. The results from 2-year studies show that the early difference persisted, but did not appear to progress over the 2-year period. As noted above, the 2-year pulmonary function data were obtained with the MedTone inhaler and 6-month pulmonary function data are available with the Gen2 inhaler; however, the decline in FEV1 (mean treatment difference) at 6 months was similar between the two devices. Controlled pulmonary safety data beyond 2 years of treatment are not available.

### 2. Bronchospasm in Patients with Underlying Lung Disease

Patients with underlying lung disease were excluded from the phase 2 and 3 clinical development program for Afrezza. However, small single dose studies were conducted with the MedTone inhaler in order to evaluate the effect of Afrezza in patients with asthma and COPD.

In one study in asthmatic patients, mean FEV1 declined approximately 400 mL from baseline when measured 15 minutes after inhaling a single-dose of Afrezza. This decline recovered towards baseline (to within 20 mL) at 2 hours. Bronchospasm and wheezing were noted in 29% (5 out of 17) and 0% (0 out of 13) of patients with and without a diagnosis of asthma, respectively. Two SAEs of bronchospasm were reported in the patients with asthma. In another study, patients with COPD had a smaller mean decline (200 mL) and a slower recovery over 8 hours towards baseline. Associated symptoms were not reported in patients with COPD in this small study.

### 3. Cough

Cough was the most common adverse event (approximately 30% incidence) associated with Afrezza, and the most common reason for discontinuation due to an adverse event (approximately 3%). Cough usually occurred within 10 minutes, was generally mild, dry, intermittent or single-defined, and tended to decrease over time.

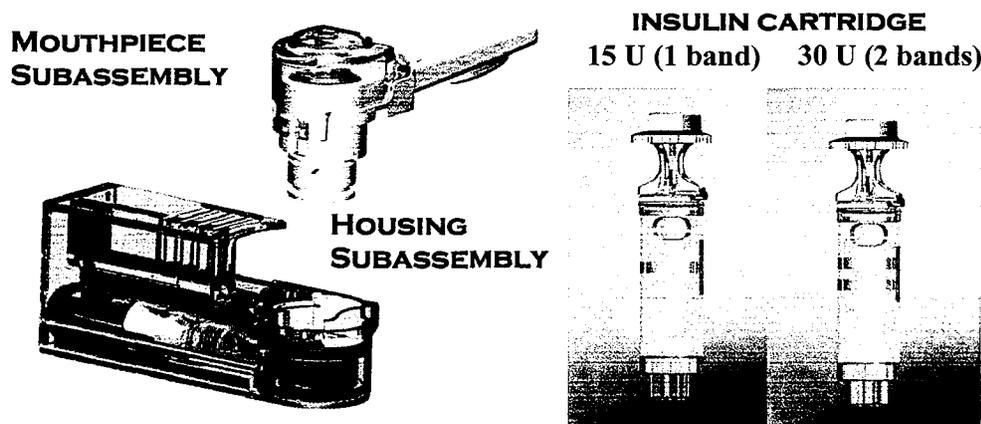
The pulmonary safety profile has been adequately captured in the labeling, including a boxed warning for acute bronchospasm, a contraindication in asthma and COPD, warnings and precautions regarding acute bronchospasm and pulmonary function decline over time. In addition, there is also a REMS for pulmonary safety. The Applicant has also been informed and has agreed to collect 5-years of pulmonary function data as a post-marketing requirement. From a pulmonary safety standpoint, there are no issues that preclude approval of Afrezza this time.

The following review covers the regulatory history of Afrezza by summarizing prior reviews completed by DPARP regarding the pulmonary safety data of TI delivered via the MedTone inhaler, as well as new data submitted by the Applicant, with respect to pulmonary safety of TI delivered via the Gen2 inhaler. Of note, a discussion of lung malignancy has not been included in our review, but is included in Dr. Yanoff's review. Following a presentation of the data, we discuss the agreed upon labeling, REMS, and post-marketing requirements relevant to the pulmonary safety of Afrezza.

## II. Background and Regulatory History

### A. Afrezza

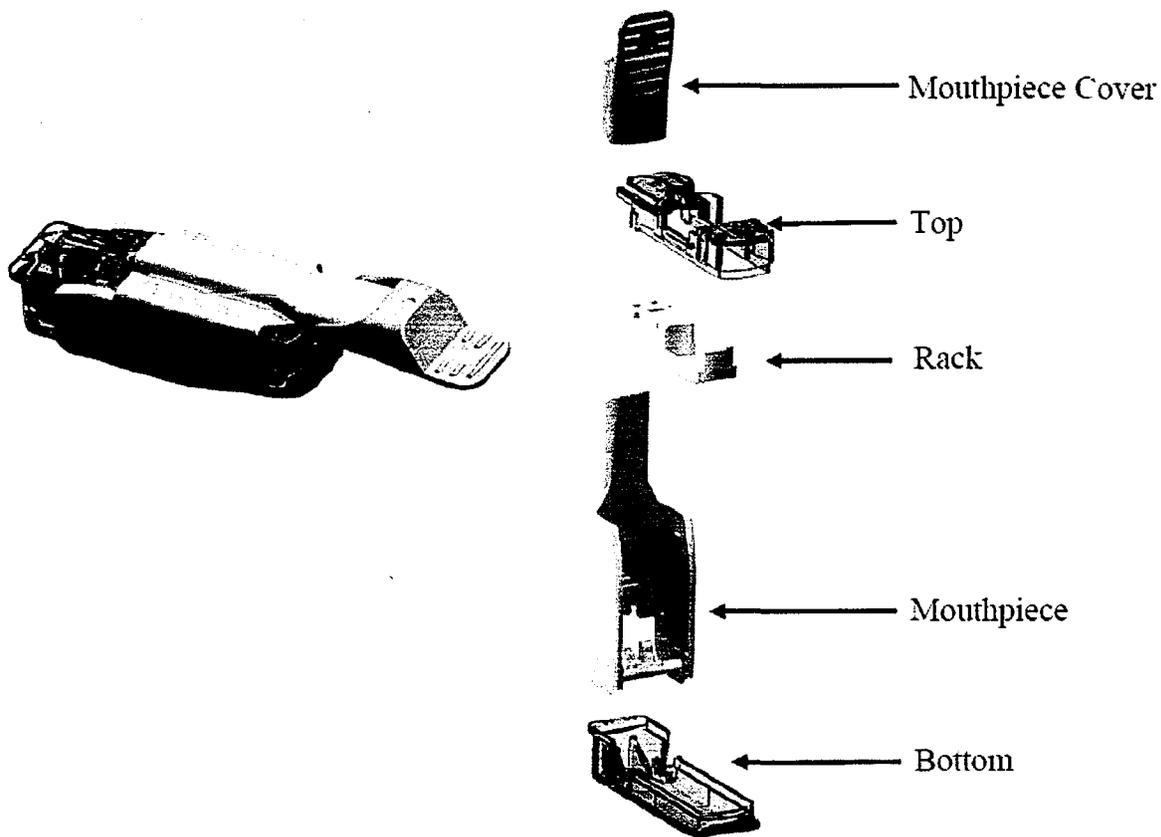
The NDA for Afrezza was originally submitted on March 16, 2009. In the original submission, Afrezza consisted of TI Inhalation Powder pre-metered into unit dose cartridges to be delivered via the MedTone Inhaler. The MedTone inhaler (Figure 1) was proposed to be breath-powered and re-usable for 12 months. A Complete Response (CR) action was taken on March 12, 2010, in which several deficiencies were cited including: 1) unproven clinical utility resulting from a failure to demonstrate adequate glycemic control versus comparators, 2) unreliability of pivotal bioequivalence study results, 3) unproven usability of the MedTone device, and 4) lack of data to support proposed 1-year in-use life of the MedTone device.



**Figure 1. MedTone Inhaler Schematic**

Source: Module 3.2.P.1 (pg 1), and Module 3.2.P.7 (pg 3)

The Applicant submitted a CR on June 29, 2010. In response to the deficiencies outlined in the letter dated March 12, 2010, the Applicant proposed to change the device to the Gen2 inhalation system (Figure 2). The Applicant noted that they did not think that modification of the MedTone inhaler would allow them to adequately address the cited deficiencies. The newly proposed product consisting of different pre-metered unit dose cartridges of TI delivered by the Gen2 inhaler was a completely different device from the MedTone Inhaler put forth in the original submission. The TI Inhalation Powder was not changed, however the pre-metered unit dose cartridges made for the Gen2 device had lower fill weights (10U and 20U) compared to those for the MedTone device (15U and 30U). Further details the device can be found in Appendix 3: Chemistry, Manufacturing, and Controls.



**Figure 2. Gen 2 Inhaler with Exploded Schematic**

Source: Module 3.2.P.1, Figure 1, p 1

A second CR letter was issued on January 18, 2011. Among the deficiencies listed in the CR letter, the issue most relevant to pulmonary safety was the lack of clinical data with the new Gen2 inhaler. In the second submission, the Applicant attempted to rely on in vitro and clinical pharmacology data to bridge the Gen2 inhaler to the phase 3 trials conducted with the MedTone inhaler. The Agency considered this approach to be inadequate because the Gen2 device had not been studied in any controlled phase 3 clinical trials. Lack of clinical data with the Gen2 device precluded determination of the safety and efficacy of TI delivered via the Gen2 inhaler. Further, the lack of clinical data precluded determination of device robustness and usability.

In order to address the deficiencies with respect to pulmonary safety, the Agency advised the Applicant to conduct two phase 3 trials with the Gen2 device, with at least one of these trials including a treatment group using the MedTone inhaler. As the majority of the available pulmonary safety data was with the MedTone inhaler, DPARP felt that it was necessary to obtain a head-to-head comparison of the pulmonary safety data between the MedTone and the Gen2 inhalers, acknowledging that the shorter duration, smaller size, and proposed “bridging” of pulmonary safety information from one device to another would provide limited information.

The second CR, which is the focus of this review, was received on October 15, 2013, which includes the two new phase 3 clinical trials (MKC-TI-171 and MKC-TI-175) requested by the Agency. The designs of both trials were discussed during a Type C meeting on August 10, 2011. Each protocol was reviewed by DPARP and found to be acceptable (November 4, 2011 (Study MKC-TI-171) and December 9, 2011 (Study MKC-TI-175)).

## **B. Exubera**

Exubera (NDA 21-868, approved January 27, 2006), a powdered form of inhaled insulin, was the first formulation of inhaled insulin to receive FDA approval. An Endocrine and Metabolic Drugs Advisory Committee Meeting was held in September 2005, to discuss the NDA and pulmonary safety was a specific discussion item. Exubera was available in the United States from September 2006 to October 2007. In October 2007, Pfizer announced that it would be discontinuing the production and sale of Exubera due to poor sales, and because Exubera failed to gain acceptance among patients and physicians.

### *Pulmonary Function – FEV1 and DL<sub>CO</sub>*

Per the package insert, the effect of Exubera on the respiratory system had been evaluated in over 3800 patients in controlled phase 2 and 3 clinical studies (in which 1977 patients were treated with Exubera). In randomized, open-label clinical trials of up to two years duration, patients treated with Exubera demonstrated a greater decline in pulmonary function, specifically FEV1 and the carbon monoxide diffusing capacity (DL<sub>CO</sub>), than comparator-treated patients. The mean treatment group differences in FEV1 and DL<sub>CO</sub>, were noted within the first several weeks of treatment with Exubera, and did not progress over the two year treatment period. Following 2 years of Exubera treatment in patients with type 1 and type 2 diabetes, the difference between treatment groups for the mean change from baseline FEV1 was approximately 40 mL, favoring the comparator. Following 2 years of Exubera treatment, the difference between treatment groups for the mean change from baseline DL<sub>CO</sub> was approximately 0.5mL/min/mmHg (type 1 diabetes), favoring the comparator, and approximately 0.1mL/min/mmHg (type 2 diabetes), favoring Exubera. Because of the effect of Exubera on pulmonary function, the package insert advised that all patients should have pulmonary function assessed prior to initiating therapy with Exubera and that periodic monitoring of pulmonary function was recommended for patients being treated with Exubera.

### *Smoking*

Smokers were excluded from the pivotal clinical efficacy and safety studies; however, some PK/PD data in smokers were available. In smokers, the systemic insulin exposure for Exubera was found to be 2 to 5 fold higher than non-smokers. In clinical studies of Exubera in 123 patients (69 of whom were smokers), smokers experienced a more rapid onset of glucose-lowering action, greater maximum effect, and a greater total glucose-lowering effect (particularly during the first 2–3 hours after dosing), compared to non-smokers. As a result, the package insert contraindicated the use of Exubera in patients who smoked or who had discontinued smoking less than 6 months prior to starting Exubera therapy. Further, the package insert stated that if a patient were to start or resume smoking, that Exubera should be discontinued immediately due to the increased risk of hypoglycemia.

### *Underlying Lung Disease*

Patients with asthma and COPD were excluded from the pivotal clinical efficacy and safety studies and only limited data with Exubera were available in these patient populations. Therefore, the use of Exubera was not recommended in patients with underlying lung disease.

### *Respiratory Adverse Events*

Common respiratory adverse events associated with Exubera were respiratory tract infection, cough increased, pharyngitis, rhinitis, sinusitis, dyspnea, sputum increased, bronchitis, epistaxis, laryngitis, and voice alteration. Cough was the most common respiratory adverse event attributable to Exubera. The cough tended to occur within seconds to minutes after Exubera inhalation, was predominantly mild in severity and was rarely productive. The incidence of cough decreased with continued use of Exubera. In clinical studies, 1.2% of patients discontinued treatment due to cough.

### *Imaging*

Baseline and end of study chest x-rays (CXRs) were performed in almost all of the clinical studies with Exubera. The CXR data did not identify a particular pulmonary safety signal.

Baseline and two year high resolution computed tomography (HRCT) scans of the thorax in 50 subjects treated with Exubera and 50 subjects treated with comparator were requested by the Agency to assess for parenchymal lung changes associated with Exubera use. The Applicant submitted controlled HRCT data at baseline and 24 weeks in 116 subjects, controlled HRCT data at baseline and 24 months in 104 subjects, and “for cause” HRCT data in 48 subjects. The controlled HRCT data did not suggest an increase in abnormal findings associated with Exubera use compared to SC insulin at 24 weeks or 24 months.

Experience with the Exubera pulmonary safety data helped to guide our review of the pulmonary safety data for Afrezza. Similar to the Exubera program, DLco data tended to be variable in the Afrezza program; additionally, imaging data was not found to contribute new information. Therefore, these variables will not be of primary focus in this review.

## **III. Review of Pulmonary Safety of Afrezza**

### **A. Original Submission – March 2009**

To support approval of Afrezza in the original NDA submission, the Applicant conducted a large clinical development program with TI delivered via the MedTone inhaler, which included 9 controlled clinical trials in patients with type 1 and 2 DM (see Table 1). The original clinical development program with the MedTone inhaler provided pulmonary safety data for a duration of up to 2 years.

<b>Table 1. Clinical Studies Used in the Evaluation of Pulmonary Safety (Original NDA Submission): TI delivered via the MedTone Inhaler</b>				
<b>Study</b>	<b>Design</b>	<b>Study Duration</b>	<b>Treatment Arms</b>	<b>N*</b>
<b>Type 1 DM</b>				
MKC-TI-101	R, OL	12 weeks	TI Injected insulin	54 56
MKC-TI-009	R, C, OL	1 year	TI Injected insulin	301 288
<b>Type 2 DM</b>				
MKC-TI-005	MC, R, DB, PC	11 weeks	TI Inhaled excipient (TP)	181 46
PDS-INS-0008	R, DB, PC, PG	12 weeks	TI Inhaled excipient (TP)	61 62
MKC-TI-026	R, C, OL	12 weeks	TI Inhaled excipient (TP)	75 15
MKC-TI-014	R, OL	24 weeks	TI Injected insulin	151 158
MKC-TI-103	R,C, OL	24 weeks	TI Oral anti-diabetic agent	358 170
MKC-TI-102	R, C, OL	1 year	TI Injected insulin	334 343
<b>Type 1 and Type 2 DM</b>				
MKC-TI-030	MC, R, OL	2 years	<b>Type 1</b>	
			TI	267
			Non-inhaled comparator	271
			<b>Type 2</b>	
TI	656			
Non-inhaled comparator	678			
*Number randomized; R: randomized; OL: open label; C: controlled; MC: multicenter; DB: double blind; PC: placebo controlled, PG: parallel group, TI: Technosphere Insulin Source: Individual Study CSRs, DPARP Review 2009, Table 4, p. 38.				

The total pooled populations used for the Applicant's analysis are listed in Table 2.

<b>Table 2. Total Subjects for Pooled Analysis in Original Submission, by Treatment Arm and Disease Type</b>			
	<b>TI MedTone</b>	<b>Comparator</b>	<b>TP MedTone</b>
Type 1	614	599	
Type 2	1795	1345	114
<b>Totals</b>	<b>2409</b>	<b>1944</b>	<b>114</b>
TI: Technosphere Insulin; TP: Technosphere particles (excipient only) Source: Module 5.3.5.3, ISS 2009, Table 9, p 60; Table 10, p 61			

In the primary clinical development program, patients were excluded if they had underlying lung disease (e.g., COPD or asthma), were current or former smokers (within 6 months), had a history of malignancy within 5 years, or abnormal lung function. The definition of abnormal lung function varied depending on the study, but generally was FEV1, FVC (forced vital capacity), and DL<sub>CO</sub> < 75% (range 70-80%) predicted normal. There were some smaller studies conducted in patients with underlying lung disease, to which these exclusions did not apply, and these will be discussed in further detail below.

In the original review of the pulmonary safety data, >600 patients with type 1 DM and >1700 patients with type 2 DM, without underlying lung disease, were exposed to TI via the MedTone inhaler (**Table 2**). This included TI exposure data of up to 2 years was for 267 patients with type 1 DM and 656 patients with type 2 DM (**Table 1**).

Based upon review of the pulmonary safety data with the MedTone inhaler in the original submission, DPARP noted issues regarding decline in FEV1 (immediately post-inhalation and over time) and cough in patients without underlying lung disease; and bronchospasm and FEV1 decline in subjects with underlying lung disease (asthma and COPD). The findings from our review of the original submission are summarized below.

### **1. Pulmonary Function in Diabetic Patients without Underlying Lung Disease**

#### **a) FEV1 Decline Over Time**

The original submission provided controlled pulmonary function data of up to 2 years duration. The specific pulmonary function tests (PFTs) evaluated included spirometry [FEV1, FVC, and Forced Expiratory Flow (FEF) 25-75%], and lung volumes (Total Lung Capacity (TLC), Residual Volume (RV)), and DL<sub>co</sub>). The DPARP review focused on the assessment of FEV1, as this parameter was considered to be the most clinically relevant and reproducible. In general, PFTs were measured every 3 months for a year and then every 6 months for up to 2 years, depending on the length of the study.

Patients with type 1 or type 2 DM treated with TI via the MedTone inhaler had a greater decline in FEV1 over time than patients treated with non-inhaled comparators. The decline was noted

during the first 3 months of therapy. The treatment differences were small (on average about 40-60 mL), as depicted in Table 3 (type 1 DM) and Table 4 (type 2 DM). The nature and magnitude of the change in FEV1 was consistent with what was observed in the Exubera clinical development program.

<b>Table 3. Change in FEV1 from Baseline in Type 1 DM with TI via the MedTone Inhaler (Safety Population, Original Submission)</b>			
<b>Timepoint</b>	<b>FEV1 (L)</b>		
	<b>TI MedTone Mean (SD)</b>	<b>Comparator Mean (SD)</b>	<b>Treatment Difference TI – Comparator (95% CI)</b>
<b>6 months</b>	<b>Applicants 2009 Pooled Type 1 (MMRM)</b>		
	-0.09 (0.01) N=370	-0.05 (0.01) N=437	<b>-0.04</b> (95% CI: -0.7, -0.1)
<b>1 year</b>	<b>MKC-TI-009 (Agency-LOCF)</b>		
	-0.07 (0.22) N=235	-0.04 (0.17) N=244	<b>-0.04</b> (95% CI: -0.08, -0.05)
<b>2 years</b>	<b>MKC-TI-030 (Agency-LOCF)</b>		
	-0.13 (0.22) N=200	-0.10 (0.19) N=246	<b>-0.04</b> (95% CI: -0.08, -0.001)

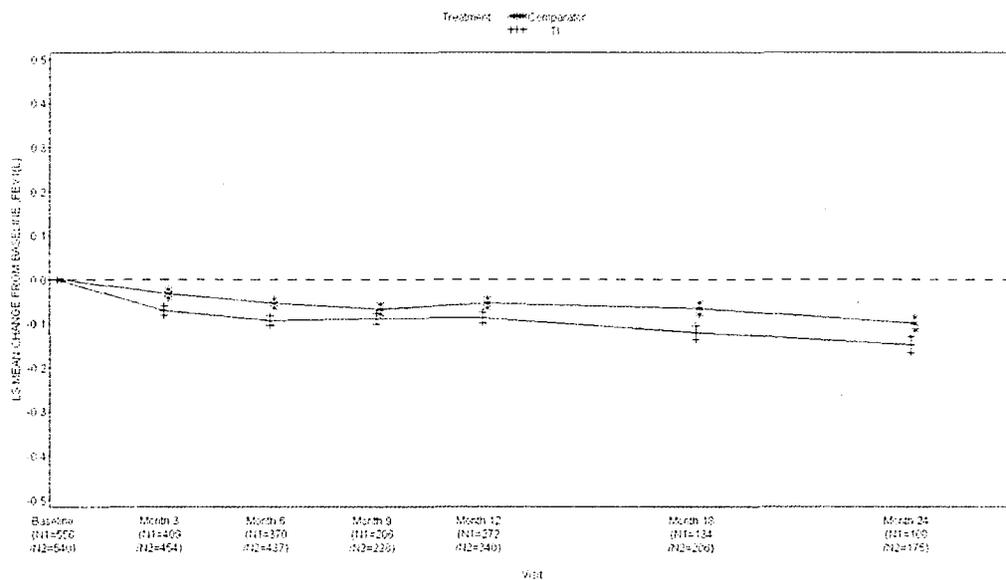
TI: Technosphere Insulin  
Source: DPARP NDA 2009 Review, Table 23, p. 69; Table 25, p. 71; Table 27, p. 76; Pulmonary CIR, ISS 2009, Table 51, p 159; DPARP NDA 2009 Review, Table 23, p. 69; Table 25, p. 71

<b>Table 4. Change in FEV1 from Baseline in Type 2 DM with TI via the MedTone Inhaler (Safety Population, Original Submission)</b>			
<b>Timepoint</b>	<b>FEV1 (L)</b>		
	<b>TI MedTone Mean (SD)</b>	<b>Comparator Mean (SD)</b>	<b>Treatment Difference TI – Comparator (95% CI)</b>
6 months	<b>Applicants 2009 Pooled Type 2 (MMRM)</b>		
	-0.13 (0.01) N=688	-0.08 (0.01) N=765	<b>-0.05</b> (95% CI: -0.07, -0.03)
1 year	<b>MKC-TI-102 (Agency-LOCF)</b>		
	-0.13 (0.23) N=266	-0.07 (0.19) N=283	<b>-0.06</b> (95% CI: -0.10, -0.03)
2 years	<b>MKC-TI-030 (Agency-LOCF)</b>		
	-0.14 (0.21) N=530	-0.10 (0.22) N=578	<b>-0.04</b> (95% CI: -0.06, -0.01)

TI: Technosphere Insulin, Afrezza  
Source: DPARP NDA 2009 Review, Table 32, p. 81; Table 25, p 71; Table 32, p. 83; Table 34, p. 84

The results from the long-term studies showed that the early difference persisted and that the results were statistically different when compared to an active control. As can be seen in the Applicant’s analysis, in both type 1 DM (Figure 3) and type 2 DM (Figure 4), after the initial separation between groups, the difference did not appear to be progressive; however controlled pulmonary safety data beyond 2 years of treatment is not available. The Applicant’s analysis represents pooled data from both 1 and 2 year trials (Studies 009, 102, and 030). The Agency’s analysis, which examined Study MKC-TI-030 (2 year data) in Type 1 DM and Type 2 DM showed similar results.

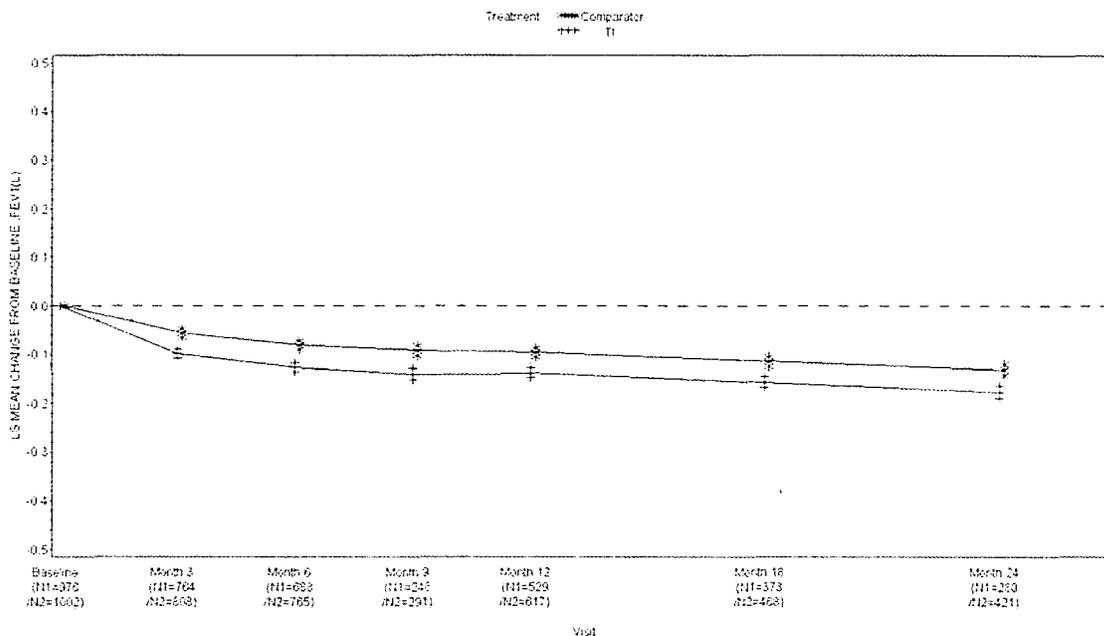
**Figure 3. LS Mean (SE) of Change from Baseline in FEV1 (L) by Visit to 2 years (MMRM Model, Type 1 DM, Applicant's Analysis)**



N1=TI; N2 = Comparator; SE=standard error

Source: Figure 35, p 159, Pulmonary CIR, ISS, Module 5; DPARP Review 2009, Figure 11, p. 77.

**Figure 4. LS Mean (SE) of Change from Baseline in FEV1 (L) by Visit to 2 years (MMRM Model, Type 2 DM, Applicant's Analysis)**



N1=TI; N2=Comparator; SE=standard error

Source: Figure 66, p 229, Pulmonary CIR, ISS, Module 5 and DPARP 2009 review, Figure 17, p. 91.

The Agency's categorical analysis showed that more patients treated with Afrezza had a significant decline in FEV1 ( $\geq 15\%$ ) than in the comparator groups, as shown in Table 5.

<b>Table 5. Proportion of Subjects with a Decline in FEV <math>\geq 15\%</math> (Original Submission, Safety Population)</b>		
Timepoint	% of Subjects	
	TI MedTone	Comparator
	<b>Type 1</b>	
1 year <sup>1</sup>	2.5	1.2
2 year <sup>2, 3</sup>	5.5	0.8
	<b>Type 2</b>	
1 year <sup>2, 4</sup>	9.0	2.8
2 year <sup>3</sup>	5.9	4.3

<sup>1</sup> Study MKC-TI-009; <sup>2</sup> Difference was statistically significant; <sup>3</sup> Study MKC-TI-030; <sup>4</sup> Study MKC-TI-102  
 TI: Technosphere Insulin, Afrezza  
 Source: DPARP 2009 review, p 73 and 88

A small number of patients from the 6-month trial (MKC-TI-103), the 1-year trials (MKC-TI-009 and MKC-TI-102), and the 2-year trial (MKC-TI-030) were followed up 8 weeks after TI

discontinuation, as part of the extension trial MKC-TI- 126. The Agency analyzed the two 1-year studies (MKC-TI-009: Table 6 and MKC-TI-102: Table 7 ) from this extension trial.

<b>Table 6. FEV1(L) Results Off Treatment – Type 1 Diabetes - MKC-TI-126 (extension of MKC-TI-009)</b>		
	<b>TI (n=81) Mean (SD)</b>	<b>Comparator (n=83) Mean (SD)</b>
<b>Last FEV1 on 009</b>		
<b>Observed</b>	3.54 (0.7)	3.53 (0.8)
<b>Change from baseline</b>	-0.07 (0.21)	-0.02 (0.19)
<b>Last FEV1 on 126</b>		
<b>Observed</b>	3.48 (0.7)	3.50 (0.8)
<b>Change from last 009</b>	+0.01 (0.14)	-0.02 (0.14)
<b>% patients with increase in FEV1 during 126</b>	42/81 51%	35/83 42%
<b>% patients returning to 009 baseline FEV1 or higher</b>	30/81 37%	43/83 52%

Source: Biometrics Review, Dr. Joy Mele

<b>Table 7. FEV1(L) Results Off Treatment – Type 2 Diabetes -MKC-TI-126 (extension of MKC-TI-102)</b>		
	<b>TI (n=69) Mean (SD)</b>	<b>Comparator (n=67) Mean (SD)</b>
<b>Last FEV1 on 102</b>		
<b>Observed</b>	2.89 (0.7)	2.80 (0.7)
<b>Change from baseline</b>	-0.11 (0.19)	-0.08 (0.17)
<b>Last FEV1 on 126</b>		
<b>Observed</b>	2.93 (0.7)	2.78 (0.7)
<b>Change from 102</b>	+0.04 (0.18)	-0.02 (0.15)
<b>% patients with increase in FEV1 during 126</b>	45/69 65%	29/67 43%
<b>% patients returning to 102 baseline FEV1 or higher</b>	22/69 32%	21/67 31%

Source: Biometrics Review, Dr. Joy Mele

Although the numbers are small, it appears as if only 37% and 32% of TI-treated patients returned to their baseline FEV1 as measured in MKC-TI-009 and MKC-TI 102, respectively. Given that both TI and comparator groups' FEV1 are simultaneously declining, return to baseline FEV1 is not an acceptable measure of reversibility. Ideally, the comparison between the treatment difference at randomization baseline and then extension follow-up would have provided the most useful data. However, Dr. Mele completed the analysis in this manner, due to the very small number of patients contributing data at the end time point, which precluded a meaningful comparison of treatment differences. Thus, the available data from the original program does not provide adequate confirmation that the change in FEV1 noted with Afrezza is

reversible off-treatment, at least at 2 months of follow-up (*Biometrics Review 2009, Dr. Joy Mele*).

b) Decline in FEV1 Post-Inhalation

Immediate post-inhalation FEV1 was also measured in three small phase 1 studies. A mean decline in FEV1 of 90-138 mL was noted in two of the trials. This magnitude of decline would not be expected to cause symptoms in someone with a normal baseline FEV1. The FEV1 data is generally consistent with the effects seen in the Exubera program.

**2. Bronchospasm in Patients with Underlying Lung Disease**

Five studies in patients with underlying lung disease were included in the clinical development program, as listed in Table 8. Three studies are completed, and outlined below. Study MKC-TI-105 was terminated early for poor enrollment and Study MKC-TI-134 is on-going with a goal enrollment of 255 patients with asthma and 255 patients with COPD.

<b>Table 8. Clinical Studies in Patients with Underlying Lung Disease with TI via MedTone Inhaler (Original Submission)</b>						
Study Status	Design	Study Duration	Population			N
			Diabetes	Asthma	COPD	
MKC-TI-027 <i>Completed</i>	OL, SD	-	x	x FEV1 > 60%		5 Asthma 15 non
MKC-TI-113 <i>Completed</i>	OL	-		x FEV1 ≥ 70%		17 Asthma 13 non
MKC-TI-015 <i>Completed</i>	OL	-		x FEV1 ≥ 50%	x	18 <sup>1</sup> COPD 20 <sup>1</sup> non
MKC-TI-134 <i>Ongoing</i>	R, OL	1 year	x	x	x	9 Asthma 8 COPD
MKC-TI-105 <i>Terminated due to poor enrollment</i>	R, OL	1 year	x	x		----

OL=open-label, SD=single-dose, R=randomized, FEV1= Forced expiratory volume in 1 second, COPD=Chronic obstructive pulmonary disease, non= non-asthmatic or non-COPD  
<sup>1</sup> Only 8 of these subjects had pulmonary function measured.

### Study MKC-TI-027

Study MKC-TI-027 studied the immediate effect of TI via the MedTone inhaler on pulmonary function in 5 asthmatic subjects and 15 non-asthmatic subjects, measured as the change in FEV1 and FVC from 5 to 120 minutes post-TI administration. Mean changes from pre- to post-TI spirometry measurements showed no clear pattern of difference in either patient population. In addition, review of the individual subject data revealed no **clinically significant decrease ( $\geq 15\%$ )** in any asthmatic or non-asthmatic subject at any time point after administration of TI Inhalation Powder.

### Study MKC-TI-113

Study MKC-TI-113 was similar in design to Study MKC-TI-027, with the following exceptions: 1) Spirometry measurements began at 15 minutes and 2) TI was administered alone and following pre-treatment with salbutamol (short-acting beta-agonist bronchodilator). Asthmatic subjects had a clinically significant mean decline in FEV1 15 minutes post-TI (~400 mL), with a return towards baseline FEV1 by 120 minutes. When TI Inhalation Powder was given after pre-treatment with salbutamol, mean FEV1 was higher at all time points after dosing than before dosing. Two SAEs of bronchospasm were reported in asthmatic subjects. One of these subjects experienced a drop in FEV1 of 45% from baseline with wheezing. Treatment with 400 mcg of salbutamol reversed his symptoms and his FEV1 recovered to baseline by 30 minutes. The other subject experienced a 33% drop in FEV1 at 15 minutes and wheezing at 30 minutes post-TI inhalation. Salbutamol was given, but no comment is made by the Applicant regarding reversal of symptoms or FEV1. Overall, bronchospasm (N=3 (18%)) and wheezing (N=2 (12%)) adverse events occurred more often in asthmatics and compared to non-asthmatics, in which neither bronchospasm nor wheezing was reported. Cough adverse events were similar between asthmatics and non-asthmatics.

### Study MKC-TI-015

Study MKC-TI-015 studied the immediate effect of TI on pulmonary function in COPD and non-COPD subjects, measured as the change in FEV1 from 18 to 485 minutes (about 8 hours) post-TI administration. COPD subjects showed a small mean decline in FEV1 by 18 minutes (200 mL), which gradually recovered by 8 hours. No SAEs were reported. Respiratory AEs (cough, dry throat) were similar across treatment groups.

### MKC-TI-134

No specific study in patients with underlying lung disease with the Gen2 inhaler was provided in this resubmission; however an update on the enrollment status of study patients with asthma or COPD using TI via the MedTone inhaler (MKC-TI-134) was included. These enrollment numbers are from the 120-day safety update.

Study MKC-TI-134 was initiated in 2007. Out of an enrollment goal of 255 asthmatic subjects, 180 have been screened, with the vast majority of subjects (166/180(92%)) failing screening. The most common reason for failing screening was HbA1c out of range. A total of 9 subjects

have been randomized, with 4 subjects prematurely discontinuing. Three subjects discontinued prior to receiving drug for peak expiratory flow out of range. One subject discontinued at month 10 due bronchitis and an SAE of lymphoma.

Out of an enrollment goal of 255 patient with COPD, 120 patients have been screened, with the majority not meeting eligibility criteria (106/120 (89%)). The most common reason for failing screening was also HbA1c out of range. A total of 9 subjects have been enrolled. One subject discontinued prior to randomization due to an SAE of myocardial infarction. Four subjects discontinued prematurely, 2 with COPD exacerbation after receiving at least one dose of TI.

### 3. Cough

Cough was the most common adverse event noted in the clinical program (approximately 30% incidence), and the most common reason for discontinuation due to an adverse event (approximately 3%). The frequency of cough was similar to what was seen in the Exubera program, but more than what is typically observed for dry powder inhalers developed for the treatment of asthma/COPD. Cough usually occurred within 10 minutes, was generally mild, dry, intermittent or single-defined, and tended to decrease over time. Other common AEs that were reported in  $\geq 1\%$  of patients and more commonly than in the comparator group for the pooled safety population included: dyspnea, lung infiltration, pharyngolaryngeal pain, productive cough, throat irritation, bronchitis, nasopharyngitis, rhinitis, and pulmonary function test decreased (Table 9).

<b>Table 9. Common Respiratory Adverse Events Occurring at <math>\geq 1\%</math> and More Commonly with Active Treatment than Comparator (Safety Population, Original Submission, Pooled Analysis)</b>			
<b>System Organ Class/PT N (%)</b>	<b>TI MedTone N = 2409</b>	<b>TP MedTone N = 114</b>	<b>Comparator N = 1944</b>
Subjects with Respiratory AE	1088 (45.2)	44 (38.6)	606 (31.2)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL</b>	794 (33)	29 (25.4)	192 (9.9)
Cough	642 (26.7)	21 (18.4)	109 (5.6)
Crackles Lung	1 (0)	2 (1.8)	0
Dyspnea	32 (1.3)	0	5 (0.3)
Lung Infiltration	1 (0)	2 (1.8)	0
Pharyngolaryngeal Pain	56 (2.3)	4 (3.5)	20 (1)
Productive Cough	56 (2.3)	3 (2.6)	16 (0.8)
Throat irritation	55 (2.3)	2 (1.8)	2 (0.1)
<b>INFECTIONS AND INFESTATIONS</b>	574 (23.8)	29 (25.4)	497 (25.6)
Bronchitis	45 (1.9)	2 (1.8)	24 (1.2)
Nasopharyngitis	184 (7.6)	16 (14)	155 (8)
Rhinitis	26 (1.1)	1 (0.9)	19 (1)
<b>INVESTIGATIONS</b>	51 (2.1)	1 (0.9)	24 (1.2)
Pulmonary function test decreased	44 (1.8)	0	22 (1.1)

TI: Technosphere Insulin; TP: Technosphere powder, excipient only  
Source: Module 5, Pulmonary CIR, Table 12, p. 53-57; DPARP Review, Table 18, p 57

### **B. First Resubmission – June 2010 (Complete Response 1)**

The Applicant submitted two, open-label, crossover, single-dose, clinical pharmacology studies in 66 healthy volunteers with the Gen2 inhaler and the MedTone inhaler (MKC-TI-140 and MKC-TI-141). Both studies included spirometry assessments at 1 and 2 hours post single-dose administration. As the original NDA (in which the MedTone inhaler was used) contained controlled pulmonary function information for up to two years, these studies added relatively little information to the overall pulmonary safety database with respect to extent of exposure. As noted in the Background section, the Applicant was advised that pulmonary safety data would be necessary with the new Gen2 inhaler, including a comparison between the Gen2 and MedTone inhalers.

### **C. Second (Current) Resubmission – October 2013 (Complete Response 2)**

In the second resubmission, the Applicant submitted two phase 3 studies which provided pulmonary safety data for up to 24 weeks with the new drug/device combination (TI delivered via the Gen2 inhaler), as well as a comparison to the pulmonary safety data obtained with the TI/MedTone inhaler drug/device combination. Table 10 outlines the two new studies. The purpose of including the MedTone inhaler in Study MKC-TI-171 was to compare the pulmonary safety data with the MedTone inhaler to the Gen2 inhaler, as the majority of the clinical safety data had been obtained with the TI/MedTone inhaler, as previously discussed.

<b>Table 10. Clinical Studies Used in the Evaluation of Pulmonary Safety (Current Submission)</b>						
<b>Study</b>	<b>Design</b>	<b>Study Duration (weeks)</b>	<b>Treatment Arms<sup>1</sup></b>	<b>N</b>	<b>Population</b>	<b>Objective</b>
MKC-TI-171	OL, R, C, FT, MC	24	TI in Gen2 Inhaler <sup>2</sup>	174	Adults: Type 1 DM suboptimally controlled with current insulin regimen	Non-inferiority to insulin aspart in HbA1c levels
			TI in MedTone Inhaler	174		
			Insulin Aspart	170		
MKC-TI-175	PC, DB, R	24	TI in Gen2 Inhaler <sup>2</sup>	177	Adults: Type 2 DM suboptimally controlled on metformin or $\geq 2$ OAD	Superiority to placebo (excipient powder)
			TP in Gen2 Inhaler <sup>2</sup>	176		

MC = multi-center, R = randomized, OL = open-label, FT = forced titration, C = controlled, DB = double-blind, PC = placebo controlled, OAD = oral antidiabetic agent, TI = Technosphere Insulin (Afrezza), TP = Technosphere particles (excipient only), DM = diabetes mellitus

<sup>1</sup> All type 1 patients had basal insulin = insulin glargine, insulin detemir, and NPH insulin

<sup>2</sup> Gen2 inhaler version C which is proposed for marketing.

Study MKC-TI-171 included two treatment arms in which TI was delivered via the new, proposed to-be-marketed device (Gen2 inhaler), and the previously studied device (MedTone inhaler) providing a head-to-head comparison in patients with type 1 DM. Additional clinical data was provided in Study MKC-TI-175, which compared the Gen2 inhaler with and without active drug in patients with type 2 DM. The populations for both studies were similar to the studies included in the original submission, as outlined in the section entitled Original Submission – March 2009, in which patients with abnormal lung function, underlying lung disease, and smokers were excluded.

In the following section, the pulmonary safety data from the new clinical studies with TI delivered via the Gen2 inhaler (MKC-TI-171 and -175) will be reviewed and compared to the data from the original clinical development program in which TI was delivered via the MedTone inhaler. It is important to note, that while we have reviewed these studies for pulmonary safety, the primary objective of these studies was to provide further evidence to support the efficacy of Afrezza. Pulmonary safety assessments were added to these studies in order to obtain pulmonary safety data with the new Gen2 device, as the majority of the pulmonary safety data was derived from TI delivered via the MedTone inhaler.

Studies MKC-TI-171 and MKC-TI-175 are reviewed in detail in Appendix 1: MKC-TI-171 (Study 171) and Appendix 2: MKC-TI-175 (Study 175).

Study MKC-TI-171 was a phase 3, open-label, randomized trial in 518 patients with type 1 DM, treated with TI delivered via the Gen2 inhaler or the MedTone inhaler compared to aspart insulin (randomized 1:1:1) over a 24-week treatment period.

Study MKC-TI-175 was a phase 3, double-blind, placebo-controlled, randomized, trial in 353 patients with type 2 DM, treated with TI (active) delivered via the Gen2 inhaler compared to Technosphere Particles (TP; FDKP excipient alone) delivered via the Gen2 inhaler (randomized 1:1) over a 24-week treatment period.

For both studies, there was a 6-week run-in phase, a 24-week treatment phase, and a 4-week safety follow-up. Spirometry was performed at screening, Weeks 0, 12, 24, and at the 4-week follow-up visit. Subjects were non-smoking adults with FEV1 and FVC  $\geq$  70%, and a normal FEV1/FVC ratio. Subjects with pulmonary disease, including COPD and asthma, and active respiratory infection within 30 days, were excluded.

### Pulmonary Safety Review

#### Exposure

Exposure for the pooled studies in the original submission and the current submission, up to the safety cut-off of July 31, 2013, are detailed for patients with type 1 DM and type 2 DM in Table 11 and Table 12, respectively.

<b>Table 11. Duration of Exposure for Type 1 DM – Original Submission Phase 2/3 Clinical Trials and Current Submission (up to safety data cut-off July 31, 2013)</b>			
<b>Exposure Duration (days)</b>	<b>TI Gen2 N = 174</b>	<b>TI MedTone N = 852</b>	<b>Comparator N = 599</b>
Mean	141	270	340
SD	56	213	222
Median	169	173	362
Range	5-206	1-743	0-800
TI: Technosphere Insulin, Afrezza Source: Summary of clinical safety, Table 3, p. 14.			

<b>Table 12. Duration of Exposure for Type 2 DM – Original Submission Phase 2/3 Clinical Trials and Current Submission (up to safety data cut-off July 31, 2013)</b>					
<b>Exposure Duration (days)</b>	<b>TI Gen2 N = 177<sup>1</sup></b>	<b>TI MedTone N=1795</b>	<b>TP Gen2 N=176</b>	<b>TP MedTone N=114</b>	<b>Comparator N = 1363</b>
Mean	158	259	152	81	369
SD	39	238	44	27	252
Median	169	127	169	91	364
Range	9-211	1-764	12-205	2-128	0-810

<sup>1</sup> Applicant's table used 196 for the TI Gen2 arm. These additional 19 subjects are added from Study MKC-TI-162 (16-week study using TI Gen2).  
TI: Technosphere Insulin; TP: Technosphere powder, excipient only  
Source: Module 5, Study MKC-TI-175, Table 22, p 94; Summary of clinical safety, Table 4, p. 14

As can be seen in Table 11 and Table 12, the majority of the safety data is derived from TI delivered via the MedTone inhaler. The two clinical studies provided in the current submission (MKC-TI-171 and -175) intend to bridge the pulmonary safety of the MedTone inhaler to the Gen2 inhaler. As was discussed previously, the bridging of pulmonary safety data between two different devices is a novel approach.

#### Deaths

A total of 23 subjects died during the clinical development program. None of these deaths were due to primary respiratory events.

#### Nonfatal Serious Pulmonary Adverse Events

All the respiratory SAEs for the clinical development program, including the two new studies with the resubmission (MKC-TI-171 and MKC-TI-174) are listed in Table 13. No SAEs were reported in the TP group (N=290, not listed).

**Table 13. All Serious Respiratory Adverse Events (Safety Population, 2013 Resubmission Safety Update)**

<b>System Organ Class/PT N (%)</b>	<b>TI N = 3017</b>	<b>Comparator N = 3307</b>
Subjects with Respiratory SAE	9 (0.5)	7 (0.5)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL</b>	9 (0.3)	2 (0.06)
Asthma	1 (0.03)	0
Atelectasis	1 (0.03)	0
Bronchial hyper-reactivity	1 (0.03)	0
Bronchial obstruction	1 (0.03)	0
Cough	1 (0.03)	0
Dyspnea	1 (0.03)	0
Hemoptysis	1 (0.03)	0
Orthopnea	1 (0.03)	0
Vocal cord polyp	1 (0.03)	0
Hydrothorax	0	1 (0.03)
Pulmonary edema	0	1 (0.03)
<b>INFECTIONS AND INFESTATIONS</b>	4 (0.13)	6 (0.18)
Pneumonia	2 (0.07)	5 (0.15)
Pulmonary tuberculosis	1 (0.03)	0
Upper respiratory tract	1 (0.03)	0
Bronchitis	0	1 (0.03)

In the controlled phase 2 and 3 trials, there were more respiratory serious adverse events (SAES), reported in patients treated with TI than in those subjects who were treated with comparator therapies.

One serious adverse event occurred in Study MKC-TI-171 for bronchial hyperreactivity. The case narrative can be found in the detailed review of Study MKC-TI-171, Appendix 1.

There were no SAEs that were reported in more than one subject in the Afrezza group and more commonly than in the comparator group. Analysis of the respiratory SAEs does not demonstrate a particular safety signal with use of Afrezza.

Dropouts and/or Discontinuations

Respiratory adverse events leading to discontinuation were more common in the TI group, both with the Gen2 inhaler and the MedTone inhaler, than the comparator group, as detailed in Table 14 and Table 15.

**Table 14. Respiratory AE Leading to Discontinuation by Preferred Term in Type 1 DM (Safety Population; >1 Subject in Any Arm)**

Preferred Term	Subject, N (%)		
	TI Gen2 N = 174	TI MedTone N = 852	Comparator N = 835
Any AE	14 (8.0)	33 (3.9)	1 (0.1)
Cough	10 (5.7)	24 (2.8)	0
Dyspnea	4 (2.3)	2 (0.2)	0
Bronchial obstruction	0	2 (0.2)	0

TI: Technosphere Insulin, Afrezza  
Source: Resubmission safety update 2013, Table 98, p. 302.

**Table 15. Respiratory AE Leading to Discontinuation by Preferred Term in Type 2 DM (Safety Population; >1 Subject in Any Arm)**

Preferred Term	Subject, N (%)				
	TI Gen2 N = 177 <sup>1</sup>	TI MedTone N = 1795	TP Gen2 N = 176	TP MedTone N = 114	Comparator N = 1363
Any AE	7 (4.0)	87 (4.8)	7 (4.0)	0	2 (0.1)
<b>INFECTIONS AND INFESTATIONS</b>					
Bronchitis	0	5 (0.3)	0	0	0
URTI <sup>2</sup>	0	3 (0.2)	0	0	0
Pneumonia	0	2 (0.2)	0	0	1 (0.1)
<b>RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS</b>					
Cough	2 (1.1)	47 (2.6)	6 (3.4)	0	0
Dyspnea	1 (0.6)	8 (0.4)	0	0	0
Oropharyngeal pain	1 (0.6)	1 (0.1)	0	0	0
Throat irritation	0	4 (0.2)	0	0	0
Asthma	0	3 (0.2)	0	0	0
Bronchial Hyperreactivity	0	2 (0.1)	0	0	0
Bronchospasm	0	2 (0.1)	0	0	0
Wheezing	0	2 (0.1)	0	0	0

<sup>1</sup> Applicant's table used 196 for the TI Gen2 arm, including an additional 19 subjects are added from Study MKC-TI-162.  
<sup>2</sup> URTI: Upper respiratory tract infection  
TI: Technosphere Insulin; TP: Technosphere powder, excipient only  
Source: Resubmission safety update 2013, Table 111, p. 327; MKC-TI-175 CSR, Table 39, p. 136.

The most common respiratory adverse event leading to discontinuation was cough, as detailed below. Respiratory adverse events that led to discontinuation of study treatment were more

common in the TI Gen2 group compared to the TI MedTone group in patients with type 1 DM, but similar between groups for patients with type 2 DM.

### 1. FEV1

The 2 new clinical studies in this resubmission included assessment of pulmonary function (FEV1 and FVC). FVC will not be discussed here, as it generally followed the same trend as FEV1. There was no significant difference in the mean change from baseline in FEV1 between the TI Gen2 and TI MedTone groups at Week 24 (TIGen2 - TI MedTone = 0.01L, 95% CI [-0.02, 0.04]) as displayed in **Table 16**. Although no analysis was done to compare the active arms in Study MKC-TI-171 to the active comparator, the numerical differences of -0.04 L for Gen2 and -0.05 L for MedTone are similar to the original submission.

<b>Table 16. Change in FEV1 (L) from Baseline in Type 1 DM at 6 months in Studies MKC-TI-171 and MKC-TI-175 Compared to Original Submission (Safety population)</b>			
<b>TI Gen 2</b> Mean (SE)	<b>TI MedTone</b> Mean (SE)	<b>Comparator</b> Mean (SE)	<b>Treatment Difference</b> Mean (SE)
<b>MKC-TI-171</b>			
-0.07 (0.01) N=127	-0.08 (0.01) N=133	-0.04 (0.01) N=146	TI Gen2 – TI MedTone <b>0.01</b> (95% CI: -0.02, 0.04)
			TI Gen2 – Comparator <b>-0.03<sup>1</sup></b>
			TI MedTone – Comparator <b>-0.04<sup>1</sup></b>
<b>Original Submission<sup>2</sup></b>			
	-0.09 (0.01) N=370	-0.05 (0.01) N=437	TI MedTone – Comparator <b>-0.04</b> (95% CI: -0.7, -0.1)
<sup>1</sup> No analysis was done to determine statistical significance; <sup>2</sup> Applicants 2009 Pooled Type 1 (MMRM) Source: Study MKC-TI-171 CSR, Table 52, p 168; Summary of clinical safety 2013, Table 29, p. 67; Pulmonary CIR, ISS 2009, Table 51, p 159.			

In patients with type 2 DM, TI was compared to TP (excipient only), both delivered via the Gen2 inhaler. The change in FEV1 from baseline was similar to the changes seen in the original submission using the MedTone device, as shown in **Table 17**. The slight numerical difference is due to the comparator arm (Gen2 device with Technosphere particles without insulin), showing a smaller change in FEV1 from baseline than in the original submission.

<b>Table 17. Change in FEV1 (L) from Baseline in Type 2 DM at 6 months in Resubmission Compared to Original Submission (Safety Population)</b>			
LS Mean (SE)			
MKC-TI-175		Original Submission*	
TI Gen2	Inhaled Excipient (TP) Gen2	TI MedTone	Non-Inhaled Insulin
-0.13 (0.01) N=177	-0.04 (0.01) N=176	-0.13 (0.01) N=688	-0.08 (0.01) N=765
<b>-0.09 (95% CI: -0.12, -0.05)</b>		<b>-0.05 (95% CI: -0.07, -0.03)</b>	

Applicant's 2009 Pooled Type 2 (MMRM)  
Source: Study MKC-TI-175 CSR, Table 43, p. 143; DPARP NDA 2009 Review, Table 37, p. 90.

As seen in the original submission, categorical analysis showed that patients with a significant decline in FEV1 ( $\geq 15\%$ ) were uncommon and similar across treatment groups for both studies.

Pulmonary function was measured 4 weeks off treatment (at Week 28) for both studies. In Study MKC-TI-171 the FEV1 adjusted mean change from baseline after 4 weeks off-treatment was similar in all treatment groups.

(Table 18).

<b>Table 18. Study MKC-TI-171: Change in FEV1 (L) from Baseline by Visit (Safety Population) – Observed values*</b>				
	Statistics	TI Gen2 N=174	TI MedTone N=173	Insulin Aspart N=173
<b>Baseline</b>	N (%)	173 (99%)	168 (97%)	168 (97%)
	Mean (SD)	3.48 (0.8)	3.42 (0.8)	3.36 (0.8)
<b>Week 24</b>	N (%)	127 (73%)	133 (77%)	146 (84%)
	Adjusted Mean (SE)	3.43 (0.8)	3.34 (0.8)	3.36 (0.8)
	Adjusted Mean Change (SE)	<b>-0.07 (0.2)</b>	<b>-0.08 (0.2)</b>	<b>-0.04 (0.1)</b>
<b>Week 28</b>	N (%)	116 (67%)	127 (73%)	135 (78%)
	Adjusted Mean (SE)	3.47 (0.8)	3.38 (0.8)	3.33 (0.8)
	Adjusted Mean Change (SE)	<b>-0.05 (0.1)</b>	<b>-0.05 (0.1)</b>	<b>-0.06 (0.1)</b>

\*Primary analysis was MMRM, but Week 28 was only analyzed as observed value  
Source: Module 5.3.5.1, Trial MKC-TI-171 CSR, Table 14.3.4.3.1; Trial MKC-TI-175 CSR, Table 14.3.4.3.1, p 1049

For Study MKC-TI-175 the FEV1 adjusted mean change from baseline after 4 weeks off-treatment was higher in the TI Gen2 group compared to placebo. (Table 19). The numerical difference of 0.04 is similar to the treatment difference seen with subjects on TI treatment compared to placebo.

	Statistics	TI Gen2 N=177	Placebo N=176
<b>Baseline</b>	N (%)	173 (98%)	166 (94%)
	Mean (SD)	2.87 (0.7)	2.84 (0.7)
<b>Week 24</b>	N (%)	144 (81%)	128 (73%)
	Adjusted Mean (SE)	2.78 (0.7)	2.78 (0.7)
	Adjusted Mean Change (SE)	<b>-0.13 (0.2)</b>	<b>-0.04 (0.1)</b>
<b>Week 28</b>	N (%)	142 (80%)	127 (72%)
	Adjusted Mean (SE)	2.84 (0.8)	2.79 (0.8)
	Adjusted Mean Change (SE)	<b>-0.06 (0.2)</b>	<b>-0.02 (0.1)</b>

\*Primary analysis was MMRM, but Week 28 was only analyzed as observed value  
Source: Trial MKC-TI-175 CSR, Table 14.3.4.3.1, p 1049

## 2. Cough

Cough was the most common adverse event (excluding hypoglycemia), with similar incident rates, discontinuation rates, and characteristics compared to the original submission (Table 20).

	MKC-TI-171			MKC-TI-175		Original submission		
	TI Gen2 N=174	TI Med Tone N=173	Insulin aspart N=171	TI Gen2 N=177	TP N=176	TI N=2409	TP N=114	Comp N=1944
<b>Incidence</b>	32%	23%	2%	24%	20%	27%	18%	6%
<b>Early d/c</b>	6%	3%	0	1%	3%	3%	0%	0%

TI=Technosphere Inhalation Powder (active); TP=Technosphere Particles (excipient alone); Comp=Comparator; d/c = discontinuation  
Source: DPARP Review 2009, Table 18, p 57, Table 14, p 50; Study 171, Table 41, p 147; Table 43, p 151; Study 175, Table 39, p 136, Table 34, p 127.

The slightly numerically higher incidence of cough and early discontinuation due to cough in the Gen2 arm of Study MKC-TI-171 as compared with the incidence with the MedTone Inhaler, is not repeated in Study MKC-TI-175, and is likely not to be concerning on its own. Notably, in Study MKC-TI-175, the excipient (TP) had similar cough rates to the excipient plus the insulin. This finding was also seen in the original submission.

Other common respiratory adverse events that occurred more often in the treatment arms compared to the active comparator were dyspnea, bronchitis, throat irritation, oropharyngeal pain, dry throat, upper respiratory tract infection, nasopharyngitis, rhinitis, and pharyngitis for Study MKC-TI-171 (type 1 DM), as seen in Appendix 1, Table 25. Other common respiratory adverse events seen in Study MKC-TI-175 (type 2 DM) occurring more often in the active arm as compared to the excipient only arm were oropharyngeal pain, throat irritation, dysphonia, nasopharyngitis, upper respiratory tract infection, and rhinitis (Appendix 2; Table 30).

#### **D. Labeling**

DMEP plans to take an Approval action. The product label has been through multiple rounds of negotiation with the Applicant. At the time of this review, the labeling has been finalized. The labeling with respect to pulmonary safety is provided below:

#### **BOXED WARNING**

#### **WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE**

- Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza. *[see Warnings and Precautions (5.1)]*.
- AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD. *[see Contraindications (4.1)]*.
- Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV<sub>1</sub>) to identify potential lung disease in all patients. *[see Dosage and Administration (2.5), Warnings and Precautions (5.1)]*

#### **Section 2: DOSAGE AND ADMINISTRATION**

##### **2.5 Lung Function Assessment Prior to Administration**

AFREZZA is contraindicated in patients with chronic lung disease because of the risk of acute bronchospasm in these patients. Before initiating AFREZZA, perform a medical history, physical examination and spirometry (FEV<sub>1</sub>) in all patients to identify potential lung disease *[see Contraindications (4) and Warnings and Precautions (5.4)]*.

#### **Section 4: CONTRAINDICATIONS**

Chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), because of the risk of acute bronchospasm *[see Warnings and Precautions (5.1)]*.

## **Section 5: WARNINGS AND PRECAUTIONS**

### **5.1 Acute Bronchospasm in Patients with Chronic Lung Disease**

Because of the risk of acute bronchospasm, AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD [see *Contraindications (4)*].

Before initiating therapy with AFREZZA, evaluate all patients with a medical history, physical examination and spirometry (FEV<sub>1</sub>) to identify potential underlying lung disease.

Acute bronchospasm has been observed following AFREZZA dosing in patients with asthma and patients with COPD. In a study of patients with asthma, bronchoconstriction and wheezing following AFREZZA dosing was reported in 29% (5 out of 17) and 0% (0 out of 13) of patients with and without a diagnosis of asthma, respectively. In this study, a mean decline in FEV<sub>1</sub> of 400 mL, was observed 15 minutes after a single dose in patients with asthma. In a study of patients with COPD (n=8), a mean decline in FEV<sub>1</sub> of 200mL was observed 18 minutes after a single dose of AFREZZA. The long-term safety and efficacy of AFREZZA in patients with chronic lung disease has not been established.

### **5.4 Decline in Pulmonary Function**

AFREZZA causes a decline in lung function over time as measured by FEV<sub>1</sub>. In clinical trials excluding patients with chronic lung disease and lasting up to 2 years, AFREZZA treated patients experienced a small (40 mL (95% CI: -80, -1)) but greater FEV<sub>1</sub> decline than comparator treated patients. The FEV<sub>1</sub> decline was noted within the first 3 months, and persisted for the entire duration of therapy (up to 2 years of observation). In this population, the annual rate of FEV<sub>1</sub> decline did not appear to worsen with increased duration of use. The effects of AFREZZA on pulmonary function for treatment duration longer than 2 years has not been established. There are insufficient data in long term studies to draw conclusions regarding reversal of the effect on FEV<sub>1</sub> after discontinuation of AFREZZA. The observed changes in FEV<sub>1</sub> were similar in patients with type 1 and type 2 diabetes.

Assess pulmonary function (e.g., spirometry) at baseline, after the first 6 months of therapy, and annually thereafter, even in the absence of pulmonary symptoms. In patients who have a decline of  $\geq 20\%$  in FEV<sub>1</sub> from baseline, consider discontinuing AFREZZA. Consider more frequent monitoring of pulmonary function in patients with pulmonary symptoms such as wheezing, bronchospasm, breathing difficulties, or persistent or recurring cough. If symptoms persist, discontinue AFREZZA. [see *Adverse Reactions (6)*].

## **Section 6: ADVERSE REACTIONS**

### **6.1 Clinical Trials Experience**

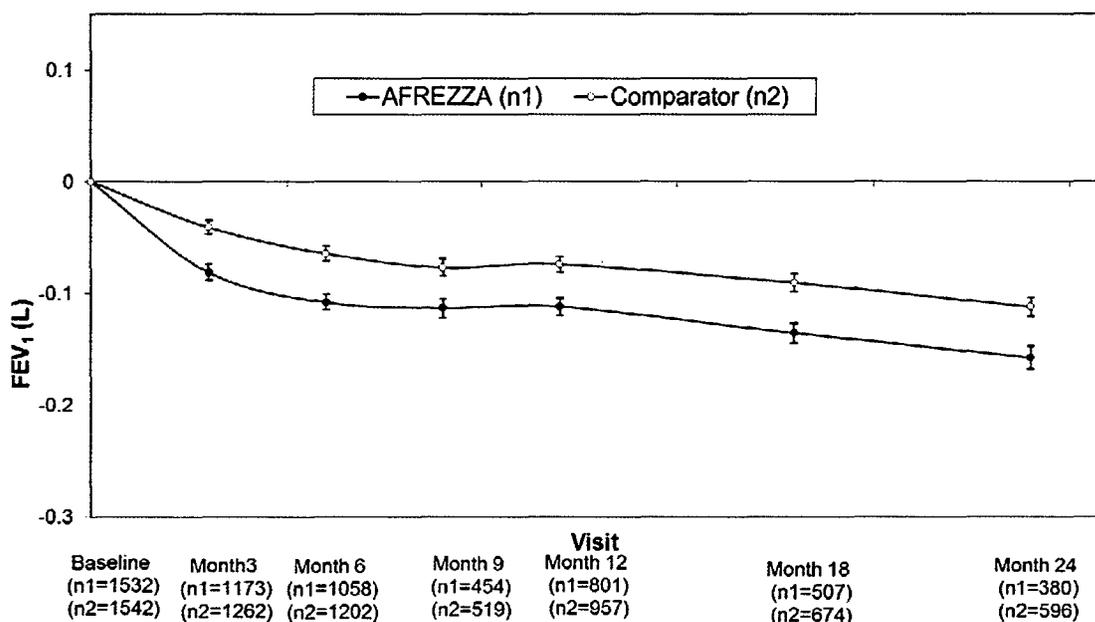
#### **Cough**

Approximately 27% of patients treated with AFREZZA reported cough, compared to approximately 5.2% of patients treated with comparator. In clinical trials, cough was the most common reason for discontinuation of AFREZZA therapy (2.8% of AFREZZA treated subjects).

### Pulmonary Function Decline

In clinical trials lasting up to 2 years excluding patients with chronic lung disease, patients treated with AFREZZA had a 40 mL (95% CI: -80, -1) greater decline from baseline in forced expiratory volume in one second (FEV<sub>1</sub>), compared to patients treated with comparator anti-diabetes treatments. The decline occurred during the first 3 months of therapy and persisted over 2 years (Figure 2). A decline in FEV<sub>1</sub> of  $\geq 15\%$  occurred in 6% of AFREZZA-treated subjects compared to 3% of comparator-treated subjects.

**Figure 2. Mean (+/-SE) Change in FEV<sub>1</sub> (Liters) from Baseline for Type 1 and Type 2 Diabetes Patients**



### **E. Risk Evaluation and Mitigation Strategy (REMS)**

A REMS was required for Afrezza because of the risk of acute bronchospasm in patients with chronic lung disease.

The goal of the Afrezza REMS is to mitigate the risk of acute bronchospasm associated with Afrezza by:

- Informing healthcare providers that there is risk of acute bronchospasm associated with AFREZZA in patients with chronic lung disease
- Informing healthcare providers that acute bronchospasm has been observed with AFREZZA in patients with asthma and COPD
- Informing healthcare providers that AFREZZA is contraindicated in patients with chronic lung disease

- Informing healthcare providers of the need to evaluate patients for lung disease before starting on AFREZZA

The REMS consists of a communication plan which includes: Letters for Healthcare Providers, Letters for Professional Societies, a factsheet, and a website. The Sponsor will also disseminate REMS information at scientific meetings.

#### **F. Post-marketing requirements**

With respect to pulmonary safety, the following post-marketing requirements were agreed to by the Applicant:

A 5-year, randomized, controlled trial in 8,000-10,000 patients with type 2 diabetes to assess the serious potential risk of pulmonary malignancy with AFREZZA use. The primary objective of the trial should be to compare the incidence of pulmonary malignancy observed with AFREZZA to that observed in the standard of care control group. Secondary endpoints should include mortality due to pulmonary malignancy and all-cause mortality. Randomization to AFREZZA or standard of care should be 1 to 1. The patient population should be enriched with respect to lung cancer risk (i.e., predicted incidence of no less than 200/100,000 patient-year). The potential for detection bias should be adequately addressed in the trial design. Subjects who discontinue randomized intervention due to lack of efficacy or tolerability issues should continue to be followed for the outcomes of interest and prospective measures to encourage subject retention and capture outcomes in patients who withdraw or are lost to follow-up should be in place. Glucose control and glycemic rescue should be per standard of care. The trial must also include an assessment of cardiovascular risk based on prospectively defined, collected and independently adjudicated major adverse cardiovascular events or MACE (i.e., cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). Also include as part of the trial a substudy (also with 1 to 1 randomization to either AFREZZA or standard of care) to evaluate the long-term effect of AFREZZA on pulmonary function. Patients in the substudy should have pulmonary function tests at baseline and every 6 months until end of treatment.

Final Protocol Submission: *April 2015*

Trial Completion: *April 2023*

Final Report Submission: *December 2023*

(b) (4)

#### **IV. Advisory Committee Meeting**

The committee was asked to discuss the pulmonary safety findings in the Afrezza clinical development program (acute bronchospasm and pulmonary function decline over time.)

In terms of pulmonary risks, the committee was concerned with the development of acute bronchospasm with the use of Afrezza in patients with undiagnosed asthma or other lung diseases with potential serious consequences. To mitigate this risk, one suggested approach was that the first dose be administered under supervision with adequate support to deal with acute bronchospasm. The committee expressed concern regarding deterioration of pulmonary function (possibly irreversible) over time, particularly in patients with undiagnosed COPD given that the lung function data covers only 2 years. The committee noted the need to evaluate a patient's pulmonary function prior to use of Afrezza and periodically over time, such as every 6 months, although the committee questioned whether prescribers would follow through on the recommendation for baseline screening.

The committee recommended that the long term effect on pulmonary function be evaluated in post-marketing studies.

The advisory committee had no particular reason for concern over the impact of changing the device from a safety perspective.

The committee voted in favor of approval for both patients with type 1 diabetes mellitus (majority 13 to 1) and type 2 diabetes mellitus (unanimous) t.

## **V. Conclusions**

The pulmonary safety data in the original NDA was comprised of 9 controlled trials in patients with type 1 and 2 DM, treated up to 2 years with TI via the MedTone inhaler. Subjects were excluded for underlying lung disease (with the exception of specific studies done in subjects with asthma and COPD), smoking, malignancy history, and abnormal lung function. Review of the pulmonary safety data with the MedTone inhaler identified issues regarding decline in FEV1 (both immediately and over time) and cough in patients without underlying lung disease, and bronchospasm and immediate post-inhalation FEV1 decline in subjects with underlying lung disease.

The two new studies with the Gen2 inhaler (MKC-TI-171 and -175) demonstrated a similar pulmonary safety profile.

A key issue in the Afrezza clinical development program was the significant change in device, from the MedTone to the Gen2 inhaler during the course of development. The two new studies with the Gen2 inhaler did not reveal any new pulmonary safety signals, however the data is limited to 6 months. The lack of long-term data with the Gen2 device is to be addressed via the post-marketing study as described above.

Pulmonary safety issues have been adequately conveyed in the product label and will also be the subject of a REMS. From a pulmonary safety standpoint, there are no issues that preclude approval of Afrezza.

## VI. Appendices

### A. Appendix 1: MKC-TI-171 (Study 171)

#### 1. Overview

**Study Title:** A Phase 3, Multicenter, Open-label, Randomized, Forced-titration Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Inhalation Powder in Combination with a Basal Insulin Versus Insulin Aspart in Combination with a Basal Insulin in Subjects with type 1 Diabetes Mellitus Over a 24-week Treatment Period.

**Study Design:** 6-week run-in phase, a 24-week treatment phase, and a 4-week safety follow-up. Spirometry was performed at screening, weeks 0, 12, 24, and at the 4-week follow-up visit.

**Population:** Non-smoking adults with FEV1 and FVC  $\geq$  70%, and a normal FEV1/FVC ratio. Subjects were excluded with underlying lung disease, including COPD and asthma, and active respiratory infection within 30 days.

#### Pulmonary Endpoints

- AEs of special interest: cough, and respiratory events (non-infective). Cough associated with a defined clinical entity (ie, diagnosis, such as upper respiratory tract infection) did not require completion of the cough case report form (CRF); however, the appropriate diagnosis associated with the cough was recorded on the AE CRF.
- Non-AE safety parameters of special interest: PFTs

#### PFT parameters

- URI within 15 days of the scheduled PFTs, rescheduled for 15 days after resolution of symptoms.
- Lower respiratory infection within 30 days of the scheduled PFTs, rescheduled for 30 days after resolution of symptoms.
- Symptoms of a respiratory tract infection at the time of or within 1 week before the PFT testing at the randomization visit (week 0); the subject was discontinued from the study (the subject could return 30 days after resolution of the infection for rescreening).

#### Study treatments

##### TI in Gen2 Inhaler

TI Inhalation Powder consists of recombinant insulin human; fumaryl diketopiperazine (FDKP), the MKC proprietary excipient which self-assembles into Technosphere particles; and polysorbate 80. TI Inhalation Powder is a dry powder formulation and is pre-metered

into unit (U) dose cartridges. It is administered by the Gen2 inhaler. Pre-metered single-dose cartridges are filled with 3.3 mg or 6.7 mg of Technosphere Insulin Inhalation Powder containing 10 U or 20 U of insulin, respectively. Details of the Gen2 inhaler are provided in Table 21.

**Table 21. Description of Gen2 Inhaler**

Investigational Device:	Gen2 Inhaler
Version:	C
Product description:	Breath-powered inhaler requiring 1 inhalation per cartridge
Inhaler Use Period	Use 1 inhaler for up to 15 days, then replace it with a new inhaler
Manufactured by:	MannKind Corporation
Storage conditions:	Store inhaler at room temperature

Source: Module 5.3.5.1, Trial MKC-TI-171 CSR, Table 6, p. 56.

#### TI in MedTone Inhaler

Pre-metered single-dose cartridges are filled with 5 mg or 10 mg of Technosphere Insulin Inhalation Powder containing 15 U or 30 U of insulin, respectively. Details of the MedTone Inhaler are provided in Table 22.

**Table 22. Description of MedTone Inhaler**

Investigational Device:	Gen2 Inhaler
Version:	C
Product description:	Breath-powered inhaler requiring 1 inhalation per cartridge
Inhaler Use Period	Use 1 inhaler for up to 15 days, then replace it with a new inhaler
Manufactured by:	MannKind Corporation
Storage conditions:	Store inhaler at room temperature

Source: Module 5.3.5.1, Trial MKC-TI-171 CSR, Table 6, p. 56.

#### Insulin aspart

Insulin aspart was used in the active comparator arm. Insulin aspart is an insulin analog packaged as 3 mL (300 U) in a prefilled pen. The Novolog FlexPens are packaged as five 3-mL pens per box. Outside of the United States, a commercially available equivalent could have been used.

## 2. Results

### Population

*Disposition:* A total of 518 patients were randomized. Patient disposition is summarized in Table 23.

<b>Table 23. Study MKC-TI-171 Subject Disposition (ITT population)</b>			
	<b>TI Gen2</b>	<b>TI MedTone</b>	<b>Insulin Aspart</b>
<b>ITT Analysis Set</b>	174	174	170
<b>Safety Analysis Set</b>	174	173	171
<b>PP Analysis Set</b>	130 (74.7%)	136 (78.2%)	147 (86.5%)
<b>Randomized treatment phase completers</b>	130 (74.7%)	138 (79.3%)	151 (88.8%)
<b>Completed study</b>	130 (74.7%)	135 (77.6%)	151 (88.8%)
<b>Prematurely Discontinued</b>	44 (25.3%)	36 (20.7%)	19 (11.2%)
<b>Reason for Discontinuation</b>			
<b>Non-Safety</b>			
Protocol violation	2 (1.1%)	2 (1.1%)	2 (1.2%)
Physician decision*	3 (1.7%)	1 (0.6%)	0
Withdrawal by subject*	21 (12.1%)	16 (9.2%)	8 (4.7%)
Non compliance	1 (0.6%)	2 (1.1%)	0
Lost to follow-up	1 (0.6%)	2 (1.1%)	4 (2.4%)
<b>Safety</b>			
AE	16 (9.2%)	9 (5.2%)	0
Death	0	0	1 (0.6%)
*One subject discontinued due to cough in Gen2 arm Source: Module 5.3.5.1, Trial MKD-TI-171 CSR, Table 19, p. 96.			

*Demographics:* Subject age (mean 37 years) was similar between the two treatment groups. The majority of subjects was Caucasian (94-98%) and divided approximately evenly by sex. Weight, height, BMI, and baseline FEV1 were similar between treatment groups, as seen in Table 24.

<b>Table 24: Study MKC-TI-171 Demographic Characteristics of Safety Population</b>						
<b>Characteristic</b>	<b>TI Gen2 N = 174</b>		<b>TI MedTone N = 173</b>		<b>Insulin Aspart N = 171</b>	
Subjects with at least one post-baseline PFT	148 (85)		157 (91)		159 (93)	
Gender						
Male	62 (42)		72 (46)		69 (43)	
Race						
Caucasian	164 (94)		166 (96)		167 (98)	
African American	8 (5)		5 (3)		3 (2)	
Other	2 (1)		2 (1)		1 (1)	
Age						
N	148		157		159	
Mean	37		41		40	
SD	12		13		13	
Range	18,71		18,76		18,76	
Age Group						
18-30	46 (31)		40 (26)		43 (27)	
31-49	81 (55)		75 (48)		80 (50)	
50 - 64	14 (10)		33 (21)		28 (18)	
≥65+	7 (5)		9 (6)		8 (5)	
Weight (Kg)						
N	148		157		159	
Mean	77		76		73	
SD	16		14		15	
Range	42, 129		48, 116		47, 120	
Height (cm)						
N	148		157		158	
Mean	170		171		169	
SD	9		9		10	
Range	150, 200		151, 194		149, 196	
BMI (kg/m <sup>2</sup> )						
N	148		157		158	
Mean	26		26		25	
SD	5		4		4	
Range	17, 39		18, 36		17, 37	
FEV1 (L)	Observed	% Predicted	Observed	% Predicted	Observed	% Predicted
N	173	173	168	168	168	168
Mean	3.5	97	3.4	97	3.4	96
SD	0.8	12	0.8	11	0.8	12
Range	1.5, 6.6	72, 129	1.8, 5.3	71, 134	1.9, 6.1	63, 133

Source: Study MKC-TI-171 CSR, Table 50, p 165-6; Table 14.1.2.1, p. 81.

## Efficacy

Efficacy was not reviewed in detail by this reviewer. Refer to DMEP's clinical review for further details.

## **Safety**

### **Exposure**

Exposure duration for TI Gen2 was a mean (SD) of 140 (56) days, compared to 150 (45) days for the TI MedTone, and 161 (36) days for insulin aspart.

### **Pulmonary safety:**

Head-to-head comparison between the TI Gen2 and TI MedTone inhalers showed that there were no significant differences in pulmonary safety parameters (i.e. cough and FEV1)

### Respiratory Adverse Events

No respiratory deaths occurred in this study. One serious adverse event of bronchial hyper-reactivity was reported in the TI Gen2 group for an incidence of 0.6% (1/174). The narrative is included below:

A 58-year-old Caucasian male with T1DM and a medical history of lingering bronchitis after pneumonia, hypertension, hypercalcemia, depression, anxiety, s/p left nephrectomy due to Wilm's tumor in 1957, and allergy to iodine (rash) was randomized on 22 Aug 2012 to receive TI Gen2 in combination with basal insulin. The subject received TI Inhalation Powder, 10 U at mealtimes plus 10 U supplemental doses as needed, by oral inhalation from 22 Aug 2012 to 05 Sep 2012. The dose was titrated to 10-20-20 U breakfast, lunch, and dinner, respectively, with 2 supplemental doses of 10 U from 06 Sep 2012 to 10 Sep 2012. On [REDACTED] (b) (6), the subject experienced cough, chest pain, and difficulties in breathing and was hospitalized with the diagnosis of "reactive airway disease." The event was considered severe. On hospital admission, the subject had oxygen saturation of 97%. Chest x-ray showed hyperinflated lung with flattened hemidiaphragm. The study medication was discontinued on [REDACTED] (b) (6) and not restarted. The subject was treated with Albuterol 2.5 mg per 3 mL 4 times daily and oral Tussinex every 12 hours until [REDACTED] (b) (6). The subject was discharged from the hospital in stable condition on [REDACTED] (b) (6). The subject was withdrawn from the study on 24 Oct 2012 due to the AE of bronchial hyperreactivity. Lung function remained stable throughout the study. FEV1 values were 3.39 L (85% predicted) at the screening visit (V1 on 09 Jul 2012) and 3.45 L (87% predicted) at the baseline V4 (10 Aug 2012). FVC values at these visits were 4.56 L (87% predicted) and 4.56 L (87% predicted), respectively. FEV1/FVC ratios were 74.5% and 75.7%, respectively. FEV1 and FVC values were not recorded at the early termination visit. In the opinion of the investigator, the bronchial hyperreactivity was related to the TI Inhalation Powder and not related the study procedure or the study device..

This SAE does not demonstrate a new safety signal associated with the use of Afrezza.

The most common respiratory adverse events are shown in Table 25.

<b>Table 25. Study MKC-TI-171 Respiratory Adverse Events by Preferred Term in &gt; 1 subject in Any Arm (Safety Population)</b>			
<b>Preferred Term</b>	<b>Subject, n (%)</b>		
	<b>TI Gen2 N=174</b>	<b>TI MedTone N=173</b>	<b>Insulin aspart N=171</b>
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>			
Cough	55 (31.6)	39 (22.5)	4 (2.3)
Dyspnea	7 (4.0)	0	0
Throat irritation	5 (2.9)	3 (1.7)	1 (0.6)
Oropharyngeal pain	3 (1.7)	6 (3.5)	3 (1.8)
Sinus headache	1 (0.6)	0	2 (1.2)
Dry throat	0	2 (1.2)	0
<b>INFECTIONS AND INFESTATIONS</b>			
Upper Respiratory Tract Infection	14 (8.0)	16 (9.2)	12 (7.0)
Nasopharyngitis	5 (2.9)	13 (7.5)	12 (7.0)
Bronchitis	6 (3.4)	1 (0.6)	4 (2.3)
Respiratory Tract Infection Viral	3 (1.7)	1 (0.6)	3 (1.8)
Sinusitis	2 (1.1)	2 (1.2)	3 (1.8)
Rhinitis	2 (1.1)	0	1 (0.6)
Tracheitis	1 (0.6)	0	1 (0.6)
Pharyngitis	0	2 (1.2)	1 (0.6)

Source: Module 5.3.5.1, Study 171, Table 41, p. 147.

Cough was the most common AE associated with TI and was reported more frequently with the Gen2 inhaler than the MedTone inhaler. Cough was generally mild, dry, intermittent or single-defined, and occurred usually within 10 minutes of the inhalation. The incidence of cough was highest during the first week after initiation of the treatment with TI and then declined rapidly over subsequent 2-7 weeks of continued use. Cough resolved quickly in all subjects when TI Inhalation Powder therapy was discontinued. Bronchitis was also higher in the TI Gen 2 treatment group (3.4%) compared to the TI MedTone treatment group (0.6%) and Insulin aspart (2.3%).

No subjects in the insulin aspart group discontinued due to respiratory AEs. Subjects did discontinue due to cough as shown in the table below. More subjects in the TI inhaled powder groups discontinued because of cough (5.7% in TI Gen2 and 2.9% in TI MedTone) compared to none in the insulin aspart group. More subjects also discontinued due to cough, dyspnea, bronchial hyperreactivity, and exertional dyspnea for Gen2 compared to MedTone and insulin aspart (Table 26).

**Table 26. Study MKC-TI-171 Respiratory AE by Preferred Term Leading to Discontinuation (Safety Population)**

Preferred Term	Subject, n (%)		
	TI Gen2 N=174	TI MedTone N=173	Insulin aspart N=171
<b>Cough</b>	10 (5.7)	5 (2.9)	0
<b>Dyspnea</b>	4 (2.3)	0	0
<b>Bronchial Hyperreactivity</b>	1 (0.6)	0	0
<b>Exertional dyspnea</b>	1 (0.6)	0	0
<b>Bronchial obstruction</b>	0	1 (0.6)	0

Source: Module 5.3.5.1, Study MKC-TI-171, Table 43, p. 151.

Overall, the findings in patients with type 1 diabetes continue to show that respiratory AEs do occur with TI. While the respiratory AEs were not serious, cough did lead to discontinuation in a small number of patients. Cough remains the most common AE with both the Gen2 and MedTone inhalers. The cough is generally mild, dry, and occurs within 10 minutes of inhalation. The cough AEs decreased over time. Comparing the Gen2 and MedTone, respiratory AEs and discontinuations due to respiratory AEs were numerically more common with the Gen2 inhaler.

#### FEV1

Baseline FEV1 was normal and comparable between the TI Gen2 and TI MedTone groups. Mean change from baseline in FEV1 at Week 24 was similar for TI delivered via the Gen2 inhaler and the MedTone inhaler (-0.01, 95% CI: -0.02, 0.04) (Table 27). The decline in the TI MedTone group of about 40 mL compared to the active comparator arm was numerically similar to the original submission.

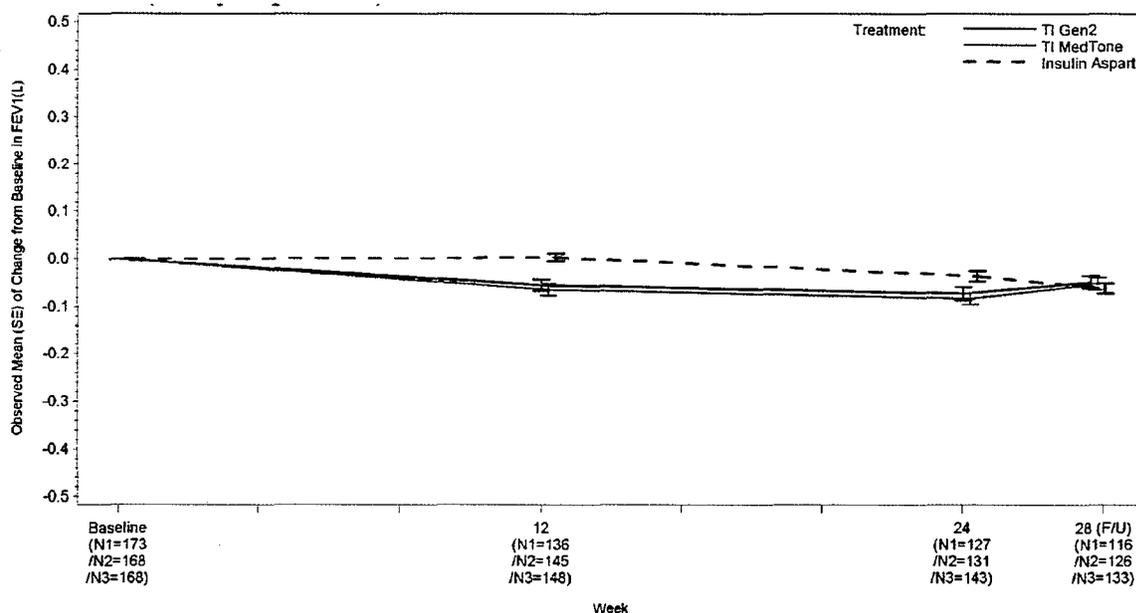
**Table 27. Study MKC-TI-171 Adjusted Mean Change in FEV1 from Baseline to Week 24 Over Time Based on MMRM Analysis (Safety Population)**

	Statistics	TI Gen2 N=174	TI MedTone N=173	Insulin Aspart N=173
<b>Baseline</b>	N (%)	173 (99%)	168 (97%)	168 (98%)
	Adjusted Mean (SE)	3.43 (0.03)	3.43 (0.03)	3.43 (0.03)
<b>Week 24</b>	N (%)	127	133	146
	Adjusted Mean (SE)	3.35 (0.03)	3.35 (0.03)	3.39 (0.03)
	Adjusted Mean Change (SE)	-0.07 (0.01)	-0.08 (0.010)	-0.04 (0.01)
	Treatment Difference (TI Gen2 – MedTone) Adjusted Mean Change (SE)	-0.01 (0.02) 95% CI: -0.02, 0.04		

Source: Module 5.3.5.1, Trial MKC-TI-171 CSR, Table 52, p 167

After 4 weeks off treatment (Week 28), the mean FEV1 value in the TI Gen2 group and TI MedTone groups returned to a level similar to that of insulin aspart, as seen in Figure 5.

**Figure 5. Study MKC-TI-171 Mean (SE) of Change from Baseline in FEV1 (L) Over Time: Observed Values (Safety Population)**



N1 = TI Gen2; N2 = TI MedTone; N3 = Insulin aspart  
 Source: Study MKC-TI-171 CSR, Figure 8, p 169.

Mean changes in PFT parameters were not driven by a small number of subjects with large PFT changes (outliers) but by the slight shift in the distribution of large number of subjects with small changes. PFT findings (defined as >15% decline from baseline in FEV1 or FVC) were uncommon and noted in only 4/518 (0.77%) subjects (2 in TI MedTone, 1 in TI Gen2 and 1 in insulin aspart group).

Subgroup analysis was performed for FEV1 by age, sex, race, mean daily, dose, and by cough status. As expected, mean FEV1 values were greater in males than females, although the magnitudes of the mean changes relative to baseline were similar for males and females within the treatment groups. No notable changes were seen by age, mean daily dose, or by cough status. There were too few subjects in other ethnic groups to draw any definitive conclusions.

#### FEV1 Summary

Mean change from baseline in FEV1 at Week 24 was similar for TI delivered via the Gen2 inhaler and the MedTone inhaler (-0.01, 95% CI: -0.02, 0.04). Numerically, both the treatment arms showed a similar mean change from baseline in FEV1 compared to placebo, as was seen in the original submission (about 40 mL). Mean changes in PFT parameters were not driven by a

small number of subjects with large PFT changes. After 4 weeks off treatment (Week 28), the mean FEV1 value in the TI Gen2 group and TI MedTone groups returned to a level similar to that of insulin aspart. No noteworthy or consistent patterns were observed in the change from baseline in FEV1 across subject characteristics, including gender, age, race/ethnicity, average daily dose of TI, and cough status.

## **B. Appendix 2: MKC-TI-175 (Study 175)**

### **1. Overview**

**Study Title:** A Phase 3, Multicenter, Double-blind, Placebo-controlled, Randomized, Clinical Trial Evaluating the Efficacy and Safety of Prandial Technosphere® Insulin Inhalation Powder Versus Technosphere® Inhalation Powder (Placebo) in Insulin Naïve Subjects With type 2 Diabetes Mellitus Poorly Controlled With Oral Antidiabetic Agents Over a 24-week Treatment Period.

The study design, population, endpoints, and PFT parameters were the same as for study MKC-TI-171 (see Appendix 1: MKC-TI-171 (Study 171)).

#### **Study treatments:**

##### TI in Gen2 Inhaler

Detailed in Study MKC-TI-171.

##### Technosphere Inhalation Powder in Gen2 Inhaler (TP; placebo/excipient only)

The MKC proprietary excipient, fumaryl diketopiperazine (FDKP), self-assembles into Technosphere particles; and polysorbate 80. No insulin is included in this treatment.

## 2. Results

### Population

**Disposition:** A total of 353 subjects were enrolled in this study. Subject disposition is summarized in Table 28.

<b>Table 28. Study MKC-TI-175 Subject Disposition (ITT population)</b>		
	<b>TI Gen2</b>	<b>TP Gen2</b>
<b>ITT Analysis Set</b>	177	176
<b>Safety Analysis Set</b>	177 (100%)	176 (100%)
<b>PP Analysis Set</b>	144 (81.4%)	131 (74.4%)
<b>Completed randomized treatment phase</b>	150 (84.7%)	139 (79.0%)
<b>Completed study</b>	149 (84.2%)	138 (78.4%)
<b>Prematurely Discontinued</b>	27 (15.3%)	37 (21.0%)
<b>Reason for Discontinuation</b>		
<b>Non-Safety</b>		
Protocol violation	1 (0.6%)	2 (1.1%)
Physician decision*	1 (0.6%)	1 (0.6%)
Withdrawal by subject*	10 (5.6%)	14 (8.0%)
Non compliance	1 (0.6%)	3 (1.7%)
Lost to follow-up	6 (3.4%)	4 (2.3%)
<b>Safety</b>		
AE	7 (4.0%)	9 (5.1%)
Death	0	0
*None of these subjects withdrew for pulmonary reasons TI: Technosphere Inhalation Powder (active), TP: Technosphere particles (excipient only) Source: Module 5.3.5.1, Trial MKC-TI-175 CSR, Table 14, p 83		

**Demographics:** Subject age (mean 57 years) was similar between the two treatment groups. The majority of subjects was Caucasian (85-88%) and divided approximately evenly by sex. Weight, height, BMI, and baseline FEV1 were similar between treatment groups, as seen in Table 29.

<b>Table 29: Study MKC-TI-175 Demographic Characteristics of Safety Population</b>				
<b>Characteristic</b>	<b>TI Gen2 N = 177, n (%)</b>		<b>TP Gen2 N = 176, n (%)</b>	
Subjects with at least one post-baseline PFT	163 (92)		155 (88)	
Gender				
Male	75 (46)		64 (41)	
Race				
Caucasian	151 (85)		155 (88)	
African American	21 (12)		17 (10)	
Other	5 (3)		4 (2)	
Age				
N	163		155	
Mean	57		57	
SD	9		8	
Range	27, 75		36, 79	
Age Group				
25-39	7 (4)		2 (1)	
40-65	133 (82)		130 (84)	
>65	23 (14)		23 (15)	
Weight (Kg)				
N	163		155	
Mean	90		91	
SD	17		18	
Range	54, 142		58, 137	
Height (cm)				
N	163		155	
Mean	168		167	
SD	10		10	
Range	146, 188		143, 197	
BMI (kg/m <sup>2</sup> )				
N	163		155	
Mean	32		33	
SD	5		5	
Range	22, 44		21, 44	
FEV1 (L)	Observed	% Predicted	Observed	% Predicted
N	173	173	166	166
Mean	2.9	98	2.8	98
SD	0.7	13	0.7	12
Range	1.7, 4.9	68, 150	1.6, 4.6	71, 125
TI=Technosphere Insulin (active); TP = Technosphere particles (excipient only)				
Source: MKC-TI-171 CSR, Table 41, p 140-1; Table 42, p 142; MKC-TI-171, Table 14.1.2.1, p. 587.				

## Efficacy

Efficacy was not reviewed in detail by this reviewer. Refer to DMEP's clinical review for further details.

## **Safety**

### **Exposure**

Exposure duration for TI Gen2 was a mean (SD) of 158 (39) days, compared to 152 (44) days for TP Gen2.

### **Pulmonary Safety**

Comparison of TI vs. TP in the Gen2 inhaler showed similar pulmonary safety results as was seen in the original submission.

### Respiratory adverse events

No respiratory SAEs or deaths were noted. The most common adverse event in both treatment groups was cough (TI Gen2: 24%; TP Gen2: 20%). Additional respiratory adverse events are listed in Table 30.

<b>Table 30. Study MKC-TI-175 Respiratory Adverse Events by Preferred Term Occurring in &gt; 1 Subject in Any Arm (Safety Population)</b>		
<b>Preferred Term</b>	<b>Subject, n (%)</b>	
	<b>TI Gen2 N=177</b>	<b>TP Gen2 N=176</b>
<b>RESPIRATORY, THORACIC, MEDIASTINAL DISORDERS</b>		
Cough	42 (24%)	35 (20%)
Oropharyngeal pain	8 (5%)	4 (2%)
Throat irritation	3 (2%)	2 (1%)
Dysphonia	2 (1%)	0
Dyspnea	1 (1%)	2 (1%)
<b>INFECTIONS AND INFESTATIONS</b>		
Nasopharyngitis	15 (9%)	8 (5%)
Upper Respiratory Tract Infection	9 (5%)	5 (3%)
Bronchitis	5 (3%)	7 (4%)
Rhinitis	3 (2%)	0
Respiratory Tract Infection*	4 (2%)	5 (3%)
Sinusitis	2 (1%)	2 (1%)
*Combined respiratory tract infection viral and respiratory tract infection		
Source: Module 5.3.5.1, Trial MKC-TI-175 CSR, Table 34, p 128		

Cough was the most common reason for discontinuation. More subjects who received the excipient powder discontinued due to cough (3%) than subjects who received TI (1%), as summarized in Table 31. Other respiratory adverse events causing discontinuation were uncommon.

<b>Table 31. Study MKC-TI-175 Respiratory AEs Leading to Discontinuation (Safety population)</b>		
<b>Preferred Term</b>	<b>Subject, n (%)</b>	
	<b>TI Gen2 N=177</b>	<b>TPGen2 N=176</b>
Cough	2 (1%)	6 (3%)
Dyspnea	1 (1%)	0
Oropharyngeal pain	1 (1%)	0
Nasal congestion	0	1 (1%)
Wheezing	0	1 (1%)

Source: Module 5.3.5.1, Trial MKC-TI-175 CSR, Table 35, p. 129.

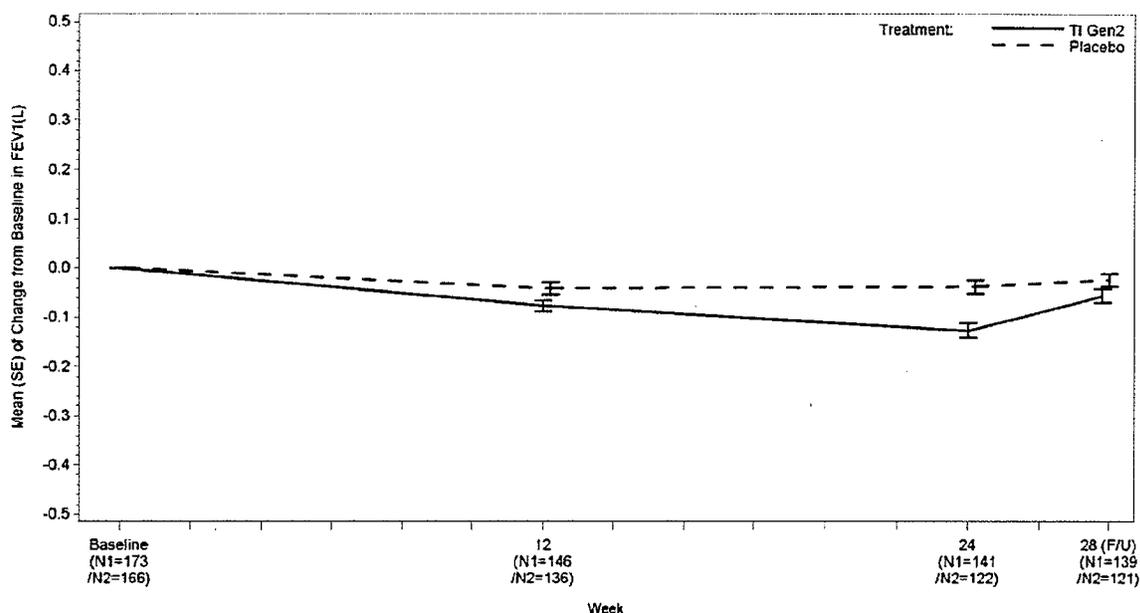
#### FEV1

Baseline FEV1 was normal and comparable between TI Gen2 and the TP Gen2 groups. The TI Gen2 group showed greater decline from baseline in FEV1 at Week 24 compared to the TP Gen2 group (Table 32). This was numerically similar to the original submission with the TI MedTone inhaler. After 4 weeks after stopping treatment (Week 28) the mean FEV1 value in the TI Gen2 group returned to a level similar to that of the TP Gen2 group (placebo), as seen in Figure 6.

<b>Table 32. Study MKC-TI-175 Adjusted Mean Change in FEV1 from Baseline to Week 24 (Safety Population; MMRM Analysis)</b>			
	<b>Statistics</b>	<b>TI Gen2 N=177</b>	<b>TP Gen2 N=176</b>
<b>Baseline</b>	N (%)	173 (98)	166 (94)
	Adjusted Mean (SE)	2.83 (0.02)	2.83 (0.03)
<b>Week 24</b>	N (%)	144 (81)	128 (73)
	Adjusted Mean (SE)	2.70 (0.03)	2.79 (0.03)
	Adjusted Mean Change (SE)	-0.13 (0.01)	-0.04 (0.01)
	Treatment Difference (TI Gen2 – TP Gen2) Adjusted Mean Change (SE)	-0.09 (0.02) 95% CI: -0.12, -0.05	

Source: Module 5.3.5.1, Trial MKC-TI-175 CSR, Table 43, p. 143.

**Figure 6. Trial MKC-TI-175 Mean (SE) Change from Baseline in Observed FEV1 (L) Values over Time (Safety Population)**



Note(s): N1 = TI Gen2, N2 = Placebo; Error bar denotes +/- standard errors  
 Source: Module 5.3.5.1, Trial MKC-TI-175 CSR, Figure 10, p 144.

Observed mean changes from baseline to Week 24 in PFT parameters were not driven by a small number of subjects with large PFT changes (outliers), but rather by the slight shift in the distribution of large number of subjects with small changes. Nine TI Gen2-treated subjects (5.1%) and 4 placebo-treated subjects (2.3%) experienced a  $\geq 15\%$  decline of FEV1 or FVC; the majority had improvement or resolution at the follow-up visit 4 weeks after the end of therapy.

Subgroup analysis was performed for FEV1 by age, sex, race, mean daily dose, and by cough status. As expected, mean FEV1 values were greater in males than females, although the magnitudes of the mean changes relative to baseline were similar for males and females within the treatment groups. No notable changes were seen by age, mean daily dose, or by cough status. There were too few subjects in other ethnic groups to draw any definitive conclusions.

### FEV1 Summary

Mean change from baseline in FEV1 at Week 24 for TI Gen2 compared to TP Gen2 (placebo) was similar to TI MedTone compared to placebo from the original submission. Mean changes in PFT parameters were not driven by a small number of subjects with large PFT changes. After 4 weeks after stopping treatment (Week 28) the mean FEV1 value in the TI Gen2 group returned to a level similar to that of the TP Gen2 group (placebo). No noteworthy or consistent patterns were observed in the change from baseline in FEV1 across subject characteristics, including gender, age, race/ethnicity, average daily dose of TI, and cough status.

## C. Appendix 3: Chemistry, Manufacturing, and Controls

### A. Drug Product: Technosphere Insulin

The drug product consists of particles of the novel excipient fumaryl diketopiperazine (FDKP) coated with recombinant human insulin, as well as trace amounts of polysorbate 80 (b) (4). The drug product is contained within cartridges as is further discussed below. Per the original NDA chemistry review, there is a significant amount of (b) (4) present in the excipient FDKP, (b) (4). The active pharmaceutical ingredient, excipients, and sources are the same for the MedTone and Gen 2 products.

*Reviewer's Comment:* (b) (4) may be a potential mechanism for the high incidence of cough noted post-inhalation.

### B. Device Characteristics: MedTone Inhaler

The Model D MedTone Inhaler (Figure 1) was designed and developed by the Applicant for exclusive use with the Afrezza-filled cartridges. The MedTone inhaler was breath-powered, and proposed to be re-usable for 12 months. The design was comprised of two subassemblies (the mouthpiece and the housing), (b) (4)

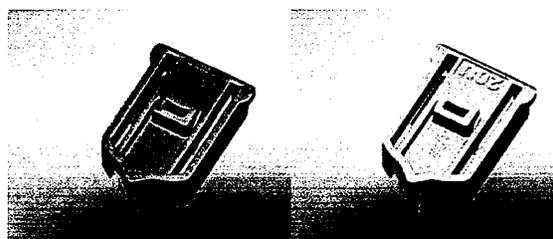
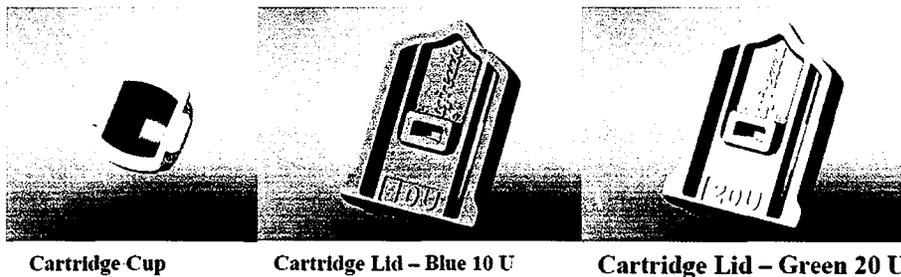
*Reviewer's comment:* The MedTone Inhaler was a complex device to operate. The usability of the device was not sufficiently evaluated in the original submission, and this constituted one of the deficiencies cited in the CR letter.

### C. Device Characteristics: Gen2 Inhalation System

The Gen2 Inhaler (Figure 2) has two distinct, but non-separable components, a Mouthpiece and Housing. The Mouthpiece is white and is the external portion of the device which users put in their mouth during inhalation. The Housing is translucent purple and serves as a grasping surface by which users can hold and manipulate the device.

In order to use the device, a cartridge containing either 10U or 20U of insulin is loaded into the Gen2 inhaler as shown below. The inhaler is then closed in to the dosing position, and the patient inhales the dry powder from the mouthpiece in one breath.

Cartridge Lids are color coded and marked to indicate cartridge strength (Figure 7). Blue Cartridges contain 10 U TI Inhalation Powder (3.3 mg) and green cartridges contain 20 U TI Inhalation Powder (6.7 mg). In addition, “Afrezza” is on the lid to identify the drug product.



10 U and 20 U Assembled Cartridges – Containment Position

### Figure 7. Gen2 Insulin Cartridges

Source: Module 3.2.P.2.4 Container closure system, Fig 4, p 12

*Reviewer’s comment: The Gen2 inhalation system has also gone through a number of iterations (Gen2A, Gen2B, and Gen2C). The clinical pharmacology and BE studies were done with the Gen2B inhaler, however it is the Gen2C that is proposed for marketing. In discussion with our CMC team, the modifications from the Gen2B to Gen2C should not impact performance.*

### D. CMC Issues Relevant to Pulmonary Safety

A summary of a discussion with the CMC and CDRH review teams is presented here as it relates to subsequent recommendations regarding the evaluation of pulmonary safety. Reviews from the CMC and CDRH disciplines are pending at the time of finalization of this review. For full details, please refer to the reviews of Dr. Edwin Jao (CMC) and Melanie Choe (CDRH).

#### Comparability of the MedTone and Gen2 inhalation systems

The Applicant proposes that the Gen2 inhalation system is a more efficient delivery system for TI (b) (4) allowing for one-third less powder per cartridge. As confirmed by the CMC review, the Gen2 inhalation system provides more efficient deagglomeration of the dry powder drug product, resulting in a total emitted dose which is (b) (4) less than what was administered by the MedTone inhaler, while the fine particle fraction

is comparable (b) (4) between the two devices. This results in lower dose cartridges (10U and 20U) for the Gen2 inhaler compared to the MedTone (15U and 30U).

Another notable difference is the proposed life of the Gen2 inhaler is 15 days compared to 1 year for the MedTone inhaler.

#### Device Robustness

The Applicant submitted robustness studies for the Gen2 device. After review of all study results, there were conditions under which modest departures from expected performance (ED and APSD) may be encountered. These included the following.

If the inhaler is:

1. inverted during use
2. dropped from the vertical orientation with a loaded cartridge prior to use
3. vigorously shaken in the vertical orientation prior to use

*Reviewer's comment: The CMC reviewer, Dr. Edwin Jao, noted the delivered dose and particle size distribution observed during dropping and shaking tests were outside the Agency's specification limits. This can be corrected by replacing the cartridge.*

#### Human Factors/Usability Study

Human factors/usability studies were conducted with the Gen2 Inhaler. See the CDRH review for further details. According to the Applicant, over 500 subjects used the Gen2 Inhaler throughout clinical studies.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MIYA O PATERNITI  
06/26/2014

BANU A KARIMI SHAH  
06/26/2014

SALLY M SEYMOUR  
06/26/2014

## Division of Oncology Products 2 Medical Officer Consult

**CONSULT REQUEST DATE:** December 19, 2013

**STN** NDA 22472\79  
**PRODUCT** AFREZZA (insulin human [rDNA origin])  
Inhalation Powder and Inhaler  
**APPLICANT** MannKind Corporation

**CONSULT REQUESTED BY** Lisa Yanoff, MD Medical Officer  
Rich Whitehead, RPM, ODEII, Div Metabolism  
and Endocrinology Products (DMEP/ODEII)

**CONSULTANT** Lee Pai-Scherf, MD DOP2/OHOP  
Gideon Blumenthal, MD DOP2/OHOP (TL)

### Consult Request/Questions

“Please evaluate lung cancer signal in Afrezza clinical development program”  
EDR Location: <\\CDSESUB1\evsprod\NDA022472\022472.enx>

### Consult Review

#### *I. Background*

Afrezza (Technosphere® Insulin Inhalation System, TI) is a drug-device combination product and consists of Afrezza Inhalation Powder pre-metered in to single unit dose cartridges and the Afrezza Inhaler as the delivery device for oral inhalation.

The proposed indication is for “*AFREZZA® is an ultra rapid acting insulin indicated to improve glycemic control in adults with type 1 or type 2 diabetes mellitus*”

NDA 22472/0 was first submitted on March 16, 2006 to the Division of Metabolism and Endocrine Products (DMEP). On March 12, 2010, DMEP issued a Complete Response (CR) letter to MannKind Corp. citing among other issues, “unclear clinical utility of Afrezza given that three of the four pivotal phase 3 trials failed to meet the primary objective for efficacy.”

MannKind Corp submitted a response to the CR letter on June 29, 2010. In the original NDA submission, the Sponsor proposed to market Afrezza with a MedTone inhaler and cartridges that contain 15 or 30 units of drug product. The new submission proposed to market Afrezza with a new Gen2 inhaler with re-designed cartridges. No clinical data to support the safety and efficacy of the new device was submitted. A second CR letter was issued by DMEP on January 18, 2011 recommending that the Sponsor conduct two randomized, controlled studies with Gen2.

Lung malignancies are of particular interest due to the mode of administration of Afrezza. At the time of the second NDA submission (June 29, 2010), two lung cancer cases were reported by the Sponsor among 3,364 Afrezza-treated patients (0.059%) and zero cases among approximately 1600 comparator-treated patients. DMEP requested (2<sup>nd</sup> cycle CR letter, January 18, 2011) the sponsor to submit “updated analyses of lung cancer cases in the Afrezza program. These analyses should include adjustments for patient-year exposure and should compare the rates of lung cancer among Afrezza-treated patients to the background rates among smokers and non-smokers”.

On October 13, 2013, MannKind Corp. submitted a response to the second CR Letter. This resubmission includes data from two new Phase 3 trials in subjects with type 1 and type 2 diabetes mellitus (DM) over 24 weeks treatment (trials MKC-TI-171 and MKC-TI-175, respectively).

## ***II. DOP2 Medical Officer’s review of the October 13, 2013 Submission with Focus on Lung Malignancies***

### **1. Safety Population and Exposure (ISS)**

In the Afrezza clinical development program, safety has been evaluated in more than 6500 adult subjects. Pooled safety data from the completed, controlled Phase 2/3 clinical studies in patients with type 1 or 2 diabetes mellitus (T1DM, T2DM), with planned continuous treatment duration of > 14 days include:

- **TI Inhalation Power: N = 3017** [N=2647 (MedTone Inhaler), N = 370 (Gen2 inhaler)]
- **Control: N = 2488** [N = 290 (placebo inhalation powder, TP), N = 2198 comparator treatments)
- **Time of exposure** (cut-off date July 31, 2013)
  - 896 for 0 to 3 months
  - 978 for >3 to 6 months
  - 419 for >6 to 12 months
  - 724 for >12 months

### **2. Sponsor’s Report of Lung Malignancies**

MannKind Corp. provided updated analyses of lung cancer cases in the Afrezza program (ISS, Resubmission Safety Update, Section 4.9.3.3, page 250 of 596). Four cases of lung malignancy were reported: two in the clinical program reported in the 2009 original NDA ISS and two spontaneously reported after the completion of participation in clinical trials.

A brief narrative of each patient is summarized below:

**Subject ID MKC-CI-102/2909:** a 62-year-old Caucasian male with T2DM was enrolled in study MKC-TI-102, “A Prospective, Multi-Center, Open-Label, Randomized, Controlled Clinical Trial Comparing the Efficacy and Safety in Subjects With Type 2

Diabetes Receiving Subcutaneous Basal Insulin and Prandial Inhalation of Technosphere® Insulin Versus Subcutaneous Premixed Insulin Therapy Over a 52-Week Treatment Period and a 4-Week Follow-up”. The subject received TI inhalation powder from an unknown date through December 21, 2007. The patients’ past medical history include stage 3A rectal carcinoma treated with surgery, radiation and 5-fluorouracil eight years prior to study entry and a 20 cigarettes per day smoking history for 41 years (from 1959 to 2000). On December 5, 2007, 200 days after initiation of TI powder inhalation, the patient was found to have elevated an elevated serum CEA and enlarged neck lymph nodes, a right upper lung lesion and enlarged mediastinal lymph nodes. A subsequent biopsy revealed neuroendocrine carcinoma (oat cell type) with immunohistochemistry positive for synaptophysin, chromogranin, CK, Ki76 60% and negative for ACL. The investigator considered the tumor as a second primary and initiated chemotherapy with carboplatin and etoposide. The patient subsequently died on [REDACTED] (b) (6) due to disease progression. The investigator assessed causality as not related to the study drug and considered the medical history of cancer and heavy smoking as possible causes.

**Subject ID 407/3316:** a 66-year-old male with T2DM was enrolled in MKC-CI-005 trial and received TI inhalation powder from November 3, 2004 to December 7, 2007. Past medical history included hypertension, peripheral vascular disease, status post orchiectomy and smoking (40 cigarettes per day for 20 years) until 1985 and a family history of lung cancer. The patient received TI inhalation powder from November 2004 to December 2006. In December 2006, approximately 627 days after initiation of the study treatment, the patient was found to have enlarged mediastinal lymph nodes and small suspicious right lung lesions during a work-up for microcytic anemia. A CT scan at baseline on February 17, 2005 had shown a small right upper lobe nodule that was considered stable and chronic. A subsequent biopsy showed non-differentiated bronchogenic carcinoma, non small cell lung cancer (NSCLC- T4 N2 M0). The patient died in [REDACTED] (b) (6). The cause of death was not reported. The investigator assessed the causality for the bronchogenic carcinoma as unlikely to be related to study drug given the risk factors of heavy smoking and family history.

**Subject ID PDC-IN-0008/358:** a 59-year-old Caucasian male with T2DM was enrolled in study PDC-INS-0008 entitled “Efficacy and Safety of Inhaled Technosphere® Insulin Compared to Technosphere® Placebo in Patients With Type 2 Diabetes Mellitus Following Diabetes Education” followed by study MKC-TI-010 “A Four Year, Safety and Tolerability, Open-Label, ‘Follow-On’ Trial Evaluating Technosphere® Insulin in Subjects With Type 2 Diabetes Mellitus.” The subject received TI inhalation powder from October 22, 2004 thru April 21, 2008. The duration of treatment was 3.5 years. Approximately 2.5 years after the last dose of TI inhalation powder, the subject developed paralysis of the left vocal cord. A CT scan of the chest revealed a large mass in the middle mediastinum and subcarinal lymph nodes. A pathology report from a needle biopsy showed poorly differentiated NSCLC favoring squamous cell histology. The investigator assessed causality as possibly related to TI. The patient’s smoking history was not provided.

**Subject ID TI-030/618:** a 73-year-old female with T2DM was enrolled in studies MKC-TI-030, entitled “Pulmonary Outcomes within a 2-Year Period in Subjects with Diabetes Mellitus Treated with Technosphere® Insulin or Usual Antidiabetic Treatment and in Subjects without Abnormalities in Glucose Control” followed by a 2-month safety follow-up study (MKC-TI-126). The patient received TI inhalation powder from April 21, 2006 through March 2, 2008. The duration of treatment was 1 year and 11 months. On July or August 2011, approximately 3.5 years after the last dose of TI inhalation powder, a CT scan revealed a focal lesion in the left lower lung with dissemination to the upper lobe, pleura and lymphadenopathy. She was diagnosed with stage II, T3, NX M0 lung cancer, presumably of squamous histology. The investigator assessed that a causal relationship of the event and the study medication can not be excluded. The patient’s smoking history was not provided.

### 3. Additional Cases with AE of Interest (Lung Neoplasm)

In addition to the four subjects with lung malignancy identified by the Sponsor, our review of the ISS identified 19 additional subjects (15 TI inhalation powder treated, 4 comparator) with adverse event preferred term (PT) of lung neoplasm, pleural, lung nodules, lung mass or squamous cell carcinoma in the submission that require closer examination.

Table 1 and Table 2, extracted from ISS 2013 Resubmission Safety Update tables G.1.14.2, page 1080 of 5305 and G.2.14.2, pages 2973 of 5305, summarize the available information for subjects with a Neoplasm AE of interest (lung, pleura, squamous cell ca) in controlled phase 2/3 studies in patients with DM type 1 and type 2, respectively. In total, 16 cases were identified. Only 1 out of the 16 cases was previously reported by the Sponsor (MKC-TI-102-2909, neuroendocrine tumor):

- **TI inhalation powder treated:**
  1. MKC-TI-009-1751
  2. MKC-TI-030/0814
  3. MKC-TI-005/8472
  4. MKC-TI-030/0108
  5. MKC-TI-102/1906
  6. PDC-INS-0008/157
  7. PDC-INS-0008-323
  8. PDC-INS-0008/399
  9. MKC-TI-175/3953
  10. PDC-INS-0008-154
  11. PDC-INS-0008-403
  12. MKC-TI-102-2909 (previously reported)
- **Comparator treated**
  13. MKC-TI-009-1200
  14. MKC-TI-030/1764
  15. MKC-TI-102/2221
  16. MKC-TI-030/3543.

A review of Appendix 1 - Narratives of the Integrated Summary of Safety identified 10 subjects with AE of lung neoplasm/nodules/mass, 8 subjects received TI inhalation powder and 2 subjects received a comparator treatment. Narratives of these cases are briefly summarized in Table 3. Side-by-side comparison of the patients identified in Tables 1 and 2 with the case narratives for overlap identified an additional 3 patients with AE of interest not previously reported by the Sponsor.

**TI inhalation powder treated:**

17. PDC-INS-0008/261
18. MKC-TI-010
19. MKC-TI-030/2973

Case report forms (CRF) are not available for review in the majority of cases. Narratives, when provided, contain insufficient information (e.g., pertinent medical history, smoking history, diagnosis, management and outcome) to draw meaningful conclusions concerning a causal relationship of the event and the study medication.

## NDA22472 Afrezza - Subjects with AE PT of Interest

**Table 1. Subjects with Neoplasm AEs - DM type 1 subjects in controlled phase 2/3 studies**

ID	Age/Sex	AE onset	AE PT	Outcome Recovered/Resolved	AE lead to withdraw	Treatment emergent
<b>TI</b>						
MKC-TI-009-1751	22yom	2008-03-12	Pulmonary mass	No/No	No	Yes
MKC-TI-030/0814	46yom	2007-11-29	Squamous cell (site?)	Yes/Yes	No	Yes
<b>Comparator</b>						
MKC-TI-009-1200	43yom	2007-10-05	Lung neoplasm	No/No	No	Yes

*Source ISS, 2013 Resubmission Safety Update, Table G.1.14.2*

**Table 2. Subjects with Neoplasm AEs - DM type 2 subjects in controlled phase 2/3 studies**

ID	Age/Sex	AE onset	AE PT	Outcome Recovered/Resolved	AE lead to withdraw	Treatment emergent
<b>TI</b>						
MKC-TI-005/8472	72yof	2005-01-27	Pleural neoplasm	No/No	No	Yes
MKC-TI-030/0108	54yof	2008-01-08	Lung neoplasm	Yes/Yes	No	Yes
MKC-TI-102/1906	55yof	2008-02-19	Lung neoplasm	No/No	No	Yes
MKC-TI-102-2909	61yom	2008-02-22	Neuroendocrine tumor	No/No	No	No
PDC-INS-0008/157	57yom	2004-06-02	Lung neoplasm	Yes/Yes	No	Yes
PDC-INS-0008-323	54yom	2004-08-27	Lung neoplasm	No/No	No	Yes
PDC-INS-0008/399	37yom	2004-10-18	Lung neoplasm	Unknown	No	Yes
<b>TP</b>						
MKC-TI-175/3953	48yom	2012-11-24	Squamous cell ca (site ?)	Yes/Yes	Yes	Yes
PDC-INS-0008-154	49yom	2004-06-04	Lung neoplasm	No/No	No	Yes
PDC-INS-0008-403	62yom	2004-10-25	Lung neoplasm	No/No	No	Yes
<b>Comparator</b>						
MKC-TI-030/1764	58yom	2008-06-20	Lung neoplasm	No/No	No	Yes
MKC-TI-102/2221	73yof	2008-04-15	Lung neoplasm	No/No	No	Yes
MKC-TI-030/3543	70yom	2007-09-04	Lung neoplasm	No/No	No	Yes

*Source ISS, 2013 Resubmission Safety Update, Table G.2.14.2*

**Table 3. Case Narratives with Adverse Events of Lung neoplasm or Lung Mass/nodules**

<b>ID/Study</b>	<b>Demographic</b>	<b>Study Treatment</b>	<b>Narrative</b>	<b>CRF</b>
<b>MKC-TI-009/1751</b> Site 112 no. 1751	22 yom, Caucasian DM1 Non smoker	TI inhalation powder and Lantus 377 days in treatment	Enlarging lung mass (per chest x rays at beginning & end of study) Not resolved Relationship to TI: possible No action taken with study drug (completed study)	Not available
<b>PDC-INS-0008/403</b> Site 006, no. 403  Study MKC-TI-010	63yom, Caucasian, Non-smoker	1 (?) day in treatment TI inhalation powder  Start 10/25/04, Visit 2 form dated 11/8/04 states investigational drug dispensed at the visit ?? terminated from study 12/13/04	3 mm pulmonary nodule RLL, lung neoplasm, unrelated, permanently discontinued CT: benign calcified granuloma. Withdrawn from study	Treatment discontinued on 12/13/04. To Sponsor: please clarify the length of treatment received.
<b>PDC-INS-0008/261</b> Site 022, no. 261 MKC-TI-010	53yom, Caucasian, TI inhalation powder  Smoker, 17 years, quit 19.8 years, 17 pack-years	340 days in treatment	Lung neoplasm, RLL nodule, enlarged mediastinal LN No action was taken concerning study drug Action specified: to repeat CT in 3 months	Not available
<b>MKC-TI-010</b> Site 23, no. 406 Studies MKC-TI-010 and PDC-INS-0008	57yof, Caucasian Non smoker	TI inhalation powder 1241 days in treatment	6.7 mm nodule in LLL No action taken with study drug. Patient out of study.	Not available
<b>MKC-TI-005/3316</b> Site 407, no. 3316 MKC-TI-005 MKC-TI-010	66yom, Caucasian Past history, 27 years smoking history, 54 pack-years, quit 20.4 years ago	TI inhalation powder 627 days in treatment	Bronchogenic carcinoma, possible permanently discontinued	
<b>MKC-TI-030/0108</b> Site 80, ID 0108 Study MKC-TI-030	54yof Caucasian, DM2 Non-smoker	677 days in treatment TI inhalation powder	2 cm nodular infiltrated inferior R lobe, never biopsied Outcome resolved in follow-up scan No action taken	
<b>MKC-TI-030/2973</b> Site 80, subject 2973 Study MKC-TI-030	55yom, Caucasian, TI inhalation powder No smoking	114 days in treatment	4 mm nodule LLL CT (1/18/07) to follow up Ct advised Subject withdrew consent (cough,	

Site 067, ID2909 Study MKC-TU-102	62yom, Caucasian DM2 Smoking history: 20/day x 41 years	137 days to onset of symptoms  TI inhalation and Lantus	inconvenience with product) Neck lymphadenopathy elevated CEA, CT mediastinal, and hilar nodes Biopsy LN - oat cell, small cell and neuroendocrine type Rx carbo/etoposide, Study treatment discontinued, Worsening tumor, stopped chemo, palliative care	
<b>CONTROL</b>				
Site 196, subject 3543 <b>MKC-TI-030/3543</b> Study MKC-TI-030	70yom, Caucasian No smoker	Control "usual anti-diabetic treatment" 242 days in treatment	4.5mm soft tissue nodule mid RL Referral to primary care physician	
Site 69, no. 1764 <b>MKC-TI-030/1764</b> Study MKC-TI-030	58yom, Caucasian DM 2	Control "usual anti-diabetic treatment" 612 days in treatment	LUL nodule	

Source ISS, 2013 Resubmission Safety Update, Appendix 1

**Table 4. Spontaneous Reports after Study Ending**

PDC-IN0008/358	59yom Smoking history: not provided	TI inhalation Duration of rx: 3 year, 6 months	Squamous cell lung ca (stage III) 2.5 year after discontinuation Possibly related to TI	No case report form
MKC-TI-030/618	73yof DM2 Smoking history: not provided.	TI inhalation powder Duration of rx: 1 year, 11 months (4/06 - 3/08)	Stage II squamous cell, 3.5 year after discontinued participation	No case report form

Source ISS, 2013 Resubmission Safety Update, Section 4.9.3.6

### **III. DOP2 Summary of Findings and Recommendation**

Our preliminary review of the Afrezza ISS report identified an additional 18 subjects with AE preferred term (PT) of lung neoplasm, pleural neoplasm, lung mass/nodule or squamous cell carcinoma in the NDA submission, which requires further examination.

In order to complete our review, we recommend that the Sponsor submit CRFs and detailed case narratives for all subjects identified in tables 1, 2, and 3 of this review. Please also provide case report forms for patients ID PDC-IN0008/358 and MKC-TI-030/618 (spontaneous reports) for review.

Detailed case narratives should contain a description of the pertinent medical history, any comorbid illnesses, smoking history, date of study treatment initiation and termination, date of pulmonary AE diagnosis, AE treatment and AE outcome information. Please include all pertinent radiographic and pathology (if available) reports. If the patient was terminated early from the study, please provide the reason.

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/s/  
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LEE HONG PAI SCHERF  
01/22/2014

GIDEON M BLUMENTHAL  
01/22/2014

**Division Director's Memo**

<b>NDA</b>	22-472
<b>Drug Name</b>	Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler
<b>Applicant</b>	Mankind Corporation
<b>Indication</b>	Treatment of hyperglycemia in adults with type 1 or 2 diabetes mellitus
<b>Date of Submission</b>	June 23, 2010
<b>PDUFA Goal Date</b>	December 29, 2010
<b>Recommended Action</b>	Complete Response

**Background**

On March 12, 2010, the Division of Metabolism and Endocrinology Products issued a *Complete Response* action on NDA 22-472 for Afrezza, an inhaled insulin product for the treatment of hyperglycemia in adults with Type 1 and 2 diabetes mellitus (T1DM and T2DM). My decisional memo dated that same day, discussed the reasons upon which I concluded that the application failed in demonstrating a favorable benefit-risk profile. The action letter specifically outlined the deficiencies under four different categories: clinical; clinical pharmacology; labeling; and device. The reader is referred to decisional memos across these different disciplines for a full account of problems in the original NDA. Please also see the Cross-Discipline Team Leader Memo prepared by Dr. Hylton Joffe for a very complete summary of this resubmission.

The original NDA was not approved for the following reasons, all inextricably linked:

- Clinical – three out of four pivotal Phase 3 trials failed to meet their stated objectives of showing either non-inferiority or superiority to a comparator anti-diabetic regimen. In two of these trials, one each in T1 and T2DM, Afrezza was inferior to the short-acting insulin aspart. Drs. Yanoff and Joffe noted that Afrezza treatment still maintained glycemic control in both T1 and T2DM, where one would expect worsening of glycemia, particularly T1DM, if current regimens were discontinued. This and data from Phase 2, placebo-controlled clinical trials in T2DM support a conclusion that Afrezza, provides for systemically absorbed insulin that can lower glucose levels in diabetes. However, the comparative effectiveness of Afrezza to other approved therapies from the Phase 3 trials showed that Afrezza was a sub-optimal insulin regimen for the treatment of diabetes mellitus. Recommendations on labeling were proposed by Dr. Yanoff, and in part by Dr. Joffe, which would convey the lesser efficacy of Afrezza relative to other anti-diabetic agents but that despite this, Afrezza might still be a reasonable option in some patients. This proposal was never acted on given the other deficiencies in the original application.

- Clinical Pharmacology – to further complicate matters from the clinical efficacy and safety trials, the original application relied on pivotal studies which employed an investigational device (Model C), not the to-be-marketed device (Model D). The applicant submitted a pivotal bioequivalence study to bridge clinical efficacy and safety data from the trials using Model C to Model D; however, DSI inspection concluded that data from this BE study were unreliable.
- Labeling – numerous concerns for medication errors were raised by the Division of Medication Errors and Prevention and Analysis (DMEPA)
- Device – deficiencies underscoring the complexity of Model D which also paralleled concerns raised by DMEPA were identified.

In their resubmission, Mannkind did not directly address all of the deficiencies outlined in the *Complete Response* letter. Instead, the applicant proposed a completely new device which had not been evaluated in any clinical efficacy and safety trial. The applicant argues that the new device, the Gen2 inhaler, is a less complex device with a more efficient delivery of insulin for which *in vitro* bridging studies and a clinical bioequivalence study will obviate the need for additional clinical trials.

**Gen2 inhaler versus Medtone inhaler (Please refer to CMC and CDRH reviews)**

In the original NDA, all Phase 2 and 3 clinical trials were conducted with the MedTone inhaler. In parallel with that program, Mannkind was developing a new inhalation system called the Gen2 inhalers for which 3 versions were tested. Of these, the Gen2C model is now being proposed for marketing. The following table adapted from Dr. Jao’s review summarizes some of the differences between the two devices.

**Table 1. MedTone vs Gen2 Inhalers**

API	MedTone (original NDA) Recombinant human insulin	Gen2 (resubmission) Recombinant human insulin
Cartridge strengths	15 U (5 mg) 30 U (10 mg)	10 U (3.3 mg) 20 U (6.7 mg)
Resistance	High resistance ranging from (b) (4) to (b) (4) kPa <sup>1/2</sup> /LPM	High resistance ranging from (b) (4) to (b) (4) kPa <sup>1/2</sup> /LPM
Simplicity	(b) (4)	2 different positions: Load Dose
Ease of use	(b) (4)	4 steps – 1 inhalation per cartridge
Care/maintenance	(b) (4)	No cleaning required Dispose after 15 days of use

Overall, the Gen2C inhaler differs from the Medtone inhaler in that it is smaller; requires fewer steps for insulin administration; requires only a single inhalation from one cartridge for powder delivery; and does not require any cleaning as it is replaced after 15 days of use. To determine how these design differences affect comparability of function between the two devices, several studies were performed including a particle characterization tests to establish equivalence between the Gen2 and MedTone inhaler. These tests assessed emitted dose (ED) and aerodynamic particle size distribution (APSD). In addition, the applicant claimed that the Gen2 inhaler deagglomerates insulin powder more efficiently than the previous device. As a result, less powder per cartridge is required to provide comparable fine particle and systemic

exposure as compared to the previous device that might theoretically result in a better pulmonary safety profile from reduced local drug exposure. These differences are considered by the applicant as improvements over the previous device.

According to CMC reviewers, the applicant has provided sufficient data to enable a conclusion of comparability between the two devices. However, they caution that these *in vitro* data are used more for quality control purposes of the device than for determining clinical implications of insulin delivered in Gen2 versus MedTone inhaler.

Although the final CMC recommendation was acceptable for approval, there were additional CMC issues identified that the applicant needs to address. Dr. Prasad noted that depending upon the final action, these issues can be postmarketing requirements (if NDA approved) or deficiencies to be addressed prior to approval.

#### **Clinical Bioequivalence Trial (Please refer to Clinical Pharmacology review)**

In addition to *in vitro* comparability studies, the applicant submitted the results of CSR MKC-T1-142, a bioequivalence study between the Gen2C inhaler and the Model C inhaler use in Phase 2/3 trials. The study was a single-center, open-label, randomized, crossover trial in approximately 70 healthy, normal volunteers. The primary objective of the study was to show bioequivalence between 20U cartridges using the Gen2C inhaler versus 30U cartridges using the Model C inhaler. A secondary objective was to show bioequivalence between two 10U cartridges and one 20U cartridge using the Gen2C inhaler.

The study was reviewed by Drs. Sang Chung and Sally Choe from Office of Clinical Pharmacology. They have concluded that the pharmacokinetics of 20 U of insulin delivered by the Gen2C inhaler is comparable to 30U of insulin delivered by Model C inhaler. All assessments of the mean ratio of insulin AUC and Cmax and their accompanying 90% CI fell within the limits of 0.80 to 1.25. Their review also supported a conclusion of bioequivalence between two 10U cartridges and a single 20U cartridge in the Gen2C inhaler.

#### **Clinical Efficacy and Safety Data with Gen2 Inhalation System**

Although the applicant has provided data showing comparability between the MedTone and Gen2 devices from the *in vitro* and clinical BE studies, there were no clinical efficacy and safety trials conducted with the Gen2C inhaler. At best, the submitted bridging studies will link efficacy and safety data to the original Phase 3 trials and the recently submitted MKC-T1-117 trial. Again, none of these trials employed the Gen2C inhaler.

MKC-T1-117 was a randomized, multi-center, open-label, 16-week trial comparing Afrezza in combination with Lantus to Humalog in combination with Lantus in patients with T1DM. The trial design and results have been thoroughly reviewed and discussed by Drs. Sahlroot and Yanoff and summarized in Dr. Joffe's CDTL memo.

The objective of MKC-T1-117 was to demonstrate that Afrezza was noninferior to Humalog based on a pre-defined non-inferiority margin of 0.4%. The following table from Dr. Sahlroot's review shows that the study met its primary objective and that Afrezza was non-inferior to Humalog.

**Table 1. Study 117 <sup>1</sup> HbA1c change from baseline to Week 16 (ITT- LOCF)**

HbA1c (% units)	Treatment group		Trt difference <sup>2,3</sup>
	Afrezza n=61	Humalog n=65	LS mean (95% CI) p-value for NI
Baseline mean (SD) LS mean <sup>2</sup> change at 16 wks	7.75 (0.55) -0.09	7.62 (0.60) -0.05	-0.04 (-0.25, +0.18) p<.001

1 Medtone inhaler device was used

2 Least squares (LS) mean and confidence interval based on ANCOVA with treatment group and country as factors and baseline HbA1c as a covariate.

3 The pre-specified NI margin (by protocol amendment) was 0.4%

However, there are limitations to this study which require some measure in endorsing these results as conclusive. As mentioned in the Background section of this memo, 3 out of the 4 pivotal Phase 3 trials failed to meet their stated objectives of showing either non-inferiority or superiority to a comparator anti-diabetic regimen. It is difficult to dismiss those studies with the results of Study 117 in hand now, especially when there are notable differences between Study 117 and previously conducted ones that may contribute to a demonstration of non-inferiority of Afrezza to Humalog in the former.

The following table summarizes the comparative effectiveness of Afrezza to several other anti-diabetic regimens. Study 117 is highlighted in yellow. Relative to the other studies, it is a small study with a limited duration of assessment. As noted by Dr. Sahlroot, Study 117 was stopped early after enrollment of only half of the planned sample size. It is not clear whether the findings from the unplanned interim analysis would have been upheld if the study had proceeded as originally planned or if a longer duration of treatment was required. Except for Study 117, all active-controlled trials favored comparator. The baseline HbA1c of patients in Study 117 was much lower than all other trials signifying a patient population that had a greater degree of diabetes control at time of enrollment. Showing non-inferiority in a reasonably controlled diabetic population may be easier than patients with higher HbA1c levels at baseline.

#### **Efficacy of Afrezza on Glycemic Control in Active Controlled Trials\***

	N	Treatments	Mean BL HbA1c	Mean Diff (95% CI)	Comments
<b>Type 2 DM Trials</b>					
Study 014 24 wks	309	T1+glargine vs Insulin aspart+glargine	8.9	0.36 (0.14,0.58)	Failed to show non-inferiority and was also inferior to aspart
Study 103 12 wks	528	T1+metformin vs metformin+insulin secretagogue	8.9	0.10 (-0.13,0.33)	Trial was designed to show superiority of T1+met to met+secretagogue. Failed on this objective
Study 102 52 wks	677	T1+glargine vs Novolog Mix 70/30	8.7	0.12 (-0.05,0.29)	Met objective in showing non-inferiority to Novolog Mix 70/30
<b>Type 1 DM Trials</b>					
Study 009 52 wks	589	T1+glargine vs Insulin aspart+glargine	8.4	0.24 (0.08,0.40)	Failed to show non-inferiority and was also inferior to aspart
Study 101 12 wks	111	T1+glargine vs Insulin	9.0	0.25 (-0.9,0.58)	Primary endpoint was not change in HbA1c from

aspart+glargine

baseline. Upper bound of 95% CI in secondary efficacy assessment did not fall below conventional cutpoint for NI

Study 117 16 wks	126	T1+glargine vs Humalog+glargine	7.7	-0.04 (-0.04,0.18)	Met objective in showing non-inferiority to Humalog
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\*Efficacy presented as the LS Mean Difference in change in HbA1c reduction in ITT with LOCF populations  
T1 = Afrezza inhaled insulin administered via MedTone C Device

Overall, the totality of clinical efficacy data with Afrezza in trials employing the MedTone inhaler does not show a consistent pattern of robust efficacy relative to other available therapies. Establishing a bridge between the Gen2C inhaler and the MedTone inhaler only revisits the clinical conundrum from the original application. The most logical approach now would be to conduct clinical trials with the Gen2C inhaler in patients with T1 and T2DM to support an indication in both of these patient populations. Given the improvements made with this new inhalation system, it is possible that better efficacy can be demonstrated in these new trials.

### **Other Issues Identified by Consultants**

#### CDRH

In her consult, Dr. Melanie Choe from the Center for Devices and Radiological Health (CDRH) has provided a detailed description of the Gen2 inhaler, its components, and operating principles. She also reviewed the bench test results comparing the Gen2 and MedTone inhalation devices. Dr. Quynh Nguyen, also from CDRH, reviewed the Human Factors Study.

Dr. Choe stated that the bench tests support the conclusion that the Gen2 inhaler system is equivalent to the MedTone inhaler system; however, she noted the limitation of bench performance tests and their ability to detect clinically relevant differences in the delivery of insulin that could only be determined through clinical trials.

Deficiencies related to user errors were identified after review of the Human Factors Study. Dr. Nguyen's review summarizes 13 use-errors. Most of these were identified as low to moderate risk (e.g., inserting inverted cartridge in inhaler whose design would not enable usage); however, high-risk errors that would result in improper dosing of insulin were identified. The applicant argues that most of the errors were due to unfamiliarity with the product and labeling, as the study did not provide any training to simulate the a worst-case scenario in a clinical setting. To address the risk of these use-errors occurring, the applicant has proposed (b) (4)

This has been deemed unacceptable by CDRH which is requiring another validation study. I concur with this conclusion and the CR letter will include this as a deficiency to be addressed by the applicant prior to approval.

The appropriateness/effectiveness of the risk mitigation strategies and the need for user training should be discussed with the applicant. If it is determined that patient training is a necessary component for the safe and effective use of Afrezza, the training and its components might be considered as part of a Risk Evaluation and Mitigation Strategy (REMS) if this NDA is approved.

#### DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the Human Factors Study and product labeling. Deficiencies were identified that preclude their recommendation for approval. DMEPA maintains that the device, although much improved, is still too complex and they recommend that the applicant re-design the device to decrease the number of steps required in administration of the

drug. A threshold for maximum number of steps was not specified but I would counter that the administration of insulin injection also involves multiple steps (e.g., mixing of long-acting and short-acting insulin from vials) that a deficiency should not focus on the number of steps necessary to use a drug-device product but that those steps can be adhered to appropriately to ensure the safe and effective use of the product. I do not believe the CR letter should require that the applicant redesign its device as I believe there are already notable improvements on this model over the MedTone inhalation system. However, I agree with DMEPA that there are areas which require improvement before approval and I concur that these other deficiencies be identified in the CR letter.

Importantly, DMEPA made note of the potential for dosing errors. This pertains to both incorrect selection of cartridges and miscalculation of deliverable dose from the labeled dose (i.e., 10 or 20 unit cartridges). I agree with DMEPA that labeling and instructions for use should be directed at ensuring safe dosing of this product including the back-calculation from Afrezza use to injections of prandial insulin. The applicant should be informed that a dosing calculation chart should be proposed in labeling and tested to ensure adequate patient comprehension.

### Pulmonary

In her review, Dr. Karimi-Shah noted that in the original NDA review there were no pulmonary safety issues which precluded approval and that any safety concerns could have been addressed through labeling and postmarketing requirements. However, the proposal to bridge all pulmonary safety data to a new inhaler device which has had limited experience in controlled clinical trials is problematic. As thoughtfully pointed out in her consult, the efficacy and safety profiles of drugs administered via inhalation are dependent upon the delivery characteristics of the device. She has recommended a 12-wk comparative trial between the Gen2 inhaler and the MedTone inhaler to assess differences in FEV1. The duration proposed is based on the observation from the original NDA that FEV1 declines were maximal between Afrezza and controls at this timepoint. If the FEV1 findings between the Gen2 inhalation and Medtone inhalation systems are comparable, long-term pulmonary safety with the Gen2 device may be collected as a postmarketing requirement.

I believe Dr. Karimi-Shah's recommendations are scientifically justified and do not find that a 12-week study is unreasonable, especially given a requirement for new clinical trials with Gen2 inhalers to establish efficacy.

I note that Dr. Joffe has remarked on a recent report of lung cancer occurring in a 59-year old man who had been receiving Afrezza for 3.5 years. Information on this patient thus far reveals limited to no cigarette smoking history but additional information will be requested as part of the CR letter.

### **Conclusions and Recommendations**

Mannkind Corporation has developed a recombinant human insulin to be administered via inhalation for the treatment of Type 1 and Type 2 diabetes mellitus. It is the second NDA for an inhaled insulin to be considered for approval. Pfizer's Exubera, which was approved in 2006, was withdrawn from the market so the availability of Afrezza will be the only option for non-injectable insulin therapy.

As appealing as this is for many patients who are averse to taking injections, this application has not provided evidence that a breakthrough promise has been fulfilled. First, we must all be reminded that this is prandial insulin. For all Type 1 diabetics, there will still be a requirement for injection of long-acting insulin. Many type 2 diabetics may also still require the addition of a long-acting insulin injection to control fasting blood glucoses. However, for some, a reduction in the number of injections may be a sufficient improvement to consider its availability. After all, the agency approved Exubera even though this only provided prandial insulin coverage.

In my opinion, the greater problem with Afrezza is the demonstrated suboptimal efficacy in several trials of T1 and T2 diabetic patients. The results from a new 16-week trial in T1DM showing comparable efficacy to Humalog do not negate the less favorable findings of 3 other earlier trials. If anything, the totality of data reveals an inconsistent pattern of efficacy leaving one to wonder what the true effect is for a drug product that is highly dependent upon the delivery mechanism and patient performance. And because efficacy and safety of an inhaled product is strongly dependent on the performance of the patient and device, the proposal by Mannkind to market Afrezza with a new inhalation system without extensive clinical trial data is unacceptable.

I agree with Dr. Joffe that controlled clinical trials are necessary for Afrezza administered with the Gen2C inhaler to be approved for either Type 1 or Type 2 diabetes. In addition to the conduct of these studies, the applicant must address the deficiencies identified by other review disciplines as part of its complete response resubmission.

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MARY H PARKS  
01/18/2011

## Cross-Discipline Team Leader Review

<b>Date</b>	January 3, 2011
<b>From</b>	Hylton V. Joffe, M.D., M.M.Sc.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	22-472
<b>Applicant</b>	MannKind Corporation
<b>Date of Submission</b>	June 29, 2010
<b>PDUFA Goal Date</b>	December 29, 2010
<b>Proprietary Name / Established (USAN) names</b>	Afrezza (insulin, human [rDNA] inhalation powder)
<b>Dosage forms / Strength</b>	Single-use cartridges containing 10 units or 20 units of human recombinant insulin
<b>Proposed Indication(s)</b>	To improve glycemic control in adults with diabetes mellitus
<b>Recommended:</b>	<i>Complete Response</i>

## Cross Discipline Team Leader Review Template

### 1. Introduction

Afrezza (insulin, human [rDNA] inhalation powder) is an inhaled insulin developed for improving glycemic control in adults with type 1 and type 2 diabetes. On March 31, 2009, MannKind Corporation submitted a New Drug Application for Afrezza, seeking permission to market the MedTone Model D inhaler and its insulin cartridges (Figure 1). We issued a Complete Response letter on March 12, 2010, because of numerous deficiencies.

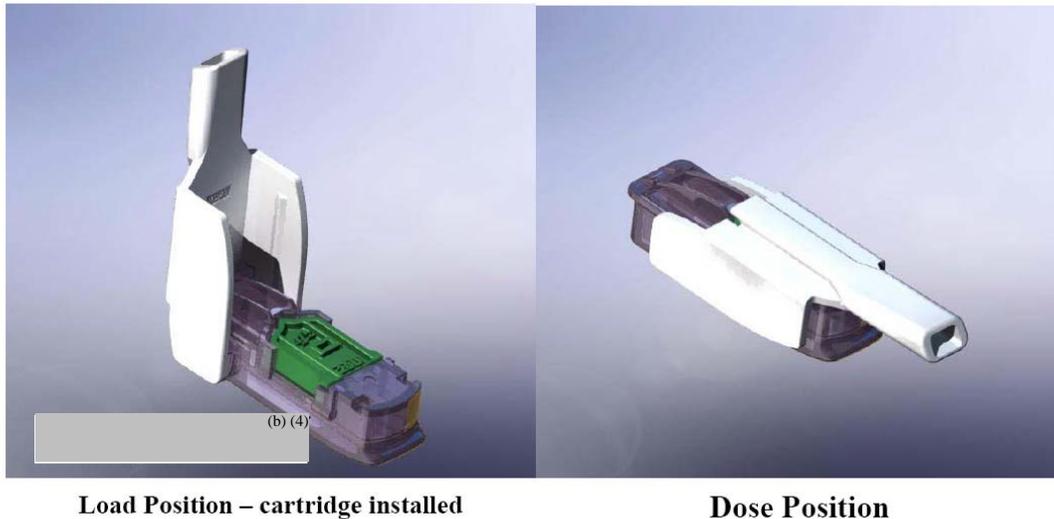
**Figure 1. MedTone Inhaler (left) and its insulin cartridges (right). The cartridge with a single band holds 15 units of insulin and the cartridge with two bands hold 30 units.**



At the End-of-Review meeting on June 9, 2010, the sponsor informed FDA of its plans to abandon the MedTone system and to submit a Complete Response seeking permission to market Afrezza using an entirely new Gen2 device (Figures 2 and 3). The sponsor states that the Gen2 device has several advantages over the MedTone device including delivery of less drug product per dose, the need for less inspiratory effort on the part of the patient, ease of handling with fewer steps needed to administer the drug product, and the need for only 1 puff per cartridge (b) (4)

. This memorandum discusses the sponsor's resubmission and the adequacy of the available data from the various review disciplines to support approvability of this new Afrezza product.

**Figure 2. Gen2 Inhaler. The mouthpiece is white. The housing is purple and is the grasping surface for users to hold and manipulate the device.**



**Figure 3. Redesigned cartridges for the Gen2 system. The blue cartridge holds 10 units of insulin and the green cartridge holds 20 units.**



## 2. Background

During the first review cycle, the sponsor proposed marketing Afrezza with the MedTone inhaler. We identified the following major deficiencies:

- Unclear clinical utility of Afrezza given that three of the four pivotal phase 3 trials failed to meet their primary objective for efficacy. We requested that the sponsor clarify why additional clinical studies are unnecessary. Dr. Mary Parks, our Division Director and the signatory authority, recommended in her memorandum that the adequacy of the efficacy findings to support approvability of the MedTone device be discussed at an advisory committee meeting after all remaining deficiencies had been resolved.
- Unreliable analytical data from the pivotal bioequivalence study comparing the to-be-marketed device (Model D inhaler) with the device tested in the phase 3 trials (Model C inhaler).

- Concerns that variations in inspiratory effort could lead to changes in Afrezza particle sizes, potentially altering Afrezza's pharmacokinetic and pharmacodynamic profile, impacting efficacy and safety.
- Concerns that the currently proposed labeling could lead to confusion and medication errors.
- Need for a Human Factors Study with the to-be-marketed Model D inhaler to show that modifications made to the Model C inhaler (used in phase 3 trials) and to the associated patient labeling mitigate usability concerns and risks.
- Lack of clinical trial data with the Model D inhaler to support the proposed 1-year in-use life.

Because the sponsor has abandoned the MedTone device and is pursuing the Gen2 device, many of the deficiencies listed above are moot. However, there are no controlled phase 2 or phase 3 clinical trials with the Gen2 device. Therefore, besides the Chemistry/Manufacturing/Controls (CMC) and device issues pertinent to the new device, a critical question is whether the sponsor has adequately bridged Gen2 to the phase 3 clinical data for the MedTone device. If such a bridge exists, another critical question is whether the clinical data with the MedTone device are adequate to support approval of Gen2 given that questions were raised about the adequacy of these clinical data to support the MedTone device itself. These issues are discussed below with reference to the deficiencies in our Complete Response letter, where applicable.

We first learned of the sponsor's plans to proceed with the Gen2 device in the briefing package for the End-of-Review meeting. We stated in our preliminary comments for this meeting that clinical evidence of pulmonary safety and evidence of adequate glycemic effect (based on HbA1c) will be needed for the new device. This approach of obtaining efficacy and safety data with a new device is in-line with the general approach used by the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) for locally-acting pulmonary drugs. At the End-of-Review meeting, the sponsor claimed that the Gen2 and MedTone devices result in comparable delivery of the Afrezza drug product permitting reliance on the efficacy and safety findings from the MedTone device. We informed the sponsor that a change in device after the completion of the phase 3 program is risky and unprecedented and recommended that the sponsor submit the *in vitro* comparative performance data for Gen2 and MedTone before we decide whether such an approach is acceptable. Instead, [REDACTED] (b) (4), the sponsor decided to directly proceed with submitting their Complete Response with the Gen2 system approximately 3 weeks after the End-of-Review meeting.

### 3. CMC/Device

The Complete Response letter did not contain Chemistry/Manufacturing/Controls (CMC) deficiencies. However, the sponsor is now proposing a new inhaler (Figure 2) with redesigned insulin cartridges (Figure 3), which requires review by CMC and the Center for Devices and Radiological Health (CDRH).

Dr. Theodore Carver reviewed the CMC issues pertaining to manufacturing of the drug substance and drug product and is recommending approval of the NDA without the need for chemistry postmarketing commitments. Dr. Carver notes that there have been no changes made to the manufacturing of the drug substance (recombinant human insulin manufactured from E. coli by (b) (4) under Drug Master File (b) (4) or bulk drug product (crystalline particles of a novel excipient, fumaryl diketopiperazine or FDKP, coated with insulin drug substance). The bulk drug product is filled into redesigned cartridges that contain 10 units (0.35 mg) or 20 units (0.69 mg) of recombinant human insulin compared to the 15-unit and 30-unit cartridges that were developed for use with the MedTone system. The sponsor claims the new cartridge system leads to (b) (4) due to improved deagglomeration, which is the basis for the reduced cartridge fill weights. Based on stability testing, Dr. Carver recommends a (b) (4) shelf-life for storage of the Gen2 drug product at 2-8 degrees Celsius with an additional 10 days of storage at room temperature. (b) (4)

The sponsor has developed three models of the Gen2 device (Gen2A, Gen2B and Gen2C) with the Gen2C device chosen for marketing. The Gen2C device was used to generate most of the CMC data in this submission and was used in the pivotal clinical pharmacology study.

The redesigned insulin cartridges are manually placed into the re-useable Gen2C inhaler. Patients inhale deeply one time per cartridge to administer the powder, (b) (4). The Gen2C inhaler is intended for a 15 day in-use period without cleaning and has a shelf-life of (b) (4). Dr. Edwin Jao reviewed the CMC issues pertaining to the inhaler device and drug product performance and is recommending approval with the following postmarketing commitments:

- An environmental study to show that performance (emitted dose and aerodynamic particle size distribution) of the 10-unit inhaler is not affected by static on the contact surfaces of inhalers at low temperatures (5 degrees Celsius) and low humidity (25% relative humidity) (an environmental study with the 20-unit inhaler has previously been conducted)
- A shipping study to show that performance (emitted dose and aerodynamic particle size distribution) of the 10-unit inhaler is not affected by settlement/leakage during shipment (a shipping study with the 20-unit inhaler has previously been conducted)
- A robustness study of Gen2 inhalers to provide in-use performance data (emitted dose and aerodynamic particle size distribution) under misuse scenarios (e.g., dropping, shaking)

Dr. Prasad Peri states that these postmarketing commitments should be listed as deficiencies if it is determined for other reasons that the application cannot be approved on this review cycle.

In the Complete Response letter, we included a deficiency that the (b) (4)

The CMC reviewers have confirmed that this deficiency does not apply to the

Gen2 device. The Gen2 inhaler has slightly lower resistance with a narrower range of resistance compared to the MedTone inhaler, which results in the Gen2 having a slightly higher and more stable flow rate.

Because the Gen2 cartridges have a lower amount of formulation (10 or 20 units) than the MedTone cartridges (15 or 30 units), the Gen2 device has lower emitted dose targets and lower emitted dose results compared to the MedTone device as shown in Table 1.

<b>Table 1. Target emitted dose and mean dose emitted for the Gen2 and MedTone inhalers</b>		
	<b>Target Emitted Dose Units</b>	<b>Mean Emitted Dose (Range) Units</b>
<b>MedTone</b> 15-unit cartridge 30-unit cartridge		(b) (4)
<b>Gen2</b> 10-unit cartridge 20-unit cartridge		

The sponsor compared the aerodynamic particle size distribution achieved with Gen2 to that achieved with the MedTone inhaler using a (b) (4) kPa constant pressure drop. This pressure drop corresponds to a flow rate of approximately (b) (4) liters per minute. The sponsor states that (b) (4) kPa (b) (4) liters per minute) is the typical pressure drop that patients can generate through the Gen2 device. In this setting, the overall mean fine particle fraction was slightly lower with Gen2 (b) (4) units) compared to MedTone (b) (4) units), a (b) (4) between-group difference. Dr. Peri states that these data support *in vitro* comparability between the two devices under patient-use scenarios of (b) (4) kPa. Higher flow rates generate significantly larger amounts of fine particle fractions compared to lower flow rates (likely a result from increased deagglomeration), although Dr. Peri notes that at (b) (4) kPa (b) (4) liters per minute) there is at least (b) (4) % less fine particle fraction for Gen2 compared to MedTone.

In summary, the emitted doses are approximately (b) (4) % less with Gen2 compared to the MedTone inhaler but the devices have comparable aerodynamic particle size distribution data under patient-use scenarios of a (b) (4) kPa pressure drop.

The CMC reviewers confirmed that the Office of Compliance found all manufacturing and testing facilities to be acceptable.

Please see the reviews by Drs. Carver, Jao, and Peri for additional details.

**CDRH Review:**

Based on bench testing, the CDRH reviewers have determined that both the Gen2 and MedTone inhalers deagglomerate and deliver respirable particles of Afrezza drug product. However, because of inherent limitations with bench testing, the CDRH reviewers state that *in vivo* equivalence between the devices can only be shown with clinical studies (bioequivalence

and/or controlled clinical trials). One issue discussed by both CMC and CDRH is that the aerodynamic particle size distribution profile is significantly affected when the Gen2 inhaler is tested in the upside down position suggesting that the formulation cannot be effectively deagglomerated in this position. In the sponsor's completed Gen2 usability study, 5 of 15 participants held the inhaler upside down on 12 occasions suggesting that this may be an important use error. The sponsor states that incorrect device orientation will be mitigated by prominently displaying the correct orientation in the Instructions for Use (IFU). The ability of this change to the IFU to mitigate this error will need to be tested in the validation usability study (see below).

The CDRH reviewers identified the following deficiencies to be addressed prior to marketing:

- The sponsor completed a usability study and is now proposing changes to the IFU and cartridge label in an attempt to minimize errors identified in this study (see Section 12 of this memorandum for further details). However, the sponsor has not conducted another usability study validating that these changes to the IFU and changes to the cartridge label minimize the previously identified user errors without introducing new risks. In addition, the sponsor is proposing training prior to clinical use yet the usability study did not validate the training or the training materials. Therefore, CDRH is requesting that the sponsor complete another usability study prior to marketing. This validation study should test representative device users, the proposed user training program and its associated materials, the to-be-marketed version of the Gen2 inhaler, and the final proposed version of the IFU. Note that the Office of Surveillance and Epidemiology (OSE) reviews the IFU during the review cycle after the package insert is substantially complete and may request edits for readability or comprehension. Whether another usability study will be needed for the OSE-revised IFU document will depend on the extent of edits needed.
- The sponsor should provide a description of the Afrezza training program.
- The sponsor states that referring to the IFU will mitigate many of the errors identified in the completed usability study. However, CDRH notes that many of these errors occurred because the user did not recognize or was not aware of the content in the IFU. Therefore CDRH would like the sponsor to explain how reference to the IFU will be an effective risk mitigation strategy.
- The claimed storage condition for the inhaler should be revised from 2-25 degrees Celsius to 5-25 degrees Celsius to reflect the actual test conditions.
- Mouthpiece retention testing after shelf-life and simulated use conditions to support the claim that the [REDACTED] <sup>(b) (4)</sup>.
- Labeling to include the statement required by 21 CFR 801.109 for prescription devices: "Caution: Federal law restricts this device to sale by or on the order of a physician."

Please see the reviews by Dr. Melanie Choe and QuynhNhu Nguyen for further details.

## 4. Nonclinical Pharmacology/Toxicology

The Complete Response letter did not include non-clinical pharmacology/toxicology deficiencies. In addition, the Gen2 device system did not trigger the need for new non-clinical pharmacology/toxicology data. Therefore, this resubmission does not contain new non-clinical pharmacology/toxicology data.

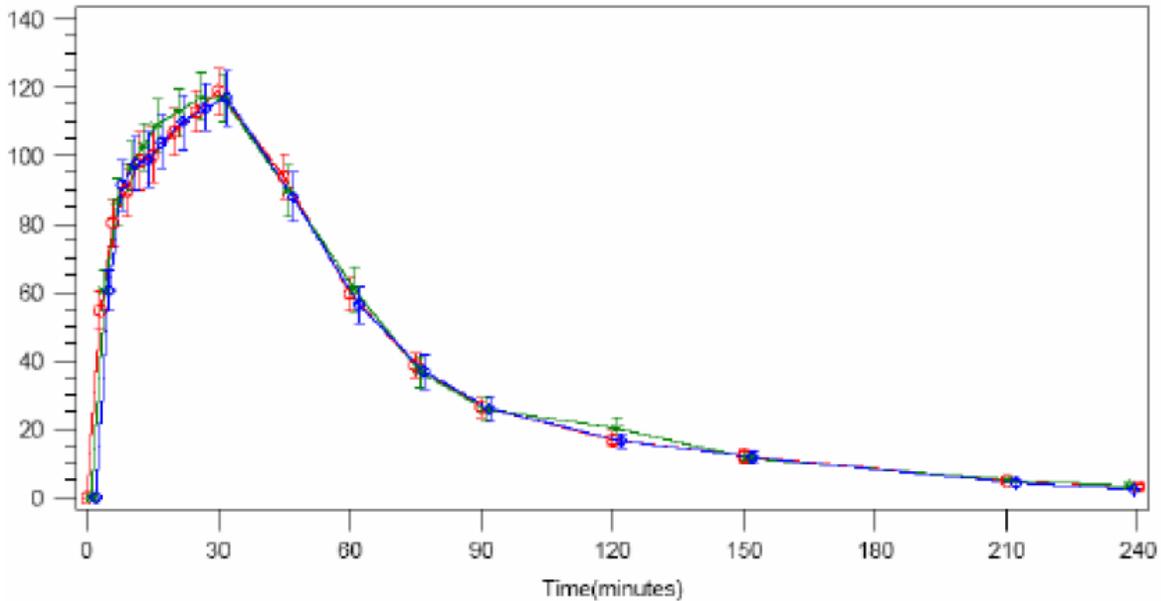
## 5. Clinical Pharmacology/Biopharmaceutics

One of the deficiencies in the Complete Response letter pertained to the pivotal bioequivalence study comparing the to-be-marketed Model D MedTone inhaler with the Model C MedTone inhaler used in the phase 3 trials. This trial had unreliable results because of problems with the insulin and glucose assays identified during inspections by the Division of Scientific Investigations (DSI). We asked the sponsor to either repeat the insulin and glucose measurements (if possible) or to repeat the study. This deficiency is now moot because the sponsor has abandoned the MedTone system and is now proposing the Gen2C inhaler as the to-be-marketed device. Because there are no pivotal clinical trials with the Gen2C inhaler, the sponsor has attempted to bridge the Gen2C system to the MedTone C inhaler (used in the pivotal clinical trials) using a pivotal pharmacokinetic (PK) comparability study (MKC-TI-142).

Study MKC-TI-142 was an open-label, randomized, crossover study in healthy volunteers. The primary objective was to show that 20 units administered by Gen2C (not Gen2B, as suggested on page 8 of the pulmonary review by Dr. Banu Karimi-Shah) yields bioequivalent PK when compared to 30 units administered by the Model C MedTone device. The secondary objective was to show that two 10-unit packages administered by the Gen2C device yields bioequivalent PK when compared to a single 20-unit package administered by Gen2C. The clinical pharmacology reviewers have concluded that these objectives for bioequivalence have been met pending DSI inspection of the clinical and analytical sites of this study. Please see the review by Drs. Sang Chung and Sally Choe for details. As shown in Table 2, adapted from Dr. Chung's review, 20 units via the Gen2C device easily meets the 0.80-1.25 bioequivalence criteria when compared to 30 units via the Model C MedTone inhaler with point estimates that range from 1.00 to 1.08. Graphically, the PK data from these devices are superimposable as illustrated in Figure 4.

<b>Table 2. Least square geometric mean ratios with 90% confidence intervals for AUC and Cmax comparing the Gen2C device and the Model C MedTone inhaler (n=46) (adapted from Dr. Chung's Tables 1 and 2)</b>		
	<b>AUC<sub>0-120</sub> (min*mcU/mL)</b>	<b>Cmax (mcU/mL)</b>
<b>20 units Gen2 vs. 30 units Model C</b>		
Baseline unadjusted	1.01 (0.95, 1.06)	1.02 (0.95, 1.10)
Baseline adjusted – method 1 <sup>a</sup>	1.00 (0.94, 1.06)	1.02 (0.94, 1.10)
Baseline adjusted – method 2 <sup>b</sup>	1.06 (0.98, 1.15)	1.08 (0.99, 1.18)
<b>2 x 10 units Gen2 vs. 1 x 20 unit Gen2</b>		
Baseline unadjusted	0.97 (0.92, 1.02)	0.95 (0.89, 1.03)
Baseline adjusted – method 1 <sup>a</sup>	0.97 (0.91, 1.03)	0.95 (0.88, 1.03)
Baseline adjusted – method 2 <sup>b</sup>	0.96 (0.89, 1.04)	0.93 (0.85, 1.01)
<sup>a</sup> Baseline adjusted using mean of three pre-dose insulin concentrations		
<sup>b</sup> Baseline adjusted using C-peptide concentrations as a measure of endogenous insulin production		

**Figure 4. Mean (SD) insulin concentration-time profiles - baseline insulin values are corrected using the mean of three pre-dose insulin concentrations (red = 30 units with Model C MedTone; green = 20 units with Gen2C; blue = 2 x 10 units with Gen2) – adapted from Dr. Chang's review**



Dr. Chang notes that pharmacodynamic (glucose) parameters were not reported in this study. He states, however, that such data would be limited because this study enrolled healthy volunteers and did not use clamp procedures. Therefore, these subjects often needed exogenous glucose to maintain euglycemia, confounding the pharmacodynamic assessments.

## 6. Clinical Microbiology

Afrezza utilizes (b) (4) powder for inhalation. During the first review cycle, Microbiology reviewed the proposed microbial limits of the insulin powder and found these to be acceptable. There have been no changes to these microbial controls with the new cartridge system; therefore, no Microbiology review was needed during the current review cycle.

## 7. Clinical/Statistical- Efficacy

The sponsor's resubmission contains the full study report for a 16-week, open-label, randomized controlled trial in patients with type 1 diabetes (MKC-TI-117). The remaining clinical studies in the sponsor's resubmission are either uncontrolled trials or phase 1 clinical pharmacology studies involving at most 3 days of dosing of study medication. Therefore, in this section of this memorandum, I will focus only on the 16-week MKC-TI-117 trial.

The original Afrezza NDA included four phase 3 trials testing the MedTone C inhaler, one trial in patients with type 1 diabetes and three trials in patients with type 2 diabetes. These trials were poorly designed and executed (e.g., inadequate titration of insulin doses in the treatment arms). Only one of these four trials, the comparison of Afrezza to NovoLog Mix 70/30 in patients with type 2 diabetes, met its primary objective for efficacy. Afrezza in combination with basal insulin was statistically inferior to subcutaneous basal-bolus therapy in both type 1 and type 2 diabetes. Based on these results, we stated in the Complete Response letter that these findings call into question the clinical utility of Afrezza to treat diabetes in an era where glycemic control has been well-established to reduce long-term complications of microvascular disease in both type 1 and 2 diabetes. We requested that the Complete Response include a detailed discussion on how the available clinical data support the utility of Afrezza in the marketplace and asked the sponsor to clarify why additional clinical studies are not necessary.

In an attempt to provide clearer evidence of efficacy in patients with type 1 diabetes, the sponsor is including in the resubmission the complete study report for MKC-TI-117, a 16-week, multicenter, open-label, randomized, non-inferiority trial comparing Afrezza to insulin lispro, both in combination with insulin glargine in patients with type 1 diabetes. Note that this trial used the MedTone C inhaler, not the Gen2 system. This trial has been reviewed in detail by Drs. Lisa Yanoff (clinical) and J. Todd Sahlroot (biostatistics). Key aspects are briefly reviewed here.

The trial enrolled patients with a >1-year history of type 1 diabetes and HbA1c 7-9% currently treated with any type of insulin regimen. A total of 130 patients were randomized 1:1 into the two treatment groups with approximately two-thirds of randomized patients from the United States and the remaining patients from Brazil. There were more men in the Afrezza arm (62%) than in the lispro arm (51%). Most patients were Caucasian (86-91%). The mean baseline HbA1c was 7.7%.

There was a 3-week run-in period during which all patients were switched to glargine (~20% were not on pre-trial glargine) and the glargine dose was then titrated to achieve fasting glucoses of 80-119 mg/dL. During the run-in period, patients continued their pre-study prandial insulin (two-thirds were already on lispro). At randomization, patients stopped their pre-study prandial insulin and began either Afrezza (premeal Afrezza dose = 3 times the pre-randomization subcutaneous prandial insulin dose then this dose was rounded down to the nearest multiple of 15 units) or lispro (1:1 conversion based on pre-randomization prandial insulin doses). Note that there were no forced treat-to-target algorithms during the 16-week treatment period. Instead, the protocol provided suggestions for dose adjustments and left titration to the discretion of the investigators.

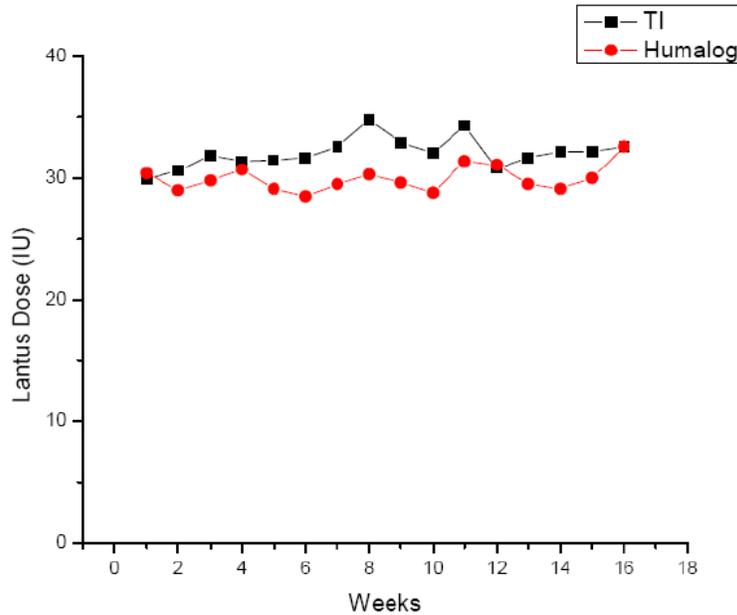
The primary objective of this trial was to show non-inferiority of Afrezza to insulin lispro based on a non-inferiority margin of 0.4%, which was changed from 0.5% by protocol amendment. The 0.4% margin is the standard margin for non-inferiority trials of insulin therapies. The sponsor met the criteria for non-inferiority in both the intent-to-treat population with last-observation-carried-forward and in the completer population as shown in Table 3, adapted from Dr. Sahlroot’s review. Specifically, the upper bound of the two-sided 95% confidence interval for the between-group treatment difference in HbA1c was 0.2% for both statistical populations, below the non-inferiority margin of 0.4%.

<b>Table 3. HbA1c (%) results for Study MKC-TI-117</b>					
<b>Study</b>	<b>N</b>	<b>Baseline mean ± SD</b>	<b>LS mean change at Week 16</b>	<b>LS Mean treatment difference (95% CI)</b>	<b>p-value</b>
<b>Intent-to-treat with last-observation-carried-forward</b>					
Afrezza	61	7.75±0.55	-0.09	-0.04 (-0.25, +0.18)	<0.001
Insulin lispro	65	7.62±0.60	-0.05		
<b>Completers</b>					
Afrezza	52	7.81±0.56	-0.10	-0.07 (-0.31, +0.16)	<0.001
Insulin lispro	60	7.59±0.62	-0.03		
SE=standard deviation; CI=confidence interval					

A small proportion of patients in both treatment groups achieved HbA1c ≤7% at Week 16 (17% with Afrezza; 24% with lispro).

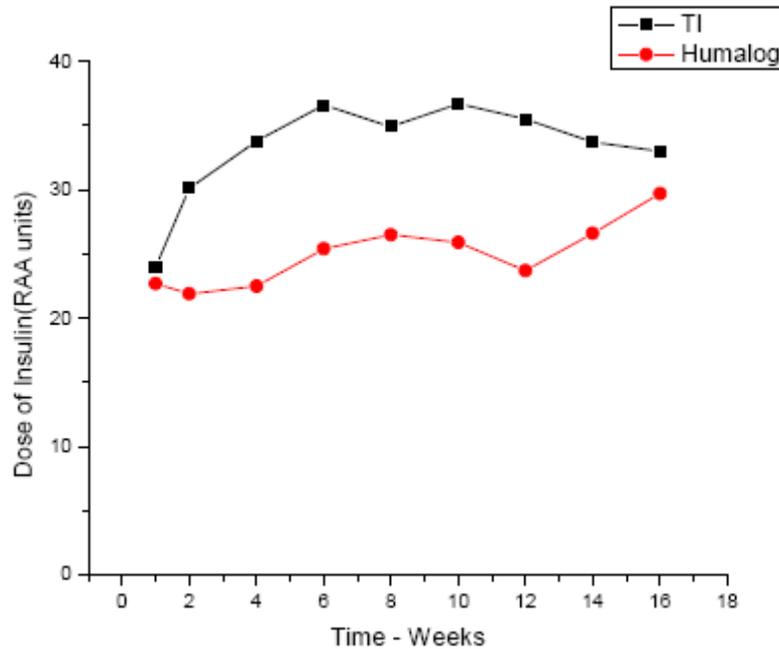
For both treatment groups, the mean daily glargine dose was 30 units at the beginning of the trial and 33 units at Week 16. However, over the 16 weeks, the glargine dose was slightly lower (~0-4 units) in the lispro arm as shown in Figure 5 below.

**Figure 5. Mean daily insulin glargine dose (units) over the 16-week treatment period (safety population)**



As shown in Figure 6, mean doses of prandial insulin were also lower in the lispro arm (the Afrezza doses are converted to subcutaneous-equivalent doses using a conversion factor of 15 inhaled units = 4 subcutaneous units). Afrezza was titrated from a mean daily dose of ~24 units at study start to ~35 units from Weeks 6-12 and then the mean dose declined slightly thereafter to ~33 units at Week 16. In contrast, there was minimal titration of the lispro dose over the first 12 weeks of the trial. As a result, there was a mean absolute difference of ~10 units (after converting Afrezza's doses to subcutaneous-equivalents) between treatment groups from Weeks 2-12. This considerable between-group difference in mean prandial insulin dose calls into question the finding of non-inferiority because of assay sensitivity concerns related to inadequate titration of the lispro comparator. Inadequate titration of insulin doses was also an important limitation of the pivotal phase 3 trials included in the original NDA. Future efficacy and safety trials for Afrezza should ensure that appropriate titration of insulin doses occurs. Strategies include use of a titration algorithm, investigator training with frequent reminders about titrating insulin doses, and review of glucose data while the trials are ongoing with feedback to investigators when there is evidence of inadequate titration. Although the mean lispro dose increased more steeply during the last 4 weeks of the trial, these doses are not fully reflected in the endpoint HbA1c measurement as HbA1c reflects glycemic control over the preceding 12 weeks.

**Figure 6. Mean daily prandial insulin dose (units) over the 16-week treatment period (safety population). Subcutaneous-equivalent doses shown for the TI (Afrezza) arm.**



In addition, Drs. Yanoff and Sahlroot have identified several important limitations of this trial with Dr. Sahlroot stating that these shortcomings have rendered results less than conclusive. These limitations include:

- This trial used the MedTone C inhaler system (the same inhaler used in the original pivotal phase 3 trials). It provides no efficacy or safety data for the Gen2 system.
- The trial was stopped early at one-half the planned sample size. The sponsor chose to do so because they stopped development of the MedTone inhaler in favor of the new Gen2 inhaler. After stopping the trial, the sponsor then calculated *post-hoc* power – apparently on the blinded standard deviation data – and estimated 90% power to meet the 0.4% non-inferiority margin. Nonetheless, the findings are derived from an unplanned, interim analysis of data from an open-label trial. Whether these findings would have been borne out upon completion of the originally planned trial is unknown.
- The baseline HbA1c values were low (mean 7.7%), which may have limited the ability of the trial to show changes in HbA1c from baseline, and, therefore, may have made it easier to show non-inferiority.
- Dr. Sahlroot notes that the size and scope of this trial are similar to the features of Study 101, a 16-week trial in 111 patients with type 1 diabetes comparing Afrezza to insulin aspart, both in combination with insulin glargine. Study 101 was a phase 2 study. Similarly, MKC-TI-117 may be more appropriately viewed as a phase 2 trial rather than as a pivotal phase 3 trial.

Nonetheless, I concur with Dr. Yanoff that MKC-TI-117 provides some clinical information on the utility of the MedTone C system in patients with type 1 diabetes based on the natural

history of the disease. In this population, substitution of Afrezza for prandial subcutaneous insulin maintained glycemic control over 16 weeks (within-group mean HbA1c change from baseline -0.1%), which would not be expected if Afrezza was not contributing glycemic efficacy.

## 8. Safety

Dr. Yanoff has reviewed the new non-pulmonary safety data available since the cutoff date for the original NDA. Note that these data are limited because there is only one newly completed phase 2/3 trial (MKC-TI-117) that enrolled few patients (~65/group). The remaining new data come from short-term dosing in phase 1 clinical pharmacology studies, several uncontrolled trials, and a compassionate use program involving 14 patients who transitioned off Exubera. The new phase 2/3 trial data from MTC-TI-117 (n=130) contributes little additional safety information for the type 1 diabetes population as this represents a small fraction of the available data on approximately 1,200 total patients in the original phase 2/3 type 1 diabetes trials. I concur with Dr. Yanoff that no new safety concerns have been identified based on these limited new data. In this memo, I will focus on all the newly available data for deaths, serious adverse events and withdrawals due to adverse events. For the other safety data, I will focus on the only new controlled phase 2/3 trial, MKC-TI-117. Please see Dr. Yanoff's review for additional details.

The sponsor states that 150 patients have been exposed to the Gen2 system. However, these data are derived from either short-term clinical pharmacology studies or MKC-TI-159, a small (n=73) uncontrolled trial with a median 45 day treatment period. There are no controlled phase 2 or phase 3 trials using the Gen2 system.

All new deaths: There were no deaths in MKC-TI-117 or in any of the clinical trials included in the resubmission. There was 1 death in the compassionate use program that occurred in a 54-year old man with type 1 diabetes and multiple cardiac risk factors, including prior myocardial infarction, who died in his sleep approximately (b) (6) after starting Afrezza. He had persistently elevated HbA1c values for years (most recently in the 12% range) and had refused injected insulin.

All new serious adverse events: Twelve patients (~3%) reported a serious adverse event in the newly available clinical data. Four of these events occurred in Study MKC-TI-117 (hypoglycemia occurring in one Afrezza-treated patient and two lispro-treated patients and one report of delayed recovery from anesthesia in a lispro-treated patient). Eight events occurred in Afrezza-treated patients participating in uncontrolled trials. The remaining event was an episode of diabetic ketoacidosis (DKA) and renal failure in a patient in the compassionate use program. However, non-compliance is the most likely explanation for DKA in this patient because the daytime Afrezza and detemir doses were skipped on two consecutive days. Please see Dr. Yanoff's review for a listing of all newly reported serious adverse events and their narratives. I concur with Dr. Yanoff that there was no pattern to these events – besides the hypoglycemia events, none of the other types of serious adverse events was reported in more than 1 patient.

*All new discontinuations due to adverse events:* In the newly available clinical data, a total of 14 patients (~3%) discontinued due to adverse events, all of whom were treated with Afrezza. Ten of these patients were participating in uncontrolled trials and the remaining four patients (6.2% of the 65 patients randomized to Afrezza) were participating in MKC-TI-117. Except for one patient who discontinued due to hypoglycemia (which was also reported as a serious adverse event), the remaining 13 patients discontinued due to non-serious adverse events related to respiratory symptoms, such as cough (n=5), dyspnea (n=3), bronchoconstriction (n=2), upper respiratory tract infections (n=2), and chest tightness (n=1). I concur with Dr. Yanoff that these adverse events leading to discontinuation are consistent with what was seen in the original NDA and do not change the overall safety profile of Afrezza.

*Lung cancer cases to date:* In the original NDA there was one case of primary lung cancer (bronchogenic carcinoma) that was diagnosed approximately 13 months after the patient started Afrezza when he presented with anemia and CT scanning showed two 2 cm lung nodules. This patient had a 40-pack year history of smoking and his father died of lung cancer.

An additional case of lung cancer in the Afrezza program was reported to FDA on December 28, 2010, as an expedited safety report. This 59 year-old patient received Afrezza for 3.5 years during the same uncontrolled extension trial (MKC-TI-010) as the patient described above. The last dose of Afrezza was taken approximately 2.5 years prior to his presenting symptoms. Chest CT showed a large mediastinal mass and bronchoscopy showed extensive ulceration in the distal trachea, carina, and bilateral main stem bronchi. Based on lymph node biopsy, he was diagnosed with poorly-differentiated non-small cell lung cancer favoring squamous cell carcinoma. Of note, the patient is essentially a non-smoker, having used at most 5 cigarette packs while in college more than 40 years ago.

These two lung cancer cases have occurred among 3,364 Afrezza-treated patients (n=0.059%). There have been no reports of lung cancer among the ~1,600 comparator-treated patients. For comparison, in the Exubera clinical trials, lung cancer was reported in 7 of 3,652 Exubera-treated patients (0.19%) and in 1 of 3,223 comparator-treated patients (0.03%), all of whom had a prior history of smoking. The sponsor did not present analyses for Afrezza using patient-year exposure and did not compare the rates of lung cancer among Afrezza-treated patients to the background rates among smokers and non-smokers. This information should be requested in the Complete Response letter.

#### **Selected safety data from MKC-TI-117:**

Deaths, serious adverse events, and withdrawals due to adverse events in MKC-TI-117 are covered in the sections above.

*Patient disposition:* As discussed by Dr. Yanoff, 65 patients were randomized into each treatment group with 52 Afrezza-treated patients (80%) and 60 lispro-treated patients (92%) completing the 16-week treatment period. The difference in completion rates was driven by adverse events (4 patients with Afrezza – 3 with cough and 1 with dyspnea – vs. 0 patients with lispro), patient withdrawal of consent (4 patients with Afrezza vs. 1 patient with lispro),

and other reasons (3 patients with Afrezza vs. 1 patient with lispro). As discussed by Dr. Yanoff, a total of three patients in the Afrezza group and no patients in the lispro group discontinued due to unacceptable hyperglycemia. These patients were listed in the “patient withdrawal of consent” and “other” discontinuation categories. However, the reasons for classifying these patients as having unacceptable hyperglycemia are unclear. For example, one of these patients had a HbA1c value of 7.3% at discontinuation after several months of therapy, which was unchanged from his baseline HbA1c value. The other two patients had an increase in HbA1c from 7.9% to 8.7% and from 7.4% to 8.8% but there is no mention as to whether the Afrezza dose had been appropriately titrated.

*Adverse events:* Cough was the most common adverse event reported in MKC-TI-117, occurring in 29 (45%) Afrezza-treated patients and in one (1.5%) lispro-treated patient. Cough was also the predominant adverse event in the original NDA and has been attributed to the irritant effects of the drug product on the lungs. There were no reports of drug hypersensitivity reactions, diabetic ketoacidosis, or other noteworthy findings.

*Hypoglycemia:* Based on the pivotal phase 3 trials in the original NDA, the sponsor has claimed that Afrezza carries a lower risk of hypoglycemia than subcutaneous basal-bolus therapy. However, in both type 1 and type 2 diabetes, Afrezza was statistically worse than subcutaneous basal-bolus therapy with regard to glycemic efficacy. These results confounded the hypoglycemia findings because improvement in glycemic control is associated with increased hypoglycemic risk. Because Afrezza was non-inferior to lispro in MKC-TI-117, this trial provides a better setting to compare hypoglycemic risk although the small sample sizes limit conclusions. There was no statistically significant difference (using nominal p-values of 0.05) between treatment groups in the proportion of patients reporting at least one hypoglycemic event (97% in both treatment groups) or in the proportion of patients reporting at least one hypoglycemic event requiring assistance (3 patients with Afrezza vs. 5 patients with lispro).

### **Pulmonary safety:**

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is recommending that additional pulmonary safety data comparing Gen2 and the MedTone devices be obtained prior to approval of the Gen2 system. Please see the review by Drs. Banu Karimi-Shah and Sally Seymour for details.

Dr. Karimi-Shah states that there is inadequate pulmonary (FEV1) data with the Gen2 device. She states that the safety of Afrezza on the pulmonary system is a local effect and she is, therefore, hesitant to extrapolate pulmonary safety from the MedTone system based only upon a comparison of CMC *in vitro* characteristics and systemic pharmacokinetic exposures. Although Dr. Karimi-Shah acknowledges that patients are being exposed to less drug product with the Gen2 device, she states that the factors that impact on pulmonary safety are unknown. In the original NDA, the sponsor provided 2-year pulmonary safety with the MedTone inhaler. Because the maximum separation in FEV1 decline with the MedTone system vs. control occurred within the first 12 weeks of exposure to Afrezza, Dr. Karimi-Shah recommends pre-approval collection of FEV1 data for Gen2 from a randomized, controlled trial comparing the

Gen2 and MedTone inhalers over at least 12 weeks. If these data are reassuring, additional pulmonary safety data can be obtained in the post-marketing setting. If the data are not reassuring, additional pulmonary safety data may be needed pre-approval. Dr. Karimi-Shah's other concern is that the Gen2 has not been evaluated in controlled phase 3 clinical trials and, therefore, meaningful information regarding patient use and device robustness is lacking.

## 9. Advisory Committee Meeting

Had the sponsor continued to propose the MedTone system for marketing and had they resolved the other deficiencies in the Complete Response Letter, we would have taken this application to advisory committee meeting, in accordance with the first cycle recommendations from Dr. Parks. However, the sponsor instead decided to pursue the Gen2 system without accompanying Gen2 phase 3 clinical trials making an approval this cycle unlikely. Therefore, an advisory committee meeting was not scheduled this review cycle.

## 10. Pediatrics

The resubmission contains a revised pediatric plan based on the comments we communicated to the sponsor during the first review cycle, incorporating recommendations from the Pediatric Review Committee (PeRC). For example, based on results from a pediatric handling study with the Gen2 system, the sponsor is now requesting a waiver for children <4 years old <sup>(b)</sup><sub>(4)</sub> and a deferral for children  $\geq 4$  years of age. This revised cutoff age is acceptable and is consistent with the cutoff age used for subcutaneous insulins. Further review and discussions with the sponsor regarding the revised pediatric plan are deferred until the next review cycle. The sponsor should include their pediatric plan together with new timelines for the pediatric studies with the next Complete Response.

## 11. Other Relevant Regulatory Issues

**Tradename:** The Division of Medication Error Prevention and Analysis (DMEPA) re-reviewed the proposed tradename, Afrezza, and found it to still be acceptable. Because approval will not occur within 90 days of the DMEPA review, the Tradename will need to undergo re-review within 90 days prior to approval. See the review by Dr. Yelena Maslov for details.

**Financial disclosures:** For MKC-TI-117, two investigators reported financial conflicts of interest, although one of these sites did not enroll any patients and the other site enrolled only one patient. I agree with Dr. Yanoff that the limited data from these sites would not impact overall conclusions.

**Division of Scientific Investigations (DSI):** On this review cycle, the only scheduled DSI inspection is for the clinical and analytical sites of MKC-TI-142, the pivotal comparative pharmacokinetic study comparing Gen2 to the MedTone C device. Because of an administrative error, this inspection was requested late in the review cycle. FDA inspectors issued a Form 483 for the clinical site on December 17, 2010, but a written report from DSI for this site and the inspection of the analytical site are still pending. However, I am recommending that the sponsor conduct new phase 3 trials with the Gen2 device. If this recommendation is upheld by Dr. Parks, the inspection of Study MKC-TI-142 will be moot as the new trials will provide direct evidence of efficacy and safety with the Gen2 system with no need to bridge to the MedTone C system.

No DSI inspection was requested for MKC-TI-117 as this trial was small (n=130), of short treatment duration (16 weeks) and did not use the Gen2 device – as such, this trial was considered supportive as opposed to pivotal.

An article published in the media stated that a former Senior Director for Regulatory Affairs at MannKind filed a lawsuit in September alleging that the company conducted potential fraud and scientific misconduct and that he was subjected to retaliatory termination. The former employee stated that Good Clinical Practice (GCP) violations occurred at a Russian site (Dr. Shvarts) and a Bulgarian site (Dr. Daskalova) that contributed data to NDA 22472 and that the sponsor did not report this information to FDA despite his recommendation to do so. Dr. Cynthia Welsh in DSI requested additional data from the sponsor and concluded that these data, including a third-party audit and internal investigation, appear to refute the allegations of GCP non-compliance. In addition, there were no regulatory violations identified at the site of Dr. Shvarts (which contributed data to Study 014 only – the 24-week trial that failed to meet its primary efficacy objective and showed statistical inferiority of Afrezza + glargine to aspart + glargine in patients with type 2 diabetes) when it was inspected on the last review cycle. Dr. Daskalova's site did not undergo FDA inspection but this site did not contribute patients to any of the pivotal phase 3 trials for the MedTone device. Therefore, Dr. Welsh concluded that no further regulatory action on this complaint is warranted at this time. I agree with this assessment, particularly because I am recommending the need for new phase 3 trials to support approvability of the Gen2 device. Please see the review by Drs. Welsh and Constance Cullity for further details.

## 12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the labeling and packaging design for Afrezza as well as results of the sponsor's Usability Test conducted with the Gen2 system. Errors occurring among the 15 patients who participated in the Usability Test included overdosing (n=2) and underdosing (n=3) due to miscalculation of the cartridges needed for one dose (to minimize this error, the sponsor has subsequently molded the cartridge strength directly into the cartridge), possible underdosing in 5 participants who held the inhaler upside down on 12 occasions (to minimize this error, the sponsor is proposing to prominently show the correct inhaler orientation in the IFU), not breathing out prior to cartridge inhalation (n=12), not inhaling deeply enough (n=9), and not removing the

mouthpiece cover prior to inhalation (n=2). Based on these findings, DMEPA is recommending the following:

- Pre-approval testing for dosing errors resulting from confusion around the difference between the labeled drug content of the cartridges (10 units or 20 units) and the deliverable dose (equivalent to ~4 or 8 units of subcutaneous insulin).
- Testing the revised IFU to show that the modifications made are effective at minimizing the identified errors, e.g., errors resulting from miscalculation of number of cartridges needed to administer doses larger than 20 units.
- Although the Gen2 device is simpler to use than the MedTone device, DMEPA is still concerned that the multiple steps involved complicate its use and recommends redesign of the device to decrease the number of required steps to administer the drug.

See the reviews by Yelena Maslov, Zachary Oleszczuk, and Carol Holquist for details.

Because I am recommending that the NDA not be approved on this cycle, further review of labeling will be deferred until the next review cycle. DMEPA's preliminary labeling comments can be included in the Complete Response letter for the sponsor to address prior to resubmission.

### **13. Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

#### **Complete Response.**

The deficiencies of this application that do not permit approval at this time include:

#### **Clinical:**

- Lack of randomized, controlled phase 3 trials with the Gen2 device (see rationale below).

#### **DMEPA:**

- Lack of testing in the Usability Study for dosing errors resulting from confusion around the difference between the labeled drug content of the cartridges (10 units or 20 units) and the deliverable dose (equivalent to ~4 or 8 units of subcutaneous insulin).
- Lack of testing the revised IFU to show that the modifications made are effective at minimizing previously identified medication errors, e.g., errors resulting from miscalculation of number of cartridges needed to administer doses larger than 20 units.
- Although the Gen2 device is simpler to use than the MedTone device, DMEPA is still concerned that the multiple steps involved complicate its use and recommends redesign of the device to decrease the number of required steps to administer the drug. It is not clear whether further simplification is possible. The sponsor should either simplify the device where possible or otherwise provide justification for why simplification is not possible.

**CDRH:**

- In line with DMEPA’s recommendations, CDRH is requesting a usability study validating that the sponsor’s changes to the IFU and changes to the cartridge label minimize the previously identified user errors without introducing new risks. According to CDRH, this study should test representative device users, the proposed user training program and its associated materials, the to-be-marketed version of the Gen2 inhaler, and the final proposed version of the IFU. I recommend that this usability study also test some patients who have not undergone the user training program. If this study shows that training mitigates important risks and ensures safe use, I would recommend that the training program be part of the Risk Evaluation and Mitigation Strategies (REMS). The sponsor should be strongly encouraged to submit a study protocol prior to implementation to ensure that the proposed study adequately addresses the concerns raised by CDRH and DMEPA.
- The sponsor should provide a description of the Afrezza training program.
- The sponsor states that referring to the IFU will mitigate many of the errors identified in the completed usability study. However, CDRH notes that many of these errors occurred because the user did not recognize or was not aware of the content in the IFU. Therefore CDRH would like the sponsor to explain how reference to the IFU will be an effective risk mitigation strategy.
- The claimed storage condition for the inhaler should be revised from 2-25 degrees Celsius to 5-25 degrees Celsius to reflect the actual test conditions.
- Mouthpiece retention testing after shelf-life and simulated use conditions to support the claim that the [REDACTED] (b) (4)
- Labeling must be updated to include the statement required by 21 CFR 801.109 for prescription devices: “Caution: Federal law restricts this device to sale by or on the order of a physician.”

**CMC:**

- Lack of an environmental study to show that performance (emitted dose and aerodynamic particle size distribution) of the 10-unit inhaler is not affected by static on the contact surfaces of inhalers at low temperatures (5 degrees Celsius) and low humidity (25% relative humidity).
- Lack of a shipping study to show that performance (emitted dose and aerodynamic particle size distribution) of the 10-unit inhaler is not affected by settlement/leakage during shipment.
- Lack of a robustness study of Gen2 inhalers to provide in-use performance data (emitted dose and aerodynamic particle size distribution) under misuse scenarios (e.g., dropping, shaking).
- Risk Benefit Assessment

The sponsor is proposing to market Afrezza using a new Gen2 inhalation device with re-designed cartridges that contain 10 units or 20 units of drug product compared to 15-unit and 30-unit cartridges previously proposed for the MedTone inhalation device. The Gen2 device

has several advantages over the MedTone device including fewer steps for administering insulin, need for only 1 puff per cartridge (b) (4) and lower amounts of drug product delivered per cartridge. However, the sponsor has not submitted any controlled phase 2 or phase 3 data with the Gen2 device to support its efficacy and safety. Instead, the sponsor is attempting to rely on *in vitro* performance data and a clinical pharmacology bridge to the phase 3 trials conducted with the MedTone inhaler. I consider this approach to be inadequate and recommend that controlled phase 3 trials with the Gen2 inhaler be conducted pre-approval for the following reasons:

- Inhaled insulin products are novel – if approved, Afrezza would only be the second inhaled insulin to market. Therefore, our knowledge of inhaled insulin is in its infancy and we do not yet know for certain that the types of *in vitro* performance changes with Gen2 are safe and effective from a clinical standpoint.
- I concur with the pulmonary reviewers that local pulmonary safety with Gen2 cannot be extrapolated from *in vitro* data and systemic pharmacokinetic profiles. Although patients are being exposed to less drug product with the Gen2 device, the pulmonary reviewers note that the factors that impact on pulmonary safety are unknown.
- In my memorandum for the first cycle review, I stated that in my mind the available phase 3 clinical data support the MedTone device given the novel route of administration, the fact that some patients can achieve adequate glycemic control on this therapy, that there is evidence of efficacy when taking into account the absolute need for insulin in patients with type 1 diabetes and the fact that glycemic control can be monitored and intervened upon, if inadequate. The adequacy of these efficacy data would have been vetted by an advisory committee meeting had the sponsor still proposed marketing the MedTone device. However, given our limited knowledge of inhaled insulin, I am hesitant to extrapolate these phase 3 data to the entirely new Gen2 device based only on *in vitro* performance characteristics and the comparative pharmacokinetic study (even if the DSI inspection is acceptable). In addition, I do not see an easy way to label the efficacy and safety findings for Gen2 based on MedTone C as the MedTone C device was never approved and has a different dosing regimen to the Gen2 device (e.g., 15 and 30 unit cartridges (b) (4) compared to 10 and 20 unit cartridges for Gen2 each requiring one puff).
- The Gen2 device has only been studied in short-term clinical pharmacology studies and in a small uncontrolled study with a median treatment duration of only 45 days. Because Gen2 has not been studied in controlled phase 3 clinical trials, meaningful information regarding patient use and device robustness is lacking.

Given that Afrezza will be a convenience product for most users, I cannot justify approving now based on the above uncertainties and deferring the conduct of controlled phase 3 trials to the postmarketing setting. For patients who have needle phobia or other reasons for clearly needing inhaled insulin (e.g., lipodystrophy), the sponsor can in the meantime set up a treatment investigational new drug application (IND) or physicians can apply for single-patient INDs.

Therefore, I recommend two pre-approval phase 3 trials with Gen2 – one in patients with type 1 diabetes and the other in patients with type 2 diabetes. Both trials should compare Afrezza in

combination with basal insulin to subcutaneous basal-bolus therapy. These trials should be of sufficient duration to permit an adequate titration of study medication and there should be a least 12 weeks of relatively stable insulin doses at the end of the treatment period so that the endpoint HbA1c adequately reflects preceding glycemic control. Adverse events of interest should include pulmonary safety (with pulmonary function testing), hypoglycemia, diabetic ketoacidosis, immunogenicity, eye events (there were 5 cases of retinal detachment with Afrezza and no cases with comparator in the original NDA for the MedTone phase 2/3 program), and device-related performance issues. The sponsor should be strongly encouraged to submit the protocols for these studies for FDA review prior to implementation.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Please see my recommendations from the first cycle review. There may be new or modified recommendations for postmarketing risk evaluation and management strategies based on the findings from the requested Gen2 phase 3 trials.

- Recommendation for other Postmarketing Requirements and Commitments

Please see my recommendations from the first cycle review. There may be new or modified recommendations for postmarketing requirements based on the findings from the requested Gen2 phase 3 trials.

- Recommended Comments to Applicant

The Complete Response letter should include the deficiencies listed above together with our rationale for these deficiencies, where applicable. The letter should also request updated analyses of lung cancer cases in the Afrezza program. These analyses should include adjustments for patient-year exposure and should compare the rates of lung cancer among Afrezza-treated patients to the background rates among smokers and non-smokers. In addition, there should be placeholder language for the anticipated Risk Evaluation and Mitigation Strategies (REMS) based on the safety concerns we identified during the first review cycle. Lastly, labeling comments from DMEPA can be included in the letter together with a statement that all other labeling comments are deferred until when the application can be approved.

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/s/  
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HYLTON V JOFFE  
01/03/2011

MARY H PARKS  
01/04/2011

**DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY**  
**PRODUCTS MEDICAL OFFICER CONSULTATION**

Date: December 13, 2010  
To: Lisa Yanoff, MD, Medical Officer, DMEP;  
Hylton Joffe, MD, Diabetes Team Leader, DMEP;  
Mary Parks, MD, Division Director DMEP  
From: Banu Karimi-Shah, M.D., Medical Officer, DPARP  
Through: Sally Seymour, M.D., Deputy Director for Safety, DPARP  
Subject: Pulmonary Safety of Afrezza (insulin monomer human [rDNA origin]) Inhalation Powder)

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**General Information**

NDA/IND#: NDA 22-472  
Sponsor: MannKind Corporation  
Drug Product: Technosphere Insulin/Afrezza  
Request From: Lisa Yanoff, Medical Officer, DMEP  
Date of Request: June 29, 2010  
Date Received: June 29, 2010  
Materials Reviewed: Complete response submission dated June 28, 2010, S0045

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This document is the response from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to the request for consultation issued by the Division of Metabolic and Endocrine Products (DMEP), requesting analysis of the new pulmonary safety data for insulin monomer human [rDNA origin] Inhalation Powder, or Afrezza (NDA 22-472). A complete response (CR) action was taken for the original NDA submission on March 10, 2010. The Applicant has now returned with additional clinical efficacy and safety information to address the deficiencies which resulted in a complete response action. In response to the deficiencies cited, the sponsor now proposes to replace the previous MedTone inhaler with a new delivery device, known as the Gen2 inhalation system. The sponsor asserts that the design of the Gen2 inhalation system allows them to address the Agency's advice and concerns as outlined in the complete response letter. The drug product, Technosphere Insulin, remains the same, although the dose strength has been changed to maintain bioequivalence to the previously studied doses in the MedTone inhaler. Although the new Afrezza product with the Gen2 inhaler is a new drug-device combination product, the Agency determined that a new NDA was not required because the dosage form (dry powder inhaler) was unchanged.

There were no specific questions for response with this consultation. As with the previous consultation dated December 28, 2009, this consult addresses the pulmonary safety of Afrezza and some general issues with inhalation products. This consult response begins with an Executive Summary of the conclusions/recommendations from DPARP, followed by a presentation of general information, CMC issues which are pertinent to pulmonary safety, a

summary of my review of the pulmonary safety from the original NDA, and the relevant new pulmonary safety data with the Gen2 inhaler. From a pulmonary safety standpoint, there are several issues which the Division of Metabolic and Endocrine Products should consider in making their decision regarding approval of Afrezza.

## **I. Executive Summary**

### **Recommendation on Regulatory Action**

After review of the pulmonary safety data that was submitted with the original NDA 22-472, it was the opinion of this reviewer that there were no pulmonary safety issues that precluded approval of Afrezza. Had the application been approved in the previous cycle, pulmonary safety issues that had been identified (bronchospasm, cough, FEV1 decline both acutely and over 2 years) could be addressed through labeling, and potential safety issues (malignancy, long-term pulmonary function decline, and use of Afrezza in patients with underlying lung disease) could be addressed as post-marketing requirements. However, the Applicant's current proposal to respond to the deficiencies cited in the Complete Response by putting forth a completely new device is problematic because of the lack of pulmonary safety data and limited patient use and device performance/reliability information with the new product. As discussed below, it is not clear that pulmonary safety data can be extrapolated based upon *in vitro* assessment and systemic exposure. Therefore, prior to approval, we recommend obtaining additional pulmonary safety data with the Gen2 and MedTone products to assure the pulmonary safety data is comparable.

From my perspective, a reviewer who deals with locally-acting, inhaled drugs, whose efficacy and safety profiles are highly dependent on the delivery characteristics of the device, it is difficult to fully accept the Applicant's attempt to "bridge" the pulmonary safety of TI in the MedTone Inhaler to TI in the Gen2 inhaler, based on *in vitro* assessments and systemic exposure. While *in vitro* assessments provide important information, the clinical implication of a difference in performance characteristics is unclear, and systemic exposure has little to no impact on pulmonary safety. Inhaled medications for pulmonary diseases act locally and a change in the device can affect performance characteristics and thus affect efficacy and safety. As a result, a new device for a pulmonary disease would generally warrant a new clinical development program for a locally acting drug. Because Afrezza is a systemically active drug delivered via the inhaled route, the Applicant proposes that the efficacy of Afrezza delivered via the two devices can be bridged via a bioequivalence approach as the pharmacodynamic effect (blood glucose) is systemically measurable. The effect of Afrezza on the pulmonary system (pulmonary safety), however, is a local effect and it is not clear that the pulmonary safety can be bridged in the same manner as efficacy.

The Applicant designed the Gen2 inhaler to have the same performance characteristics as the MedTone inhaler, however the performance characteristics of these two devices are not the same. CMC review of the performance characteristics shows that the Gen2 inhalation system is a more efficient delivery system for TI with a total emitted dose <sup>(b)</sup><sub>(4)</sub> % less than what was administered by the MedTone inhaler, so patients are being exposed to less drug product via the Gen2 inhaler, which is reassuring, however it is important to note that the exact factors which impact upon pulmonary safety are unknown.

Therefore, the most definitive way to ensure that the pulmonary safety of TI delivered via the Gen 2 inhaler is similar to that of TI delivered via the MedTone inhaler is to collect pulmonary safety information (adverse events, FEV1) in a controlled clinical trial setting. Based on the data we have from the original NDA submission in which pulmonary safety data were collected for 2 years, we know that the maximum separation in FEV1 declines between TI-treated and control patients occurs within the first 12 weeks of exposure to Afrezza, and therefore, we recommend collection of FEV1 data comparing Afrezza administration in the Gen2 and MedTone inhalers over at least a 12 week time period to compare the pulmonary safety of the two products. If the results of a short term (e.g. 12 week study) are reassuring, additional pulmonary safety data with the Gen2 inhaler could be obtained post-marketing. If the results of the short term pulmonary safety study suggest a larger effect on pulmonary function, additional pulmonary safety data may be necessary prior to approval to assure the pulmonary safety of the Gen2 product.

In addition to the need for more pulmonary safety data, the resubmission with the Gen2 inhaler is also lacking important information regarding patient use and device robustness. The Gen2 product has not been evaluated in large scale, phase 3 clinical trials. Although a usability/human factors study has been conducted, actual use of the Gen2 product by patients in a clinical trial setting is necessary to ensure that the device can be used safely prior to marketing.

#### **Recommendation for Post-market Requirements**

If this application is to be approved, the following are recommended post-marketing requirements regarding pulmonary safety:

- The Applicant should conduct a large controlled study designed to further assess the long-term pulmonary safety of Afrezza with the Gen2 device. In the absence of a safety signal, the most appropriate duration and size of the study are uncertain. We suggest a minimum of 5,000 patients in each treatment arm for a duration of at least 5 years. Ideally, the study will include an assessment of FEV1.
- The Applicant should design and conduct a long-term epidemiologic lung cancer study in order to collect more data regarding the risk of malignant lung neoplasm in patients that use Afrezza in the Gen2 device.
- The Applicant should evaluate the safety and efficacy of Afrezza in the Gen2 device in patients with underlying lung disease, such as asthma and COPD.

#### **Labeling Recommendations**

Initial review of the proposed product label has revealed some notable omissions. (b) (4)

High-level labeling comments pertaining to the inclusion of pulmonary safety data include:

##### Section 2: Dosage and Administration

- A recommendation for baseline and periodic monitoring of PFTs should be included.

##### Section 4: Contraindications

(b) (4) The following contraindications should be included:

- Smokers

- Unstable or poorly controlled lung disease

#### Section 5: Warnings and Precautions

- [REDACTED] (b) (4)  
This statement should be corrected to read that Afrezza is not recommended for patients with any concomitant or underlying lung disease, as it has not been studied in this patient population. In addition, the concern for bronchospasm in patients with asthma should be noted.
- A warning and precaution regarding the decline in pulmonary function should also be included. More detailed information regarding the change in pulmonary function can be presented in Section 6.
- A recommendation that patients have baseline spirometry and periodic monitoring of spirometry. In addition, underlying lung disease should be ruled out.

#### Section 6: Adverse Reactions

- A section entitled “Respiratory Adverse Events” and “Pulmonary Function” should be added to this section. A full explanation of change in PFTs, including figures, in both Type 1 and Type 2 diabetics, as well as a table of common respiratory adverse reactions should be included.

#### **Risk Evaluation and Mitigation Strategy**

If Afrezza is approved, DPARP recommends a REMS to include a Medication Guide for patients and possibly a communication plan for healthcare providers. The Medication Guide is recommended because Afrezza has effects on pulmonary function and should not be used in patients with asthma or COPD. Patients should be made aware of this information as this could affect patients’ decision to use Afrezza. A communication plan should be considered for healthcare providers regarding the appropriate patient population for Afrezza, baseline screening spirometry, and periodic monitoring of spirometry. The safety concern is the possibility of harm due to use by inappropriate patient populations and the risk of respiratory difficulty immediately post-inhalation and the risk of pulmonary function decline over time.

## **II. General Information**

In NDA 22-472, MannKind Corporation has developed Afrezza, insulin monomer human [rDNA origin] Inhalation Powder (also referred to as Technosphere Insulin, or TI), as an ultra-rapid acting prandial insulin for the treatment of Type 1 and Type 2 Diabetes Mellitus in adults 18 years of age and older. Technosphere® Insulin (TI) Inhalation Powder is a dry powder formulation of recombinant human insulin and contains a novel proprietary excipient, fumaryl diketopiperazine (FDKP).

The NDA was originally submitted on March 16, 2009. In that submission, Afrezza consisted of Technosphere® Insulin Inhalation Powder pre-metered into unit dose cartridges to be delivered via the MedTone® Inhaler. The MedTone inhaler was proposed to be breath-powered, re-usable for 12 months, [REDACTED] (b) (4)

[REDACTED] The applicant conducted the pivotal phase 2 and 3 clinical trials with the Model C inhaler; however, the Applicant planned to market the Model D inhaler, which had been modified to address issues noted with the Model C inhaler.

To support approval of the Afrezza product in the original NDA submission, the Applicant conducted a large clinical development program with the MedTone inhaler which included 9 controlled clinical trials, including one with a 2 year duration in patients with diabetes, which also evaluated pulmonary safety. Based upon review of the pulmonary safety data with the MedTone inhaler in the original submission, DPARP noted issues regarding the following: 1) bronchospasm and cough; 2) (b) (4); 3) device durability and patient use data; and 4) pulmonary safety. These were not necessarily deficiencies, but issues for DMEP to consider in determining the regulatory action.

A complete response action was taken on March 12, 2010, in which several deficiencies were cited including: 1) unproven clinical utility, 2) unreliability of pivotal bioequivalence study results, 3) unproven usability of the MedTone device, and 4) lack of data to support proposed 1-year in-use life of MedTone device.

An end-of-review meeting was held with the Applicant on June 9, 2010, to discuss the deficiencies. The Applicant proposed that they would be submitting information with the Gen2 inhaler in the Complete Response. In the meeting comments dated June 8, 2010, the Applicant was informed that clinical evidence of pulmonary safety would be required with the new device. The Applicant was cautioned that a change in device after completion of the phase 3 program was considered to be extremely risky. During the meeting, the Applicant claimed that the device characteristics for Gen2 would allow for comparable delivery of TI as compared with the previously studied MedTone inhaler. The Agency indicated that the Applicant would need to establish adequate comparability between the two devices to consider bridging the pulmonary safety data from the MedTone inhaler to the Gen2 inhaler. Because it is unclear what causes the effects on the pulmonary system and the process of bridging pulmonary safety between devices was unprecedented, any differences between the products would be concerning.

The Applicant submitted a Complete Response June 29, 2010. In response to the deficiencies, the sponsor has now proposed to change the device to the Gen2 inhalation system. The Applicant noted that they did not think that modification of the MedTone inhaler would allow them to adequately address the Agency's deficiencies. The new product now consists of different pre-metered unit dose cartridges of TI to be delivered by the Gen2 inhaler, a completely different device. The TI Inhalation Powder has not changed, however the sponsor asserts that the deagglomeration of the TI powder is more efficient in the Gen2 inhaler, therefore supporting lower fill weights in the new cartridges. The CR submission includes the following:

- two single dose clinical pharmacology studies with the Gen2 inhalation system and the MedTone inhalation system (MKC-TI-140 and MKC-TI-141) in which spirometry was assessed
- bioequivalence study of the Gen2 inhaler to the previously studied MedTone inhaler in order to support the device switch from an efficacy standpoint (MKC-TI-142).
- new clinical data from Study MKC-TI-117 to support the clinical utility of Afrezza (conducted with the MedTone inhalation system)
- revised labeling, REMS, safety update, pediatric program
- CMC data to support the Gen2 inhalation system
- usability study and human factors evaluation

The current submission contains pulmonary safety information from two studies with the Gen2 inhaler in which pulmonary function was measured post single dose out to two hours after TI administration. As the original NDA (in which the MedTone inhaler was used) contained controlled pulmonary function information for two years, these studies add relatively little information to the overall pulmonary safety database with respect to extent of exposure, but does provide some useful information regarding FEV1 immediately post-dose.

### III. Chemistry, Manufacturing, and Controls

#### A. Drug Product: Technosphere Insulin

The drug product consists of particles of the novel excipient fumaryl diketopiperazine (FDKP) coated with recombinant human insulin, as well as trace amounts of polysorbate 80 (b) (4). The drug product is contained within cartridges as is further discussed below. Per the original NDA chemistry review, there is a significant amount of (b) (4) present in the excipient FDKP, (b) (4). The active pharmaceutical ingredient, excipients, and sources are the same for the MedTone and Gen 2 products.

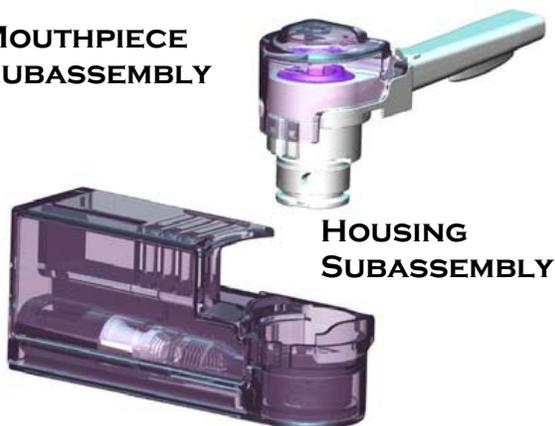
*Reviewer's Comment:* (b) (4) may be a potential mechanism for the high incidence of cough noted post-inhalation.

#### B. Device Characteristics: MedTone Inhaler

The Model D MedTone Inhaler was designed and developed by the Applicant for exclusive use with the Afrezza-filled cartridges shown below. The MedTone inhaler was breath-powered, proposed to be re-usable for 12 months, (b) (4).

The design was comprised of two subassemblies (the mouthpiece and the housing), (b) (4).

**MOUTHPIECE  
SUBASSEMBLY**



**HOUSING  
SUBASSEMBLY**

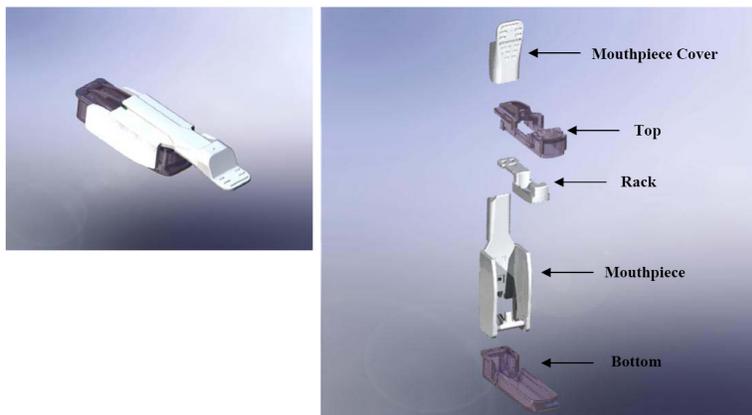
**INSULIN CARTRIDGE**  
15 U (1 band) 30 U (2 bands)



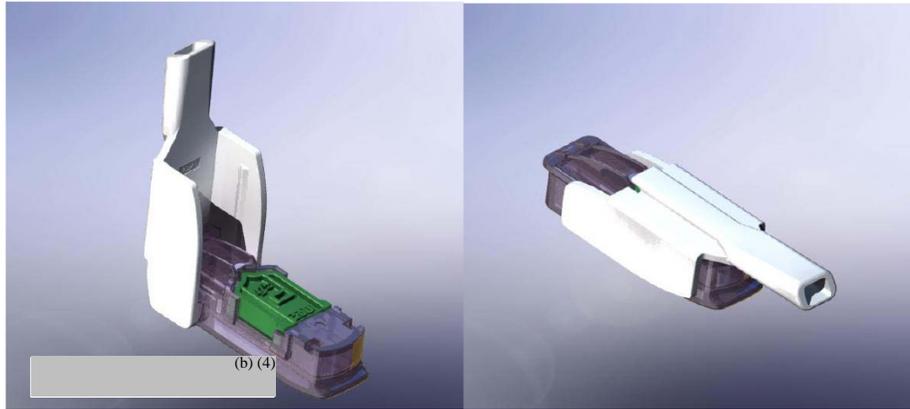
*Reviewer's comment: The MedTone Inhaler was a complex device to operate. The usability of the device was not sufficiently evaluated in the last submission, and this constituted one of the deficiencies cited in the CR letter. The 1-year life of the product had also not been established.*

### **C. Device Characteristics: Gen2 Inhalation System**

The Gen2 Inhaler has two distinct, but non-separable components, a Mouthpiece and Housing. The Mouthpiece is white and is the external portion of the device which users put in their mouth during inhalation. The Housing is translucent purple and serves as a grasping surface by which users can hold and manipulate the device.



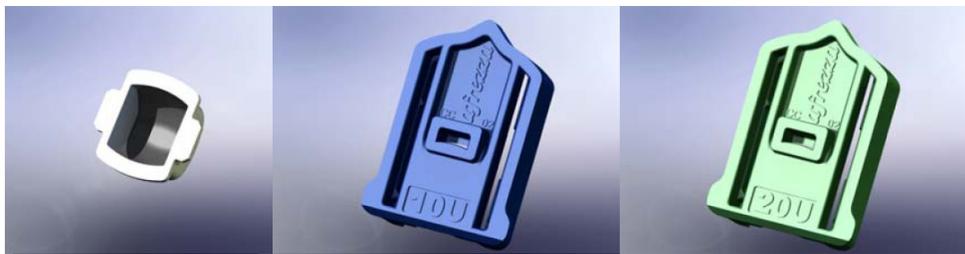
In order to use the device, a cartridge containing either 10U or 20U of insulin is loaded into the Gen2 inhaler as shown below. The inhaler is then closed in to the dosing position, and the patient inhales the dry powder from the mouthpiece in one breath.



**Load Position – cartridge installed**

**Dose Position**

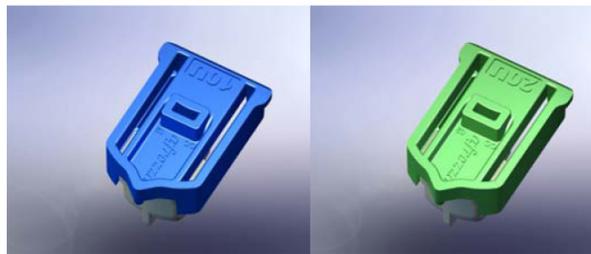
Cartridge Lids are color coded and marked to indicate cartridge strength. Blue Cartridges contain 10 U TI Inhalation Powder (3.3 mg) and green cartridges contain 20 U TI Inhalation Powder (6.7 mg). In addition, “afrezza” is on the Lid to identify the drug product.



**Cartridge Cup**

**Cartridge Lid – Blue 10 U**

**Cartridge Lid – Green 20 U**



**10 U and 20 U Assembled Cartridges – Containment Position**

*Reviewer’s comment: The Gen2 inhalation system has also gone through a number of iterations (Gen2A, Gen2B, and Gen2C). The clinical pharmacology and BE studies were done with the Gen2B inhaler, however it is the Gen2C that is proposed for marketing. In discussion with our CMC team, the modifications from the Gen2B to Gen2C should not impact performance.*

**D. CMC Issues Relevant to Pulmonary Safety**

A summary of a discussion with the CMC and CDRH review teams is presented here as it relates to subsequent recommendations regarding the evaluation of pulmonary safety. Reviews from the CMC and CDRH disciplines are pending at the time of finalization of this review. For full details, please refer to the reviews of Dr. Edwin Jao (CMC) and Melanie Choe (CDRH).

### Comparability of the MedTone and Gen2 inhalation systems

The Applicant proposes that the Gen2 inhalation system is a more efficient delivery system for TI (b) (4) allowing one-third less powder per cartridge. As confirmed by the CMC review, the Gen2 inhalation system provides more efficient deagglomeration of the dry powder drug product, resulting in a total emitted dose which is (b) (4) % less than what was administered by the MedTone inhaler, while the fine particle fraction is comparable (b) (4) between the two devices. When looked at in the Next Generation Impactor (NGI), with a pressure drop of (b) (4) kPa (which corresponds to flow rates of (b) (4) LPM), the Gen2 delivers (b) (4) U of insulin while the MedTone delivers about (b) (4) U of insulin.

*Reviewer's comment: The flow rates at which the Applicant purports similarity/comparability of the two devices are lower than those at which inhalation devices are typically evaluated. For example, inhalation products indicated for asthma are usually evaluated at (b) (4) LPM. However, the Applicant states that the typical pressure drop which patients can generate through this high resistance device is (b) (4) kPa, making this the more relevant in vitro testing condition. Although this may be accurate, the CMC reviewers caution that lower flow rates may be less discriminating of differences between the two devices.*

### Device Robustness

The Applicant did not submit any studies evaluating the robustness of the Gen2 device. These studies typically include drop testing, shipping stability, and dose counter studies. These studies are typically included in applications for inhalation products.

*Reviewer's comment: It is an atypical situation here in which the device proposed for marketing has never been evaluated in a large scale, phase 3, clinical trial, but rather has been bridged to the studied device (the MedTone inhaler) in a bioequivalence PK study. As a result, we don't have controlled data regarding the robustness of the device. However, the proposed life of the Gen2 inhaler is 15 days, as opposed to the MedTone Inhaler, which was 1 year.*

### Human Factors/Usability Study

A human factors/usability study was conducted. See the CDRH review for further details. According to the Applicant, as of 15 May 2010, 250 subjects have received at least one dose of TI Inhalation Powder through a Gen2 inhaler in clinical trials.

#### IV. Summary of Pulmonary Safety from Original NDA Submission

The pulmonary safety results from the original NDA submission are summarized below. In the original review of the pulmonary safety data, we concluded that the number of subjects exposed to Afrezza in the MedTone inhaler in the controlled clinical trials (>600 type 1 diabetics and >1700 type 2 diabetics) was adequate to assess the pre-marketing pulmonary safety of Afrezza in subjects without underlying lung disease. In addition, the duration of exposure of up to two years in 538 type 1 diabetics and 1334 type 2 diabetics was reasonable to assess the pulmonary safety of subjects without underlying lung disease.

##### A) Bronchospasm and cough

Afrezza was noted to cause irritation of the upper respiratory tract, as manifested by cough and occasional bronchospasm, particularly in patients with underlying lung disease, such as asthma. Cough was the most common adverse event noted in the original clinical program (25-30% incidence) with Afrezza. Although cough was generally mild, dry, intermittent, and tended to decrease over time, cough was the reason for discontinuation in approximately 3% of patients treated with Afrezza. There were a number of other respiratory adverse events reported that suggested irritation of the upper respiratory tract including, asthma, bronchial hyperreactivity, bronchospasm, dyspnea, laryngospasm, throat irritation, throat tightness, and wheezing.

*Reviewer's comment: The frequency of coughing was similar to what was seen in the Exubera program, but much more than what we tend to see in asthma/COPD programs with dry powder inhalers.*

##### B) Pulmonary function

The submitted data were adequate to assess pulmonary safety over 2 years. Patients with type 1 or type 2 DM treated with Afrezza had a greater decline in FEV1 over time than patients treated with comparators. The decline was noted during the first 3 months of therapy. The treatment differences were small (on average about 40-50 mL) and the results from the long-term studies showed that the early difference persisted and that the endpoint results were statistically significantly different when Afrezza was compared against a non-inhaled anti-diabetic product. There was insufficient data to draw definitive conclusions regarding reversal of the FEV1 effects. Categorical analysis showed that more patients treated with Afrezza had a significant decline in FEV1 ( $\geq 15\%$ ) than in the comparator groups. Overall, a treatment group difference of 40-50mL was thought unlikely to be clinically significant if the treatment groups did not continue to separate over time. The FEV1 data was generally consistent with the effects seen in the Exubera program. Based upon the two year data, it was unclear if the groups would separate more with longer treatment, thus, additional long term data was recommended as a post-marketing requirement, similar to what was requested with the Exubera program.

The Applicant also characterized serial pulmonary function (FEV1) immediately post-inhalation of Afrezza, up to 2 hours in asthmatic patients (n=22), and up 4 hours in patients with COPD (n=8) and in patients without asthma or COPD in three small phase 1 studies. In patients without asthma, a mean decline in FEV1 up to 90mL-138mL post Afrezza was noted in two of the trials. Thus, there was a decline in FEV1 noted post inhalation, albeit likely not large enough to cause symptoms in someone with normal FEV1. In asthmatic patients, FEV1 declined approximately

400 mL when measured 15 minutes after administering Afrezza. This decline recovered towards baseline (to within 20 mL) at 2 hours. In addition, the Applicant noted difficulties with bronchospasm in an ongoing clinical trial (MKC-TI-134) in patients with asthma. Patients with COPD had a smaller decline (200 mL) and a slower recovery over 4 hours towards baseline. Although Afrezza was not proposed to be labeled for patients with asthma or COPD, there was significant concern that a patient with undiagnosed underlying lung disease may receive the drug and experience respiratory difficulty post-inhalation.

### C) Malignancy

Malignancy was an adverse event of interest, given the properties of insulin and the findings with Exubera. While a pulmonary malignancy signal was not noted, the database was likely too small to identify such a signal. As a result, additional post-marketing data was recommended to evaluate for malignancy, similar to what was requested for the Exubera program.

## V. New Pulmonary Safety Data with the Gen2 Inhalation System

### Study MKC-TI-140

*Reviewer's comment: This study was done with the Gen2A inhaler which is two models previous to the one which is proposed for marketing. The changes that have occurred from Gen2A to Gen2C may impact the performance characteristics of the device, and therefore, this study is only briefly reviewed here.*

This was a phase 1, open-label, crossover, 2-part study in 20 normal healthy volunteers. The primary endpoint of the trial was the tolerability and safety of 2 fill weights (10 mg and 15 mg) of dry powder containing only excipient (FDKP) as measured by a VAS for cough and by FEV<sub>1</sub>. Results for the Gen2A Inhaler were compared to those for the MedTone® Inhaler Model C. Inspiratory training was done with the BluHale™ Inspiratory System (a proprietary experimental system developed by MKC for determining pressure and flow through MKC inhalers) at the screening visit, with additional inspiratory training at each clinic visit. Subjects trained and performed practice inhalations until they were comfortable with the inspiratory maneuver.

Part 1 was a 2-way, 3-period crossover study. Ten subjects received 10 mg and 15 mg of Technosphere® Inhalation Powder inhaled through the Gen2A Inhaler and 10 mg inhaled through the MedTone Model C. Safety and tolerability measurements (VAS and FEV<sub>1</sub>) were recorded. Each dose of FDKP dry powder was preceded by an overnight washout period. Dosing was completed within 72 hours. The PK of FDKP was assessed with each treatment. Part 2 was a 2-part, 2-way crossover using 10 mg of excipient-only powder in the Gen2A Inhaler. The effect of altering inspiratory effort (lower versus higher) and inhalation time (short versus long) were evaluated. For both parameters, all other parameters were held constant. Ten subjects were crossed over for each of the 2 parameters with an overnight washout period between doses for a total of 20 subjects. The PK of FDKP was assessed for each treatment.

Reviewer's comment:

(b) (4)

The most common TEAE in all 3 cohorts was cough, which occurred in 40% to 70% of subjects. The incidence of cough was similar with the Gen2A inhaler and the MedTone Model C, with 10 mg and 15 mg Technosphere® Inhalation Powder doses, with long and short inhalations, and with higher and lower effort. Cough is typically observed after inhalation of a dry powder, and the incidence of cough was similar to that seen across studies using the MedTone® Inhaler Model C and the Gen2A inhaler, regardless of inhalation effort.

For all subjects, irrespective of inhaler type or FDKP dose, mean FEV1 decreased about 70 cc at 15 minutes after dosing, but had returned towards baseline by 30 minutes after dosing.

### **Study MKC-TI-141**

The Applicant conducted study MKC-TI-141 in which the MedTone C and Gen2 inhalation systems were compared in approximately 46 healthy volunteers. The study was a single center, open label, randomized, crossover study to evaluate the bioavailability of TI in the Gen2B inhaler as compared with the MedTone Model C inhaler. Pulmonary function tests were measured. The study was conducted in 4 parts, the design and pulmonary safety results of which are summarized below.

*Reviewer's comment: The Gen2B inhaler is not the model intended for marketing, but rather it is the Gen2C which is the model that is proposed for marketing. However, according to our CMC review team, the changes from Gen2B to Gen2C do not impact the delivery characteristics in a significant way.*

#### A. Study Design

##### *Part 1*

Twelve subjects participated in a 2-way, 2-period crossover trial of 20U of TI through the Gen2B inhaler and 30U through the MedTone Model C. Subjects entered the clinic on Day 0 for inhalation training. To acclimate the subjects to inhaling a dry powder, after completing admission tests subjects were dispensed 10 mg of Technosphere® Inhalation Powder (excipient only) and the Gen2B inhaler, and three test inhalations were performed. Subjects remained overnight in the clinic. On Day 1, 6 subjects received TI using the Gen2B inhaler and 6 subjects received TI using the MedTone Model C. Immediately after inhalation, subjects were fed a standardized breakfast. Blood samples were obtained over 6 hours for glucose, insulin, FDKP, and C-peptide measurements. FEV1 was measured pre-dose (baseline), 17, 33, 63, and 123 minutes post-administration of TI. After an overnight washout period, subjects received TI using the alternate inhaler, and followed the same procedures as on Day 1. Subjects were discharged from the clinic at the discretion of the PI after the last PK sampling at 360 minutes and a physical examination.

*Part Ib:*

This part of the trial was conducted because the insulin PK of the Gen2B inhaler was lower than desired versus the MedTone® Inhaler Model C using the initial doses of TI Inhalation Powder. The TI dose used with the Gen2B inhaler was increased to 22 U based on the difference in exposure between inhalers. Part I was repeated using the adjusted dose with 12 new subjects who were TI naïve.

*Part II:*

The design of this part of the trial was also similar to Part 1, except that the treatment groups consisted of 10U TI delivered by the Gen2B vs. 15U TI delivered by the MedTone Model C.

*Part III:*

This part of the trial was conducted in a similar fashion to Part I, however this was a 3 period cross over trial in which patients received the dose of TI from the same inhaler for 2 dosing periods (to examine for intra-subject variability), and were then crossed over to the alternate inhaler. Each period was separated by an overnight washout.

B. Extent of Exposure

Forty-eight subjects were randomly assigned to treatment, but only 45 were exposed to TI. Three subjects discontinued the trial and were exposed only to excipient; these 3 subjects were not included in the safety population.

In Part I (relative exposure), 11 subjects received single doses of TI 20 U and 30 U using the Gen2B inhaler and MedTone® Inhaler Model C, respectively. In Part Ib (relative exposure), 12 subjects received single doses of TI 22 U and 30 U using the Gen2B inhaler and MedTone® Inhaler Model C, respectively. In Part II, 10 subjects received single doses of TI 10 U and 15 U using the Gen2B inhaler and MedTone® Inhaler Model C, respectively. The remaining 12 subjects in Part III (intra-subject variability) received 2 single doses of TI of 20 U or 30 U using the same inhaler and corresponding dose and a single dose of TI using the alternate inhaler model from the one previously used.

C. Adverse Events

The most common treatment-emergent adverse events (TEAEs) for subjects who received excipient only inhalation during training were headache (16.7%) and cough (77.1%). The only other TEAEs that occurred for more than 1 subject were dizziness and throat irritation. There were also 2 episodes of mild wheezing experienced by 1 subject when using each inhaler in part 1 of the study. These wheezing episodes were accompanied by a 5-6% decline in FEV1 and returned to baseline ~30 min after inhalation. All TEAEs during training with the excipient only formulation were mild and all subjects used the Gen2B inhaler. No deaths, SAEs, discontinuations due to TEAEs, or other significant AEs were reported for subjects who received Technosphere® Inhalation Powder during training.

The most common respiratory TEAEs for subjects who received TI in Parts I – III was cough, which occurred in 10% to 91.7% of subjects (see Table 1). The incidence of cough was comparable between the Gen2B inhaler and the MedTone® Inhaler Model C in Parts I –III. All

cough TEAEs were mild in severity. The only other TEAEs that occurred for more than 1 subject who received TI were headache and dizziness. No deaths, SAEs, discontinuations due to TEAEs, or other significant AEs were reported for subjects treated with TI .

<b>Table 1: Adverse Event of Cough in Study MKC-TI -141 (Safety Population, n = 45)</b>								
	<i>Part I</i>		<i>Part Ib</i>		<i>Part II</i>		<i>Part III</i>	
	Gen 2B 20 U n = 11 (%)	Mod C 30U n = 11 (%)	Gen2B 22U n=10 (%)	Mod C 30U n=12 (%)	Gen2B 10U n=10 (%)	Mod C 15U n = 10 (%)	Gen2B 20U n= 12 (%)	Mod C 30U n=12 (%)
Cough	3 (36.4)	5 (45.5)	3 (30.0)	5 (41.7)	1 (10.0)	2 (20.0)	11 (91.7)	10 (83.3)

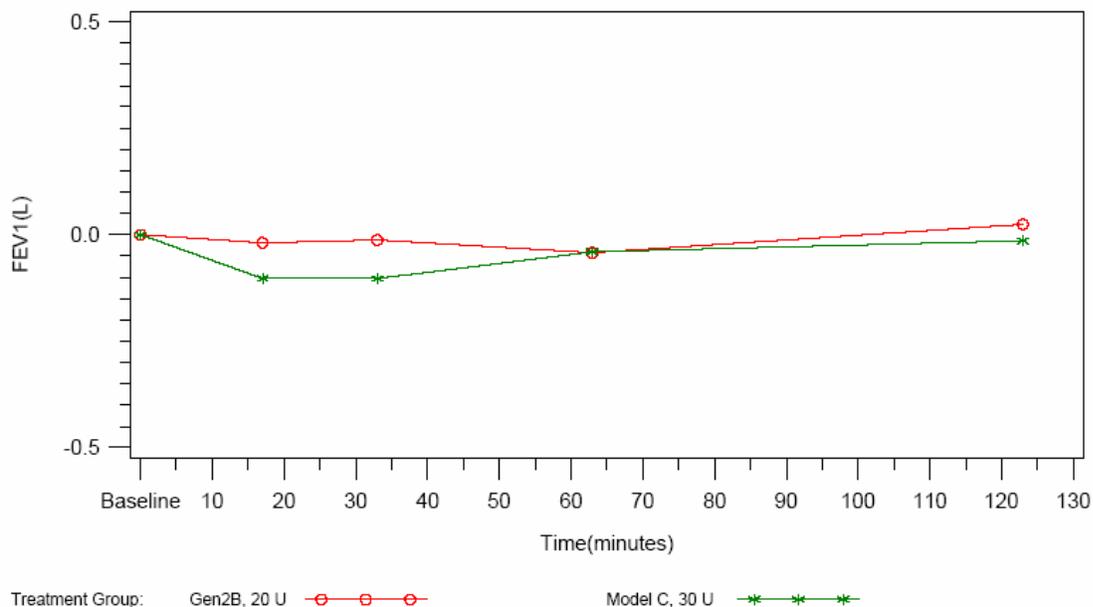
Source: Table 12, p. 53, MKC-TI-141 Clinical Study Report, Module 5.

*Reviewer’s comment: Although it is difficult to draw definitive conclusions from such small study, it does not appear that the incidence of cough has changed as a result of the change in device. The frequency of cough as an adverse event is still higher than what we are accustomed to in our inhalation programs for pulmonary indications such as asthma and COPD, but there doesn’t seem to be any dose or device dependence.*

#### D. Pulmonary Function: FEV1

Mean changes in FEV1 from pre- to 17, 33, 63, and 122 minutes post-administration of TI using either the Gen2B inhaler or the MedTone Model C are shown in the figures below.

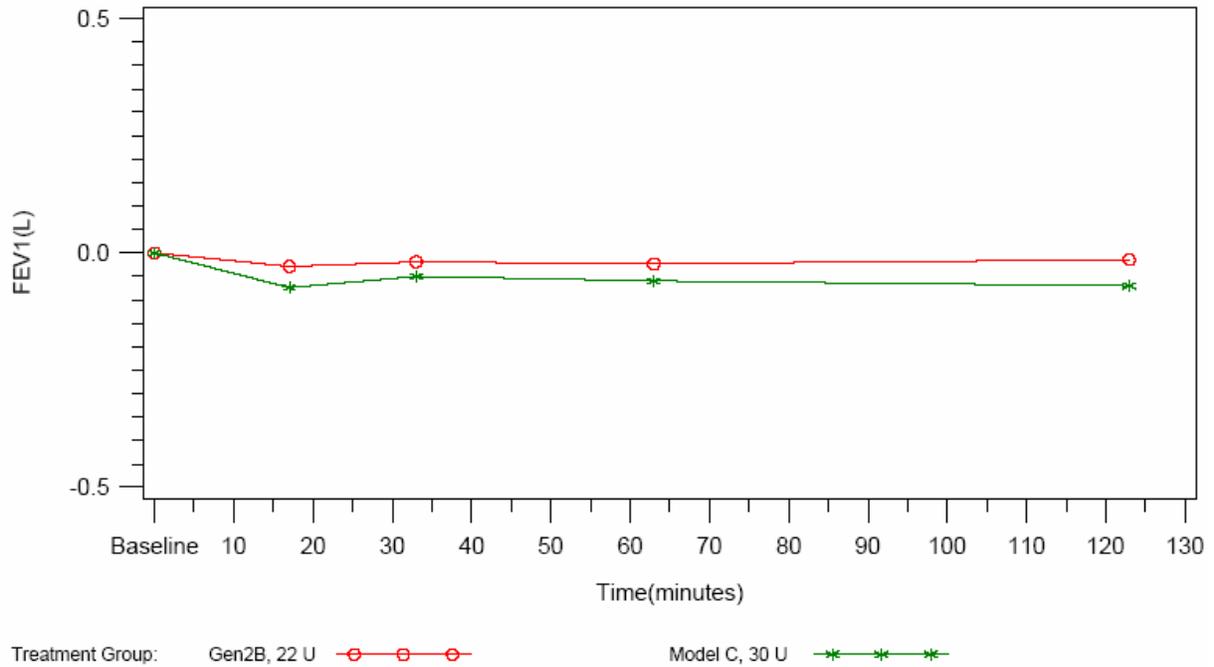
**Figure 1: Mean FEV1 Change (L) from Baseline by Treatment in Part 1**



With the Gen2B inhaler, the mean change in FEV<sub>1</sub> from baseline in Part I was -0.02 L at 17 minutes, -0.01 L at 33 minutes, -0.04 L at 63 minutes, and 0.02 L at 123 minutes after administration of TI. With the MedTone Model C, the mean changes in FEV<sub>1</sub> in Part 1 from baseline to 17, 33, 63, and 123 minutes post inhalation were -0.10 L, -0.10 L, -0.04 L, and -0.01 L, respectively.

*Reviewer's comment: Overall, it appears that the MedTone inhaler was associated with a larger FEV<sub>1</sub> decline at 17 and 33 minutes post-dose. The declines noted with the MedTone inhaler were consistent with those noted in the original NDA submission. The declines with the Gen2 inhaler were smaller, and are unlikely to be of clinical significance.*

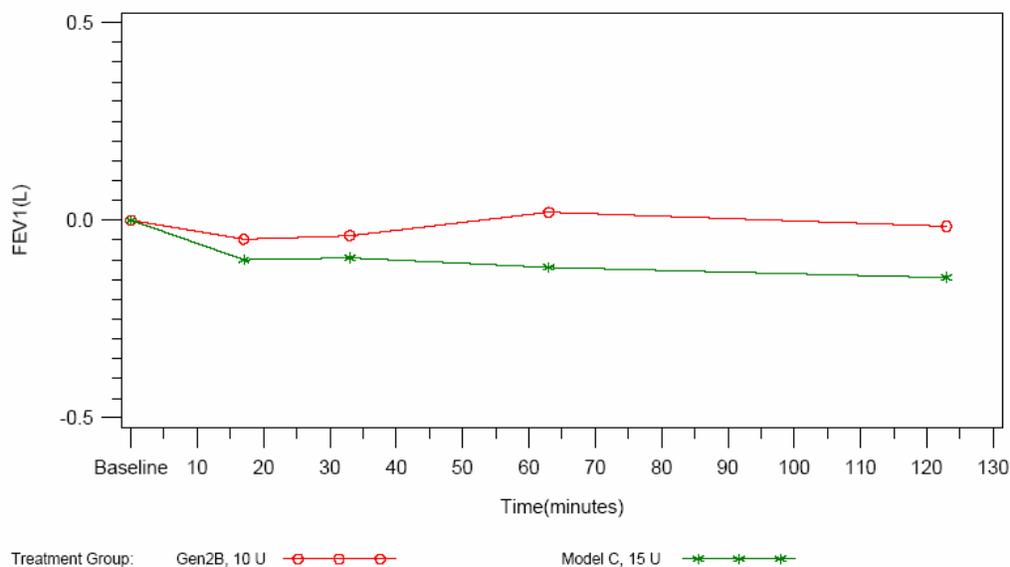
**Figure 2: Mean FEV1 Change (L) from Baseline by Treatment in Part 1B**



In part IB, the mean change in FEV<sub>1</sub> from baseline in Part Ib was -0.03 L at 17 minutes, -0.02 L at 33 minutes, -0.02 L at 63 minutes, and -0.01 L at 123 minutes with the Gen2B. After inhalation with the MedTone® Inhaler Model C, mean changes in FEV<sub>1</sub> were -0.07 L, -0.05 L, -0.06 L, and -0.07 L, respectively.

*Reviewer's comment: In Part IB, the declines in FEV<sub>1</sub>, though small for both groups, appeared to be larger with the MedTone inhaler over the 2 hours post-dose period as compared with the Gen2 inhaler.*

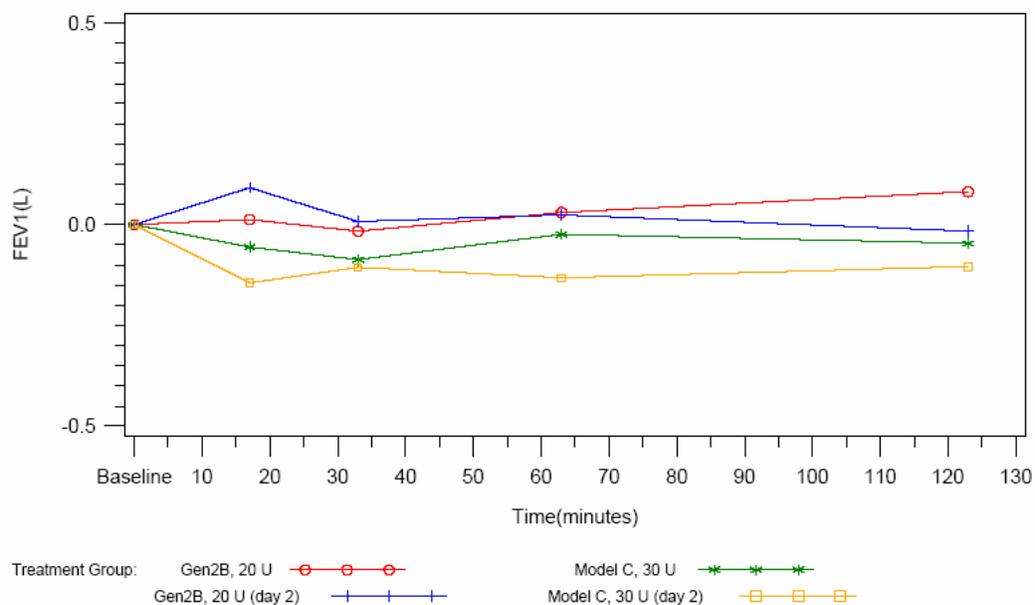
**Figure 3: Mean FEV1 Change (L) from Baseline by Treatment in Part II**



The mean change in FEV<sub>1</sub> from baseline in Part II was -0.05 L at 17 minutes, -0.04 L at 33 minutes, 0.02 L at 63 minutes, and -0.02 L at 123 minutes with the Gen2B inhaler. After inhalation with the MedTone® Inhaler Model C, mean changes from baseline in FEV<sub>1</sub> in Part II were: -0.10 L, -0.09 L, -0.12L, and -0.15 L, respectively;

*Reviewer's comment: This part of the study had the largest numerical declines in FEV1 noted with the MedTone inhaler, although the values were still consistent with other parts of this study and the information available from the original NDA submission. There was relatively little to no change in FEV1 associated with the Gen2 inhaler.*

**Figure 4: Mean FEV1 Change (L) from Baseline by Treatment in Part III**



The mean change in FEV<sub>1</sub> from baseline in Part III was 0.04 L at 17 minutes, -0.01 L at 33 minutes, 0.03 L at 63 minutes, and 0.05 L at 123 minutes with the Gen2B. After inhalation with the MedTone® Inhaler Model C, mean changes from baseline in Part III were: -0.08 L, -0.09 L, -0.06 L, and -0.06 L, respectively.

*Reviewer's comment: The Gen2 inhaler performed more consistently from Day 1 to Day 2 than did the MedTone inhaler, in which there was more variability in FEV1 declines from Day to Day 2. The reason for this is unclear.*

The data from all parts of the study are summarized in Table 2 below.

<b>Table 2: Mean FEV1 Change from Baseline by Treatment (Safety Population)</b>								
	<i>Part I</i>		<i>Part Ib</i>		<i>Part II</i>		<i>Part III</i>	
	Gen2B 20 U n = 11	Mod C 30U n = 11	Gen2B 22U n=10	Mod C 30U n=12	Gen2B 10U n=10	Mod C 15U n = 10	Gen2B 20U n= 12	Mod C 30U n=12
<b>Time Post-TI administration</b>								
17 min	-0.02	-0.10	-0.03	-0.07	-0.05	-0.10	0.04	-0.08
33 min	-0.01	-0.10	-0.02	-0.05	-0.04	-0.09	-0.01	-0.09
63 min	-0.04	-0.04	-0.02	-0.06	0.02	-0.12	0.03	-0.06
123 min	-0.02	-0.01	-0.01	-0.07	-0.02	-0.15	0.05	-0.06
Note: There were no notable differences between baseline FEV1 between treatment groups. Legend: Mod C: MedTone Model C Inhaler; U: units of insulin,								

In conclusion, FEV1 was measured out to 2 hours post-dose following TI inhalation from both the Gen2B and MedTone Model C inhalers. Overall, the FEV1 decline with the MedTone inhaler was consistent with what was observed in the original NDA submission with maximum FEV1 declines of about 100 mL. The FEV1 declines with the Gen2B inhaler appear to be less when compared to the MedTone inhaler, with maximum declines in FEV1 ranging from about 20-40 mL.

*Reviewer's comment: The small changes in FEV1 noted with the Gen2 inhaler up to 2 hours post-dose are unlikely to be of clinical consequence. The Applicant proposes that the smaller total emitted dose from the Gen2 inhaler, while maintaining a comparable fine particle fraction (respirable fraction), is the mechanism behind smaller acute changes in FEV1. It is of note however, that the reduction in total emitted dose did not reduce the incidence of cough.*

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/s/  
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BANU A KARIMI SHAH  
12/14/2010

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12/14/2010

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 22,472 Resubmission  
Priority or Standard S

Submit Date(s) 28 Jun 2010  
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Reviewer Name(s) Lisa B. Yanoff, M.D.  
Review Completion Date 8 Dec 2010

Established Name Technosphere insulin  
(Proposed) Trade Name Afrezza  
Therapeutic Class Inhaled insulin  
Applicant MannKind

Formulation(s) Inhalation powder (pre-metered)  
Dosing Regimen Dose-titrated premeal inhalation  
Indication(s) The treatment of adults with type  
1 or type 2 diabetes mellitus for  
the control of hyperglycemia.  
Intended Population(s) Adult Type 1 and Type 2  
Diabetics

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

In the original clinical NDA review, based on my review of clinical non-pulmonary safety and clinical efficacy, I recommended approval of Afrezza for the treatment of Type 1 and Type 2 diabetes in adults without the need for additional pre-approval clinical studies. My review of the resubmission for non-pulmonary clinical safety corroborates my original recommendation. For clinical efficacy, the findings of the resubmission are supportive of my original recommendation but may not address the concerns identified by Dr. Parks in her Division Director Complete Response (DDCR) memo (13 Mar 2010) for reasons discussed in section 1.2. I reiterate that in my view there is a patient population in which the benefits of Afrezza outweigh the risks, and Afrezza should be approved for these patients with the appropriate labeling language to address concerns related to somewhat lesser efficacy than injected prandial insulins. In addition, the new less complex Gen2 device has the potential to eliminate some of the device concerns that precluded approval during the first review cycle. However, since there is no phase 2/3 data with the new Gen2 device, this recommendation is predicated upon the finding that the Gen2 device is functionally similar to the MedTone device so that safety and efficacy data can be bridged from the old MedTone inhalation system to the new Gen2 inhalation system; the Clinical Pharmacology, Chemistry Manufacturing and Controls, and Center for Devices and Radiologic Health reviews are pending at the time of this clinical review.

### **1.2 Risk Benefit Assessment**

In the original clinical NDA review, among four phase 3 trials, one conducted in patients with type 1 diabetes mellitus and three conducted in patients with type 2 diabetes, only one of these four trials (Study 102, the comparison of Afrezza to NovoLog Mix 70/30 in patients with type 2 diabetes) met its primary objective for efficacy. In study 009 in patients with type 1 diabetes Afrezza was found to be statistically inferior to comparator. These findings along with the complex MedTone inhalation device led Dr. Parks to conclude that the risk/benefit profile of Afrezza was not favorable enough for approval at that time, although she noted that “Despite the multiple deficiencies in this application precluding its approval, I believe the applicant has demonstrated that systemic absorption of Technosphere insulin does lower blood glucose levels making it a viable candidate for the treatment of type 1 and 2 diabetes. In addition, the non-injectable route of administration might make it more acceptable to patients than subcutaneous administration of prandial insulins.”

In the resubmission, I have found the clinical risk/benefit assessment to be somewhat more favorable from the original NDA. First, a continued favorable safety profile has been demonstrated. Second, a review of efficacy in the resubmission was based on the positive results of trial 117, a randomized, open-label substitution study in patients with type 1 diabetes that demonstrated that the efficacy of Afrezza in combination with insulin glargine was noninferior to insulin lispro in combination with insulin glargine in effects on HbA1c after 16 weeks of treatment. Third, the new Gen2 inhalation system appears to be much less complex than the MedTone inhalation system.

Starting from a baseline HbA1c of 7.75%, the mean change from baseline in the Afrezza + glargine arm was -0.09% compared with the lispro + glargine arm which showed a mean change from baseline (7.62%) of -0.05%. The between-group difference in change from baseline in HbA1c was 0.04% (favoring Afrezza) with a corresponding 95% CI of (-0.25 to 0.18) supporting a non-inferiority claim for Afrezza (pre-specified inferiority margin < 0.4%). Secondary endpoint analyses (fasting plasma glucose, glycemic goals, and postprandial glucose) were consistent with the primary efficacy analysis.

Dr. Parks noted in her original DDCR memo that when patients in the pivotal type 1 diabetes trial 009, a switch study, replaced their regimen of insulin injections to one that replaced prandial injection with prandial Afrezza inhalation, they were not able to achieve better or maintain glycemic control as did the standard injection regimen. She wrote that for a drug such as Afrezza to be approvable, such a switch should provide either improved glycemic control or maintenance of glycemic control that could have been achieved if the patient were to have remained on standard injection therapies. Unlike trial 009, trial 117 has been able to demonstrate that maintenance of glycemic control can be achieved with Afrezza as the prandial insulin therapy. Therefore, the results of trial 117 are somewhat reassuring in supporting effectiveness of Afrezza.

However, there are caveats to my conclusions and recommendation. In the original NDA clinical review I asserted that statistical significance (or lack thereof) should not be the primary focus of interpretation of the clinical trials in the Afrezza development program and that the natural history of T1DM should be taken into consideration. Likewise, just because Trial 117 has “made it” on statistical significance of the primary endpoint, this fact should not be the primary focus in consideration of support of a claim of efficacy; there were notable problems with the design and conduct of trial 117 that need to be taken into consideration (discussed in the next paragraph). Further, it is not appropriate to disregard the entire Afrezza clinical development program and focus only on trial 117, just as it wouldn't be appropriate to ignore negative studies and focus on positive studies in an original review. As with the first review cycle, my recommendation includes the caveat of strict labeling to ensure the proper patient population uses Afrezza.

Concerns with the design and conduct of trial 117 include the trial's small size, short duration, open-label design and early trial termination. Additionally, in a non-inferiority trial, the effect of the comparator must be understood in order to interpret the results of the study. As noted above the comparator group began with a baseline mean HbA1c of 7.62% and decreased by 0.05%.

The most plausible explanation for this small change is that trial 117 was a switch study and merely maintenance of glycemic control can be anticipated. Nevertheless, because the control group showed essentially no improvement in HbA1c, the planned non-inferiority analysis becomes less than optimal, and the results must be interpreted with caution. Unfortunately, it seems that trial 117 may be plagued by design and conduct concerns, similarly to trials submitted in the original NDA. A review from the Office of Biostatistics is pending at the time of this review.

In sum, I believe the data in the resubmission support my original conclusion that Afrezza does have a place in the armamentarium of diabetes products, because it offers the advantage of an alternative route of administration. Patients on Afrezza, like those on any antidiabetic medication(s), should be monitored regularly for adequate glycemic control and the patient can be switched to an alternative therapy if glycemic control becomes unacceptable. The degree of “inferiority” vs. comparators one is willing to accept when recommending approval of an insulin product with the benefit of a non-injectable route of administration is a personal judgment. In my view, Afrezza has met that threshold of a favorable benefit/risk profile, and I support its approval given the issues with similarity of the old and new devices are adequately addressed.

### **1.3 Recommendations for Postmarket Risk Management Activities**

Unchanged from the original clinical NDA review.

### **1.4 Recommendations for Postmarket Studies/Clinical Trials**

Unchanged from the original clinical NDA review.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

#### Product description

MannKind Corporation has developed a dry powder formulation of recombinant human insulin (called Technosphere insulin) designed to be delivered systemically via pulmonary inhalation with a proprietary inhalation device. The first generation drug-device combination reviewed in the original NDA was Technosphere insulin with the MedTone Inhaler while in this

resubmission the Sponsor has replaced the first generation inhalation system (MedTone) with the Gen 2 inhalation system, which they propose to market as the (b) (4)™ Inhaler (the sponsor is presently not pursuing marketing of the old device). However, note that the one clinical trial reviewed in this document was conducted with the MedTone inhalation system. No phase 2/3 clinical trials have been conducted with the new device.

The drug product is manufactured from recombinant human insulin and the proprietary excipient fumaryl diketopiperazine (FDKP). The Technosphere Insulin Inhalation Powder / Gen2 Inhaler system includes single-use, pre-metered cartridges that are manually inserted into disposable breath-powered, high resistance dry powder inhalers. Using the same formulation of TI Inhalation Powder as with the MedTone inhaler, the cartridges used with the Gen2 inhaler are supplied at nominal strengths of 10 U/cartridge and 20 U/cartridge, which are lower than the 15 unit and 30 unit cartridge strengths for the MedTone device). The 10 U and 20 U product presentations have fill weights of 3.3 mg and 6.7 mg, respectively. The filled cartridges are packaged into foil overwrapped blisters. On average, inhalation of 10 U of TI Inhalation Powder using the Gen2 inhaler has been shown to approximate 4 IU of sc insulin. Similarly, inhalation of 20 U of TI Inhalation Powder using the Gen2 inhaler has been shown to approximate 8 IU of sc insulin.

#### Established name and proposed trade name

The established name of this product is Technosphere Insulin. The proposed trade name is Afrezza. This trade name has been tentatively approved by the Division of Medication Error Prevention and Analysis (DMEPA).

For the purposes of this review, Technosphere Insulin administered through inhalation is abbreviated "TI."

#### Chemical class

Recombinant human insulin

#### Pharmacologic class

Inhaled insulin. Afrezza is the second NDA for an inhaled insulin to be reviewed by the Agency. The first, Exubera (NDA 21,868) was approved by the Division of Metabolism and Endocrinology Products in January 2006. Exubera was subsequently withdrawn from the market for reported business reasons (see section 2.4).

#### Sponsor's proposed indication, dosing regimen, age group

The Sponsor proposes the following language for the "Indications and Usage" section of the product label:

AFREZZA™, an ultra rapid acting insulin, is indicated for the treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia. For type 1 patients, AFREZZA should be used in regimens that include a long acting insulin. AFREZZA should not be used for the treatment of diabetic ketoacidosis.

**Dosage and Administration:**

AFREZZA is administered via oral inhalation using the AFREZZA Inhaler. AFREZZA should be administered at the beginning of a meal. (b) (4)



The proposed age group, as stated in “indications and usage” is adults.

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

Patients with type 2 diabetes (T2DM) often undergo an initial trial of diet and exercise. If control is inadequate, a variety of oral agents is available (Table 2.1). If adequate blood glucose control is not achieved with oral agents, subcutaneous insulin is often used.

**Table 2.1. Currently approved pharmacologic therapies for type 2 diabetes mellitus**

Drug Class	Examples	Mechanism of action	Expected decrease in HbA1c (%)*	Pros	Cons
Biguanides	Metformin	Decreases hepatic glucose production Increases insulin sensitivity	1.5	Weight neutral Inexpensive Low risk of hypoglycemia	GI side effects Rare lactic acidosis Contraindicated in renal failure
Sulfonylureas	Glimepiride Glyburide Glipizide	Insulin secretagogue	1.5	Inexpensive	Hypoglycemia Weight gain
Thiazolidinediones	Rosiglitazone Pioglitazone	Increases insulin sensitivity	0.5-1.4	Lower risk of hypoglycemia	Fluid retention Weight gain Contraindicated in heart failure Expensive
Insulin	Lispro NPH insulin Glargine	Stimulates glucose uptake in muscle and adipose tissues	1.5-2.5	No dose limit Improved lipid profile	Injections Frequent monitoring Hypoglycemia Weight gain
Alpha-glucosidase inhibitors	Acarbose Miglitol	Slows GI absorption of carbohydrates	0.5-0.8	Weight neutral	Frequent GI side effects Three times/day dosing Expensive
Meglitinides	Repaglinide Nateglinide	Insulin secretagogue	1-1.5	Short duration	Three times/day dosing Expensive
Amylin analogues	Pramlintide	Slows gastric emptying Suppresses glucagon secretion Promotes satiety Decreases appetite	0.5-1.0	Weight loss	Three times/day dosing Frequent GI side effects Expensive Limited clinical experience
GLP-1 analogues	Exenatide Liraglutide	Stimulates glucose-dependent insulin release Slows gastric emptying Inhibits glucagon secretion Reduces food intake	0.5-1.0	Weight loss Theoretically lower risk of hypoglycemia	Frequent GI side effects Expensive Limited clinical experience Pancreatitis
DPP-IV inhibitors	Sitagliptin Saxagliptin	Inhibits the enzyme DPP-IV prolonging the action of endogenous GLP-1 and GIP	0.5-0.8	Weight neutral Lower risk of hypoglycemia	Limited clinical experience Expensive Hypersensitivity reactions
Bile acid sequestrant	Colesevelam	Unknown	0.4-0.8	Favorable lipid effects	Frequent GI side effects
Dopamine agonist	Bromocriptine	Unknown	0.4-0.6	Weight neutral Minimal hypoglycemia	Gastrointestinal side effects

\* Expected decrease in HbA1c is not placebo-corrected. Note: Part of the extent of reduction depends on the patient characteristics – e.g., baseline HbA1c etc.

GI = gastrointestinal; GLP-1 = glucagon-like peptide-1, DPP-IV = Dipeptidyl peptidase 4, GIP = glucose-dependent insulinotropic polypeptide

Source: Adapted from Stumvoll et al. (2005), Nathan et al. (2008), Cycloset prescribing information, and WelChol prescribing information

Type 1 diabetes (T1DM) is currently treated with subcutaneously administered insulin, which is available in a variety of formulations and analogs, with a spectrum of time-action profiles. Because Type 1 diabetics have virtually no residual pancreatic islet beta cell function, these patients have an absolute requirement for administered insulin for survival after the honeymoon phase, and cannot be managed with diet and exercise alone. Patients generally receive one or two subcutaneous injections per day of a relatively long-acting insulin as "basal" insulin, and take a short-acting subcutaneous insulin before each meal (prandial insulin). Continuous subcutaneous infusion via insulin pump of short-acting insulin, with mealtime boluses, is also used. Pramlintide, an amylin analog, was recently approved as the first agent other than insulin for treatment of Type 1 diabetes, but pramlintide is an adjunct to mealtime insulin, rather than a substitute for subcutaneous insulin.

The applicant considers Afrezza faster in time-action profile to subcutaneously administered rapid-acting insulin analogs, which have a rapid onset of action (about 15 minutes), a short time to peak action (0.5- 1.5 hours), and a short duration of action (2-5 hours). Currently marketed rapid-acting analogs available in the United States include insulin aspart and insulin lispro. Regular soluble crystalline zinc insulin is also sometimes used as a prandial insulin; it has an onset of action at 30-45 minutes, peak action between 1.5 and 4 hours, and a duration of action of 5-8 hours.

There are no currently available inhaled insulin therapies for diabetes. As is discussed in section 2.1 and 2.4, Exubera is an inhaled insulin therapy that was approved for the treatment of type 1 and type 2 diabetes in adults in January 2006. Pfizer withdrew Exubera from the market in early 2009 for business reasons (presumably poor sales). If approved, Afrezza would be the only marketed non-subcutaneously delivered insulin therapy.

### **2.3 Availability of Proposed Active Ingredient in the United States**

The active ingredient used in the production of the inhalation powder is a recombinant human insulin formulation which is not approved for marketing in the United States. (b) (4)  
the manufacturer of the active ingredient insulin, has authorized MannKind to cross reference the Drug Master File (DMF) for this insulin.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Only one inhaled insulin product, Exubera (NDA 21,868, recombinant human insulin powder for oropulmonary inhalation) has been approved in any country. It was approved in January 2006 but subsequently withdrawn by the Sponsor for marketing reasons.

Please see the original NDA clinical review for discussion of important safety issues related to Exubera.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The original new drug application (NDA) for Afrezza was dated and received 16 Mar 2009. For information regarding Presubmission regulatory activity prior to the original NDA submission please see the original NDA clinical review.

After review of the original NDA submission, the Agency issued a Complete Response (CR) letter dated 12 Mar 2010 to the Sponsor. Several deficiencies were included; these are discussed throughout this review in the sections pertaining to the corresponding disciplines.

The clinical deficiency was as follows:

“Your NDA contained four phase 3 trials, one conducted in patients with type 1 diabetes mellitus and three conducted in patients with type 2 diabetes. An important limitation of these trials is that there was inadequate titration of insulin doses in the treatment arms for both Afrezza and comparator. Based on our analyses, only one of these four trials (Study 102, the comparison of Afrezza to NovoLog Mix 70/30 in patients with type 2 diabetes) met its primary objective for efficacy. Afrezza failed to demonstrate non-inferiority to comparators in two trials, Studies 014 and 009. In Study 103, Afrezza failed to demonstrate superiority to the comparator. More notable was the finding of statistical inferiority of Afrezza to comparators in Studies 014 and 009. These findings call into question the clinical utility of your product to treat diabetes in an era where glycemic control has been well-established to reduce long-term complications of microvascular disease in both type 1 and 2 diabetes. Your complete response should include a detailed discussion on how currently available clinical data support the utility of Afrezza in the marketplace and clarify why additional clinical studies are not necessary.”

The Sponsor requested and was granted an end of review meeting in June 2010.

In the meeting package, the Sponsor stated that MannKind will prepare a resubmission as a response to the Complete Response Letter, which will include information that addresses clinical deficiencies with:

- New clinical data available from study MKC-TI-117
- Additional analyses of clinical data previously submitted in NDA 22-472

The Sponsor’s meeting package clinical question and FDA preliminary response is as follows:

Question C: Does the Agency agree that MannKind’s presented approach of new data from MKC-TI-117 and new analyses of data presented in the original NDA is adequate and complete for a successful resubmission to address the clinical utility of AFREZZA with the Gen2 inhaler?

FDA Preliminary Response: New analyses of data presented in the original NDA are not adequate to address the clinical utility of Afrezza, because these data were already taken into consideration during the review of the original NDA. New data from study MKC-TI-117 may be adequate to support the MedTone device but this will be a review issue. Given your intention to proceed with the Gen2 inhaler, there will be further clinical requirements for resubmission. For example, clinical evidence of pulmonary safety and evidence of adequate glycemic effect (based

on HbA1c) will be required with the new device. The extent of clinical data needed can be discussed at the End-of-Review meeting.

During the face-to-face End-of-Review meeting (9 Jun 2010) the Division informed the Sponsor of concerns regarding the similarity of the Gen2 and MedTone inhalers and whether clinical data could be extrapolated from the previous MedTone device to the new Gen2 device. The Division informed the Sponsor that further clinical requirements would be a review issue depending on the CMC findings of device similarity. The Sponsor was encouraged to submit CMC data to support their claim that the two devices were essentially functionally the same prior to submitting their formal NDA re-submission. However, the Sponsor chose to submit these data along with the formal NDA re-submission which was received by the FDA on 28 Jun 2010.

## **2.6 Other Relevant Background Information**

Foreign Commercial Marketing History: Afresa is not approved in any other country, nor is it submitted to any foreign health authority.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The quality and integrity of the resubmission documents were adequate.

### **3.2 Compliance with Good Clinical Practices**

For the original clinical NDA review, the Division of Scientific Investigations (DSI) conducted audits for site-specific issues regarding good clinical practices. Site selection was performed by the clinical reviewer along with Dr. Susan Leibenhaut, DSI reviewer, based on relatively larger numbers of subjects enrolled at the selected sites. There was no potential financial conflict of interest influencing the site selection. Five clinical investigator sites and one CRO were inspected in support of this NDA. Audits of all the clinical sites were able to validate the primary endpoint. The contract research organization (CRO) inspection was issued to verify the pulmonary function testing results submitted as safety data. According to Dr. Leibenhaut the data are considered reliable in support of this NDA.

Recently, allegations into non-compliance with FDA policies during the development of

Afrezza, made by a former MannKind employee, have come to the attention of the Division. Coincidentally, one of the sites mentioned by the former employee where he noted irregularities of trial conduct was also a site chosen by this reviewer for inspection (the “Russian” site mentioned in the allegations). The site and inspection findings are as follows:

Prof. Yury Shvarts  
State Educational Institution of High Professional Education  
Saratov State Medical University Clinical Hospital  
No. # 137 Bolshaya Sadovaya str., Saratov, 410054, Russia

**Note:** Observations noted for this site are based on communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected:** For Protocol #MKC-TI-014, 50 subjects were screened, 29 subjects were randomized, and 29 subjects completed the study. An audit of 15 subjects' records was conducted.

b. **General observations/commentary:** There was no under reporting of adverse events by the site to the sponsor and the primary endpoint data were verifiable. The following adverse events were reported to the sponsor, but were not contained in the line listings submitted in the NDA:  
1. Subject 054(control): ischemic event. This event was not listed in the line listings or narrative, but the Case Report Form (CRF) documenting this event was submitted in the NDA.  
2. Subject 409(control): arterial hypertension.

This information was communicated to the review division in an e-mail on December 18, 2009.

c. **Assessment of data integrity:** At this site, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. It appears that some AEs at the Russian sites were not reported by the sponsor to the NDA. This does not appear to be a systemic issue with respect to underreporting of AEs by the sponsor. The review division may consider an information request to the sponsor concerning their under-reporting of adverse events to the NDA from this site.

Dr. Cindy Welsh, MD, Medical Officer, Division of Scientific Investigations, Office of Compliance reviewed information submitted by the Sponsor regarding the allegations. She concluded that no further investigation of this complaint is warranted at this time because:

- Actions taken by the sponsor are appropriate - including conducting their own independent third party audit as well as an internal investigation into the allegations of GCP non-compliance
- Foreign sites – given the Agency’s limited inspection resources, Dr. Welsh’s opinion is that re-inspection of the Russian site (Shvarts) is not warranted as the first inspection was classified NAI. Additionally, the second site with alleged non-compliance with FDA policies, a Bulgarian site (Daskalova), had internal audits performed. The data were only ~10% of enrolled subjects per site. The two clinical investigators’ data were not included in the only supportive clinical trial submitted. Their data were in the negative/non-supportive trials.
- No violation of GCP/HSP/data integrity determined during evaluation of this complaint by Dr. Welsh

Depending upon the review division's opinion regarding the approvability of the NDA based on the resubmission, Dr. Welsh stated that we may want to consider asking the sponsor to reanalyze the data with and without the data from the sites of Drs. Shvarts and Daskalova. However, she stated this may be unnecessary as the trials in which they participated were not supportive of efficacy. Alternatively, GCP2 may consider PDUFA related inspections, if the review division requests inspection of the sponsor and/or clinical sites.

### 3.3 Financial Disclosures

The Sponsor submitted a completed Financial Certification Form FDA 3454 and Financial Disclosure Form FDA 3455. All investigators who participated in the MannKind Corporation clinical program for NDA 22-472 were reviewed.

Please see the original clinical NDA review for discussion of financial disclosures for investigators participating in clinical trials reviewed during the first cycle. There were no significant conflicts of interest that would be expected to bias study results. In the resubmission, there is one major clinical trial – Trial 117. The Sponsor reported two potential financial conflicts of interest.

- 1) [REDACTED] (b) (6), Site [REDACTED] (b) (6) - The Principal Investigator at Site [REDACTED] (b) (6), Dr. [REDACTED] (b) (6), reported financial interests. However Site [REDACTED] (b) (6), did not enroll any subjects in trial MKC-TI-117.
- 2) [REDACTED] (b) (6), Site [REDACTED] (b) (6) A sub-investigator at Site [REDACTED] (b) (6), Dr. [REDACTED] (b) (6), reported financial interests (significant equity). This site enrolled [REDACTED] (b) (6) subject under the direct supervision of the Principal Investigator, Dr. [REDACTED] (b) (6). The Principal Investigator has no financial interests to disclose.

**Reviewer's comment: These reports are extremely unlikely to have biased study results.**

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The Chemistry review is pending. Therefore, I am unable to comment at this time on how the *in vitro* characteristics of the Medtone C inhaler compare to that of the newly proposed device.

## 4.2 Clinical Microbiology

(b) (4) Microbiology review is not required. In the first cycle, ONDQA asked Microbiology to review the proposed microbial limits and test method, which were concluded to be acceptable in a review completed by Dr. Denise A. Miller on 22 Sep 2009. In this current cycle, the resubmission has no change to the microbial limits or test method, so a Microbiology review was not needed.

## 4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology reviewer, Dr. Tsai-Turton, recommended approval of the NDA during the first cycle with no further nonclinical studies.

An overview of nonclinical findings (excerpted from Dr. Tsai-Turton's original pharm/tox review) is included in the original clinical NDA review.

There are no new non-clinical pharmacology/toxicology data included in the resubmission.

## 4.4 Clinical Pharmacology

See section 5.1 for tables of clinical studies.

Clinical Pharmacology deficiencies outlined in the CR letter were as follows:

2. The pivotal bioequivalence study results are not reliable based on the inspection results from the Division of Scientific Investigations (DSI). Because of unreliable data from this study, the comparability of the to-be-marketed device (Model D inhaler) to the device used in your pivotal clinical trials (Model C inhaler) is not known.

Since the Sponsor is no longer developing the MedTone device, the above deficiency listed in the CR letter is moot. The re-submission contains a pivotal bioequivalence study (MKC-TI-142) comparing the new device to the Model C MedTone inhaler. This study was reviewed by Drs. Chang and Choe from the Office of Clinical Pharmacology / Division of Clinical Pharmacology 2. Their review has not been finalized but preliminarily they find the two devices to be bioequivalent. DSI inspection of this bioequivalence study is pending.

Their preliminary review summarizes that "The sponsor assessed insulin pharmacokinetic comparability following the new proposed to-be-marketed inhaler (Gen2C) compared to that of inhaler used in Phase 3 trials (MedTone Inhaler Model C) in healthy subjects (MKC-TI-142). The insulin pharmacokinetic parameters following Gen2C met the bioequivalence (BE) criteria to those of Model C. In the same study, the sponsor assessed comparability of two difference

strengths of insulin package (10U and 20U) and it was concluded that insulin pharmacokinetics following two packages of 10U was BE to that of one package of 20U when Gen2 was used.”

## 5 Sources of Clinical Data

The sources of clinical data for this review were clinical trial data submitted by the applicant.

### 5.1 Tables of Studies/Clinical Trials

**Table 5.1 – Clinical Trials in the Safety Update**

Type of Study	Study Identifier/ Study Status	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects Enrolled <sup>a</sup>	Healthy Subjects or Diagnosis of Patients <sup>b</sup>	Duration of Treatment
<b>Completed Studies</b>								
BA	MKC-T-140  Completed Full	5.3.1.1.	To assess the safety and tolerability of 2 fill weights (10 mg and 15 mg) of Technosphere <sup>®</sup> Inhalation Powder as measured by a VAS for cough and FEV <sub>1</sub> resulting from delivery by the Gen2A inhaler as compared to the MedTone <sup>®</sup> Inhaler Model C  To assess the effect of altering inspiratory effort and inhalation time on the PK of FDKP inhaled as Technosphere <sup>®</sup> Inhalation Powder using the Gen2A inhaler	Open-label, crossover, 2-part trial	<u>Test Product:</u> Technosphere Inhalation Powder  <u>Dosage:</u> Part 1: single daily doses of inhaled Technosphere Inhalation Powder for 3 days 2 single 10-mg doses via Gen2A for 1 dose and MedTone Model C inhaler for the other dose 1 single 15-mg dose via Gen2A inhaler Part 2: single daily doses of inhaled Technosphere Inhalation Powder for 2 days 2 single 10-mg doses via Gen2A inhaler  <u>Route:</u> Inhaled (Gen2A inhaler)	Part 1: 10 subjects randomized  Part 2: 20 subjects randomized	Healthy normal volunteers	Short: single daily doses administered over 2 to 3 days
BA	MKC-TI-141  Completed Full	5.3.1.1.	To assess the relative exposure of TI as delivered by the Gen2B inhaler (test inhaler) compared to the MedTone <sup>®</sup> Inhaler Model C (reference inhaler) using C-peptide-corrected serum insulin for C <sub>max</sub> and AUC (AUC <sub>0-240</sub> for Parts I, Ib, and Ic, and AUC <sub>0-120</sub> for Parts II and III). If the C-peptide-	Single-center, open-label, randomized, crossover trial	<u>Test Product:</u> TI <u>Dosage:</u> Part I: single daily doses of TI for 2 days 1 single 20 U or 30 U TI dose using Gen2B inhaler or MedTone Inhaler Model C respectively, then crossed over to alternate inhaler Part Ib: Part I was	Part I: 12 subjects randomized  Part Ib: 12 subjects randomized  Part II: 12 subjects	Healthy normal volunteers	Short: single daily doses administered over 2 to 3 days

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Type of Study	Study Identifier/ Study Status	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	No. of Subjects Enrolled <sup>a</sup>	Healthy Subjects or Diagnosis of Patients <sup>b</sup>	Duration of Treatment
			<p>corrected insulin values did not appear to accurately reflect the inhaled insulin PK. FDKP PK was to be substituted for the purpose of evaluating relative exposure and variability.</p> <p>Intrasubject variability of the PK parameters of inhaled insulin (<math>C_{max}</math> and AUC [AUC<sub>0-240</sub> for Parts I, Ib, and Ic, and AUC<sub>0-120</sub> for Parts II and III]) following administration of TI using the Gen2B inhaler and the MedTone<sup>®</sup> Inhaler Model C (Part III only)</p> <p>Time to reach maximum concentration (<math>t_{max}</math>)</p> <p>Confirm the ability to determine exogenous serum insulin by C-peptide correction in HNVs</p>		<p>repeated with the Gen2B inhaled dose increased to 22 U</p> <p>Part Ic: no further doses were tested; therefore Part Ic did not occur.</p> <p>Part II: single daily doses of TI for 2 days</p> <p>1 single 10 U or 15 U TI dose using Gen2B inhaler or MedTone Inhaler Model C respectively, then crossed over to alternate inhaler</p> <p>Part III: single daily doses of TI for 3 days</p> <p>2 single 20 U or 30 U TI doses using Gen2B inhaler or MedTone Inhaler Model C respectively, for 2 consecutive days then crossed over to alternate inhaler on Day 3</p> <p>Route: Inhaled (MedTone Inhaler Model C and Gen2B inhaler)</p>	<p>randomized</p> <p>Part III: 12 subjects randomized (48 total subjects)</p>		

Type of Study	Study Identifier/ Study Status	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	No. of Subjects Enrolled <sup>a</sup>	Healthy Subjects or Diagnosis of Patients <sup>b</sup>	Duration of Treatment
BA/BE	MKC-TI-142  Completed Full	5.3.1.2.	<p>To show that the calculated CI for the ratio of the average log-transformed insulin AUC<sub>0-120</sub> and <math>C_{max}</math> for the 20 U cartridge using the Gen2 inhaler and the 30 U cartridge using the MedTone Inhaler fell between 0.80 and 1.25. Insulin exposure was evaluated using C-peptide correction for serum insulin AUC<sub>0-120</sub> and <math>C_{max}</math></p> <p>To show that the calculated CI for the ratio of the average log-transformed insulin AUC<sub>0-120</sub> and <math>C_{max}</math> for the 20 U cartridge using the Gen2 inhaler and two 10 U cartridges using the Gen2 inhaler fell between 0.80 and 1.25. Insulin exposure was evaluated using C-peptide correction for serum insulin AUC<sub>0-120</sub> and <math>C_{max}</math></p>	Single-center, open-label, randomized, crossover trial	<p>Test Product: TI</p> <p>Dosage: Daily doses of TI in a predetermined sequence for 3 days</p> <p>Two 10 U or one 20 U TI dose using Gen2C inhaler</p> <p>One 30 U dose using MedTone Inhaler Model C</p> <p>Route: Inhaled (MedTone Inhaler Model C and Gen2C inhaler)</p>	74 subjects were randomized to treatment with TI Inhalation Powder	Healthy normal volunteers	Short; daily doses administered over 3 days

Type of Study	Study Identifier/ Study Status	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	No. of Subjects Enrolled <sup>a</sup>	Healthy Subjects or Diagnosis of Patients <sup>b</sup>	Duration of Treatment
Other	MKC-143  Completed Full	5.3.5.4.	To determine whether a pediatric population can successfully handle, assemble, and operate the Gen2C and MedTone Inhaler Model D delivery systems with an empty cartridge and to characterize the inspiratory profiles achieved by pediatric use of the Gen2C and MedTone Inhaler Model D delivery systems with an empty cartridge	Single-center, randomized, pediatric trial	<p>Test Product: None</p> <p>Dosage: Not applicable</p> <p>Route: Inhaled (MedTone Inhaler Model D and Gen2C inhalers)</p>	74 subjects randomized to study procedures	Healthy pediatric volunteers	Short; Single visit

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Type of Study	Study Identifier/ Study Status	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	No. of Subjects Enrolled <sup>a</sup>	Healthy Subjects or Diagnosis of Patients <sup>b</sup>	Duration of Treatment
Clinical Efficacy and Safety	MKC-TI-117  Completed Full	5.3.5.1.	To demonstrate that the efficacy of TI in combination with Lantus (TI group) was noninferior to Humalog in combination with Lantus (comparator group) in effects on HbA1c To evaluate the effect of the 2 treatment regimens on: <ul style="list-style-type: none"> <li>Achieving HbA1c accepted target goals of <math>\leq 7.0\%</math> and <math>\leq 6.5\%</math></li> <li>PPG excursions following the ingestion of a standardized liquid meal (meal challenge)</li> <li>Glycemic excursions and variability as assessed through CGM</li> <li>Body weight</li> <li>Subject treatment satisfaction</li> <li>Safety expressed as the incidence of hypoglycemia, cough, other AEs, changes in pulmonary function and, in a subset of subjects, Doppler echocardiogram data</li> </ul>	Multicenter, open-label, randomized trial	<u>Test Product:</u> TI <u>Dosage:</u> individualized; doses of TI could be adjusted in increments of 15 U, as needed, up to a maximum of 90 U per meal <u>Route:</u> Inhaled (MedTone Model C inhaler)	65 subjects randomized to TI and Lantus  65 subjects randomized to Humalog and Lantus	Subjects with type 1 diabetes	Medium; 16 weeks
Type of Study	Study Identifier/ Study Status	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	No. of Subjects Enrolled <sup>a</sup>	Healthy Subjects or Diagnosis of Patients <sup>b</sup>	Duration of Treatment
Other	MKC-TI-118  Completed Full	5.3.5.4.	To assess EGP after dosing with TI and compare it to EGP after sc administration of insulin lispro or inhalation of Exubera insulin during a meal challenge with 12 fluid ounces of Boost Plus <sup>®</sup> To assess EGP after dosing with TI in comparison to EGP after sc administration of insulin lispro or inhalation of Exubera insulin during a euglycemic glucose clamp procedure To characterize the PK and pharmacodynamic (PD) properties of TI, insulin lispro, or Exubera insulin To assess the effect of TI, insulin lispro, or Exubera on endogenous insulin secretion To assess the effect of the 3 test treatments on C-peptide concentrations, glucagon, and free fatty acid (FFA) concentrations.	Randomized, open-label, 2-way crossover arm with 7 visits for each completed subject	<u>Test Product:</u> TI <u>Dosage:</u> 60 U to 90 U of TI depending on effect at initial visit <u>Route:</u> Inhaled (MedTone Model C Inhaler)	Original protocol: 18 subjects randomized  Amended protocol: 12 subjects randomized	Subjects with type 2 diabetes	Medium Original protocol: 3 treatment visits for meal challenge followed by minimum 8-week blood loss recovery period, and 3 sequential visits for glucose clamp procedure  Amended protocol: 2 treatment visits for the meal challenge, followed by 2- to 6-week blood-loss recovery period, and 2 visits for glucose clamp procedure, 1 with TI as treatment drug

Type of Study	Study Identifier/ Study Status	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	No. of Subjects Enrolled <sup>a</sup>	Healthy Subjects or Diagnosis of Patients <sup>b</sup>	Duration of Treatment
Other	MKC-TI-159  Completed Abbreviated	5.3.5.4.	To collect Gen 2 inhalers after their 15-day intended lifespan for evaluation of in-use characteristics and technical performance in the clinical setting and to evaluate inhaler safety	Multicenter, open-label, single-arm trial	<u>Test Product:</u> TI <u>Dosage:</u> individualized; doses of TI may be adjusted in increments of 10 U, as needed, up to a maximum of 60 U per meal <u>Route:</u> Inhaled (Gen2C inhaler)	73 subjects randomized	Subjects with type 1 or type 2 diabetes	Medium; 45 ± 3 days
<b>Ongoing Studies As of 15 May 2010</b>								
Other	MKC-TI-119  Ongoing	5.3.4.2.	To evaluate postprandial glucose (PPG) excursions following the ingestion of lunch or breakfast meals with varying carbohydrate content	Single-center, open-label, PD trial	<u>Test Product:</u> TI <u>Dosage:</u> individualized; doses of TI may be adjusted in increments of 15 U, as needed, up to a maximum of 90 U per meal for MedTone Inhalers <u>Route:</u> Inhaled (MedTone Models C and D Inhaler)	15 subjects randomized	Subjects with type 1 or type 2 diabetes	Medium; 16 weeks

## 5.2 Review Strategy

For the review of clinical efficacy, the clinical reviewer emphasized trial data from one new clinical trial that was not complete at the time of the original NDA submission – trial MKC-TI-117. The Sponsor also submitted re-analyses of trial 102 (the one-year pivotal study in type 2 diabetes patients) demonstrating that the lower rates of hypoglycemia in the TI group seen throughout the course of the study were not related to differences in glycemic control, and that the differences in weight gain between the groups were also not related to differences in glycemic control. However, as noted in the Agency’s preliminary responses to the End-of-Review meeting package, these data were already taken into consideration during the original NDA review. These are *post hoc* analyses that, at best, are hypothesis-generating. Therefore, the Sponsor’s re-analyses were not included in this review.

The clinical safety review was based on the applicant’s Safety Update with a cutoff date of 15 May 2010. This safety update includes 441 new subjects added since the original NDA. Of the new subjects, 130 were subjects with type 1 diabetes from trial 117 that was not complete at the time of original NDA submission (65 of these were in the group randomized to TI), and the remainder were from pharmacokinetic and uncontrolled studies. A total of 250 subjects have used the new Gen2 inhaler in clinical studies. Duration of treatment ranged from single-dose studies to up to 45 days. However, there are no controlled clinical safety and efficacy trials with the Gen2 inhaler.

Separate reviews are being conducted by Biostatistics, Non-Clinical Pharmacology and Toxicology, Biopharmacology, and Chemistry (multiple reviewers). Dr. Karimi-Shah from the Division of Pulmonary and Allergy Products is reviewing the pulmonary safety of Afrezza.

## 5.3 Discussion of Individual Studies/Clinical Trials

**Trial 117** (TI + Lantus vs. Humalog [Insulin lispro] + Lantus)

Study Title: A Phase 3, Multicenter, Open-label, Randomized, Clinical Trial Evaluating the Efficacy and Safety of Technosphere Insulin Inhalation Powder in Combination with Lantus® Versus Humalog® in Combination with Lantus® in Subjects with Type 1 Diabetes Mellitus Over a 16-week Treatment Period

Study Phase: 3

Study Purpose: The primary objective was to demonstrate that the efficacy of TI in combination with Lantus (TI group) was noninferior to Humalog in combination with Lantus (comparator group) in effects on HbA1c.

Study Design: Randomized, open-label substitution study conducted from 30 May 2008 to 23 Mar 2010

**Reviewer's comment: The open-label design is acceptable for most insulin development programs because it is not practical to blind most insulin therapies. In addition, it is considered unethical to incorporate placebo arms without other insulin therapy in trials in type 1 diabetes. The choice of glargine and lispro insulin is acceptable because these insulin products are commonly used and are considered to be standard of care.**

Study Sites: Multicenter in United States and Brazil

Subjects: Approximately 230 subjects were planned to be enrolled to achieve 184 evaluable subjects who meet eligibility criteria and complete the trial. However, the study was ended early (after 130 patients were randomized) because the Sponsor stopped development of the MedTone Inhaler in favor of the Gen 2 inhaler. Study enrollment stopped in September 2009. All enrolled subjects were allowed to complete the trial. The last subject completed the trial on 23 Mar 2010. The Sponsor then evaluated the data (i.e. calculated the variance to determine if there was enough power) in a reportedly blinded fashion to determine if the sample size was adequate to analyze study.

**Reviewer's comment: Since this was an open-label trial we cannot be sure as to whether the data were truly reviewed in a blinded fashion.**

Inclusion Criteria: Non-smoking generally healthy male and female subjects  $\geq 18$  and  $\leq 80$  years of age, with clinical diagnoses of type 1 diabetes mellitus for more than 12 months currently receiving subcutaneous (sc) insulin therapy of any regimen at a total daily dose (TDD)  $< 1.5$  IU/kg/day. Body mass index (BMI) of  $\leq 30$  kg/m<sup>2</sup>. HbA1c  $> 7.0\%$  and  $\leq 9.0\%$ . Please see Dr. Karimi-Shah's pulmonary review for a discussion of pulmonary function entry criteria in the trials.

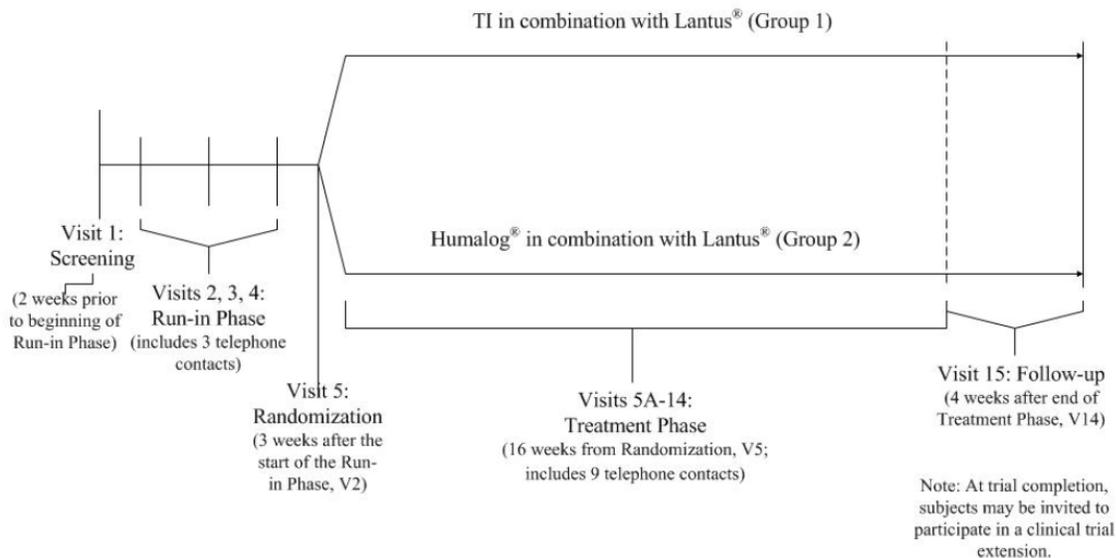
Key Exclusion Criteria:

1. Treatment with any type of antidiabetic drugs, other than sc insulin, within the preceding 12 weeks
2. Two or more severe hypoglycemic episodes within 6 months of screening or episode of severe hypoglycemia between screening (Visit 1) and randomization (Visit 5)
3. Any hospitalization or emergency room visit due to poor diabetic control within 6 months of Visit 1, or hospitalization or emergency room visit due to poor diabetic control between Visit 1 and Visit 5
4. Severe complications of diabetes, in the opinion of the PI, including symptomatic autonomic neuropathy; disabling peripheral neuropathy; active proliferative retinopathy; nephropathy with renal failure, renal transplant, or dialysis; history of foot ulcers; nontraumatic amputations due to gangrene; or vascular claudication
5. Previous exposure to an inhaled insulin product within 3 months of Visit 1
6. History of insulin pump use within 6 weeks of Visit 1
7. Significant improvement in pre- to postbronchodilator spirometry at Visit 1 (defined as an increase of 12% and 200 mL in either FEV<sub>1</sub> or FVC)
8. History of chronic obstructive pulmonary disease (COPD), clinically proven asthma, or any other clinically important pulmonary disease (e.g., obstructive sleep apnea) confirmed by pulmonary function testing or radiologic findings
9. Active respiratory infection (subject could return after 30 days from resolution for rescreening); if respiratory infection manifested after Visit 1 but before Visit 1 PFTs, subject was to be scheduled for PFTs after 30 days from resolution of respiratory infection.
10. Use of medications prescribed for weight loss (e.g., sibutramine, orlistat) within 12 weeks of Visit 1.

Study Procedures: The clinical trial consisted of up to 13 clinic visits, including:

- 1 screening visit/Visit 1 (Week -5)
- 3 visits during the run-in period/Visits 2, 3, and 4 (Weeks -3, -2, and -1, respectively)
- 1 randomization visit/Visit 5 (Week 0)
- 7 visits (1 optional) during the treatment period/Visits 6 (optional), 7, 9, 10, 12, 13, and 14 (Weeks 1, 2, 5, 8, 12, 14, and 16, respectively)
- 1 follow-up visit/Visit 15 (Week 20)
- In addition, there were 3 telephone contacts during the run-in period and approximately 9 telephone contacts during the treatment period

**Figure 5.1 – Trial 117 Schematic**



**Treatments and titration:** Subjects were randomly assigned to receive TI in combination with Lantus (TI group) or Humalog in combination with Lantus (comparator group). They received diabetes education before starting dosing. All insulin regimens were used in conjunction with an appropriately prescribed diabetic diet.

Subjects underwent a 3-week run-in phase for adjustment of basal insulin at which time all subjects were to be switched to Lantus as their basal insulin for the duration of the clinical trial. (Note: The trial results showed that roughly 80% of subjects were already on Lantus at this point with the remainder on other long acting insulins) During the run-in phase investigators titrated Lantus based on telephone contacts with subjects (see study schematic). The protocol stated “Subjects already taking Lantus once a day (QD), in the morning, will change the time of their daily doses to bedtime continuing with their usual daily doses. Subjects who take Lantus twice a day (bid) may continue to do so at the discretion of the PI. Subsequent adjustments of Lantus will occur with the goal of achieving fasting blood glucose (FBG) values of < 120 mg/dL and ≥ 80 mg/dL. During the Run-in Period, there will be clinic visits or telephone calls between the PI, or designee, and the subject, at least twice weekly for the purpose of Lantus dose adjustments and optimization. PIs will be allowed to split the doses of Lantus under the following circumstances:

- o PI or subjects’ choices,
- o Risks of hypoglycemia,
- o Inability to adjust the doses of Lantus to overall glycemic goals. For subjects with split Lantus dosing, the evening doses will be adjusted to achieve a FBG of < 120 mg/dL and ≥ 80 mg/dL and the morning doses will be adjusted to achieve pre-dinner BG levels of <120 mg/dL and ≥ 80 mg/dL
- Subjects taking Levemir or other basal insulins will convert their basal insulin doses to Lantus as follows:

- Initiation of dosing with Lantus will be at 60% of the current total pre-Run-in Period basal insulin doses. Subsequent adjustment of Lantus will occur with the goal of achieving FBG values of < 120 mg/dL and  $\geq$  80 mg/dL.

During the Run-in Period, subjects continued on their pre-study prandial insulin. During the run-in period the prandial insulins used were: insulin aspart (roughly 25% of subjects), regular human insulin (roughly 8% of subjects), insulin lispro (roughly 64% of subjects) and a few other insulins and insulin analogues (about 2-3% of subjects).

Note: there was only one subject [eventually randomized to TI] who was taking 70/30 premix insulin analogue prior to randomization. It appears that this patient was continued on 70/30 premix + Lantus during the run-in period instead of being temporarily switched to an injected prandial insulin.

At randomization subjects stopped their pre-study prandial insulin and began their study treatment prandial insulin. For initiation of TI, subject replaced each pre-randomization sc prandial insulin dose with a corresponding dose of TI, calculated as 3 times the current prandial insulin dose at each meal; The calculated TI initiation prandial dose was to be rounded *down* to the nearest multiple of 15 U to avoid potential hypoglycemia. In the Humalog group, subjects were to be converted from pre-randomization short-acting insulin or rapid acting insulin analogue to Humalog on a 1:1 basis with each meal.

After randomization, subjects in the TI group inhaled TI immediately before the first mouthful of food 2 to 4 times a day (typically 3 times daily). Dosing was individualized using combinations of 15 U and 30 U cartridge strengths up to a maximum dose of 90 units. Humalog and Lantus doses were also individualized. Dosing information was captured in the e-diary database.

The dosing guideline for both groups was as follows. However, forced treat-to-target algorithms were not employed in this study. Only suggestions for dose adjustments were recommended.

#### A. Goals of Treatment/Titration

- Target BG and HbA1c goals for all subjects, in both treatment groups, included:
  - Pre-prandial and bedtime BG levels < 120 mg/dL
  - 2-hour PPG levels < 140 mg/dL
  - HbA1c < 7.0% (ADA), < 6.5% (AACE, IDF);

#### B. SBGM

- All subjects are to be instructed to measure BG at home and to communicate their SBGM results to the PI, or designee, frequently:
  - Fasting blood glucose (FBG) results will be used to adjust basal insulin doses,
  - 2-hour PPG results will be used to adjust prandial insulin doses
  - Pre-prandial glucose and bedtime BG results may also be used to adjust prandial insulin

Further insulin dose adjustments were permitted based on carbohydrate counting, meal size, high or low SBGM results, or snacks. Split dosing in the TI group was allowed for subjects who ate

high fat or very large meals, for subjects who had delayed gastric emptying, or subjects who did not achieve optimal glycemic control on a maximum premeal dose of 90 U. However, the total prandial dose of TI could not exceed 90 U (including meal-time and post-meal-time dose). Correction doses based on the 2- to 3-hour PPG value were also permitted.

Continuous glucose monitoring was also used to help titrate insulins more aggressively; the DexCom™ Seven™ System records 288 glucose measurements every 24 hours and can be worn for up to 7 days before downloading the data onto a computer with the CGM system software. Subjects wore glucose monitors for one week intervals prior to certain visits: [Visit 7 (Week 2), Visit 9 (Week 5), Visit 10 (Week 8), and Visit 13 (Week 14)].

Efficacy Endpoints: The primary efficacy measurement was to compare the mean change from randomization/Visit 5 (Week 0) to Visit 14 (Week 16) in the percent HbA1c value between treatment groups.

#### Statistical Methods:

The Sponsor defined the following analysis populations:

- Safety Population

The Safety Population included all randomized subjects who received at least one dose of study medication.

- Intention-to-treat (ITT) Population

The ITT Population included all randomized subjects who received at least 1 dose of TI or comparator, had a baseline value and at least 1 post-baseline value for the study-specific primary efficacy endpoint.

- Per Protocol (PP) Population

The PP Population included all subjects in the ITT Population who completed the trial according to the requirements of the protocol, including the following:

- They met the eligibility criteria, i.e., there were no inclusion/exclusion violations.
- They received treatments according to the randomization schedule.
- In addition, subjects had to provide complete measurements for the study specific primary efficacy variable at baseline and study end.

The objective of this clinical trial was to show noninferiority of TI plus basal insulin over the comparator drug with a predetermined margin of 0.4%. If non-inferiority was met, superiority of TI plus basal insulin over the comparator drug was then tested. Analysis of covariance (ANCOVA) was conducted to implement these approaches. The analysis model included the treatment group and country as the class variable and baseline HbA1c (%) values as the covariates. Adjusted (least-squares) estimates of the mean differences along with their 95% CIs were calculated and used for the noninferiority/superiority assessments. For both noninferiority and superiority assessments, the ITT population was the primary analysis population.

## 6 Review of Efficacy

### Efficacy Summary

- After 16 weeks of treatment, TI was noninferior to Humalog with respect to HbA1c change from Baseline.
- Mean Lantus use over the course of the study period was similar between the two treatment groups.
- More subjects in the TI Inhalation Powder group than the Humalog group reached the goal of HbA1c  $\leq 6.5$  by Week 16.
- Both groups had a similar percentage of subjects achieving the ADA goal of HbA1c  $< 7.0\%$ .
- After 16 weeks of treatment, the sponsor reports that TI reduced fasting blood glucose to a statistically significantly greater degree than did Humalog.
- Postprandial glucose excursions, as measured during meal challenge testing, were numerically lower in the TI group at time 0 and 30, 60, 90, 105, and 120 minutes after dosing.
- Postprandial glucose exposure (AUC<sub>0-240</sub>) was significantly lower for the TI group.
- Three subjects withdrew for lack of efficacy in the TI group and none in the comparator group.
- No difference between the groups was observed in weight gain.

### 6.1 Indication

Afrezza is indicated for the treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia.

#### 6.1.1 Methods

The review of clinical efficacy is based on Trial 117. See section 5 for the trial design and procedures.

#### 6.1.2 Demographics and Disease History

Table 6.1 shows the demographic characteristics of the ITT population. There were more male than female subjects in the TI group (61.5% vs. 38.5%) while the Humalog group was better balanced.

**Table 6.1 – Trial 117 - Demographics of the ITT population**

Study	Treat-ment Group	N	Sex (%)	Age (years) mean (range)	Race (%)	BMI (kg/m <sup>2</sup> ) Mean (range)	Duration of Diabetes (years) Mean median (range)	Study Location and Sites
117	TI + insulin glargine	65	M=61.5% F=38.5%	38.6 (19,65)	Caucasian (86.2%) Hispanic (7.7%) Black (4.6%) Other (1.5%)	25.1 kg/m <sup>2</sup> (18.3 –38.7)	16.8 12.3 (2,50)	Argentina 2 sites United States
	Insulin lispro + insulin glargine	65	M=50.8% F=49.2%	39.4 (20,66)	Caucasian (90.8%) Hispanic (7.7%) Black (0%) Other (1.5%)	25.7 kg/m <sup>2</sup> (20.8–34.4)	17.6 16.2 (1,47)	

Source: Table 4, trial 117 report

Prior Antidiabetic Medications

As expected due to the nature of T1DM, all T1DM subjects were using insulin at trial entry. The percentages of subjects using specific insulin types have been requested from the Sponsor; this information is pending and will be addressed in the cross discipline team leader memo. The duration of diabetes at trial entry (roughly 17 years) was sufficient to ensure that subjects were not being studied during the “honeymoon” phase of T1DM when insulin requirements are often reduced.

Generalizability of Trial population

In trial 117 most of the subjects were from the U.S., and this trial should be considered generalizable based on demographic characteristics except that there was a relatively low percentage of African American subjects, similar to other clinical trials in the Afrezza development program.

6.1.3 Subject Disposition

In trial 117, 130 subjects were randomized before enrollment was stopped and 126 comprised the ITT population. Five subjects (7.7%) prematurely discontinued in the insulin lispro + Lantus arm (Table 6.2). Thirteen subjects discontinued in the TI + Lantus arm (20%). This difference in discontinuation rate was driven by adverse events (6.2% s. 0%) and by subject withdrawal of consent (6.2% vs. 1.5%). See Section 7 of this review for more details.

<b>Table 6.2 – Trial 117 Subject Disposition (16 Week Treatment Period)</b>			
Population	TI + Lantus	Lispro + Lantus	Overall Total
Number of Subjects (%)			
Screened			276
• Screen failures			138 (50.0)
• Eligible			138 (50.0)
Randomized	65	65	130
Safety Population	65	65	130
Completed	52 (80.0)	60 (92.3)	112 (86.2)
Prematurely Discontinued	13 (20.0)	5 (7.7)	18 (13.8)
• Adverse Event	4 (6.2)	0 (0.0)	4 (3.1)
• Protocol Violation	0 (0.0)	1 (1.5)	1 (0.8)
• Subject Withdrew Consent	4 (6.2)	1 (1.5)	5 (3.8)
• Investigator Decision	2 (3.1)	1 (1.5)	3 (2.3)
• Lost to follow-up	0 (0.0)	1 (1.5)	1 (0.8)
• Other	3 (4.6)	1 (1.5)	4 (3.1)
Intention to Treat Population	61 (93.8)	65 (100)	126 (96.9)
Per Protocol Population	52 (80.0)	60 (92.3)	112 (86.2)
Source: Table 3, trial 117 report			

Nine subjects in the TI group discontinued the study for reasons other than adverse events:

Withdrew consent:

- Subject 275-0098: time constraints
- Subject 611-0133: started working and work schedule was not flexible
- Subject 028-0145: taking 90 U of TI and blood sugars were elevated
- Subject 021-0225: could not comply with visit schedule

Investigator decision:

- Subject 610-0118: Lack of efficacy
- Subject 610-0249: Poor glycemic control

Other:

- Subject 484-0230: pregnancy
- Subject 609-0034: severe hypoglycemia events before Visit 5 and failed protocol exclusion criterion 2 (severe hypoglycemia between Visit 1 and Visit 2)
- Subject 023-0243: required to serve prison time

Of these subjects, 3 (Subjects 028-145, 610-0118, and 610-0249) discontinued for reasons related to unacceptable hyperglycemia:

Subject 028-0145 was a 31-year-old Caucasian male whose screening, baseline, and discontinuation visits were on 28 Mar 2009, 04 Jun 2009, and 24 Nov 2009, respectively. He was withdrawn on 24 Nov 2009 because of increased blood sugars while taking 90 U of TI. On 10 Aug and 17 Aug 2009, the subject had severe episodes of hypoglycemia with BGs of 23 mg/dL

and 27 mg/dL, respectively. Both episodes were treated with food and both were possibly related to study drug. No ketoacidosis or episodes of infection were reported. His HbA1c value at discontinuation was 7.3%, unchanged from an assessment in June 2009.

Subject 610-0118 was a 24-year-old Caucasian female whose screening, baseline, and end of study visits were on 27 Feb 2009, 19 May 2009, and 11 Aug 2009, respectively. She received her last dose of TI on 11 Aug 2009 when she was withdrawn because of lack of efficacy. The only treatment emergent adverse events (TEAEs) recorded included rash at the CGM insertion site, intermittent cough, and psoriasis, all either not related or unlikely related to study drug, except for the cough which was probably related. All TEAEs had either resolved or were resolving (psoriasis) when the subject withdrew. Her HbA1c was 7.9% at Baseline and 8.7% at the time of withdrawal.

Subject 610-0249 was a 53-year-old Caucasian male whose screening, baseline, and end of study visits were on 30 Jul 2009, 28 Sep 2009, and 04 Nov 2009, respectively. He withdrew on 03 Nov 2009 because of an investigator decision of poor glycemic control. His HbA1c was 7.4% on entering and 8.8% on withdrawal. The only TEAE was an intermittent cough that began on 28 Sep 2009 and ended on 15 Nov 2009, was considered moderate in severity, resolved off drug, and was probably related to drug.

**Reviewer's comment: Although coded under different categories, 3 subjects withdrew for lack of efficacy in the TI group and none in the comparator group.**

#### 6.1.4 Analysis of the Primary Endpoint

The primary efficacy variable was change from baseline in HbA1c (%) at the end of the treatment period. It is particularly important to have an objective measure of efficacy such as HbA1c in the TI clinical development program because the pivotal trials were open-label.

See the original NDA clinical review for a discussion of HbA1c as a surrogate endpoint.

Baseline HbA1c was similar between treatment groups. In an ANCOVA model including treatment group and country as fixed effects and baseline HbA1c as covariate, and using the ITT population with LOCF, the mean change from baseline in the TI + glargine arm was -0.09% compared with the lispro + glargine arm which showed a mean change from baseline of -0.05% (Table 6.3). The between-group difference in change from baseline in HbA1c was 0.04% (favoring TI) with a corresponding 95% CI of (-0.25 to 0.18) supporting a non-inferiority claim for TI (inferiority margin < 0.4%).

**Table 6.3 – Trial 117 ANCOVA of Mean Change from Baseline in HbA1c (%) at Week 16, ITT Population with LOCF**

Time Point	Statistic	TI + Glargine	Insulin Lispro + Glargine	TI + Glargine vs. Insulin Lispro + Glargine
Baseline	N	61	65	
	Mean	7.75	7.62	
	SD	0.553	0.602	
	95% CI	7.61 – 7.90	7.47 – 7.76	
Week 16	N	61	65	
	Mean	7.69	7.61	
	SD	0.800	0.720	
	95% CI	7.48 – 7.89	7.43 – 7.78	
Change from Baseline to Week 16	N	61	65	
	LS Mean	-0.09	-0.05	-0.04
	SE	0.079	0.076	0.108
	95% CI	-0.24 – 0.07	-0.20 – 0.10	<b>-0.25 – 0.18</b>
Noninferiority margin = 0.4% upper bound of the 95% CI				
Source: Table 8, Trial 117 report				

**Reviewer’s comments:** The Agency statistician Dr. Sahlroot has informed this reviewer by email that he has verified the statistical results based on both the observed data and additional analyses imputing data (conservatively) for the patients who were planned but didn't make it into the study because it was stopped early (see his review for details). However, he still has concerns about the adequacy of the design and conduct of the trial, particularly because of the small size, short duration, and open-label, non-inferiority design.

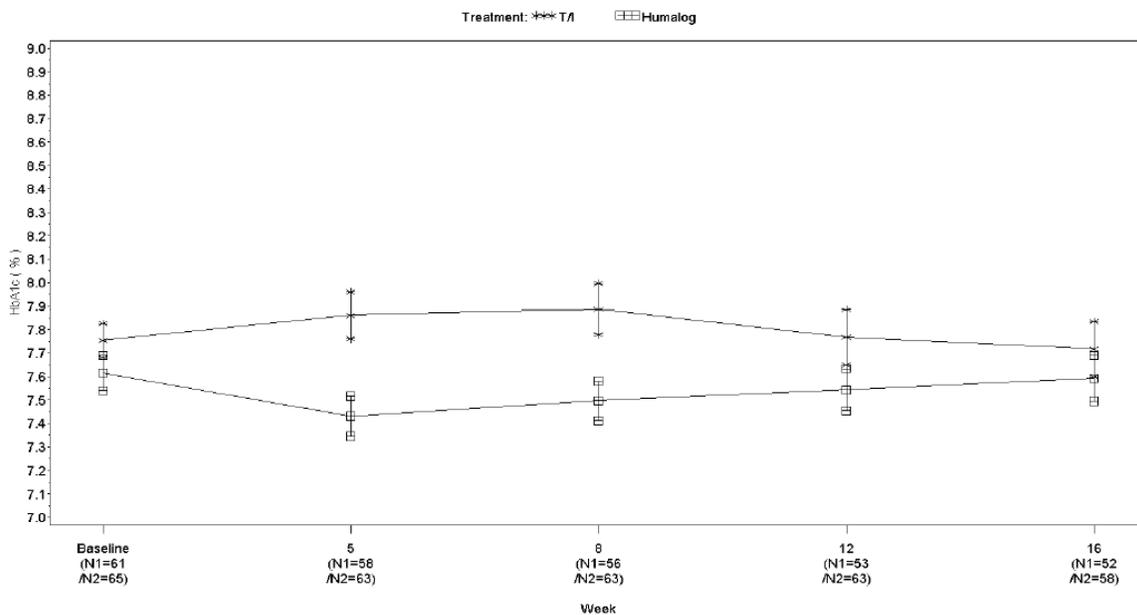
Dr. Sahlroot’s preliminary comments note that in a non-inferiority trial, the effect of the comparator must be understood in order to interpret the results of the study. Because the control group showed no improvement in HbA1c, it is not difficult for TI to be non-inferior to control. In other words, in order to obtain a valid comparison of TI to comparator insulin, the comparator insulin must be titrated effectively to achieve reasonable glycemic control. Less than one-fourth of patients in both arms of trial 117 achieved glycemic control <7%, the American Diabetes Association recommendation.

However, considering these data from a clinical perspective, both arms of the trial showed control of blood glucose over a 16 week period. It is important to interpret these data in the context of the pathophysiology of T1DM in which patients do not produce sufficient endogenous insulin; therefore, T1DM patients not given sufficient exogenous insulin would inevitably show increases in HbA1c over time. Sixteen weeks is a sufficient duration for deterioration of glycemic control to become noticeable. As long as there is not a notable difference in the amount of basal insulin each study group receives on average, it can be inferred that TI is equally as effective as Humalog at maintaining blood glucose control

over a 16 week period. This reviewer expressed the same reasoning in the original clinical review to recommend approval of TI at that time, even though the pivotal one year trial in type 1 diabetic patients did not meet the primary endpoint of non-inferiority.

Figure 6.1 shows the mean change in HbA1c over 16 weeks. The Sponsor states that the dose of TI increased from Weeks 1 to 4, then reached a plateau dose that was maintained during the remaining 12 weeks of treatment in the trial, and that this is the reason for the brief rise in the HbA1c levels in the TI group over the first 4 weeks of the trial with the gradual improvement in HbA1c levels over final 12 weeks of stable treatment. The insulin dose data are reviewed in more detail below.

**Figure 6.1 – Trial 117 Mean (SE) Change in HbA1c (%) Over 16 Weeks (ITT Population)**



Source: Figure 4, Trial 117 report

**Reviewer’s comment:** One possible explanation for the data pattern in the Humalog (lispro) group is an early improvement in HbA1c due to trial participation itself (i.e. more early follow up with physicians) and then a regression to baseline. Many patients in the Humalog group were already on Humalog during the run-in period and would not have to deal with the difficulty of learning how to use the inhaler (a plausible explanation for why the TI group showed a slight increase in HbA1c early on in the trial).

Additional analyses related to the Primary Endpoint

HbA1c Change from Baseline by HbA1c Subgroup

Table 6.4 shows the statistical analysis (LS means from ANCOVA model with terms of treatment, country, and baseline HbA1c) of HbA1c (%) change from Baseline by baseline subgroups for the ITT population. For subjects in the prespecified  $\geq 6.5\%$  to  $7.5\%$  subgroup, HbA1c in both the TI and Humalog groups was higher at Week 16 than at Baseline. For subjects in the  $> 7.5\%$  to  $9.0\%$  subgroup, HbA1c in both groups was lower at Week 16 than at Baseline. In both subgroups, the numerical change in HbA1c favored TI and were consistent with the overall results. As expected, the magnitude of the change at the end of the study was greater for the  $> 7.5\%$  to  $9.0\%$  group. Subjects with a lower starting HbA1c were under better glycemic control and thus did not have the same potential to decrease HbA1c as the higher group.

**Table 6.4 - HbA1c (%) Change from Baseline by Baseline Subgroups (ITT Population)**

Baseline HbA1c	Time Point	Statistic	TI (n = 61)	Humalog (n = 65)	TI – Humalog	
$\geq 6.5$ to $7.5$	Baseline <sup>a</sup>	N	18	30		
		Mean	7.21	7.16		
		SD	0.197	0.242		
		95% CI	(7.11, 7.31)	(7.07, 7.25)		
	Week 16 <sup>a</sup>	N	18	30		
		Mean	7.24	7.29		
		SD	0.926	0.603		
		95% CI	(6.78, 7.71)	(7.06, 7.51)		
	Change from Baseline to Week 16 <sup>b</sup>	N	18	30		
		LS Mean	0.05	0.14	-0.09	
		SE	0.176	0.140	0.217	
		95% CI	(-0.31, 0.40)	(-0.15, 0.42)	(-0.53, 0.35)	
	$> 7.5$ to $9.0$	Baseline <sup>a</sup>	N	33	26	
			Mean	8.09	8.08	
SD			0.381	0.368		
95% CI			(7.96, 8.23)	(7.93, 8.23)		
Week 16 <sup>a</sup>		N	33	26		
		Mean	7.93	7.90		
		SD	0.667	0.689		
		95% CI	(7.70, 8.17)	(7.62, 8.17)		
Change from Baseline to Week 16 <sup>b</sup>		N	33	26		
		LS Mean	-0.19	-0.15	-0.04	
		SE	0.089	0.100	0.135	
		95% CI	(-0.37, -0.01)	(-0.35, 0.05)	(-0.31, 0.23)	

Source: Table 15 trial 117 report

**Reviewer’s comment: One of the concerns with the conduct of the trial, as noted by Dr. Sahlroot in an email to this reviewer, is that the mean baseline HbA1c may have been too low to allow changes needed to show any treatment differences, if in fact they exist. It is interesting to note here that in the subgroup of subjects with higher mean baseline HbA1c, TI was similarly effective compared with Humalog. Although this finding supports the efficacy of TI, it must be considered exploratory because it is a subgroup analysis.**

HbA1c Responder Rates ( $\leq 6.5\%$  and  $\leq 7.0\%$ ) at Week 16

The treatment difference in HbA1c responder rates at Week 16 was evaluated using a logistic regression analysis (Table 6.5). The odds of reaching the  $\leq 6.5\%$  goal was slightly higher in the TI group (nominal p-value 0.03) but conclusions are substantially limited by the small sample sizes (only 7 total patients achieved this HbA1c goal). In addition, the p value cut-off used to determine statistical significance should be adjusted for multiple comparisons and the observed p-value of 0.03 would likely be non-significant after adjustment. The odds of reaching the ADA goal of  $<7\%$  was similar between the two groups although numerically higher for the comparator group.

**Table 6.5 – Trial 117 Treatment Difference in HbA1c (%) Responder Rates at Week 16 (ITT Population)**

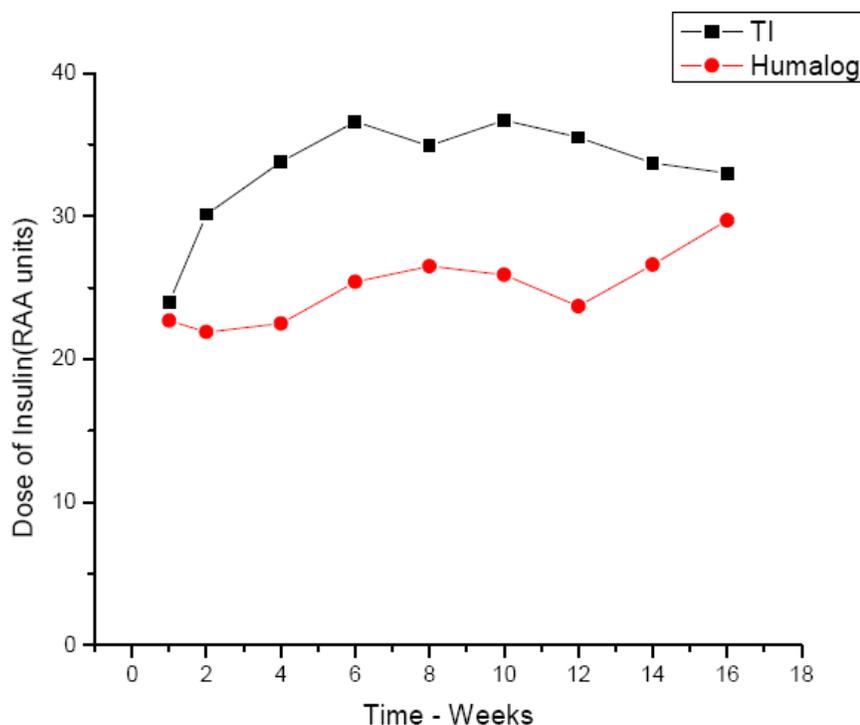
Responder Category	TI + Glargine (n=202)	Insulin Lispro + Glargine (n=210)	TI + Glargine vs. Insulin Lispro + Glargine		
	n (%)	n (%)	Odds Ratio	95% CI	p Value
HbA1c $\leq 6.5\%$ at Week 16	5 (9.62)	2 (3.45)	13.825	1.3 – 143.3	0.0277
HbA1c $\leq 7.0\%$ at Week 16	9 (17.31)	14 (24.14)	1.121	0.4 - 3.3	0.8367

Statistics based on logistic regression analysis with terms for country, treatment and baseline HbA1c  
 Source: Table 13 Trial 117 report

**Reviewer’s comment: These data, are consistent with the non-inferiority finding of TI.**

Insulin doses achieved by subjects

**Figure 6.2 – Trial 117 - Dose of TI (U) and Insulin Lispro (IU) Over 16 Weeks (Safety Population)**



Source: Figure 2, Trial 117 report

Subjects on TI were treated at Week 1 with a mean of 91.4 U, approximately equivalent to 24 IU of rapid acting insulin analogue (RAA) (based on an approximate bioavailability of 26.7% for TI). Daily mealtime doses of TI gradually increased over the first 4-6 weeks of the trial, then reached a mean plateau of approximately 132 U (equivalent to 35 IU of RAA) which remained relatively constant over the course of the final 12 weeks of the trial. Subjects in the Humalog group received somewhat less mealtime insulin during the course of trial.

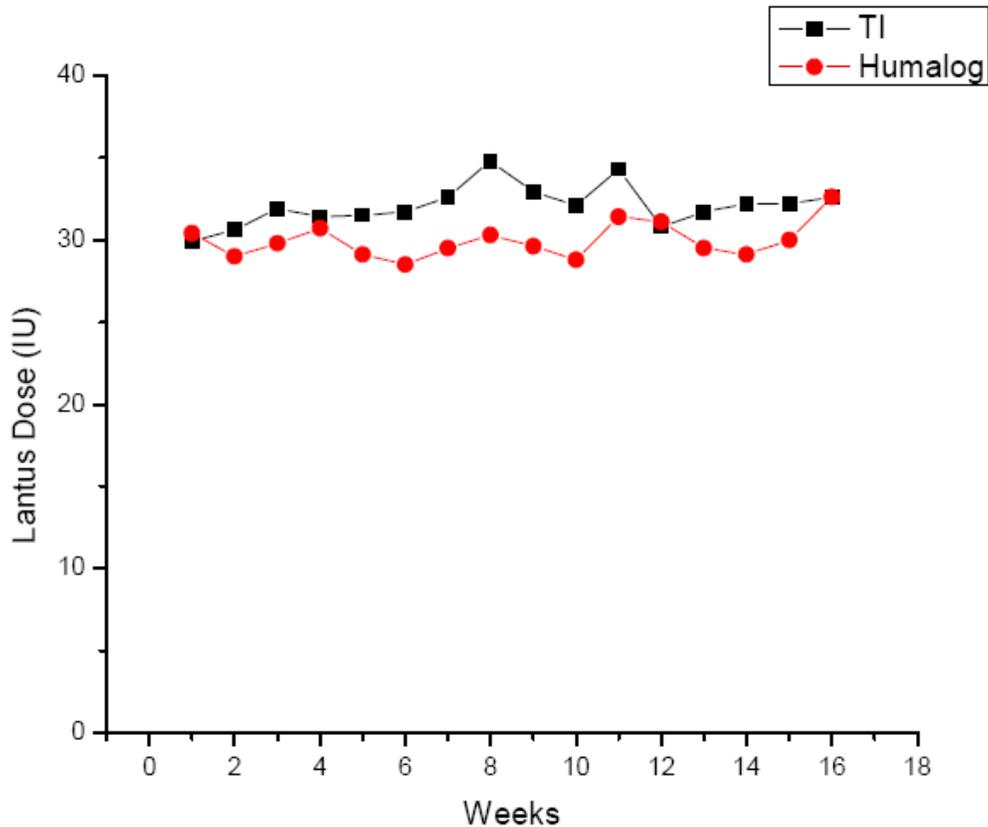
**Reviewer’s comment: These data suggest TI is less potent than Humalog, even when accounting for the relative bioavailability, since more units of TI than Humalog were used to reach similar HbA1c levels.**

A key component of the efficacy analysis is a comparison of the use of glargine between the two treatment groups. If TI were effective, one would expect the average dose of glargine over the course of the trial to be roughly equivalent between the two treatment groups. In fact, a valid comparison of TI and insulin lispro as prandial insulins is only possible if the mean daily dose of insulin glargine is roughly equivalent between the two treatment groups. Figure 6.3 shows the average dose of glargine by week between treatment groups.

The average daily dose of basal insulin was similar throughout the 16 weeks of the trial for both groups. For the TI group, the average daily dose of basal insulin ranged between 30 U and 35 U

(0.401 IU/kg to 0.467 IU/kg); the corresponding range for the Humalog group was 29 U to 33 U (0.384 to 0.439 IU/kg). The final mean Lantus dose at Week 16 was 32.6 IU for each treatment group.

**Figure 6.3 – Trial 117 – Mean Dose of Lantus (IU) Over 16 Weeks (Safety Population)**



Source: Figure 3 Trial 117 report

**Reviewer’s comment:** Numerically, the mean glargine dose was slightly higher in the TI arm at most timepoints but the between group differences were small (~1-3 units) relative to the daily glargine dose (~30 units); therefore, a meaningful comparison of the effect of TI vs. lispro is possible.

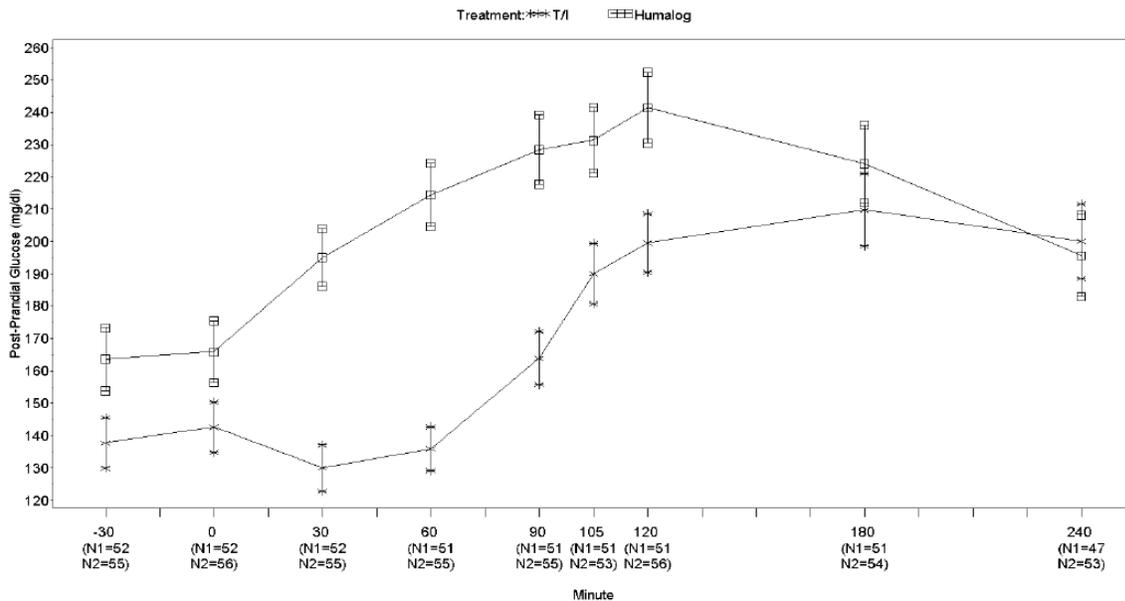
#### 6.1.5 Analysis of Secondary Endpoints(s)

##### Effect on Postprandial Glucose Control

The Sponsor has argued that because of TI’s rapid onset of action, it has an improved postprandial glucose excursion profile over other mealtime insulins. Meal Challenge tests were performed at week 0 and week 16 using a standardized liquid meal (12 oz. Boost Plus®, Novartis). Subjects were to take their usual pre-breakfast study medications at their usual doses prior to Meal Challenge testing. In the submission, the Sponsor presented the baseline data for all subjects together, instead of by randomization group.

Figure 6.4 shows glucose excursions during 240 minutes after a standardized meal challenge for the TI + basal insulin group vs. the insulin lispro + basal insulin group at Week 16 (study endpoint).

**Figure 6.4 – Mean Postprandial Glucose (mg/dL) After a Meal Challenge at Week 16 (ITT Population)**



Source: Figure 5, Trial 117 report

The TI group started with a lower mean blood glucose 30 minutes before dosing and at time 0. Subjects in the TI group had their mean BG level decrease after 30 minutes (–11.31.mg/dL), remain slightly below baseline at 60 minutes (–6.10 mg/dL less than baseline) then gradually increase over time (mean increase 21.65 mg/dL at 90 minutes, 47.78 mg/dL at 105 minutes, 57.24 mg/dL at 120 minutes, 67.47 mg/dL at 180 minutes, and 55.53 mg/dL at 240 minutes). The maximum PPG excursion from baseline was 67.47 mg/dL and occurred at 180 minutes. Subjects in the Humalog group had an initial rise in their PPG levels that persisted until 120 minutes when their PPG levels began to fall (mean increase 29.37 mg/dL at 30 minutes, 49.39 mg/dL at 60 minutes, 63.24 mg/dL at 90 minutes, 67.90 mg/dL at 105 minutes, 77.28 mg/dL at 120 minutes,

56.42 mg/dL at 180 minutes, and 28.49 mg/dL at 240 minutes). The maximum PPG excursion from baseline for the Humalog group was 77.28 mg/dL and occurred at the 120 minutes.

The postprandial plasma glucose (mg/dL) baseline-normalized AUC at week 16 was lower for TI than for Humalog (nominal p=0.02 based on an ANCOVA analysis).

**Reviewer’s comment: These results are similar to what was shown for trials reviewed during the original clinical review and are consistent with the different pharmacodynamic properties of each prandial insulin.**

Effect on Fasting Plasma Glucose

Fasting plasma glucose (FPG) is a common secondary endpoint in DM trials. One of the methods of diagnosing diabetes mellitus is a confirmed FPG  $\geq$  126 mg/dL.

Table 6.6 shows the statistical analysis of FPG change from Baseline to Week 16 for the ITT population based on data collected during the meal challenge tests.

<b>Table 6.6 – Trial 117 ANCOVA of Treatment Difference in Change From Baseline in Fasting Plasma Glucose (mg/dL) at Week 16, ITT Population without LOCF</b>				
Time Point	Statistic	TI	Insulin Lispro	TI vs. Insulin Lispro
Baseline	N	52	52	
	Mean	179.4	177.7	
	SD	73.1	69.1	
	Range	41 - 315	54 - 385	
Week 16	N	52	52	
	Mean	137.8	169.3	
	SD	56.3	75.0	
	95% CI	46 - 264	51 - 378	
Change from Baseline to Week 16	LS Mean	-41.5	-9.16	-32.4
	SE	9.0	8.9	12.4
	95% CI	-59.2 – (-23.9)	-26.6 – 8.3	<b>-57.1 – (-7.7)</b>
				<b>P=0.01</b>
ANCOVA model included country and treatment as fixed effects and baseline FPG value as covariate				
Source: Table 16 Trial 117 report				

**Reviewer’s comment: These results are similar to those seen with trials reviewed during the first cycle, particularly trial 102, i.e. the reduction in HbA1c was less or the same in the TI treatment groups but the FPG reduction was better in the TI treatment groups. The reason for these findings is unclear. However, they do support the efficacy of TI given that this difference cannot be fully explained by the very small differences in mean glargine**

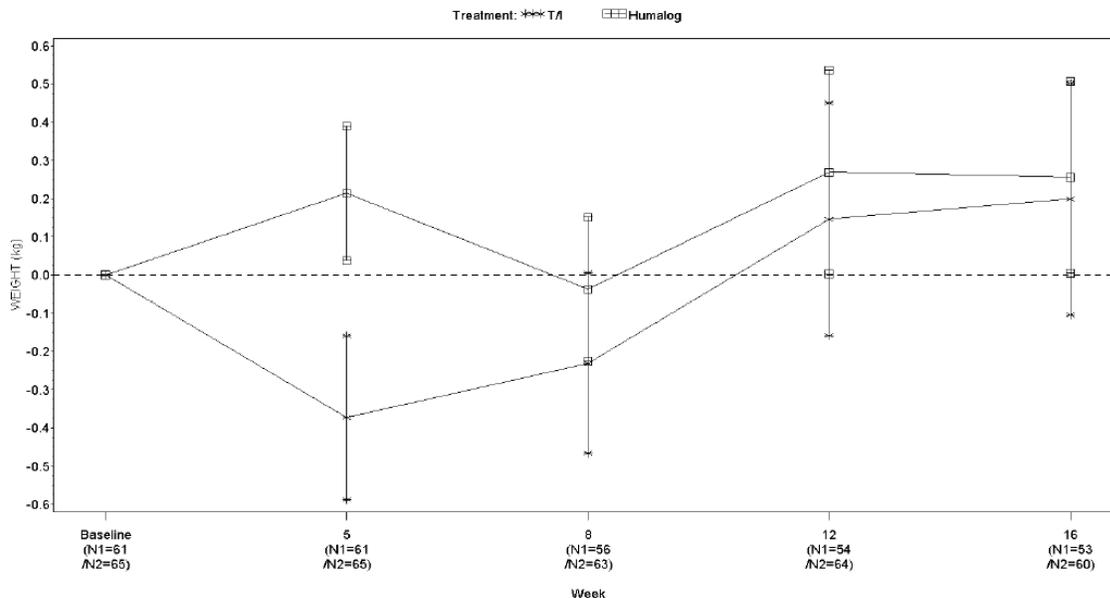
**doses between treatment groups. One consideration is that TI treated patients are experiencing better prandial coverage at dinner-time. Measurement of mean 3AM glucose values may have helped explore this finding further.**

### 6.1.6 Other Endpoints

Insulin therapy is often accompanied by the undesirable side effect of body weight gain. Data from the original clinical review suggested that TI predisposes to less weight gain than other commonly used insulin therapies in both T1 and T2 DM but this finding was confounded by differential effects of TI vs. comparators on glycemic control.

Figure 6.5 shows the mean body weight change over the 16 week trial duration for trial 117. By Week 16, both groups had gained an average of approximately 0.3 kg. The difference between the groups was in favor of TI, but was small and not statistically significant.

**Figure 6.5 – Trial 117 Mean (SE) Change in Body Weight (kg) Over 16 Weeks (ITT Population)**



Source: Figure 7, Trial 117 report

### 6.1.7 Subpopulations

Please see Dr. Sahlroot's statistical review for comments on subpopulations. These data are limited because of small sample sizes. Per the Sponsor's analyses, no particular subgroup was found of interest from baseline and demographic characteristics. HbA1c was analyzed by baseline HbA1c subgroups to study the treatment comparisons among subjects with different baseline HbA1c control (see Table 6.4).

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See original NDA clinical review. There is no new information relevant to dosing recommendations.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See original NDA clinical review.

#### 6.1.10 Additional Efficacy Issues/Analyses

None

## 7 Review of Safety

### Safety Summary

#### Exposure and Demographics

Only 1 newly completed controlled clinical trial (117) in type 1 diabetes met the criteria for pooled analyses presented in the Integrated Summary of Safety (ISS) of the NDA. There were no additional completed trials in type 2 diabetic patients that met the pooling criteria.

After combining the ISS 2009 data with new data from trial 117, the T1DM safety population included 679 TI -treated subjects and 664 subcutaneous insulin comparator-treated subjects. The total additional exposure from trial 117 is 19 pt years for the type 1 diabetes population yielding a total exposure of 559 pt years for subjects with type 1 diabetes and 1833 pt year of exposure for the combined type 1 and type 2 diabetes population.

The demographic profile of the updated safety population was essentially unchanged from the original NDA safety population.

#### Major Safety Results

There was one death in the Safety Update, which includes all completed and ongoing clinical trials and patient exposure outside of clinical trials (e.g. the Named Patient Program/Compassionate Use Program in Europe which allows access to Afrezza for patients who previously used Exubera) since the safety update for the original NDA. A 54-year old man in the Named Patient Program/Compassionate Use Program died from likely sudden cardiac death. A relationship to Afrezza cannot be concluded as cardiac death is very common in the diabetic population.

Characteristics and incidence rates of serious adverse events and events leading to dropout were similar to the original NDA pooled safety review. There were no additional reports of lung malignancy in the Safety Update.

Hypoglycemia incidence rates from trial 117 numerically favored TI but were generally not statistically significant.

Findings related to common adverse events, laboratory values, vital signs and ECGs were unchanged from the original NDA pooled safety review.

## 7.1 Methods

The clinical reviewer used the Sponsor's re-submission Safety Update as the primary source of data for the safety review. The re-submission Safety Update (cutoff date 15 May 2010) provides an update of the safety information for the Technosphere Insulin Inhalation System presented in the original NDA which was submitted 16 Mar 2009, and the 120-day Safety Update submitted on 16 July 2009.

For deaths, serious adverse events, adverse events leading to withdrawals, and adverse events of interest the clinical reviewer considered all available controlled and uncontrolled data in the Safety Update. For comparisons of incidence rates of safety data between Afrezza and comparator, new controlled data is available for type 1 diabetes patients only (i.e. none for type 2 patients). Therefore, in regards to controlled safety data the review and conclusions from the original NDA review for type 2 diabetes patients is still applicable and only updates to the type 1 population are discussed.

Note: for the Safety Update the Sponsor was asked for the following:

When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

New studies/clinical trials used to evaluate safety in the Safety Update are shown in Table 7.1. Please see the original NDA clinical review for tables of all prior studies/clinical trials used to evaluate safety.

**Table 7.1 – Clinical Trials in the Safety Update: Status and Exposure**

Trial	Phase	Study Design/Inhaler	Number of Subjects Exposed <sup>1</sup>	Population	Exposure ≥ 14 days	Status
<b>Pharmacokinetic/Biopharmaceutical Studies</b>						
MKC-T-140	1	PK, crossover; Gen2A inhaler	30	Healthy volunteers	No	Completed
MKC-TI-141	1	PK, crossover; Gen2B, MT Model C inhalers	45	Healthy volunteers	No	Completed
MKC-TI-142	1	PK, BE, crossover; Gen2C, MT Model C inhalers	68	Healthy volunteers	No	Completed
(b) (4)						
MKC-143	1	Device handling, no exposure to drug; Gen2C, MT Model D inhalers	0	74 healthy pediatric volunteers	No	Completed
MKC-TI-118	2	PK/PD, crossover; MT Model C	30	Type 2 DM	No	Completed
<b>Uncontrolled Studies</b>						
MKC-TI-119	2	Uncontrolled, PD; MT Inhaler Models C and D	15	Type 1 and 2 DM	Yes	Ongoing
MKC-TI-139	3	Uncontrolled; MT Models C and D Inhaler	16	Type 1 and 2 DM	Yes	Ongoing
MKC-TI-158	Pilot	Uncontrolled, PD; Gen2C inhaler	6	Type 2 DM	Yes	Ongoing
MKC-TI-159	2	Uncontrolled, device use; Gen2C inhaler	73	Type 1 and 2 DM	Yes	Completed
<b>Controlled Studies</b>						
MKC-TI-117	3	Controlled, open label, efficacy and safety; MT Model C	130	Type 1 DM	Yes	Completed
MKC-TI-134	3	Controlled, open label	0	Type 1 and 2 DM with asthma and COPD	Yes	Ongoing

<sup>1</sup> Exposed to study drug.

<sup>2</sup> The drug formulation used in this trial differs from the formulation used in all other trials in the Safety Update and is not a part of this submission.

BE; bioequivalence; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; MT, MedTone Inhaler; PD, pharmacodynamic; PK, pharmacokinetic.

Source: Sponsor's Table 1, ISS

### 7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA 7.1. The clinical reviewer compared investigator verbatim terms to the Sponsor's preferred terms for any deaths, serious adverse events and events leading to dropout. The Sponsor's MedDRA coding was appropriate.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As in the original NDA submission, the pooling strategy applied for the Integrated Summary of Safety (ISS) in this Safety Update was:

- Completed Phase 2/3 controlled trials - a completed trial was considered one with a completed data base lock at the cut-off date
- Adult subjects with type 1 or 2 diabetes
- Continuous duration of exposure for  $\geq 14$  days

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the original NDA review, the overall exposure at appropriate doses/durations and demographics of target populations was concluded to be adequate and there were no clinical deficiencies related to inadequate exposure and/or inability to fully assess Afrezza's safety profile.

Dating from the original NDA to the cut-off date of the re-submission Safety Update (15 May 2010), 441 additional subjects have been exposed to study drugs (i.e. Afrezza or control) in clinical trials of the Technosphere Insulin Inhalation System (6 completed and 5 ongoing). Of these, 191 subjects had been exposed as of the cut-off date of the original NDA's 120-safety update.

Of the 441 subjects exposed in the new trials, 130 were type 1 diabetes patients from trial 117 and 160 were healthy volunteers in 4 clinical pharmacology studies. In addition, 74 pediatric subjects have completed a device handling study that did not include exposure to inhaled insulin, and 14 subjects have been exposed in an ongoing Named Patient Program/Compassionate Use Program in the European Union. (These 14 subjects are not included in the total of exposed subjects in Table 7.1). Therefore, the majority of the new data are from short-term clinical pharmacology studies or other studies that yield limited safety information.

A total of 250 subjects have used the new Gen2 inhaler in clinical studies. Duration of treatment ranged from single-dose studies to up to 45 days. However, there are no controlled clinical safety and efficacy trials with the Gen2 inhaler.

#### 7.2.2 Exposure in pooled controlled phase 2/3 trials safety population

The overall clinical development program for the original NDA submission included 5128 adult subjects. The integrated pooled safety database (pooled phase 2/3 studies of greater than 14 days duration) submitted in the original NDA included 2409 subjects with type 1 or type 2 diabetes exposed to TI (1814 pt year of exposure), 114 subjects exposed to Technosphere Inhalation Powder (i.e. without insulin) (25 pt year of exposure), and 1944 subjects exposed to comparator treatments (2051 pt year of exposure). There were 661 subjects included in Clinical Pharmacology studies.

Only 1 newly completed controlled clinical trial (117) in type 1 diabetes met the criteria for pooled analyses presented in the ISS of the NDA (referred to by the Sponsor as ISS 2009). A pooled analysis of subjects with type 2 diabetes is not included in the Safety Update as there were no additional completed trials that met the pooling criteria.

After combining the ISS 2009 data with new data from trial 117, the T1DM safety population included 679 TI -treated subjects and 664 subcutaneous insulin comparator-treated subjects (Sponsor refers to this as Safety Update population). The total additional exposure from trial 117 is 19 pt years for the type 1 diabetes population yielding a total exposure of 559 pt years for subjects with type 1 diabetes and 1833 pt year of exposure for the combined type 1 and type 2 diabetes population.

The demographic profile of the updated safety population was essentially unchanged from the original NDA safety population. This is not surprising given that the updated phase 2/3 data for T1DM involves only the small 16-week trial and this trial essentially had the same demographic profile as the overall Afrezza clinical development program (see Table 6.1).

#### 7.2.2 Explorations for Dose Response

Hypoglycemia is an adverse event for which the risk is directly proportional to TI dose. Hypoglycemia was discussed in Ms. Mele's original NDA statistical safety review. No additional explorations for dose response were conducted for the re-submission.

### 7.2.3 Special Animal and/or In Vitro Testing

Please refer to the original NDA nonclinical and clinical reviews.

### 7.2.4 Routine Clinical Testing

See original NDA clinical review.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the original NDA clinical and clinical pharmacology reviews.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See original NDA clinical review.

## 7.3 Major Safety Results

### 7.3.1 Deaths

In the original NDA there was no imbalance in the rate of deaths between TI-treated subjects and comparator-treated subjects. There were no deaths reported in the completed and ongoing clinical trials included in this Safety Update.

There was 1 death in the Named Patient Program/Compassionate Use Program in Europe. The narrative for this subject is as follows:

A 54-year-old Caucasian male patient in Switzerland with type 1 diabetes participating in a Compassionate Use Program of TI began treatment on 07 Dec 2009 and continued to an unknown date in 2010. TI was administered at 30 U TID with breakfast, lunch, and dinner and at 15 U before bedtime for the treatment of type 1 diabetes mellitus. On [REDACTED]<sup>(b) (6)</sup>, the patient died during his sleep. The patient was found to be unresponsive by his wife at 04:30 and the paramedics were called. The paramedics arrived 10 minutes later and found the patient still warm but not breathing, with pupils nonreactive to light and in asystole on ECG. CPR was administered for 20 minutes with no success, and the patient was later declared dead by the arriving physician. There were no signs of crime or suicide. Paramedics found no clinical signs

of hypoglycemia; they reported the body was warm and dry; glycemia during paramedic evaluation was not checked. Information about the last dose of TI, including the time, was unknown by the investigator. The investigator reported that the patient had never had a problem with hypoglycemia and that the cause of death was probably a heart attack. The investigator reported that the patient had several cardiovascular risk factors including coronary heart disease, a myocardial infarction 2 years earlier, and uncontrolled hypertension that had become problematic to control over the prior weeks. In addition, the patient had poorly-controlled diabetes. On 20 Jan 2010, the patient's HbA1c was 12.7%, the same value as had been reported in July 2009. Recent blood glucose (BG) values were reported as 468 mg/dL on 28 Nov 2009 and 522 mg/dL on 20 Jan 2010. According to the investigator, the patient had been used to extremely high BG levels for some years, never wanted to receive injected insulin, and was fully aware of diabetes and its complications. Medical history was significant for coronary artery disease, myocardial infarction, hypertension, severe peripheral arterial occlusive disease, diabetic retinopathy, and diabetic neuropathy. Concomitant medications included aspirin QD, Plavix QD, atorvastatin QD, ramipril BID, amlodipine QD, Lyrica BID, and Torasemid QD. The investigator considered the death to be not related to TI and the probable cause of death was a heart attack. He confirmed no autopsy was performed, and the death certificate reported cause of death as a natural death.

**Reviewer's comment: The cause of death was concluded to be likely sudden cardiac death. Since death from cardiovascular disease is common among the diabetic population, a causal relationship to Afrezza cannot be concluded. Hypoglycemia as contributor to death was not ruled out completely but was believed by the investigator to be unlikely.**

### 7.3.2 Non-fatal Serious Adverse Events

In the original NDA, among T2DM subjects there was no pattern of a single type of SAE that occurred with significantly greater frequency among TI-treated subjects than among comparator-treated subjects. However, among T1DM subjects, there was a higher rate of diabetic ketoacidosis (DKA) seen in TI-treated subjects vs. comparator-treated subjects.

A listing of patients with serious adverse events (n=12) newly reported in the Safety Update is shown in Table 7.2. There is no apparent pattern of SAEs, as they cover a wide range of system organ classes/preferred terms. Most have alternative causality and come from uncontrolled trials. There was one case of DKA in a TI treated patient. However, this patient was not in a clinical trial, but rather in the Named Patient/Compassionate Use program in Europe for patients who previously used Exubera before it was withdrawn from the market. These patients often have histories of non-compliance with insulin regimens. Indeed, in this particular case (see narrative below Table 7.2) the patient refused proper treatment because of needle phobia.

<b>Table 7.2 – Listing of Patients with Serious Adverse Events (SAEs)^ since the original NDA cutoff</b>						
<b>Trial</b>	<b>Sex/Age</b>	<b>SAE PT</b>	<b>Duration of Event (Days)</b>	<b>Duration of Treatment (Days) before event</b>	<b>Severity Characteristic of SAE</b>	<b>Outcome</b>
<b>TI</b>						
117	52/F	Hypoglycemia requiring assistance	1	30	Life-threatening	recovered
119	60/M	Hypoglycemia	1	45	Important medical event	recovered
119	63/M	Bradycardia	3	Post-treatment	Hospitalization	recovered
119/158	66/M	Renal papillary necrosis	7	94	Important medical event	Withdrawn/recovered
139	52/M	Syncope	1	97	Hospitalization	recovered
139	63/F	Abdominal discomfort	6	87	Hospitalization	unknown
139	56/F	Atrial fibrillation	2	196	Hospitalization	recovered
159	61/M	Anal fistula	3	Post-treatment	Hospitalization	recovered
Named patient program*		Diabetic ketoacidosis, acute renal failure				
<b>comparator</b>						
117	47/F	Hypoglycemia requiring assistance	1 (two events)	117 and 128	Life-threatening	recovered
117	22/M	Hypoglycemia requiring assistance	1 (two events)	61 and 63	Life-threatening Hospitalization	Withdrawn/recovered
117	F/39	Delayed recovery from anaesthesia	1	Post-treatment	Hospitalization	recovered
^Includes subjects from controlled and uncontrolled studies						
*The Compassionate Use Program in Europe is not a clinical study, thus there was no collection of clinical data on CRF pages.						
Source: ISS						

### Narratives of SAEs among TI treated subjects

#### **Hypoglycemia requiring assistance**

Site Number/Subject ID Number: 028/0214

A 52-year-old Caucasian female in the U.S. received TI and Lantus for T1DM in trial 117. The subject was treated with TI 15 U to 60 U TID before meals and 15 U to 30 U at one other time during the day beginning 16 Jul 2009, and Lantus 14 IU sc QD at 9 AM since 2007. The duration of treatment from the start of therapy with TI until the onset of the event was 30 days. On 14 Aug 2009 while at home, the subject experienced hypoglycemia. Her morning blood glucose level at 09:47 was 299 mg/dL. She took TI 45 U and ate half a bagel. The subject was very busy that day with errands and cleaning. Her blood glucose level at 18:17 was 59 mg/dL. She ate 15 grams of carbohydrate and did not recheck her blood glucose. Her blood glucose at 20:13 was 163 mg/dL. She took TI 15 U before dinner, which consisted of chicken and cheese. Subject stated she does not remember what happened next. She lives in a duplex and her neighbors heard some noise and called 911. The subject slid to the floor and paramedics found her sitting awake on the floor. The investigator confirmed the subject did not lose consciousness. The paramedics gave the subject oral carbohydrates and orange juice and the event resolved. No glucagon or i.v. dextrose was given. The subject was under a lot of stress, with increased activity for the day, the duplex was warm, and she had consumed no carbohydrates with dinner. The subject took TI 4 minutes before eating dinner. The subject has a history of 4 severe hypoglycemic episodes since being diagnosed in 1959. The last severe hypoglycemia episode was August 2007.

TI dosage was reduced from 15 U to 60 U before meals to 15 U to 30 U before meals in response to the event. The subject was also instructed to ingest 2 to 3 carbohydrates with each meal (1 to 2 liquid and 1 food), eat at least every 6 hours, and check blood glucose regularly. No action was taken with Lantus in response to the event.

#### **Hypoglycemia**

Site Number/Subject ID Number: 017/0013

A 60-year-old Caucasian male in the U.S. with T2DM was treated with TI 15 U TID from 23 Jul 2009 to 10 Sep 2009 in Study 119 (an uncontrolled phase 2 pharmacodynamic study). The duration of treatment at the onset of the event was 45 days. The subject's antidiabetic regimen included glimepiride 4 mg po QD since 1997, metformin 2000 mg po QD since 2000, pioglitazone (Actos) 45 mg po QD since 2002, and sitagliptin 100 mg po QD since Feb 2009. On 05 Sep 2009, the subject experienced possible hypoglycemia although alcohol intoxication is possible alternate explanation for his symptoms. He was attending a wine tasting party and had not eaten a meal since 09:00. He inhaled 15 U TI at 22:00 after consuming wine and cheese but without eating a meal, and felt light-headed, dizzy, and confused. He did not check his blood glucose level at that time. The subject fell asleep at the party and awoke on 06 Sep 2009 at 03:00. He returned home and checked his blood glucose level via finger stick, obtaining a result greater than 100 mg/dL at 10:00 but not recording the result. At that time, the subject felt nauseous and vomited a pink clear liquid. After that, the subject felt better and ate a meal, inhaling 15 U TI before the meal. The subject felt fully recovered after eating the meal at 11:30 on 06 Sep 2009. The subject stopped taking TI Inhalation Powder on 10 Sep 2009 at Visit 17 of the trial per the protocol.

#### **Bradycardia**

Site Number/Subject ID Number: 017/0014

A 63-year-old Caucasian male in the U.S. with T2DM in Study 119 (an uncontrolled phase 2 pharmacodynamic study) received TI 30 U TID prandially from 23 Jul 2009 to 10 Sep 2009. The subject's antidiabetic regimen also included metformin 2 g po QD.

On [REDACTED]<sup>(b) (6)</sup>, the subject had an ECG as part of the study procedures during the last study visit and was found to have a heart rate of 44 bpm. He was referred to the ER for further evaluation. He was admitted the same day with a diagnosis of symptomatic bradycardia secondary to 2nd degree AV block. Symptoms reported were mild tingling of the fingers and toes, mild exercise intolerance, and mild fatigue. An ECG on the same day showed changes consistent with 2 to 1 AV block, right bundle branch block, and left anterior ventricular block. Troponin series were negative. He underwent an adenosine thallium stress test with normal results (LVEF 79%); he had no chest pain during the test and there was no significant myocardial perfusion defect. Oxygen saturation was 100% on 2 L nasal cannula. The subject underwent dual pacemaker placement on [REDACTED]<sup>(b) (6)</sup> and subsequently noticed substantial improvement in energy level and well-being and noted that his hands and feet felt warmer. He was discharged and the event was considered resolved as of [REDACTED]<sup>(b) (6)</sup>. Discharge diagnosis included sinus bradycardia secondary to 2 to 1 AV block and left anterior hemiblock. The subject's medical history was significant for right bundle branch block since screening, but his heart rate was always > 60 bpm. The subject had no referable symptoms except, in retrospect, fatigue.

### **Renal papillary necrosis**

Site Number/Subject ID Number: 017/0021

A 66-year-old Caucasian male in the U.S. in study 119 (an uncontrolled phase 2 pharmacodynamic study) received prandial TI for T2DM. The subject's first dose of TI was on 09 Feb 2010 at 15 U with meals, and was increased to 30 U at meals on 16 Mar 2010. The last dose of study drug in trial MKC-TI-119 was on 20 Apr 2010. The subject was initiated into the extension trial MKC-TI-158, receiving the first dose of TI in that protocol on 21 Apr 2010. The duration of treatment at the onset of the event was 94 days. TI was permanently discontinued as of 13 May 2010. The subject's antidiabetic regimen also included metformin 1 g po QD and subcutaneous insulin glargine 70 IU BID.

On [REDACTED]<sup>(b) (6)</sup>, the subject went to the emergency room (ER) with symptoms of kidney stones (right lower quadrant pain) and was diagnosed with right-sided renal papillary necrosis by the ER physician. The narrative does not mention analgesic use. Diagnostic laboratory results on [REDACTED]<sup>(b) (6)</sup> included glomerular filtration rate estimated at 43 ml/min/1.73m<sup>2</sup> (reference range: > 60 ml/min/1.73m<sup>2</sup>). Urinalysis showed a urine protein of 100 mg/dL (reference range: <20 mg/dL) and urine ketones of 40 mg/dL (reference: negative). Findings of a CT IVP urogram included significant right perinephric stranding with mild right hydronephrosis and hydroureter and delayed excretion of the right kidney. Laboratory results showed a blood urea nitrogen (BUN) of 31 mg/dL (reference range: 8 – 25 mg/dL) and serum creatinine of 1.6 mg/dL (reference range: 0.7 – 1.3 mg/dL). Treatment included hydrating with 2 L of normal saline, and the subject received 1 acetylcysteine (Mucomyst) dose and 3 doses to go home. The subject was discharged from the ER pain free and alert, with normal oxygen saturation on [REDACTED]<sup>(b) (6)</sup>. Serum creatinine had dropped to 0.8 mg/dL as of 12 May 2010. Follow-up with a urologist was planned. The subject was withdrawn from the study due to a renal dysfunction exclusion criterion on 13 May 2010.

The renal papillary necrosis was reported resolved on 13 May 2010.

### **Syncope**

Site Number/Subject ID Number: 626/0004

A 52-year-old Caucasian male in the U.S. with T1DM in trial 139 (an uncontrolled phase 3 device study) received prandial TI 45 U at breakfast, 60 U at lunch, and 75 U at dinner beginning [REDACTED] (b) (6). The duration of treatment at the onset of the event was 97 days. On [REDACTED] (b) (6), the subject experienced severe back pain, went to the emergency room, and was treated with Percocet (oxycodone hydrochloride, paracetamol) 5/325 for the pain. The subject experienced near syncope secondary to the pain medication and was hospitalized overnight for observation. The subject was discharged the next day. The event of syncope was considered mild in severity and resolved on [REDACTED] (b) (6). No relevant tests were performed and no action was taken with TI.

### **Abdominal discomfort**

Site Number/Subject ID Number: 631/0011

A 63-year-old Caucasian female in the U.S. in trial 139 (an uncontrolled phase 3 device study) started treatment with TI beginning on [REDACTED] (b) (6). Current daily dosage was prandial TI 15 U at breakfast and lunch, and 30 U at dinner for diabetes mellitus (unreported type). Treatment duration at the onset of the event was 87 days. The subject's antidiabetic medication also included glimepiride (Amaryl) 0.5 mg po, metformin 1000 mg po, and sitagliptin phosphate (Januvia) 100 mg po daily.

On [REDACTED] (b) (6), the subject experienced lower abdominal discomfort one day after receiving a transfusion for myelodysplasia and was hospitalized for unspecified treatment. An abdominal CT scan was negative, and the subject was referred to neurology for evaluation for neuropathic pain. No action was taken with TI; the subject continued TI treatment throughout hospitalization. The subject was subsequently discharged from the hospital on [REDACTED] (b) (6); the event had resolved. Final diagnosis and outcome were unknown at the time of this report.

### **Atrial fibrillation**

Site Number/Subject ID Number: 624/005

A 56-year-old Caucasian female in the U.S. with T1DM in trial 139 (an uncontrolled phase 3 device study) began treatment with prandial TI on [REDACTED] (b) (6) at 30 U TID and 15 to 30 U as needed for other meals or snacks. TI dosing was increased to 45 to 60 U at each meal, beginning 18 Jul 2009. Treatment with TI was interrupted on 20 Dec 2009 due to the onset of bronchitis, which resolved on 15 Jan 2010. In the interim, the subject received subcutaneous (sc) insulin aspart (Novolog) and sc insulin glargine (Lantus) on a sliding scale. Treatment with TI subsequently resumed on 16 Jan 2010 at 45 to 60 U TID at meals with dosage depending on glucose levels. The duration of treatment prior to the onset of the event was 196 days.

On [REDACTED] (b) (6) while at home, the subject experienced a sudden episode of "fluttering" and was sent to the emergency room by her internist. The diagnosis was atrial fibrillation of mild severity. Per hospital records, the subject presented with chest pain and palpitations with no peripheral edema; shortness of breath with no cough; dyspnea on exertion; no abdominal pain, nausea, vomiting, diarrhea nor rectal bleeding; no fever, chills, nor sweating; and no recent increase in alcohol or caffeine use. The subject also presented with elevated blood glucose (BG) of 400

mg/dL that had been present over the previous 5 days and was not lowered through self-titrated insulin.

Later that day pulse was elevated at 131. The subject was subsequently diagnosed with atrial fibrillation with rapid ventricular response and treated with Diltiazem 125 mg until conversion to normal sinus rhythm. Anticoagulants were not used because of the significant contraindication of spontaneous subconjunctival hemorrhage in left eye within 24 hours of presenting to the ER. The subject was admitted to telemetry for observation and was kept overnight for observation and released in the morning. No further episodes were reported. The subject had no cardiac history and had never experienced atrial fibrillation prior to (b) (6).

### **Anal fistula**

Site Number/Subject ID Number: 023/3012

A 61-year-old Asian male in the U.S. in trial 159 (an uncontrolled phase 2 device use study) received TI for T2DM. Prandial TI 10 U TID was administered from 09 Mar 2010 to 18 Apr 2010. The subject's antidiabetic regimen also included sitagliptin phosphate (Januvia) 100 mg po QD, pioglitazone hydrochloride (Actos) 45 mg po QD, and glimepiride 4 mg po QD.

On (b) (6), after completing the treatment period of the trial, the subject saw his proctologist for follow up on hemorrhoids. He was diagnosed with an anal fistula and admitted to the hospital for surgery. Diagnostic tests and results were unknown at the time of this report. The event resolved and the subject was discharged on (b) (6) after unspecified treatment.

### **Diabetic ketoacidosis/acute renal failure**

Site Number/Subject ID Number: Not applicable

A 31-year-old Caucasian female with T1DM in the United Kingdom was participating in a Compassionate Use Program of TI due to severe needle phobia. TI was administered daily at 15 U with breakfast, 45 U with lunch, and 60 U with dinner beginning on 22 Oct 2009. The duration of treatment at the onset of the event was 9 days. The patient's antidiabetic regimen included an unknown basal dose of insulin detemir (Levemir) by subcutaneous injection. On the evening of 31 Oct 2009, the patient drank alcohol. The patient missed the daytime TI and Levemir doses on 01 and 02 Nov 2009 because she felt unwell. She was subsequently hospitalized and refused blood testing and intravenous cannulation due to her needle phobia and remained in severe metabolic acidosis (pH 6.94, BE 28.7). Glasgow Coma was reported as 12. She recovered on (b) (6) and was extubated on (b) (6). The investigator reported the ketoacidosis and acute renal failure as severe and life-threatening and confirmed that the patient recovered from both events without sequelae. Per the patient, her new physician confirmed that she would be able to restart TI.

### Pooled Safety Analyses of SAEs

In the pooled Safety Update population for P2/3 trials in T1DM there was only one new serious adverse event in a TI treated patient (this was the 52 year old women in trial 117 with hypoglycemia requiring assistance listed above), and 3 patients with SAEs in the comparator group (Table 7.3). As expected, these few events change the overall SAE incidence comparisons very little, and hence have little to no impact on the overall safety assessment of TI.

**Table 7.3 - SAEs, Type 1 Diabetes, Pooled Phase 2/3 Trials (Safety Population)**

	2009 ISS		2010 Safety Update	
	TI (n=614) SYE=540 n (%)	Comparator (n=599) SYE=682 n (%)	TI (n=679) SYE=559 n (%)	Comparator (n=664) SYE=703 n (%)
Any SAE	78 (12.7)	74 (12.4)	79 (11.6)	77 (11.6)
SYE = Subject years exposure Source: Table 4 Summary of Clinical Safety				

As requested by the FDA, in the re-submission the Sponsor presented tabulations broken down by system organ class and preferred term of the new safety data combined with the original NDA data and included tables that compared frequencies of safety data in the original NDA with the re-tabulated frequencies. The Sponsor's tables can be found in Table D.G.1.9.6.1.1 (General Safety Tables and Figures document).

### 7.3.3 Dropouts and/or Discontinuations

In the original NDA, premature discontinuation from clinical trials was higher among TI-treated subjects for both T2DM and T1DM populations. The reason for the imbalance was primarily due to withdrawals for adverse events and subjects withdrawing consent. More than half of the dropouts for adverse events were respiratory-related. This reviewer concluded that the higher rate of withdrawals for non-pulmonary adverse events was likely due to the open-label nature of the trial designs because an examination of the incidence rate of adverse events overall showed no difference between TI and comparators suggesting that subjects treated with TI were dropping out at a higher rate for essentially the same adverse events. It is possible, though, that the severity of those adverse events could have been different between treatment groups and prompted a differential dropout rate.

In the original NDA, several discontinued subjects who were classified as "withdrew consent" were found to have withdrawn for reasons related to lack of efficacy. This also occurred in trial 117 with 3 subjects (see section 6 of this review).

In the Safety Update population for pooled Phase 2/3 T1DM trials (which adds only Study 117 to the previously available data), the cumulative disposition data is consistent with that previously reported in the ISS 2009 for subjects with type 1 diabetes (Table 7.4). Subject disposition data for trial 117 alone is shown in Table 6.2 in the Efficacy section of this review.

**Table 7.4 - Subject Disposition and Exposure, Pooled Phase 2/3 Trials, Type 1 Diabetes (Safety Population)**

	ISS 2009	Safety Update	Difference*
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	TI n (%)	Comparator n (%)	TI n (%)	Comparator n (%)	TI n (%)	Comparator n (%)
Randomized	624	615	689	680	65	65
Safety Population	614	599	679	664	65	65
Completed study treatment	373 (60.7)	475 (79.3)	425 (62.6)	535 (80.6)	52 (1.9)	60 (1.3)
Prematurely Discontinued	241 (39.3)	124 (20.7)	254 (37.4)	129 (19.4)	13 (-1.9)	5 (-1.3)
• Adverse Event	43 (7.0)	3 (0.5)	47 (6.9)	3 (0.5)	4 (-0.1)	0
• Protocol Violation	13 (2.1)	16 (2.7)	13 (1.9)	17 (2.6)	0 (-0.2)	1 (-0.1)
• Subject Withdrew Consent	129 (21.0)	58 (9.7)	133 (19.6)	59 (8.9)	4 (-1.4)	1 (-0.8)
• Subject Died	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.2)	0 (-0.1)	0
• Physician Decision	22 (3.6)	7 (1.2)	24 (3.5)	8 (1.2)	2 (-0.1)	1 (0)
• Lost to Follow-up	16 (2.6)	28 (4.7)	16 (2.4)	29 (4.4)	0 (-0.2)	1 (-0.3)
• Other	16 (2.6)	11 (1.8)	19 (2.8)	12 (1.8)	3 (0.2)	1 (0)
• Unknown	1 (0.2)	0	1 (0.1)	0	0 (-0.1)	0
Source: Table 5 Safety Update						
*The difference reflects events occurring in Study 117, which is the only new controlled trial in T1DM.						

### 7.3.3.1 Discontinuations due to SAEs:

There were two discontinuations due to SAEs in the Safety Update. These are the 22 year-old man with severe hypoglycemia in the comparator group in trial 117 and the 66 year-old man with renal papillary necrosis in the uncontrolled trial 119 (with extension trial 158) described in section 7.3.2. Therefore, there is no meaningful change in the incidence of discontinuations due to SAEs with respect to the 2009 ISS and 2010 Safety Update.

### 7.3.3.2 Discontinuations due to any AEs:

Ten subjects discontinued due to AEs in the uncontrolled studies. One subject discontinued due to hypoglycemia. Two subjects discontinued due to mild bronchoconstriction, one of whom had pre-existing moderate obstructive lung disease; 2 subjects discontinued due to dyspnea; 2 subjects discontinued due to upper respiratory tract infections (URI and pharyngitis); 2 subjects discontinued due to cough; and 1 subject discontinued due to chest tightness. None of these events were serious or required medical intervention.

For the pooled data the cumulative incidence of discontinuations due to adverse events was 47/679 subjects (6.9%) for TI and 4/664 (0.6%) for comparator. There was no meaningful change in the incidence of discontinuations with respect to the 2009 ISS and 2010 Safety Update.

Only 4 subjects had adverse events leading to discontinuation in the new trial (trial 117). The adverse events leading to discontinuation were cough (3 subjects) and 1 subject with dyspnea. These events are likely due to TI, but are consistent with adverse events leading to discontinuation seen in the original NDA submission, and therefore, do not change the overall safety profile of TI. Complete tables of discontinuations due to adverse events by system organ class and preferred term for subjects with type 1 diabetes in the pooled Phase 2/3 trials are presented in Table D.G.1.9.4.1.1 of the Sponsor's Safety Update.

### 7.3.4 Significant Adverse Events

Significant adverse events are those that are discussed in section 7.3.5.

### 7.3.5 Submission Specific Primary Safety Concerns

#### 7.3.5.1 Hypoglycemia

Since rates of hypoglycemia are tightly linked to degree of glycemic control, comparative hypoglycemia incidence rates between TI and comparator are best examined within the individual trial 117, where study groups achieved similar HbA1c levels at the study endpoint, rather than among the entire safety population which included some trials in which TI subjects achieved lesser glycemic control than comparators.

In the original clinical development program the Sponsor used slightly different definitions for hypoglycemia among the trials making an integrated analysis somewhat challenging. In trial 117 the definition of hypoglycemia was as follows:

#### Mild or Moderate Hypoglycemia:

- Hypoglycemia-like symptoms (e.g., lightheadedness, sweats, palpitations, tremulousness, headache), and a BG measurement of  $\leq 63$  mg/dL; OR
- In the absence of a BG measurement, hypoglycemia-like symptoms that are relieved with carbohydrate intake or self-administered glucagon injections; OR
- Any BG measurements of  $\leq 49$  mg/dL and  $> 36$  mg/dL with or without symptoms

#### Severe Hypoglycemia: the following occurred simultaneously:

- Subject requires the assistance of another person; AND
- Subject exhibits at least 1 cognitive neurological symptom (memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, seizure, loss of consciousness); AND

- Measured BG is  $\leq 49$  mg/dL or in the absence of a BG glucose measurement, clinical symptoms are reversed by oral carbohydrates, sc glucagon, or intravenous glucose administration; OR
- Measured BG is  $\leq 36$  mg/dL

In trial 117, subjects were provided an e-diary for the collection of hypoglycemia, facilitating the collection of data by the subject. This provided more detailed information on hypoglycemia and may have increased the amount of events recorded in both treatment groups.

Incidence rates and event rates for hypoglycemia in trial 117 are shown in Table 7.5. The incidence rates of hypoglycemia numerically favors TI in listed categories, although none of these differences were statistically significant based on nominal p-values of 0.05, and the event rates adjusted for patient-exposure favor TI in most categories.

<b>Table 7.5 – Incidence of Hypoglycemia Events – Trial 117</b>		
	TI N=65	Humalog N=65
<b>Total hypoglycemia events</b>		
Number (%) of subjects with events	63 (96.92)	63 (96.92)
Odds ratio	1.000	
p value	1.000	
Number of events	1381	2113
Event rate (per 100 subject months)	6.17	8.19
<b>Mild/moderate hypoglycemia events</b>		
Number (%) of subjects with events	63 (96.92)	63 (96.92)
Odds ratio	1.000	
p value	1.000	
Number of events	1338	2067
Event rate (per 100 subject months)	5.97	8.01
<b>Severe hypoglycemia events</b>		
Number (%) of subjects with events	15 (23.08)	23 (35.38)
Odds ratio	0.548	
p value	0.1251	
Number of events	43	46
Event rate (per 100 subject months)	0.19	0.18
<b>Events requiring assistance</b>		
Number (%) of subjects with events	3 (4.62)	5 (7.69)
Odds ratio	0.581	
p value	0.4700	
Number of events	4	11
Event rate (per 100 subject months)	0.02	0.04
	TI N=9	Humalog N=14
<b>Events for subjects with HbA1c <math>\leq 7\%</math> at week 16</b>		
Number (%) of subjects with events	9 (100)	14 (100)
Odds ratio	NA	NA
p value	NA	NA

Number of events	223	514
Event rate (per 100 subject months)	6.52	9.11
p values are based on logistic regression with terms for treatment, country, and baseline HbA1c Source: Tables 21-26, trial 117 report		

### 7.3.5.2 Immunogenicity

There is no new information related to immunogenicity in the re-submission.

### 7.3.5.3 Device Safety issues:

There were several device-related deficiencies outlined in the complete response letter. However, as the Sponsor intends to change the device to the Gen2, these deficiencies may no longer be applicable. Please see Dr. Melanie Choe's CDRH review for details.

The Sponsor completed a 45 day uncontrolled device handling study – study 159 “A Phase 2, Multicenter, Open-label, Single-arm Clinical Trial in Subjects with Type 1 or Type 2 Diabetes to Provide In-use Handling Data for the Gen 2 Inhaler. The study period was 03 Feb 2010 (first subject screened) to 29 Apr 2010 (last subject completed). Seventy-three subjects were enrolled; 28 subjects had type 1 diabetes and 45 had type 2 diabetes. Fifty-nine subjects completed the trial.

The primary objective was to collect Gen 2 inhalers after their 15-day intended lifespan for evaluation of in-use characteristics and technical performance in the clinical setting. Please see Dr. Choe's review for details.

A secondary objective was to evaluate inhaler safety. Safety results were consistent with the findings of the controlled phase 2/3 data. No deaths were reported. One subject had an SAE of anal fistula that was discussed in section 7.3.2. The most common AEs were hypoglycemia and cough, reported by 38.4% and 28.8% of subjects, respectively. Both hypoglycemia and cough were more common in subjects with type 1 diabetes than in subjects with type 2 diabetes. Eight subjects (11%) discontinued because of AEs. All AEs leading to discontinuation were respiratory in nature, except for 1 AE of chest discomfort. The AEs leading to discontinuation were bronchospasm in 1 subject, cough with dyspnea in 1 subject, cough and hyperglycemia in 1 subject, dyspnea in 1 subject, upper respiratory tract infection in 1 subject, pharyngitis in 1 subject, and chest discomfort in 1 subject.

## **7.4 Supportive Safety Results**

### 7.4.1 Common Adverse Events

#### 7.4.1.1 Eliciting adverse events data in the development program

See the original NDA clinical review.

#### 7.4.1.2 Incidence of common adverse events

The incidence of overall treatment emergent adverse events in the pooled type 1 diabetes Safety Update population was essentially unchanged from the original NDA integrated review of safety (Table 7.6). The comparative incidence rates of common adverse events were also similar between the original NDA and the Safety Update.

Because the only data in the pooled Safety Update population are from trial 117, and that sample size is considerably smaller than the original NDA pooled sample size, the incidence rates of common adverse events are also shown for Study 117 alone (Table 7.7).

	2009 ISS		2010 Safety Update	
	TI (n=614) SYE=540 n (%)	Comparator (n=599) SYE=682 n (%)	TI (n=679) SYE=559 n (%)	Comparator (n=664) SYE=703 n (%)
Any TEAE	544 (88.6)	539 (90.0)	596 (87.8)	584 (88.0)
Any TEAE Excluding Cough	527 (85.8)	539 (90.0)	573 (84.4)	584 (88.0)
Hypoglycemia	466 (75.9)	485 (81.0)	487 (71.7)	508 (76.5)
Cough	179 (29.2)	36 (6.0)	208 (30.6)	36 (5.4)
Upper respiratory tract infection	85 (13.8)	89 (14.9)	90 (13.3)	95 (14.3)
Nasopharyngitis	61 (9.9)	70 (11.7)	64 (9.4)	74 (11.1)
Influenza	34 (5.5)	37 (6.2)	37 (5.4)	48 (7.2)
Headache	33 (5.4)	19 (3.2)	36 (5.3)	19 (2.9)

SYE = Subject years exposure  
 Source: Table 6 Summary of Clinical Safety

	TI (n=65) n (%)	Comparator (n=65) n (%)
Any TEAE	52 (80.0)	45 (69.2)
Any TEAE Excluding Cough	46 (70.8)	45 (69.2)
Cough	29 (44.6)	0 (0)
Hypoglycemia	21 (32.3)	23 (35.4)
Upper respiratory tract infection	5 (7.7)	6 (9.2)
Sinusitis	5 (7.7)	2 (3.1)
Chest discomfort	4 (6.2)	0 (0)
Pharyngolaryngeal pain	4 (6.2)	2 (3.1)
Nasopharyngitis	3 (4.6)	11 (16.9)
Influenza	3 (4.6)	4 (6.2)

Source: Table 18, trial 117 report

#### 7.4.2 Laboratory Findings

In the original NDA, review of laboratory results revealed no statistically significant or clinically important differences between TI and comparators. In the Safety Update, the Sponsor stated that

no clinically relevant mean laboratory value changes were observed. In trial 117, clinically significant laboratory abnormalities were reported as TEAEs. Individual laboratory abnormalities reported as TEAEs were blood creatine phosphokinase increased (Subject 484-0211), urine leukocyte esterase positive and white blood cells urine (Subject 608-0115), and C-reactive protein increased (Subject 609-0015). Narratives were not provided. These few events do not change the overall safety profile of TI with regard to laboratory findings.

#### 7.4.3 Vital Signs

In the original NDA, review of vital signs revealed no statistically significant or clinically important differences between TI and comparators. In the Safety Update the Sponsor stated that no clinically relevant individual vital sign measurements were observed. No vital sign measurements were reported as adverse events in the Safety Update. Analyses of changes in FEV1 are deferred to the pulmonary reviewers.

#### 7.4.4 Electrocardiograms (ECGs)

The Sponsor reported no significant ECG measurements in trial 117.

#### 7.4.5 Special Safety Studies/Clinical Trials

There were no additional special safety studies included in this submission.

##### 7.4.5.1 Thorough QT Study

See original NDA clinical review.

#### 7.4.6 Immunogenicity

See original NDA clinical review.

## 7.5 Other Safety Explorations

As the Safety Update showed that the non-pulmonary safety profile was substantially unchanged from the original NDA safety review; other safety explorations were not performed.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Because of the post-marketing cases of lung cancer associated with Exubera which led to the Exubera product labeling changes, malignant (based on pathology findings) neoplasms were examined as an AE of interest for TI. There were no additional cases of lung malignancy reported in the Safety Update.

### 7.6.2 Human Reproduction and Pregnancy Data

One subject (number 484-0230) in the TI group in Trial 117 discontinued due to pregnancy.

A 30-year-old Caucasian female with type 1 diabetes mellitus (Subject 484/0230) in Brazil was randomized to the TI Inhalation Powder arm of MKC-TI-117. Treatment on study included daily prandial TI Inhalation Powder 45 U at breakfast, 75 U at lunch, 60 U at dinner, and 45 U at snacks beginning 21 Jul 2009, and sc Lantus (insulin glargine) 32 IU at bedtime since 30 Jun 2009.

On 14 Oct 2009 while the subject was in the clinic for study Visit 12, a urine pregnancy test was performed per protocol and the pregnancy test was positive. A serum beta-HCG test taken the same day was also positive with a result of 1.219 MIU/mL. The subject had been taking birth control medication Gynera (ethinylestradiol, gestodene) since 1999. The subject's last menstrual period was 01 Aug 2009.

TI and Lantus were discontinued; the last dose for both medications was taken on 13 Oct 2009. The subject was withdrawn from the study on 22 Oct 2009. Duration of exposure to TI Inhalation Powder was reported as 4 weeks. A pelvic ultrasound on 22 Oct 2009 showed a viable fetus with a gestational age of 5 weeks. A pelvic ultrasound on 18 Nov 2009 showed a viable fetus with a gestational age of 8 weeks. No abnormalities were seen on either date. Echographic examination and transvaginal ultrasound were normal on 10 Dec 2009. Obstetric ultrasound on 15 Dec 2009 showed a fetus with good vitality and a gestational age of 13 weeks and 3 days. The subject continued on regular pre-natal care and had a normal echography on 25 Feb 2010, showing good fetal growth in the 50th percentile at gestational age of 23 weeks and 6 days and

no observed malformations. On [REDACTED] (b) (6), the subject was hospitalized due to poor glycemic control, and she was discharged on [REDACTED] (b) (6). Antidiabetic treatment since discontinuing TI included sc Humalog (insulin lispro) 24 IU QD and sc Lantus 32 IU QD beginning 14 Oct 2009. Lantus was stopped on 25 Oct 2009. Since 26 Oct 2009, antidiabetic treatment included sc Humalog 25-28 IU QD and sc NPH insulin 26-31 IU QD. Beginning on 18 Mar 2010, the NPH insulin dose was 54 IU QD, which was decreased to 42 IU QD on 10 May 2010.

On 23 Mar 2010, a fetal echocardiogram was normal. On 14 Apr 2010, obstetric ultrasound showed a normal fetus, weighing 1754 grams, in the 75th percentile. As of 12 May 2010, the subject was on regular prenatal care with no complications. The expected delivery date was [REDACTED] (b) (6).

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Human pediatric studies were not performed prior to submission of the original NDA. As of the resubmission, 74 pediatric subjects (ages 4 to 17) participated in a device handling study without exposure to TI. The sponsor claims that these data indicate that pediatric subjects as young as 4 years of age can operate, assemble, and appropriately inhale from Gen2C inhalers. The Sponsor asserts [REDACTED] (b) (4)

[REDACTED] These data should be reviewed by the Agency's DPAP review team.

The Sponsor has requested a partial waiver of pediatric assessment for age birth to less than 4 years of age for reasons that the product would be ineffective or unsafe in this age group. The Sponsor requested a deferral of pediatric assessment for ages 4 to up to 17 years because additional safety data from adults are needed. This is reasonable and is in line with the Pediatric Review Committee recommendations during the last review cycle.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See original NDA clinical review. There is no new information on overdose, drug abuse potential, withdrawal and rebound.

## 7.7 Additional Submissions

## **8 Postmarket Experience**

Not applicable as this product is not marketed in any country.

## 9 Appendices

### 9.1 Literature Review/References

Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31: 1-11.

Welchol Prescribing Information, revised January, 2008

Cycloset Prescribing Information, revised April, 2009

Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet*. 2005; 365: 1333-46.

### 9.2 Labeling Recommendations

There were several labeling deficiencies outlined in the March 2010 complete response letter. However, these pertained to the MedTone device, and since the resubmission pertains to the Gen2 device, the deficiencies may not be applicable.

Labeling for the Gen2 device could be complicated by the fact that the pivotal trials were done with the MedTone inhaler, and the dosage forms with the MedTone inhaler (15U and 30U) are different from the dosage forms with the new device (10U and 20U). However, if the pharmacokinetic comparability for the two devices has been conclusively demonstrated (both for area under the curve and Cmax) the Gen2 device can likely be safely labeled simply by replacing “15U” with “10U” and “30U” with “20U” in the Gen2 label. [REDACTED] (b) (4) [REDACTED]. This is an unusual approach and would need to clearly include language that the trials were conducted with the old device and that pharmacokinetically equivalent doses with the new device are shown.

### 9.3 Advisory Committee Meeting

There was no advisory committee meeting for this NDA.

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/s/  
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LISA B YANOFF  
12/10/2010

HYLTON V JOFFE  
12/10/2010  
Please see CDTL memorandum.

## Cross-Discipline Team Leader Review

<b>Date</b>	March 11, 2010
<b>From</b>	Hylton V. Joffe, M.D., M.M.Sc.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	22-472
<b>Applicant</b>	MannKind Corporation
<b>Date of Submission</b>	March 31, 2009
<b>PDUFA Goal Date</b>	January 16, 2010
<b>Proprietary Name / Established (USAN) names</b>	Afrezza (insulin, human [rDNA] inhalation powder)
<b>Dosage forms / Strength</b>	Single-use cartridges containing 15 units or 30 units of human recombinant insulin
<b>Proposed Indication(s)</b>	To improve glycemic control in adults with diabetes mellitus
<b>Recommended:</b>	<i>Complete Response</i>

## Cross Discipline Team Leader Review

### 1. Introduction

MannKind Corporation has submitted a new drug application (NDA) for Afrezza, an inhaled insulin developed for improving glycemic control in patients with type 1 and type 2 diabetes. If approved, Afrezza will be the second-in-class inhaled insulin product. This memorandum discusses the Afrezza NDA with a focus on key findings from the various review disciplines and the phase 2/3 development program.

### 2. Background

Exubera, the first (and only) inhaled insulin to be approved, was voluntarily withdrawn from the market by the sponsor. The sponsor claimed that withdrawal was prompted by business decisions (poor sales) and not because of an efficacy or safety concern. Because Exubera directly deposits insulin in the lung and insulin is a growth factor, there is a theoretical concern for development of lung cancer with long-term treatment. As a postmarketing commitment, the sponsor agreed to conduct a 12-year epidemiologic lung cancer cohort study. Exubera was discontinued before this study could be conducted and completed. Approximately 1 month after Pfizer announced the decision to stop manufacturing Exubera, the Division requested updated information regarding cases of lung cancer in the Exubera clinical trials and from postmarketing reports. This request was not prompted by Pfizer's decision to stop marketing Exubera. Upon review of the submitted data, FDA noted 6 reported cases of primary lung malignancies among Exubera-treated patients and 1 case among comparator-treated patients. One postmarketing report in an Exubera-treated patient was also received. In controlled trials, the incidence rate for these malignancies (per 100 patient-years) was 0.13 for Exubera and 0.02 for comparator. All patients who developed lung cancer had a prior history of smoking. FDA concluded that there were too few cases to determine causality but requested that this information be added to the Warning section of the package insert and that the sponsor issue a Dear Healthcare Provider Letter. Because Afrezza also directly administers insulin into the lung, this safety concern with Exubera carries over to Afrezza. Other relevant safety concerns with Exubera include:

- Smokers had a 2-5-fold higher systemic insulin exposure compared to non-smokers
- Exubera-treated patients had a greater mean reduction in forced expiratory volume in 1 second (FEV<sub>1</sub>) and in diffusing capacity of the lung for carbon monoxide (DL<sub>CO</sub>) compared to control. This reduction occurred within the first few weeks of use but the mean treatment difference (~40 mL favoring comparator) persisted over 2 years of study. Based on these findings, the Exubera package insert recommended that patients undergo pulmonary function testing prior to initiating Exubera, after 6 months of treatment, then annually thereafter. Exubera was not recommended if the baseline FEV<sub>1</sub> or DL<sub>CO</sub> was <70% predicted. Discontinuation of Exubera was recommended if there was a confirmed decline in FEV<sub>1</sub> ≥20%.

- Insulin antibodies were increased in Exubera-treated patients compared to those only receiving subcutaneous insulin but no clinical consequences were identified.
- Efficacy and safety were not established in patients with underlying lung disease. Therefore, Exubera was not recommended for use in this patient population.
- Bronchospasm was reported as a serious adverse event in 1 (0.1%) Exubera-treated patient.

The Exubera program consisted of 7 phase 3 trials (two in type 1 diabetes and five in type 2 diabetes). The phase 3 trials were powered to rule out a non-inferiority margin of 0.5% for the treatment difference in HbA1c. Use of this less stringent margin did not ultimately affect approvability because in these trials Exubera was able to meet the 0.4% non-inferiority margin that is used by FDA for insulin trials.

Exubera was discussed at an advisory committee meeting where most (7 vs. 2) panel members agreed that it should be approved for the treatment of type 1 and type 2 diabetes. One of the panel members who voted against approval raised concerns about how patients and healthcare providers will be adequately trained on the correct use of the device. The other panel member who voted against approval raised the need for more data to support pulmonary safety.

### 3. CMC/Device

**Chemistry/Manufacturing/Controls (CMC):** The CMC reviewers recommend approval of the NDA pending satisfactory facility inspections by the Office of Compliance. All other CMC issues identified during the review have been adequately resolved. The Drug Master File for the insulin drug substance is acceptable. Please see reviews by Drs. Theodore Carver, Alan Schroeder, and Prasad Peri for further details.

Afrezza consists of a breath-powered inhaler device and plastic cartridges containing a powdered formulation of human insulin. Each cartridge contains 5 mg or 10 mg of inhalation powder. The 5 mg dosage strength contains 15 units (b) (4) of insulin and the 10 mg dosage strength contains 30 units (b) (4) of insulin. Based on *in vitro* testing, the emitted dose target is (b) (4) units for the 15 unit cartridge and (b) (4) units for the 30 unit cartridge. The powder is inhaled through a plastic mouthpiece. (b) (4)

The drug substance consists of (b) (4) human recombinant insulin isolated from *Escherichia coli*. The drug product is a white powder filled in (b) (4) plastic cartridges sealed in (b) (4) foil (b) (4) packs that are intended to be opened immediately before use. The

drug product consists of crystalline particles of fumaryl diketopiperazine (FDKP) coated with insulin drug substance. There are also trace amounts of polysorbate 80 (b) (4)

FDKP is a novel excipient that forms the particle matrix. It crystallizes under acidic conditions and the crystals self-assemble to form particles with a median particle diameter of approximately 2-2.5 µm. These particles dissolve under physiological conditions at neutral pH. The manufacturer of the excipient used during the Afrezza development program (b) (4) differs from the manufacturer that will produce the marketed lots of excipient (b) (4). However, the CMC reviewers note no significant differences between the excipient produced by these two manufacturers and state that there are appropriate bridging stability studies.

Throughout this review, the term “Technosphere particles” (TP) refers to the self-assembled particles of crystallized FDKP. These particles do not contain insulin. The term “Technosphere Insulin” (TI) refers to the (b) (4) Technosphere particles coated with insulin.

According to the CMC reviewers, impurities (b) (4) are controlled to acceptable levels.



The model of the Afrezza inhaler used in the phase 3 clinical trials (Model C) differs from the proposed to-be-marketed inhaler (Model D). The sponsor states that the changes were made to address problems encountered with the Model C inhalers (e.g., (b) (4) and that these changes did not alter the air flow path or functionality of the device. The CMC reviewers confirmed that Model C and Model D showed similar emitted doses and particle size distributions based on *in vitro* testing. These Models were also compared in a pivotal bioequivalence study that is discussed in the clinical pharmacology section of this memorandum.

The CMC reviewers have granted a (b) (4)-month shelf-life for the drug substance. They have also granted a (b) (4) month shelf-life for storage of the drug product at 2-8 degrees Celsius with an additional (b) (4) of storage at room temperature. The shelf-life for the device is (b) (4), including (b) (4) of use-life, when stored at (b) (4) degrees Celsius. The device should be brought to room temperature prior to use.

CMC has determined that the application qualifies for a categorical exclusion from an environmental assessment report based on expected levels of environmental exposure.

The sponsor has agreed to fulfill several CMC postmarketing commitments that are fully described in Dr. Carver's and Dr. Schroeder's reviews. When Afrezza can be approved, these post-approval agreements should be included in the action letter.

**Device:** The Center for Devices and Radiological Health (CDRH) reviewed the Afrezza inhaler. Please see Dr. Melanie Choe's review for details. Dr. Choe had several recommendations, including limiting labeling claims to tested storage conditions as well as tightening acceptance criteria/specifications for the design verification tests to better reflect the test results.

(b) (4)

(b) (4)  
Based

on all these considerations, a human factors study should be required for Afrezza.

#### 4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology reviewers recommend approval of the NDA pending agreement on labeling. Please see reviews by Drs. Miyun Tsai-Turton and Karen Davis-Bruno for details.

TI and Technosphere particles alone were evaluated in non-clinical studies. Doses of TI were limited because of hypoglycemia. Higher doses of Technosphere particles alone were used to maximize FDKP exposure, which is the focus of the non-clinical pharmacology/toxicology review given that the pharmacology and toxicology of insulin itself has been well-established.

The mechanism by which insulin is absorbed systemically from Technospheres has not been established. Per Dr. Davis-Bruno, *in vitro* studies show no evidence of disruption in cellular tight junctions or increased permeability of cell membranes. FDKP alone has no effect on blood glucose.

Safety margins discussed in this section of the memorandum are based on total systemic exposure (AUC or area under the time-concentration curve) in animals relative to AUC based on the maximum recommended human dose. For these calculations, the maximum recommended human dose of TI is defined as 315 units per day (or 105 mg of TI powder). This total daily dose corresponds to a maximum recommended dose of 90 units of TI with each of three meals and 45 units with a single snack.

The sponsor tested TI and Technosphere particles in a 2-year carcinogenicity study in rats and in an acceptable 26-week carcinogenicity study in transgenic mice expressing human c-Ha-ras oncogenes. Study drug was administered nasally in the rat study and subcutaneously in the mouse study. Neither study showed evidence of drug-induced neoplastic findings. FDKP systemic exposures were 13-times the maximum recommended daily human exposure in the rat study and at maximum recommended clinical exposures in the mouse study. There were no concerning findings based on cell proliferation activity, which was assessed in alveolar and bronchiolar cells in the rat study. All genotoxicity studies with Technosphere were negative.

Based on review of the rat and dog chronic toxicology studies, the non-clinical reviewers have concluded that there is potential for pulmonary irritation with Afrezza at maximum clinical exposures. This observation is based on minimal to mild lung irritation observed in these animals at 2-fold higher exposures relative to the maximum recommended human dose. The respiratory irritation appeared to recover with discontinuation of Technosphere inhalation and the finding had no functional significance on respiratory function. There was no evidence of

chronic inflammation in the lung in rats and dogs. Other findings from these chronic toxicology studies are discussed in more detail below.

TI and Technosphere particles alone were administered nasally in the 6-month rat toxicology study and oronasally in the 9-month dog toxicology study. In the 6-month rat study, there was an increase in cell proliferation activity in bronchiolar cells but not in alveolar cells. Dr. Davis-Bruno considers this finding to represent an adaptive response because these cells did not show neoplastic findings and the cell proliferation activity analysis was negative after lifetime exposure in the 2-year rat carcinogenicity study.

In the 6-month rat study, some males treated with Technosphere particles alone developed myocardial regeneration/necrosis at 1.5-2-times maximum recommended daily clinical exposures. This finding was not observed in the TI-treated groups (although these groups received lower doses of test drug than the Technosphere particle alone-treated group), in female rats, or in the dog. In addition, the 2-year rat carcinogenicity study did not show any increase in treatment-related cardiac findings above concurrent controls.

In the 9-month dog toxicology study, the TI and Technosphere particles alone groups developed thymic atrophy, hypocellularity of the seminiferous epithelium, and germ layer degeneration. Dr. Davis-Bruno notes these findings are commonly associated with initiation of dosing in young dogs and that these male reproductive effects were not observed in the reproductive toxicity test battery.

Technosphere particles were administered subcutaneously in rat and rabbit reproductive toxicology studies. These particles had no adverse effects on fertility in male rats at exposures 180-fold above the maximum recommended daily dose. In female rats, there was increased pre- and post-implantation loss at 180-times maximum recommended human exposure but not at 50-times maximum recommended human exposure. FDKP was detected in rat fetal circulation at concentrations comparable to maternal plasma concentrations and was present in rat milk at ~10% of the maternal systemic exposure. In rabbits, all tested doses of Technosphere particles resulted in decreased body weight. Mortality occurred in pregnant rabbits dosed with 100 mg/kg/day (2 mg/kg/day represents a 10-fold safety margin). Up to 3 fetuses had malformations at 10-times maximum recommended human exposure, including cleft palate, non-patent nares, absent intermediate lung lobe and gallbladder and skeletal malformations. Dr. Davis-Bruno notes that there is clear evidence of co-existing maternal toxicity that may explain the fetal malformations. In addition, rabbits have 10-fold greater systemic exposures to Technosphere particles than the rat at the same mg/kg dose, which may account for the increased toxicity.

Pregnant rats given subcutaneous Technosphere particles from organogenesis through weaning had pups with decreased epididymis and testes weights (without histopathological correlates) and impaired learning. Dr. Davis-Bruno notes that these findings occur at 50-times the maximum recommended human exposure.

Per Dr. Davis-Bruno, subcutaneous or nasal administration of TI or Technosphere particles had no adverse effects on lymphoid tissue, lymphocyte subpopulations or T-cell dependent

antibody responses in a 28-day rat study with a 28-day recovery period. Anti-drug antibody responses were not evaluated.

Dr. Davis-Bruno reviewed data pertaining to FDKP manufacturing process impurities, extractables, leachables and foreign particles. She notes that the seven FDKP process impurities have been identified and qualified and that leachables are present at concentrations significantly below qualification thresholds. She also notes that the material used to construct the mouthpiece and chamber are used in an approved metered-dose inhaler and have been considered safe in that setting, which likely has a higher risk of extractables than does Afrezza

(b) (4)  
(b) (4)  
) The sponsor tested for water extractables

Dr. Davis-Bruno notes that it is not possible to compare these findings under extreme conditions to the findings during normal use of the Afrezza inhaler with momentary contact during inhalation and no drug stored in the inhaler device. In addition, Dr. Davis-Bruno notes that the same material was approved for a different product that has continuous contact with a metered-dose inhaler propellant, which carries a higher risk for potential exposure to extractables. She concludes that the risk of exposure to (b) (4) under typical use is small.

## 5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewers have concluded that the NDA is not acceptable for approval because the Division of Scientific Investigations (DSI) identified important deficiencies affecting reliability of the data generated from the pivotal bioequivalence study. This trial compared the Model C inhaler (used in the phase 3 clinical trials) with the Model D inhaler (the to-be-marketed product). The clinical pharmacology reviewers are recommending that the sponsor either conduct a new pivotal bioequivalence study or attempt to salvage the data from the completed study. Please see Dr. Sang Chung's reviews for details.

Dr. Chung has noted important design differences between Afrezza's various pharmacokinetic/pharmacodynamic studies. For example, these studies used different endpoints (ranging from  $AUC_{0-235min}$  to  $AUC_{0-540min}$ ), different adjustments for baseline insulin concentrations, different inhalers, different clamp procedures, and different types of subjects. Dr. Chung states that these important differences substantially limit cross-study comparisons.

In healthy subjects using a prototype inhaler, the absolute bioavailability of TI was approximately 15% compared to 5 units of intravenous regular insulin and the relative bioavailability was approximately 30% compared to 10 units of subcutaneous regular insulin.

In healthy subjects, insulin exposures increased proportionally with TI doses ranging from 25 to 100 units.

Dr. Chung shows that both TI and subcutaneous insulin have high between-subject variability based on insulin  $AUC_{0-240min}$  (coefficient of variation 32-64% with TI vs. 17-62% with subcutaneous regular or rapid-acting insulin).

In patients with type 1 diabetes, the median time to reach maximum serum insulin concentrations (Tmax) was 10 minutes with TI compared to 60 minutes with a rapid-acting insulin analog. The median time to reach maximum glucose infusion rate (GIR) was 35 minutes with TI (30 units administered via Model C inhaler) compared to 110 minutes with 10 units of subcutaneous rapid-acting insulin. In this study, the GIR with TI was approximately 20% of the GIR with the subcutaneous insulin.

Ten units of technetium-labeled TI was administered to healthy subjects using the Model C inhaler. On average, (b) (4) of the labeled dose was delivered to the body, (b) (4) of the dose was distributed to the lung, (b) (4) was found in the oropharynx and (b) (4) was found in the stomach.

With intravenous administration, FDKP is mostly eliminated renally. FDKP is not protein-bound in plasma and is not metabolized.

The sponsor evaluated the effect of an upper respiratory tract infection, chronic obstructive pulmonary disease, asthma, and smoking on FDKP and insulin pharmacokinetics (Table 1). The sponsor also evaluated the effect of mild and moderate (but not severe) renal impairment and hepatic impairment on FDKP pharmacokinetics. Dr. Chung notes no need for adjustment of Afrezza in patients with renal or hepatic impairment based on FDKP exposures. However, as with all insulins, patients with renal or hepatic impairment may need lower doses of Afrezza for glycemic control. Dr. Chung notes that insulin exposures were slightly lower in patients with asthma or chronic obstructive pulmonary disease, but did not raise particular concerns based on this finding because Afrezza is titrated to effect. This finding is somewhat moot at the present time because of a safety concern for acute bronchospasm in this patient population that will preclude use in these patients until further data are available (see the Safety section of this memorandum for further details).

<b>Table 1. Summary of FDKP and insulin exposures in various disease states and with smoking (ratios are exposures with disease or smoking compared to exposures with control) (adapted from Dr. Chung’s review)</b>		
	<b>FDKP AUC Ratio<sup>1</sup> (ng*min/mL)</b>	<b>Insulin AUC Ratio<sup>1</sup> (mU*min/L)</b>
Chronic obstructive pulmonary disease	1.13	0.91
Asthma	0.43	0.71
Smoking	0.71	1.25
Upper respiratory tract infection	~1.0	- <sup>2</sup>
Renal impairment		
Mild vs. normal	1.18	- <sup>2</sup>
Moderate vs. normal	1.25	- <sup>2</sup>
Hepatic impairment		
Mild vs. normal	1.16	- <sup>2</sup>
Moderate vs. normal	1.22	- <sup>2</sup>

<sup>1</sup>AUC<sub>0-240 min</sub> and geometric mean ratios for chronic obstructive pulmonary disease study; AUC<sub>0-480 min</sub> and arithmetic mean ratios for all other studies  
<sup>2</sup>Not studied

According to Dr. Chung, in a study in healthy volunteers, inhalation of albuterol and fluticasone did not significantly alter the insulin or FDKP pharmacokinetics of Afrezza. The sponsor evaluated FEV<sub>1</sub> in patients with and without asthma who received a short-acting beta-agonist bronchodilator prior to TI. Pre-treatment with the beta-agonist resulted in mean FEV<sub>1</sub> values that were higher at all assessed timepoints after TI dosing than before dosing.

As mentioned above, the sponsor conducted a pivotal bioequivalence study in patients with type 1 diabetes comparing the to-be-marketed Afrezza inhaler (Model D) with the Model C inhaler used in the phase 3 clinical trials. This study met the standard bioequivalence criteria, but the data are not reliable because of deficiencies identified by DSI during inspection of the clinical and analytical site (see Section 11 for further details). (b) (4)



The sponsor showed bioequivalence between two 15-unit cartridges and one 30-unit cartridge based on insulin exposures (AUC and C<sub>max</sub>) in patients with type 1 diabetes with the Model D inhaler.

The sponsor conducted a Thorough QT Study that tested FDKP doses of 20 mg and 40 mg and included a moxifloxacin positive control arm and a placebo treatment arm. The insulin component of Afrezza was not evaluated for QT effects given the extensive clinical experience with insulin to date. Pfizer did not conduct a Thorough QT Study for Exubera. The choice of 40 mg as the suprathreshold dose of FDKP was found to be acceptable by the QT Interdisciplinary Review Team (IRT) and was based on the maximum recommended Afrezza dose of 90 units with meals, which contains (b) (4) mg of FDKP. The 40 mg FDKP dose sufficiently covers known increases in FDKP C<sub>max</sub> that occur with various disease states (e.g., renal impairment) or concomitant medications (e.g., albuterol). The QT IRT agrees with the sponsor's conclusions that FDKP does not prolong the QT interval and that the moxifloxacin control arm showed adequate assay sensitivity. The largest upper bounds of the 2-sided 90% confidence interval for the mean treatment difference between FDKP and placebo were below the 10 msec threshold for regulatory concern as described in the International Conference on Harmonisation (ICH) E14 guideline.

## 6. Clinical Microbiology

Technosphere Insulin is a (b) (4) powder for inhalation. The microbiology reviewers found the NDA acceptable and are recommending approval. Please see the reviews of Drs. Denise Miller and Bryan Riley for details.

## 7. Clinical/Statistical- Efficacy

This section will focus on the efficacy findings from the key phase 2 and 3 clinical trials. These trials all used the Model C inhaler. Please see Dr. Lisa Yanoff's clinical review and Dr. Cynthia Liu's statistical review for details. Dr. Liu used the intent-to-treat population with last-observation-carried-forward for missing values as the primary statistical population for all trials.

### **TYPE 1 DIABETES:**

The sponsor conducted one 12-week phase 2 trial (Study 101) and one 52-week phase 3 trial (Study 009) in patients with type 1 diabetes. Both studies were open-label trials that compared pre-meal TI vs. pre-meal insulin aspart in patients receiving insulin glargine at bedtime.

#### **Study 009 (52-week, open-label trial of TI + glargine vs. insulin aspart + glargine)**

This randomized, open-label trial enrolled patients with inadequately-controlled ( $HbA1c >7\%$  to  $\leq 11\%$ ) type 1 diabetes. At screening, most patients (85-90%) were using a fast-acting insulin with either an intermediate-acting insulin or long-acting insulin.

Insulin dose titration was permitted throughout the treatment period but visits dedicated to insulin titration occurred only during the first 10 weeks of the treatment period. Titration was to be based on results of 7-point meter glucoses obtained on any 3 days during the week immediately preceding the clinic visit. Part way through the trial, the sponsor started a "Glycemic Monitoring Program" that sent blinded summary HbA1c data for 451 patients to clinical sites on a monthly basis to provide investigators with information on how they were doing with respect to achieving glycemic goals. The NDA does not include analyses of the impact of this program on insulin titration.

The starting dose of TI was based on the assumption that a 15 unit cartridge of TI corresponds to 5 units of subcutaneous insulin. TI was titrated in increments of 15 units up to a maximum dose of 90 units with meals.

The study was designed to have  $>90\%$  power to show non-inferiority based on a margin of 0.4%, a HbA1c standard deviation of 1.2% and a 1-sided alpha of 0.025. A total of 590 patients were to be randomized to have 500 completers, assuming a 15% drop-out rate. A total of 539 patients were included in the primary efficacy analysis. Approximately 66% of the TI-treated patients and 76% of the aspart-treated patients completed the trial. This high and somewhat differential dropout rate was predominantly driven by adverse events consistent with inadequate efficacy (e.g., hyperglycemia, blood glucose increased, diabetes mellitus inadequate control), which were reported as reasons for withdrawal in 7.6% of TI-treated patients and 0.7% of aspart-treated patients. The high and differential dropout rate was also driven by other adverse events (excluding those suggestive of inadequate efficacy), which were reported in 6.6% of TI-treated patients and 1.4% of aspart-treated patients (see the Safety section of this memorandum for further details).

As shown in Table 2 and discussed by Dr. Liu, TI was not non-inferior to insulin aspart because the upper bound of the 95% confidence interval for the HbA1c treatment difference was 0.404%, which is above the pre-specified non-inferiority margin of 0.4%. Dr. Liu notes that similar results were obtained with various sensitivity analyses, including the completers analysis (of interest because of the high dropout rates), which had an upper bound of the 95% confidence interval for the HbA1c treatment difference of 0.45%. Furthermore, TI is statistically worse (i.e., inferior) than insulin aspart because the lower bound of the 95% confidence interval for the HbA1c treatment difference was 0.1% (i.e., excludes 0%) for the primary efficacy analysis. Note that the mean treatment difference in HbA1c is small (~0.2%).

Interestingly, there is a treatment-by-gender interaction in this trial ( $p=0.01$ ), which is not seen in the other phase 2/3 trials. For men, the mean change in HbA1c from baseline to Week 52 was 0.0% in the TI treatment arm compared to -0.5% in the insulin aspart treatment arm. For women, the mean change in HbA1c from baseline to Week 52 was -0.2% in the TI treatment arm and -0.3% in the insulin aspart treatment arm.

Importantly, the insulin glargine dose was similar in both treatment groups throughout the treatment period, making it unlikely that differential dosing of long-acting insulin contributed to the efficacy results. In the TI treatment arm, the mean daily glargine dose increased from approximately 28 units at baseline to ~33 units by Week 8 and remained at ~33 units for the duration of the trial. In the aspart treatment group, the mean daily glargine dose increased from approximately 29 units at baseline to ~30 units by Week 12 and remained at ~30 units for the duration of the trial.

Few patients in both treatment groups achieved HbA1c  $\leq 7\%$  at Week 52 based on the intent-to-treat analysis with last-observation-carried-forward (13.4% with TI and 14.1% with insulin aspart).

An important limitation of the trial is that there was minimal titration of insulin doses during most of the treatment period. Had the insulins been better titrated, it is possible that there may have been even larger treatment differences favoring the aspart-treated group. For example, the mean total daily dose of insulin aspart increased from approximately 27 units at baseline to only ~31 units by Week 12 and remained at ~31 units for the duration of the trial. The mean total daily dose of TI increased from approximately 80 units at baseline to ~150 units at Week 5 with little further change over the remainder of the treatment period. These mean doses of TI are considerably lower than the maximum permitted dose of 270 units. Note that in both treatment groups, the mean prandial insulin dose is similar to the mean glargine dose (150 units of TI corresponds to approximately 40 units of subcutaneous insulin). Therefore, the prandial insulins comprised approximately 50% of the total daily insulin dose.

There were some patients in this trial who were able to achieve adequate glycemic control with 1-year of treatment with Afrezza+glargine. Because patients with type 1 diabetes would not be expected to achieve adequate glycemic control on glargine alone, it is reasonable to conclude that Afrezza (which comprised ~50% of the median total daily insulin dose) has demonstrated sufficient evidence of efficacy for some patients with type 1 diabetes. Patients treated with Afrezza who do not achieve optimal glycemic control can return to subcutaneous pre-meal

insulin, if needed. For patients who can achieve adequate glycemic control with Afrezza, inhaled insulin offers a unique advantage (no pre-meal injections) over subcutaneous insulins, which is of value for those patients who prefer to limit the number of daily subcutaneous doses of insulin.

### Study 101 (12-week trial in type 1 diabetes)

Study 101 is not discussed in detail because it had a treatment period of only 12 weeks in duration and was likely underpowered for a non-inferiority assessment based on HbA1c as there were fewer than 60 patients per treatment group. In addition, HbA1c was a secondary endpoint with no prespecified non-inferiority margin (the primary endpoint was change in glucose following a standardized meal). Nonetheless, it is noteworthy that the HbA1c results in this study are consistent with the results in Study 009, with both trials showing that TI + glargine is not non-inferior to insulin aspart + glargine. In Study 101, the upper bound of the 95% confidence interval for the treatment difference in HbA1c is 0.6% (Table 2), which exceeds the standard non-inferiority margin of 0.4% for insulins.

Interestingly, the within-group change from baseline in HbA1c was greater for both treatment groups in Study 101 than in Study 009 (Table 2). These larger within-group changes from baseline in HbA1c may be due to regression to the mean and are doubtfully related to the treatments themselves because there were modest, if any, changes in insulin doses over the course of the trial. For example, in the insulin aspart group (which had a mean change from baseline in HbA1c of 1%), the median daily glargine dose was 20 units at Week -3 (randomization visit) and 20 units at Week 8 and the median daily aspart dose was 20 units at Week -3 and 22 units at Week 8 (reliable data on insulin dose are only available up until Week 8 because patients switched back to their pre-treatment regimens immediately after the morning meal challenge at Week 12 and investigators did not reliably collect information on total daily insulin dose around the Week 12 visit). Similar findings with regard to total daily insulin doses were seen in the TI treatment group.

**Table 2. HbA1c (%) results for the phase 2/3 trials in patients with type 1 diabetes**

Study	N	Baseline <sup>1</sup> mean ± SD	Change from baseline Adj. mean ± SE	Difference in adjusted mean change 95% CI	p-value
<b>Study 009 (52-week phase 3 non-inferiority trial in type 1 diabetes)</b>					
<b>1-year data</b>					
TI + glargine	277	8.4±0.9	-0.1±0.1	+0.2 (0.1, 0.404)	<0.01
Aspart + glargine	262	8.5±1.0	-0.4±0.1		
<b>26-week data (post-hoc)</b>					
TI + glargine	276	8.4±0.9	-0.1±0.1	+0.3 (0.1, 0.43)	<0.001
Aspart + glargine	261	8.5±1.0	-0.4±0.1		
<b>Study 101 (12-week phase 2 trial in type 1 diabetes)</b>					
TI + glargine	51	9.0±1.2	-0.8±0.1	+0.3 (-0.1, 0.6)	0.15
Aspart + glargine	56	8.9±1.2	-1.0±0.1		

<sup>1</sup>Baseline visit = Week -4 (screening visit) for Study 101 because TI was started during the 3-week (Week -3 to Week 0) substitution period to gradually replace subcutaneous prandial insulin in the TI + glargine group

## **TYPE 2 DIABETES:**

The sponsor conducted six phase 2/3 trials in patients with type 2 diabetes, including two phase 2, double-blind, placebo-controlled trials (Study 0008 and Study 005) and three phase 3, open-label, active comparator-controlled trials (Study 014, Study 102, and Study 103). Study 026, another phase 2 trial, had only 15 patients in the control arm. This small sample size limits conclusions regarding efficacy. Therefore, this trial is not discussed here. Please see Dr. Yanoff's review for details.

Note that the two phase 2 trials (studies 005 and 0008) used different formulations of TI compared to the formulation used in the phase 3 trials and that these phase 2 formulations have not been bridged to the to-be-marketed formulation (no bioequivalence study and the changes to the manufacturing process are not biowaiverable). It is unknown whether these older formulations and the to-be-marketed formulation would yield similar efficacy findings.

### **Study 005 (12-week placebo-controlled trial)**

This randomized, double-blind trial compared several doses of TI (14 units, 28 units, 42 units, and 56 units) to placebo (Technosphere particles without insulin) in patients with type 2 diabetes. TI or placebo were to be inhaled immediately prior to meals. To be eligible for enrollment, patients were to be treated for a minimum of 2 months with a stable dose of at least one oral anti-diabetic medication with or without glargine. The objective of the study was to show a relationship between TI dose and glycemic response but the study design was not ideal. For example, within 1 month prior to the beginning of the 11-week treatment period, all patients discontinued oral antidiabetic medications and glargine was initiated in the 80% of patients not already taking glargine. In addition, glargine could be titrated during the month preceding the 11-week treatment period or if there was inadequate glycemic control on the randomized dose of TI. A more ideal trial design would have maintained stable doses of background anti-diabetic medications over the course of the trial. In addition, not all TI treatment groups received 11 weeks of the randomized TI dose. Instead, all patients randomized to TI were initiated on 14 units that was force-titrated in weekly intervals by 14-unit increments to the goal TI dose. Therefore, patients randomized to 56 units of TI were treated for 1 week with 14 units, 1 week with 28 units, 1 week with 42 units, and only 8 weeks with 56 units. Therefore, the endpoint HbA1c value may not accurately reflect the full effect of the higher doses of TI.

The placebo-corrected mean change in HbA1c was -0.5% with TI 14 units and 0.7-0.8% with TI 28-56 units, suggesting a plateau effect for pre-meal doses of TI above 28 units (Table 3). This conclusion is limited by the trial design features described above. For example, there may have been more convincing evidence of a dose-response relationship had patients received the 56-unit dose for the entire 11-week treatment period.

The mean glargine dose increased in all treatment groups during the course of the trial. The mean glargine dose was 15 units at Week -1, 20 units at Week 0 and 27 units at Week 11 with comparable glargine doses across the treatment groups at the various timepoints. It is likely

that the between-group changes from baseline in HbA1c would not be greatly affected by these somewhat comparable changes in glargine doses across treatment groups.

### **Study 0008 (12-week placebo-controlled trial)**

This randomized, double-blind trial compared 12-weeks of treatment with TI vs. placebo (Technosphere particles without insulin) in patients with type 2 diabetes. All enrolled patients were taking a stable dose of at least one oral anti-diabetic medication for at least 3 months. Patients assigned to TI started 6 units with meals that was titrated in increments of 6 units up to a maximum permitted dose of 48 units with meals. As shown in Table 3, the mean placebo-corrected reduction in HbA1c with TI was -0.4% (95% confidence interval -0.6, -0.1;  $p < 0.01$ ). Of note, mean doses of TI were 6 units at Week 0, 20 units at Week 4 and approximately 30 units at Weeks 8 and 12. Because the treatment period was only 12 weeks, this uptitration of TI would not be fully reflected in the endpoint HbA1c, which may have resulted in underestimation of the treatment effect.

### **Study 014 (24-week open-label trial of TI + glargine vs. insulin aspart + glargine)**

This randomized, open-label, trial was conducted exclusively in Russia and compared 24-weeks of treatment with TI + glargine vs. insulin aspart + glargine in patients with type 2 diabetes. All enrolled patients were to be taking subcutaneous insulin for at least 3 months prior to study entry. At Week -3, patients discontinued all anti-diabetic medications and initiated glargine 10 units or 20 units at bedtime. Aspart was substituted for previous prandial insulin. During these 3 weeks, glargine could be titrated weekly at the investigator's discretion based on fasting glucose values. At Week 0, patients began pre-meal TI ( $n=151$ ) or insulin aspart ( $n=158$ ). TI-treated patients started 15 units with meals that could be titrated to a maximum of 60 units with meals. Aspart-treated patients started 4-8 units with meals and were titrated in increments of 2-4 units. Titration of both TI and aspart occurred at the investigator's discretion based on clinic or home blood glucose monitoring data. Approximately 80% of TI-treated patients and 97% of aspart-treated patients completed the 24-week treatment period. This differential dropout rate is driven predominantly by adverse events (10% with TI - with more than one-half of these due to cough – and 0% with aspart) and by patient withdrawal of consent (6% with TI vs. 0% with aspart) – see the Safety section of this memorandum for more details.

Study 014 was designed as an equivalence trial. The sponsor specified that equivalence would be established if the lower bound of the 95% confidence interval for the treatment difference in HbA1c was greater than -0.4% and the upper bound was less than 0.4%. Dr. Liu also conducted a non-inferiority analysis using the standard margin for insulins of 0.4%.

Based on the sponsor's equivalence definition, the two treatment groups were not comparable using the intent-to-treat population with last-observation-carried forward. The sponsor concluded equivalence based on the intent-to-treat population without last-observation-carried-forward. However, Dr. Liu notes that this analysis is biased because it excludes patients who had some missing data even though available data from these patients could contribute to the treatment estimates. Based on a non-inferiority analysis, Dr. Liu notes that TI add-on to

glargine was not non-inferior to insulin aspart add-on to glargine because the upper bound of the 95% confidence interval for the HbA1c treatment difference was 0.6%, which is above the pre-specified non-inferiority margin of 0.4% (Table 3). Similar results were obtained using the completers analysis, which yielded an upper bound of the 95% confidence interval for the HbA1c treatment difference of 0.5%.

In addition, TI was statistically worse than insulin aspart because the lower bound of the 95% confidence interval for the HbA1c treatment difference for the intent-to-treat population using last-observation-carried-forward was 0.1% (i.e., excludes 0%).

The median total daily dose of TI increased from 45 units at baseline to 135 units at Week 24. The median total daily dose of aspart increased from 22 units at baseline to 24 units at Week 24. In both treatment groups, the median glargine dose increased from 30 units at baseline to 35 units at Week 20. However, at Week 24, the median glargine dose was 40 units in the TI group and 34 units in the aspart group. Because the glargine dose is comparable in both treatment groups for the majority of the treatment period, it is reasonable to conclude that the between-group difference for HbA1c is not likely impacted substantially by the changes in glargine dose towards the end of the treatment period. However, the within-group change from baseline in HbA1c (e.g., reduction of 0.9% with TI and reduction of 1.3% with aspart) likely overestimates the treatment effect of TI and aspart because part of these reductions is driven by uptitration of the glargine dose both during the 3-week run-in period and during the 24-week treatment period.

Note that TI was statistically worse than aspart even though the median aspart dose did not change appreciably (22 units at baseline vs. 24 units at Week 24) whereas the TI dose increased 3-fold from 45 units at baseline (equivalent to ~12 subcutaneous units according to the sponsor) to 135 units at Week 24 (equivalent to ~36 subcutaneous units).

About 25% of TI-treated patients and 33% of aspart-treated patients achieved HbA1c  $\leq$ 7%.

At endpoint, the median TI dose comprised ~50% of the median total daily insulin dose; however, it is not possible to determine from this trial the extent of incremental efficacy contributed by TI over-and-above the efficacy resulting from uptitration of the glargine dose. Nonetheless, there is some evidence for efficacy of TI in patients with type 2 diabetes based on the other trials conducted in this population.

### **Study 102 (52-week open-label trial of TI + glargine vs. NovoLog Mix 70/30)**

This multinational, randomized, open-label, trial compared 52 weeks of treatment with TI + glargine vs. twice-daily NovoLog Mix 70/30 in patients with type 2 diabetes. To be eligible for enrollment, patients were to be on insulin with no more than 3 injections per day and a total daily insulin dose  $<$ 1.4 units/kg. Oral anti-diabetic medications were permitted except for insulin secretagogues (sulfonylureas, glinides) and alpha glucosidase inhibitors. Doses of all background anti-diabetic medications were to be stable during the 6 weeks prior to screening.

For patients assigned to TI, 50% of the total daily pre-randomization insulin dose was replaced with TI and the remaining 50% was replaced by glargine. TI was then uptitrated in 15-unit increments up to a maximum dose of 90 units with meals. Glargine was titrated based on fingerstick fasting glucoses.

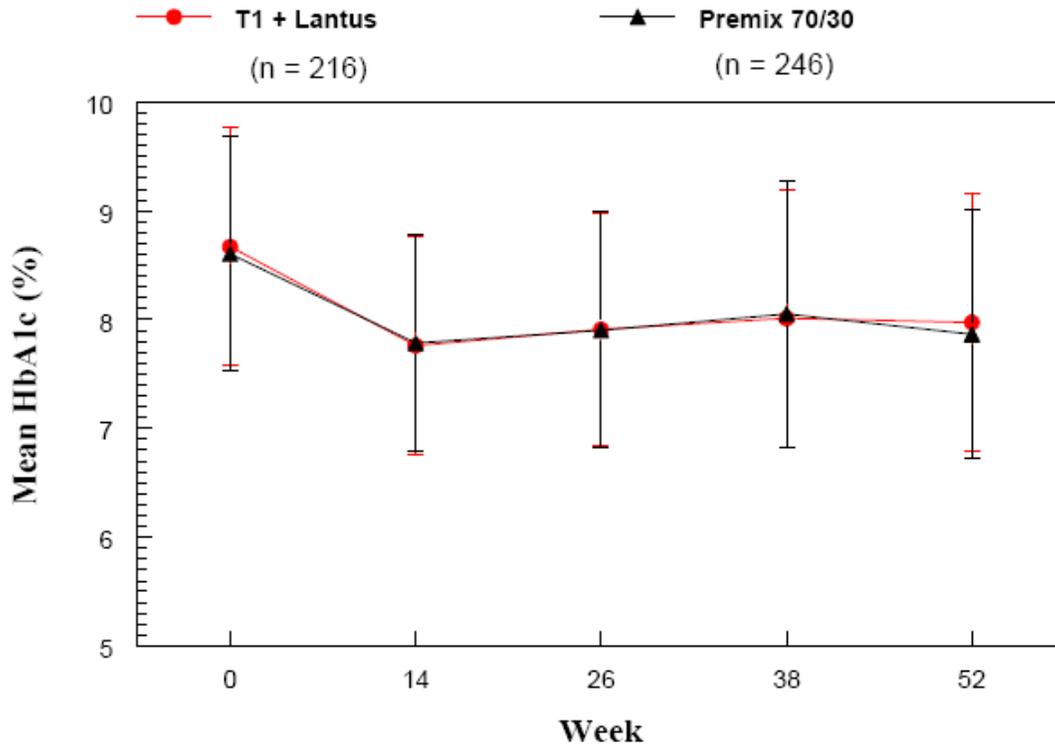
For patients randomized to NovoLog Mix 70/30, the initial dose of NovoLog Mix 70/30 depended on the type and doses of insulin used pre-randomization.

Although the protocol contains fasting and post-prandial glycemic goals for investigators to target, titration was only prioritized early during the trial. The protocol states that the insulin dose was titrated during the first 10 weeks of the treatment period with 3 telephone visits between Weeks 4 and 14 to further titrate the dose, if needed. Because this is a 52-week trial, titration should have been optimized until Week 40 (3 months prior to the endpoint HbA1c measurement).

Approximately 65% of the TI-treated patients and 72% of the NovoLog Mix 70/30-treated patients completed the trial. This high and somewhat differential dropout rate was predominantly driven by patient withdrawal of consent (11.1% of TI-treated patients and 8.2% of NovoLog Mix 70/30-treated patients) and by adverse events (excluding those suggestive of inadequate efficacy), which were reported in 9.6% of TI-treated patients and 2.9% of NovoLog Mix 70/30-treated patients. Withdrawal due to adverse events suggestive of lack of efficacy (e.g., hyperglycemia, blood glucose increased, diabetes mellitus inadequate control) occurred in 4.2% of TI-treated patients and 2.9% of NovoLog Mix 70/30-treated patients.

TI + glargine was non-inferior to twice daily NovoLog Mix 70/30. The mean treatment difference for change from baseline in HbA1c was 0.1% (favoring NovoLog Mix 70/30) with an upper bound of the corresponding 95% confidence interval of 0.3%, which is less than the pre-specified margin of 0.4%. The completers analysis (of interest because of the high dropout rates) yielded similar results. As shown in Figure 1, the two treatment groups had superimposable HbA1c curves over time. Most of the reduction in HbA1c occurred during the first 14 weeks of the trial, which is consistent with the timing of titration. Approximately 20% of TI + glargine-treated patients and 23% of NovoLog Mix 70/30-treated patients achieved HbA1c  $\leq$ 7% at Week 52 (intent-to-treat with last-observation carried forward).

**Figure 1. Mean HbA1c over the 52-week treatment period in Study 102 (adapted from Dr. Liu’s review)**



In the TI group, the mean dose of glargine increased from approximately 32 units at baseline to 44 units at Week 10 and 47 units at Week 52. The TI mean total daily dose increased from approximately 80 units at baseline to ~185 units by Week 10 and ~198 units by Week 52. The NovoLog Mix 70/30 mean total daily dose was approximately 60 units at baseline, 80 units by Week 10, and 88 units by Week 52. Therefore, most of the increase in the insulin doses occurred during the first 10 weeks of the trial.

Of note, the glargine dose of 47 units at Week 52 is lower than the dose of the intermediate-acting component of NovoLog Mix 70/30 at Week 52 (70% of 88 units or 62 units). The TI dose of 198 units at Week 52 is approximately equivalent to ~50 units of subcutaneous insulin and is higher than the aspart component of NovoLog Mix 70/30 (30% of 88 units or 26 units). Therefore, the total daily dose of insulin at Week 52 is ~100 units in the TI group and 88 units in the NovoLog Mix 70/30 group. Importantly, non-inferiority of TI + glargine to NovoLog Mix 70/30 was established in the setting of a higher prandial insulin dose in the TI group together with a lower dose of glargine compared to the dose of the intermediate-acting component of NovoLog Mix 70/30. This provides reassurance that the non-inferiority finding is driven by TI and not by glargine.

**Study 103 (12-week open-label trial of TI vs. TI+metformin vs. sulfonylurea+metformin)**

This randomized, open-label trial enrolled patients with type 2 diabetes and inadequate glycemic control (HbA1c 7.5-11%) on a stable dose (no change within the preceding 6 weeks) of metformin ( $\geq 1000$  mg/day) and at least one-half the maximum-recommended dose of an

insulin secretagogue (either sulfonylurea or glinide). No other anti-diabetic therapy was permitted. Patients were randomized to 12 weeks of continued treatment with the secretagogue + metformin (n=170) or TI + metformin (i.e., replacement of the insulin secretagogue with TI; n=175) or TI alone (i.e., discontinuation of the secretagogue and metformin and initiation of TI; n=183). This treatment period was then followed by a 12-week non-randomized treatment period, which is not discussed in this memorandum.

Patients randomized to a TI-containing regimen started TI at 15 units per meal and titrated, as needed, to a maximum dose of 90 units with meals. The protocol permitted adjustments of the metformin and insulin secretagogue doses.

Note that this study design is not ideal. Background anti-diabetic therapy should have remained constant and the controlled treatment period should have been longer (e.g., 24 weeks) to allow sufficient time for titration of TI to be fully reflected in the endpoint HbA1c measurement.

The completion rate for the 12-week treatment period was 68% with TI+metformin, 73% for TI alone, and 89% for secretagogue+metformin. The sponsor reviewed the reasons for discontinuation and concluded that the premature discontinuations were predominantly driven by lack of efficacy (18% with TI+metformin, 12% with TI alone, and 1.2% with secretagogue+metformin) and patient withdrawal of consent (7% with TI+metformin, 7% with TI alone, 6% with secretagogue+metformin). Dr. Liu notes that these findings differ somewhat from the reasons listed on the case report form (e.g., no patients on the case report form were listed as discontinuing due to lack of efficacy).

The primary objective was to show superiority of TI+metformin vs. secretagogue+metformin with respect to change in HbA1c from baseline to Week 12. Substitution of TI for secretagogue and continued treatment with metformin was not superior to continued treatment with secretagogue+metformin (p=0.51). The mean reduction from baseline in HbA1c was -0.7% in the TI+metformin group compared to -0.8% in the secretagogue+metformin group. The sponsor did not specify a non-inferiority margin. However, Dr. Liu notes that TI+metformin is non-inferior to secretagogue+metformin when the standard margin of 0.4% for insulins is used (the upper bound of the 95% confidence interval for the treatment difference in HbA1c is 0.3%). Non-inferiority (and lack of superiority) is also shown when the completers population is used.

Note that the TI alone group had a mean increase in HbA1c of 0.2% from baseline to Week 12. This is not necessarily surprising because two anti-diabetic medications were replaced by a single anti-diabetic medication in this treatment arm.

The sponsor calculated the median doses of study medication during Weeks 1-4, 5-8, and 9-12. In the TI alone group, the median total daily TI dose increased from ~100 units during Weeks 1-4 to ~200 units during Weeks 4-8, and ~240 units during Weeks 8-12. The metformin+secretagogue arm had relatively stable doses of metformin (~2,000 mg daily) and insulin secretagogue throughout the treatment period, making it less likely that dose increases of the oral agents contributed to greater efficacy in this treatment group. In the TI+metformin arm,

the median dose of metformin was ~1700 mg during Weeks 1-4 and 2000 mg during Weeks 4-12, and the median daily dose of TI was ~80 units during Weeks 1-4, 160 units during Weeks 4-8, and 190 units during Weeks 8-12.

Note that the trial design and implementation limits conclusions with respect to lack of superiority and the claim of non-inferiority. For example, for one-third of the treatment period, the TI+metformin group had a lower median metformin dose (1700 mg) than the metformin+secretagogue group (2000 mg). In addition, the full effects of TI titration were not reflected in the endpoint HbA1c measurement (titration mostly occurred during the preceding 4-8 weeks). These findings may have contributed to the inability of TI+metformin to show superiority against metformin+secretagogue. Also, the trial should not have compared a newly prescribed TI regimen to continued treatment with metformin+insulin secretagogue. Patients newly starting the comparator medications would be expected to have an initial reduction in HbA1c whereas patients continuing the comparator medications may have stable or slowly increasing HbA1c values, making TI appear more favorable than it otherwise is. This may limit a conclusion of non-inferiority.

<b>Table 3. HbA1c (%) results for key phase 2/3 trials in type 2 diabetes (adapted from Dr. Cynthia Liu's review)</b>					
<b>Note that TI provides numerically less glycemic control than comparator in the active-controlled trials</b>					
<b>Study</b>	<b>N</b>	<b>Baseline mean±SD</b>	<b>Change from baseline Adj. mean ± SE</b>	<b>Difference in adj. mean change with 95% CI</b>	<b>p-value</b>
<b>Study 005 (11-week phase 2, double-blind, placebo-controlled, forced-titration)</b>					
TI 14 units	43	8.9±1.4	-0.3±0.1	-0.5 (-1.0, 0.0)	0.04
TI 28 units	43	8.6±1.4	-0.6±0.1	-0.8 (-1.3, -0.3)	<0.001
TI 42 units	41	8.7±1.2	-0.5±0.2	-0.7 (-1.2, -0.2)	<0.01
TI 56 units	42	8.8±1.2	-0.6±0.2	-0.8 (-1.3, -0.3)	<0.001
Placebo	41	8.7±1.3	0.2±0.2		
<b>Study 0008 (12-week phase 2, double-blind, placebo-controlled)</b>					
TI	58	7.9±1.2	-0.7±0.1	-0.4 (-0.6, -0.1)	<0.01
Placebo	61	7.8±1.1	-0.3±0.1		
<b>Study 014 (24-week phase 3, open-label, with aspart + glargine comparator)</b>					
TI + glargine	150	8.9±1.1	-0.9±0.1	+0.4 (0.1, 0.6)	<0.01
Aspart + glargine	155	9.0±1.3	-1.3±0.1		
<b>Study 102 (52-week phase 3, open-label with NovoLog Mix 70/30 comparator)</b>					
TI + glargine	302	8.7±1.1	-0.6±0.1	+0.1 (-0.1, 0.3)	0.16
BID NovoLog Mix 70/30	316	8.7±1.1	-0.7±0.1		
<b>Study 103 (12-week phase 3, open-label comparison of TI + metformin to secretagogue + metformin)</b>					
TI alone	176	8.9±1.0	0.2±0.1	-	-
TI + metformin	169	9.0±1.0	-0.7±0.1	+0.1 (-0.1, 0.3) <sup>1</sup>	0.51
Secretagogue + metformin	162	8.9±0.9	-0.8±0.1		
<sup>1</sup> TI+metformin vs. secretagogue+metformin; study was designed to demonstrate superiority between these two treatment groups					

**Demographics:** Drs. Yanoff and Liu discuss the patient demographics for the phase 2/3 trials in detail. This memorandum will focus on the baseline demographics of the phase 3 trial in type 1 diabetes (Study 009) and the three active-comparator trials in type 2 diabetes (studies 014, 102, and 103). As expected, the mean age and mean body mass index were lower in the type 1 diabetes trial (~38 years old; ~26 kg/m<sup>2</sup>) compared to the type 2 diabetes trials (~55-60 years old; ~31 kg/m<sup>2</sup>). Baseline HbA1c was lower in the type 1 diabetes trial (~8.4-8.5%) compared to the type 2 diabetes trials (~8.7-9.0%). Study 014 (type 2 diabetes trial comparing TI+glargine to aspart+glargine) was conducted entirely in Russia. This trial had the lowest proportion of men (~20-25%) compared to the other type 2 diabetes trials (~40-50%) and compared to the type 1 diabetes trial (~50%). Because Study 014 was conducted in Russia alone, it is not surprising that virtually every patient in that trial was Caucasian. For the other trials, blacks comprised 5-8% of randomized patients and Asians comprised up to 3% of randomized patients. Dr. Yanoff notes that blacks were under-represented in these trials and that blacks have been reported to have lower normative values for baseline lung function compared to Caucasians. Therefore, she questions whether pulmonary safety has been adequately evaluated in blacks. This is discussed further in the Recommendations section of this memorandum. Hispanics comprised 14-20% of randomized patients in the two other type 2 diabetes trials and ~5% of patients in the type 1 diabetes trial. Smoking up to 6 months prior to study entry was an exclusion criterion for all clinical trials, but former smokers could be enrolled. In the pooled phase 2/3 dataset, approximately one-fourth of TI- and comparator-treated patients were past smokers. The mean pack-year history of smoking was ~10 in patients with type 1 diabetes and ~20 in patients with type 2 diabetes.

**Subgroup analyses for HbA1c:** Dr. Liu performed HbA1c analyses for subgroups of age (<65 years vs. ≥65 years), gender, race, and body mass index (≤25, 25-30, >30 kg/m<sup>2</sup>) for the 2 trials in type 1 diabetes and the 3 active-comparator trials in type 2 diabetes. Except for the above-described treatment-by-gender interaction for Study 009 (52-week trial in type 1 diabetes), there were no other significant treatment-by-subgroup interactions (p-values >0.10)

## 8. Safety

Dr. Yanoff reviewed the general safety of Afrezza and Dr. Banu Karimi-Shah reviewed the pulmonary safety.

Adverse events were coded using MedDRA version 7.1. Dr. Yanoff did not identify any miscoding concerns. The safety dataset consists of randomized patients who received at least one dose of study medication. Data from the type 1 diabetes trials and type 2 diabetes trials are pooled (e.g., deaths) or presented separately (e.g., hypoglycemia), as appropriate. Trials included in the pooled type 1 diabetes dataset include Study 009 (52-week comparison of TI+glargine vs. aspart+glargine) and 101 (12-week comparison of TI+glargine vs. aspart+glargine) as well as the patients with type 1 diabetes from Study 030 (2-year pulmonary safety trial, which is further described below). Trials included in the pooled type 2 diabetes dataset include Study 005 and 0008 (the phase 2, double-blind, placebo-controlled trials) as well as studies 014 (24-week comparison of TI+glargine vs. insulin aspart+glargine), 102 (52-week comparison of TI+glargine vs. twice daily NovoLog Mix 70/30), 103 (12-week

comparison of TI substitution for insulin secretagogue vs. continuing treatment with the insulin secretagogue, both in combination with continued treatment with metformin), and 026 (12-week open-label phase 2 trial that randomized 75 patients to TI and 15 patients to no treatment), as well as the patients with type 2 diabetes from Study 030 (2-year pulmonary safety trial).

As noted by Dr. Yanoff, the February 2008 draft guidance *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* recommends that an NDA contain data on at least 2,500 patients exposed to the investigational agent with at least 1,300-1,500 patients exposed to the investigational agent for  $\geq 1$  year and at least 300-500 patients exposed to the investigational agent for  $\geq 18$  months.

Over 3,000 patients have been exposed to TI as of the cut-off date for the 120-day safety update. As shown in Table 4, exposures to Afrezza are generally consistent with the recommendations in the draft guidance, although the number of patients exposed to TI for  $\geq 1$ -year (~1,200) is slightly below the recommended exposures (1,300-1,500) for that timepoint. However, this is sufficiently offset by the number of patients exposed to Afrezza for  $\geq 2$ -years (which is considerably higher than that typically seen for diabetes development programs, largely due to our request for a controlled 2-year pulmonary safety trial pre-approval).

<b>Table 4. Number of patients exposed to Technosphere Insulin (safety population from all submitted studies)</b>			
	<b>Type 1 diabetes</b>	<b>Type 2 diabetes</b>	<b>Combined</b>
<b>At NDA filing (unchanged in 120-day safety update)</b>			
$\geq 24$ weeks	400	1258	1658
$\geq 52$ weeks	355	844	1199
$\geq 76$ weeks	135	567	702
$\geq 104$ weeks	112	498	610

Most of the phase 3 trials permitted titration of TI up to 90 units with meals. Approximately 220 patients (<10%) achieved a TI dose >240 units, with one-half of these patients exposed to this dose for >12 months. This finding reflects the fact that there was generally poor titration of Afrezza in the clinical trials and should be taken into consideration when interpreting the safety findings.

<b>Table 5. Patients with type 1 or type 2 diabetes exposed to defined doses of TI (pooled, controlled phase 2/3 trials)</b>		
<b>Average Daily Dose (units)</b>	<b>Overall n (%)</b>	<b>&gt;12 months exposure n (%)</b>
$\leq 60$	475 (20)	28 (1.2)
>60-120	658 (27)	234 (9.7)
>120-180	638 (27)	278 (11.5)
>180-240	415 (17)	182 (7.6)
>240-300	197 (8.2)	98 (4.1)
>300	24 (1.0)	10 (0.4)

**Patient disposition:** Table 6 shows the patient disposition data for the controlled phase 2/3 trials. TI-treated patients had the lowest completion rates (61% with TI vs. 79% with comparator for type 1 diabetes and 65% with TI vs. 75% with comparator for type 2 diabetes). Because of this differential dropout rate, some analyses in this memorandum also report data by patient-year exposure. For patients with type 1 diabetes, the difference in completion rates was driven predominantly by adverse events (7% vs. 0.5%) and patient withdrawal of consent (21% vs. 10%). For patients with type 2 diabetes, the difference in completion rates was driven predominantly by adverse events (8% vs. 2%).

<b>Table 6. Patient disposition for the pooled, controlled phase 2/3 trials</b>						
	<b>Type 1 diabetes</b>		<b>Type 2 diabetes</b>			
	<b>TI n (%)</b>	<b>Comparator n (%)</b>	<b>TI n (%)</b>	<b>Comparator n (%)</b>		
				<b>Other insulin</b>	<b>Non- insulin</b>	<b>All</b>
Randomized and treated	614	599	1795	953	392	1345
Completed	373 (61)	475 (79)	1166 (65)	733 (78)	281 (70)	1014 (75)
Discontinued	241 (39)	124 (21)	629 (35)	214 (22)	117 (30)	331 (25)
Adverse events	43 (7.0)	3 (0.5)	142 (7.9)	19 (2.0)	5 (1.3)	24 (1.8)
Protocol violation	13 (2.1)	16 (2.7)	37 (2.1)	8 (0.8)	5 (1.3)	13 (1.0)
Withdrew consent	129 (21)	58 (9.7)	251 (14)	106 (11)	67 (17)	173 (13)
Death	1 (0.2)	1 (0.2)	7 (0.4)	4 (0.4)	0	4 (0.3)
Investigator decision	22 (3.6)	7 (1.2)	42 (2.3)	9 (0.9)	6 (1.5)	15 (1.1)
Lost to follow-up	16 (2.6)	28 (4.7)	53 (3.0)	53 (5.6)	30 (7.7)	83 (6.2)
Other	16 (2.6)	11 (1.8)	97 (5.4)	15 (1.6)	4 (1.0)	19 (1.4)
Unknown	1 (0.2)	0	0	0	0	0

Discontinuations due to adverse events are discussed in more detail below.

There was a high incidence of withdrawal of consent in the pooled phase 2/3 database. Table 7 summarizes these data across the individual phase 3 trials, showing imbalances not favoring TI in most of the clinical trials. As shown in table 7, patient dissatisfaction (~1-3% of TI-treated patients) and issues related to glycemic control (~2-8% of TI-treated patients) were the predominant reasons for withdrawal of consent in TI-treated patients across trials.

<b>Table 7. Patient withdrawal of consent across the main phase 3 trials, including the most common reasons leading to withdrawal of consent</b>		
	<b>TI n (%)</b>	<b>Comparator n (%)</b>
<b>Type 1 diabetes</b>		
Study 009	47/301 (15.6)	19/288 (6.6)
Unspecified reason	11 (3.7)	2 (0.7)
Lack of efficacy	8 (2.7)	0
Dissatisfied	6 (2.0)	1 (0.4)
Glycemic control issues	5 (1.7)	1 (0.4)
Study 030	79/269 (29.4)	39/271 (14.4)
Glycemic control issues	13 (4.8)	0
Unspecified reason	12 (4.5)	8 (3.0)
Lack of efficacy	9 (3.4)	0
Dissatisfied	8 (3.0)	1 (0.4)
Work related	7 (2.6)	2 (0.7)
<b>Type 2 diabetes</b>		
Study 014	10/151 (6.6)	0
Unspecified reason	4 (2.7)	0
Family reasons	3 (2.0)	0
Dissatisfied	2 (1.3)	0
Moved	1 (0.7)	0
Study 030	13/669 (20.8)	127/680 (18.7)
Unspecified reason	24 (3.6)	19 (2.8)
Dissatisfied	15 (2.2)	3 (0.4)
Glycemic control issues	12 (1.8)	1 (0.2)
Study 102	50/334 (15.0)	32/343 (9.3)
Unspecified reason	14 (4.2)	8 (2.3)
Glycemic control issues	7 (2.1)	3 (0.9)
AE other than hyperglycemia	5 (1.5)	0
Study 103	20/175 (11.4) <sup>1</sup>	10/170 (5.9) <sup>2</sup>
Lack of efficacy	6 (3.4)	0
Unspecified reason	5 (2.9)	3 (1.8)
Dissatisfied	3 (1.7)	0

<sup>1</sup>TI+metformin; <sup>2</sup>secretagogue+metformin

**Deaths:** Dr. Yanoff notes that a total of 16 deaths were reported in the Afrezza program at the time of NDA submission. Fourteen of these deaths occurred in the controlled phase 2/3 clinical trials with 9/2409 (0.37%) among TI-treated patients and 5/1944 (0.26%) among comparator-treated patients. There were two additional deaths during uncontrolled treatment periods – one in a TI-treated patient (myocardial infarction) and another in a comparator-treated patient (heart failure).

Dr. Yanoff notes that there were 4 additional deaths reported in the 120-day safety update that occurred in completed trials after database lock for the NDA. All 4 deaths occurred in TI-treated patients, but 3 of these deaths (bronchogenic carcinoma, prostate cancer, pancreatic cancer) occurred in a long-term uncontrolled trial, limiting interpretability. The remaining death occurred (b) (6) months after the patient's last dose of study medication and was due to a neuroendocrine tumor with lung involvement (the abnormal CT scan finding led to treatment discontinuation but the patient received only 4 months of treatment with TI, making a causal link unlikely).

As expected, most of these 20 deaths were related to cardio- or cerebrovascular causes (8 with TI vs. 5 with comparator) and neoplasms (5 with TI vs. 0 with comparator). The 2 remaining deaths were attributed to sepsis from a gangrenous toe (TI-treated patient) and a car accident (comparator-treated patient).

Note that 3 of the 5 neoplasm-related deaths (bronchogenic carcinoma, prostate cancer, pancreatic cancer) occurred during a long-term, uncontrolled trial (days of treatment with TI ranging from 372-693 days), the fourth case is the neuroendocrine tumor discussed above, and the fifth case was cholangiocarcinoma occurring after ~6 months of treatment with TI. The bronchogenic carcinoma was diagnosed approximately 13 months after the patient started TI when he presented with anemia and CT scanning showed two 2 cm lung nodules. This patient had a 40-pack year history of smoking and his father died of lung cancer. The patient who died of prostate cancer received (b) (6) months of treatment with TI. He had an elevated prostate specific antigen since 1993. The patient who died of pancreatic cancer had been treated with TI for approximately (b) (6) year.

With regard to cardiovascular deaths, during the controlled trials, there were 7/2409 (0.30%) events with TI (1 patient with both stroke and myocardial infarction, 1 patient with both stroke and heart failure, 1 patient with hemorrhagic stroke in the setting of hypertensive emergency, 1 patient with myocardial infarction alone, and 3 patients with cardiac arrest) and 4/1944 events (0.21%) with comparator (2 patients with cardiac arrest and 2 patients with acute coronary syndrome).

In summary, death rates were low and there is no apparent imbalance between TI and comparator based on controlled clinical data. Deaths occurring during the long-term uncontrolled treatment periods yield limited information because of the lack of a control group. The 1 event of primary lung cancer occurred after 1 year of treatment with TI in a patient with a significant history of smoking.

**Serious adverse events:** Because serious adverse event rates were low, the controlled phase 2/3 trials for type 1 diabetes and type 2 diabetes were pooled to improve the likelihood of detecting potentially important imbalances between treatment groups. In this pooled phase 2/3 dataset, the overall incidence of serious adverse events was 8.3% (11.1 per 100 patient-years) with TI and 9.4% (8.9 per 100 patient-years) with comparator. Most of the serious adverse events were reported in only 1-2 patients. Noteworthy findings are summarized below. Note that cardiac events, pulmonary safety, diabetic ketoacidosis, hypoglycemia, and neoplasms are discussed separately under Adverse Events of Interest.

There was 1 report each of hepatitis toxic, hepatotoxicity, and angioneurotic edema among TI-treated patients and no reports of these events among comparator-treated patients. Key features of these events are summarized below.

The event of hepatitis toxic was attributed to a Chinese herb used for weight loss. The abnormal liver tests were noted at a clinic visit when the patient's ALT was 2.5x ULN and his total bilirubin was 1.4x ULN. The liver abnormalities resolved despite continued treatment with TI and the patient completed the trial. Of note, this patient also had a history of liver test abnormalities attributed to alcohol intake.

The event of hepatotoxicity was attributed to paracetamol and ibuprofen overdose although this diagnosis is in doubt. The patient reportedly used paracetamol up to 500 mg per dose and up to 3,500 mg per day as well as ibuprofen 200-400 mg per dose up to 1,200 mg per day for 5 days to treat a sore throat. These doses do not exceed the maximum recommended doses of paracetamol (500-1,000 mg every 4-6 hours, not to exceed 4,000 mg per day) or ibuprofen (800 mg three times per day). (b) (6) later, the patient was hospitalized with an upper respiratory tract infection and diabetic ketoacidosis (pH 7.1, pCO<sub>2</sub> 13 mmHg). There is no mention of interruption of insulin therapy in the patient narrative. Approximately 1 week later, the ALT was 33 U/L. Three days after the 33 U/L measurement, the ALT was 734 U/L (24x ULN) and AST was 1291 U/L (40x ULN). Total bilirubin remained normal; therefore, the patient does not meet the biochemical criteria for Hy's Law. Liver ultrasound reportedly showed hepatomegaly. TI was temporarily interrupted but the patient subsequently completed the trial and had normal liver tests at the remaining 2 clinic visits. It is reassuring that the liver test abnormalities did not recur with resumption of TI, that this patient did not meet biochemical criteria for Hy's Law, and that overall liver test abnormalities were balanced between treatment groups in the phase 2/3 program.

The patient who developed angioneurotic edema had facial edema and respiratory difficulties after the second dose of TI. The patient had not eaten nuts, pears or apples prior to the onset of the event (which had caused angioedema in the past). The patient self-treated by injecting an anti-histamine, which resolved her symptoms. TI was discontinued. The patient had a history of urticaria from her first insulin injection in 2001 but was using glargine daily since 2003 (and received TI in 2005). There was no reported coadministration of other culprit medications such as angiotension converting enzyme (ACE) inhibitors. Based on this narrative, it appears that TI may cause serious allergic reactions. This safety issue should be labeled if/when TI is approved.

Other serious adverse events of note include 5 cases of pancreatitis (4 with TI vs. 1 with comparator), 3 cases of retinal detachment (all 3 with TI), and 3 cases of intraocular hemorrhage (1 case with TI vs. 2 with comparator).

When considering all adverse events (serious and non-serious) in the pooled phase 2/3 trials there are 5 cases of retinal detachment (all with TI) and 17 cases of intraocular hemorrhage (5 with TI vs. 12 with comparator). Therefore, retinal detachment or intraocular hemorrhage occurred in a total of 10 TI-treated patients (0.4%; 0.55 per 100 patient-years) and 12

comparator-treated patients (0.6%; 0.59 per 100 patient-years). In the Exubera program, retinal detachment was reported at a rate of 0.06 per 1,000 patient-months with Exubera vs. 0.07 per 1,000 patient-months with comparator.

When considering all adverse events (serious and non-serious) in the pooled phase 2/3 trials, there are 15 cases of pancreatitis (10 with TI vs. 5 with comparator). Six of the 10 cases of pancreatitis among TI-treated patients (0.3 per 100 patient-years) and all 5 cases of pancreatitis among comparator-treated patients (0.2 per 100 patient-years) were reported as chronic pancreatitis or acute exacerbations of pancreatitis in patients with a history of pancreatitis. The 4 remaining cases of acute pancreatitis were reported as serious adverse events in patients without a history of pancreatitis and were reported only in TI-treated patients. None of these patients permanently discontinued TI. One of these patients had acute cholecystitis. A precipitant was not clearly identified in the remaining 3 cases as summarized below.

- One patient presented simultaneously with pancreatitis and diabetic ketoacidosis after approximately 7 months of treatment with TI. The pancreatitis probably precipitated the ketoacidosis. No precipitant was reported for the pancreatitis.
- One patient had 2 episodes of pancreatitis while taking TI. The second episode occurred 6 months after the first episode and was associated with elevated alanine aminotransferase (560 U/L) and elevated total bilirubin (3.0 mg/dL) with normal alkaline phosphatase. The patient reportedly had normal findings on endoscopic retrograde cholangiopancreatography but subsequently underwent cholecystectomy. Pathology results were not included in the hospital records but the discharge diagnosis was gallstone pancreatitis. After the patient resumed TI, the highest ALT was 2.3x ULN and there were no further abnormal measurements of total bilirubin.
- One patient was diagnosed with pancreatitis after ~4.5 months of treatment with TI. No precipitant was identified.

Insulins have not been associated with pancreatitis and there was no suggestion of pancreatitis in the non-clinical studies with FDKP. The small numbers of patients with unexplained acute pancreatitis (3 with TI vs. 0 with comparator) limit conclusions.

**Withdrawals due to adverse events:** The controlled phase 2/3 trials for type 1 diabetes and type 2 diabetes were pooled for this analysis to improve the likelihood of detecting potentially important imbalances between treatment groups. Adverse events leading to discontinuation occurred in 7.7% of TI-treated patients and 1.2% of comparator-treated patients. This difference was driven predominantly by discontinuations due to adverse events in the Respiratory, Thoracic, and Mediastinal Disorders System-Organ Class (4.2% with TI vs. 0.1% with comparator). Most of the other reported adverse events leading to discontinuation occurred in isolated TI- or comparator-treated patients. Cough was the only adverse event leading to discontinuation that occurred in >1% of TI-treated patients in the controlled phase 2/3 database. Respiratory adverse events, including cough, are discussed in detail under Adverse Events of Interest. Table 8 summarizes less frequent adverse events leading to discontinuation that are of potential interest. Narratives for these selected events are summarized below.

Three TI-treated patients had hypersensitivity or drug hypersensitivity leading to premature discontinuation from the trial; no such events occurred in the comparator groups. One of these patients discontinued TI after 2 days due to an “allergic event”. The event was considered mild and no treatment was given. No other details are provided. Another patient received TP (not TI) for 2 days during a run-in period then developed aphthae on the mouth and laryngeal mucosa and urticaria on the fingertips that prompted medication discontinuation. This patient had a history of cold-induced urticaria. The third patient received TI for 1 day and experienced throat irritation, pain, and itching that was considered hypersensitivity to TI. No treatment was given.

The patient with alanine aminotransferase increased had ALT 1.3x ULN prior to dosing with TI that prompted premature discontinuation 2 weeks later. ALT was normal 2 days after the last dose of TI. This does not represent a case of serious hepatotoxicity.

The patient who discontinued due to angioneurotic edema is discussed under Serious Adverse Events.

The patient who discontinued due to elevated creatine phosphokinase (CPK) had a value of 414 U/L (1.3x ULN) on the early termination visit. Of note, the pre-treatment CPK was 831 U/L. This does not represent a case of rhabdomyolysis.

<b>Table 8. Withdrawals due to selected adverse events in the controlled phase 2/3 trials (excludes respiratory adverse events)</b>				
<b>Preferred Term</b>	<b>TI N=2409 1814 PY</b>		<b>Comparator N=1944 2051 PY</b>	
	<b>n (%)</b>	<b>Per 100 PY</b>	<b>n (%)</b>	<b>Per 100 PY</b>
Any	185 (7.7)	10.2	24 (1.2)	1.2
Hypersensitivity	2 (0.1)	0.1	0	0
Drug hypersensitivity	1 (<0.1)	0.1	0	0
Alanine aminotransferase increased	1 (<0.1)	0.1	0	0
Blood creatine phosphokinase increased	1 (<0.1)	0.1	0	0
Angioneurotic edema	1 (<0.1)	0.1	0	0

**Common adverse events:** The most common adverse events are presented separately for each of the main phase 3 trials in patients with type 2 diabetes. These data were not pooled because these trials used different comparators. The phase 2 and phase 3 type 1 diabetes trials were pooled because these trials used similar treatments.

Common adverse events for the two phase 2 placebo-controlled trials in type 2 diabetes are not presented here. These trials were small, limiting conclusions.

The most common adverse events (incidence >2% and occurring  $\geq 0.5\%$  more frequently with TI than comparator) are shown in Table 9 for the type 1 diabetes population and in Table 10 for the type 2 diabetes trials. Note that this section does not discuss cough or hypoglycemia – see Adverse Events of Interest for a discussion of those events. As shown for the common (incidence >2%) adverse events in Tables 9 and 10, TI-treated patients consistently reported headache, pharyngolaryngeal pain/throat irritation, and hyperglycemia  $\geq 0.5\%$  more frequently than comparator-treated patients. Upper respiratory tract infection, nasopharyngitis, bronchitis, diarrhea, nausea and fatigue were reported  $\geq 0.5\%$  more frequently with TI compared to control in 2 of the 4 trials in patients with type 2 diabetes summarized in Table 10.

<b>Table 9. Common adverse events (incidence &gt;2% and occurring <math>\geq 0.5\%</math> more frequently with TI than comparator) in the phase 2/3 trials in patients with type 1 diabetes (Note: Cough and hypoglycemia discussed separately under Adverse Events of Interest)</b>		
<b>Preferred Term</b>	<b>TI + glargine N=614</b>	<b>Aspart + glargine N=599</b>
	<b>n (%)</b>	<b>n (%)</b>
Any	544 (89)	539 (90)
Headache	33 (5.4)	19 (3.2)
Pulmonary function test decreased	27 (4.4)	8 (1.3)
Pharyngolaryngeal pain	23 (3.7)	9 (1.5)
Hyperglycemia	16 (2.6)	9 (1.5)

<b>Table 10. Common adverse events (incidence &gt;2% and occurring ≥0.5% more frequently with TI than comparator) in the main phase 3 trials in patients with type 2 diabetes (Note: Cough and hypoglycemia discussed separately under Adverse Events of Interest)</b>		
<b>Study 014</b>	<b>TI + glargine N=151</b>	<b>Aspart + glargine N=158</b>
Any	67 (44)	71 (45)
Upper respiratory tract infection	5 (3.3)	3 (1.9)
Osteochondrosis	5 (3.3)	1 (0.6)
Pyelonephritis	3 (2.0)	2 (1.3)
<b>Study 102</b>	<b>TI + glargine N=323</b>	<b>NovoLog Mix 70/30 N=331</b>
Any	272 (84)	296 (89)
Upper respiratory tract infection	39 (12.1)	24 (7.3)
Nasopharyngitis	30 (9.3)	28 (8.5)
Headache	18 (5.6)	12 (3.6)
Back pain	16 (5.0)	9 (2.7)
Bronchitis	16 (5.0)	7 (2.1)
Diarrhea	13 (4.0)	9 (2.7)
Throat irritation	11 (3.4)	0
Pharyngitis	10 (3.1)	8 (2.4)
Pharyngolaryngeal pain	10 (3.1)	8 (2.4)
Nausea	9 (2.8)	6 (1.8)
Muscle cramp	9 (2.8)	2 (0.6)
Fatigue	9 (2.8)	1 (0.3)
Blood creatine phosphokinase increased	8 (2.5)	2 (0.6)
Hyperglycemia	7 (2.2)	3 (0.9)
Abdominal pain upper	7 (2.2)	3 (0.9)
<b>Study 103</b>	<b>TI alone or TI + met N=355</b>	<b>Insulin secretagogue + met N=166</b>
Any	201 (57)	73 (44)
Headache	10 (2.8)	2 (1.2)
Hyperglycemia	9 (2.5)	1 (0.6)
<b>Study 030</b>	<b>TI N=656</b>	<b>Comparator N=678</b>
Any	<b>512 (78)</b>	<b>451 (67)</b>
Nasopharyngitis	48 (7.3)	41 (6.0)
Arthralgia	28 (4.3)	22 (3.2)
Influenza	27 (4.1)	23 (3.4)
Diarrhea	20 (3.0)	15 (2.2)
Pharyngolaryngeal pain	18 (2.7)	2 (0.3)
Throat irritation	17 (2.6)	1 (0.1)
Bronchitis	14 (2.1)	11 (1.6)
Headache	16 (2.4)	9 (1.3)
Fatigue	16 (2.4)	7 (1.0)
Nausea	16 (2.4)	7 (1.0)
Dyspnea	14 (2.1)	2 (0.3)

**Adverse events of interest:**

Pulmonary safety: The Division of Pulmonary and Allergy Products (DPAP) reviewed the pulmonary safety of Afrezza, with a focus on respiratory adverse events, pulmonary function tests, chest x-rays, and high resolution computed tomography of the chest. Please see the review by Drs. Banu Karimi-Shah and Sally Seymour for details.

Dr. Karimi-Shah has concluded that Afrezza likely causes irritation of the upper respiratory tract, based on reports of cough and several other pulmonary adverse events such as bronchial hyperreactivity, bronchospasm, dyspnea, laryngospasm, throat irritation, throat tightness, and wheezing. Dr. Karimi-Shah states that pulmonary irritation may be a safety issue in patients with undiagnosed lung disease because patients with reduced lung reserve could potentially develop life-threatening respiratory difficulty after inhalation if there is an acute decline in FEV<sub>1</sub>. Dr. Karimi-Shah bases this concern on data from serial pulmonary function tests obtained up to 2 hours after inhalation of Afrezza in patients with asthma (n=22) and up to 4 hours after inhalation of Afrezza in patients with chronic obstructive pulmonary disease (n=8). After inhalation of TI, patients with asthma had an acute mean decline in FEV<sub>1</sub> of ~400 mL and patients with chronic obstructive pulmonary disease had an acute mean decline in FEV<sub>1</sub> of ~200 mL. Dr. Karimi-Shah notes that this is a clinically meaningful decline in FEV<sub>1</sub>.

Of note, the sponsor suspended Study 134 (12-month phase 3 trial in patients with type 1 diabetes and mild obstructive pulmonary disease) in June 2009 after the Data Safety Monitoring Board raised concerns about acute bronchoconstriction and exacerbations in patients with asthma and chronic obstructive pulmonary disease. These concerns were based upon review of data from TI clinical pharmacology studies in patients with asthma and chronic obstructive pulmonary disease. In one of these studies, 5/17 (29%) patients with asthma had bronchoconstriction, wheezing or asthma exacerbation after inhalation of a single 45-unit dose of TI. Note that short-acting bronchodilators were held for  $\geq 6$  hours and long-acting bronchodilators were held for 24 hours prior to administration of TI. Three of these patients had spontaneous recovery. The remaining 2 patients discontinued due to bronchoconstriction after inhalation of TI – one with a 45% decline in FEV<sub>1</sub> and the other with a 33% decline in FEV<sub>1</sub>. In both cases, the event resolved after treatment with a beta-agonist. In another clinical pharmacology study, patients with chronic obstructive pulmonary disease had a mean decline in FEV<sub>1</sub> of 8.3% at 18 minutes post-dose, although there were no reports of bronchoconstriction.

The sponsor and Division subsequently held a teleconference to discuss this suspended trial. Agreement was reached to permit reinitiation of an amended protocol that included additional safeguards for enrolled patients with a goal of further evaluating risks associated with TI in these patients prior to continuing full enrollment and completion of the trial. DPAP is recommending that this trial be a postmarketing required study, if/when Afrezza is approved. I concur with this proposal. The Division did not require that Pfizer establish the efficacy and safety of Exubera in patients with underlying lung disease prior to approval; therefore, a higher standard would be applied to Afrezza if Study 134 is required pre-approval. In addition, there

would be safeguards to protect against inappropriate use of Afrezza by patients with underlying lung disease (see the Recommendations section of this memorandum).

Dr. Karimi-Shah acknowledges that Afrezza will not be labeled for patients with known asthma or chronic obstructive pulmonary disease but raises concerns that patients with undiagnosed lung disease may inadvertently receive Afrezza and have life-threatening airway emergencies after inhalation. Therefore, DPAP is recommending that patients have an evaluation of pulmonary function prior to initiating Afrezza to exclude asthma and chronic obstructive pulmonary disease. DPAP is also suggesting that the first dose of Afrezza be given in the clinic to ensure bronchospasm does not occur and that the patient understands how to correctly use the device.



Dr. Karimi-Shah has also raised concerns with the to-be-marketed Model D inhaler



Another option is to list the lack of clinical data with Model D as a deficiency in the Complete Response letter and require pre-approval trials with Model D. Note that at several points during the Afrezza development program, we recommended that the sponsor use the to-be-marketed device in phase 3 trials. However, as recently as the Pre-NDA meeting, we did not state that it was a requirement to do so. Therefore, I favor the first option of obtaining the data in the postmarketing setting. However, if there is a determination that additional pre-approval trials are needed to support efficacy then testing of Model D should be incorporated into those trials. Alternatively, if the sponsor will anyhow have clinical data on Model D

durability based on trials that are currently ongoing, those data should be required with the sponsor's Complete Response.

Dr. Karimi-Shah notes that the inhaler is complex and that patients with diabetes and their healthcare providers are not necessarily familiar with inhalation devices. She recommends that the sponsor conduct a label comprehension and use study to ensure that patients are able to read, comprehend and use the device as labeled.

With regard to pulmonary safety, Dr. Karimi-Shah has concluded that the submitted data are adequate to assess pulmonary safety over 2 years. A pulmonary malignancy signal was not noted but the database is too small to identify such a signal and further assessment of this risk will need to take place in the postmarketing setting (see below).

Dr. Karimi-Shah notes that Afrezza-treated patients had a greater decline in FEV<sub>1</sub> over time compared to controls. This decline occurred during the first 3 months of therapy and persisted during the long-term trials. DPAP considers the mean treatment differences in FEV<sub>1</sub> to be small (~40-50 mL) and consistent with that seen with Exubera. Based on the sponsor's analyses, Dr. Karimi-Shah notes no relationship between Afrezza dose and FEV<sub>1</sub> changes. The FEV<sub>1</sub> data are discussed in more detail below.

Based on the above concerns, DPAP is recommending that baseline and periodic monitoring of pulmonary function tests be obtained in Afrezza-treated patients. DPAP is also recommending a contraindication for smokers and those with unstable or poorly controlled lung disease, as well as statements in Warnings and Precautions recommending against use in patients with underlying lung disease and noting the risk of bronchospasm in patients with asthma.

DPAP is also recommending Risk Evaluation and Mitigation Strategies (REMS) consisting of a Medication Guide and possibly a Communication plan to ensure the benefits of Afrezza outweigh the risk. The REMS would address use by inappropriate patient populations (e.g., those with known lung disease), the risk of acute respiratory difficulty after inhalation of Afrezza (particularly in those with undiagnosed lung disease), the need for baseline pulmonary function tests, and the risk of pulmonary function decline over time and the need for periodic monitoring of pulmonary function tests.

Based on the above concerns, DPAP is recommending the following 3 postmarketing required studies under the FDA Amendments Act:

- A large ( $\geq 5,000$  patients per treatment arm), long-term ( $\geq 5$  years) controlled trial to further assess the long-term safety of Afrezza, including effects on FEV<sub>1</sub>.
- A long-term epidemiologic study to evaluate the risk of malignant lung tumors in Afrezza-treated patients.
- Completion of Study 134 (ongoing phase 3 trial in patients with type 1 diabetes and mild obstructive pulmonary disease – see above) to provide additional data in patients with underlying lung disease.

Key findings from Dr. Karimi-Shah's review are summarized below.

There were no deaths due to primary respiratory events in the controlled phase 2/3 trials.

There were no respiratory serious adverse events reported in more than 1 Afrezza-treated patient and more commonly than with comparator. There were isolated reports of asthma, cough, hemoptysis, and respiratory failure reported as serious adverse events in TI-treated patients. The event of asthma was diagnosed after ~5 months of treatment with Afrezza when the patient was hospitalized with cough and dyspnea. The patient with hemoptysis reported repeated episodes of bloody cough starting ~4 months after the first dose of TI. The episodes continued for ~1-month despite discontinuation of TI. A full work-up (e.g., CT imaging) was not conducted because of spontaneous resolution. The event of respiratory failure occurred in the setting of a large stroke. Dr. Karimi-Shah did not identify a safety signal with Afrezza based on her review of the serious respiratory adverse events.

Cough was the most common adverse event leading to premature discontinuation, occurring in 2.7% of Afrezza-treated patients and no comparator-treated patients in the controlled phase 2/3 database. Other adverse events in the Respiratory, Thoracic, and Mediastinal Disorders System-Organ-Class leading to discontinuation and reported by 2 or more Afrezza-treated patients included dyspnea (n=10 or 0.4%), asthma (n=4 or 0.2%), throat irritation (n=4 or 0.2%), bronchial hyperreactivity (n=2 or 0.1%), bronchospasm (n=2 or 0.1%), respiratory tract congestion (n=2 or 0.1%), and wheezing (n=2 or 0.1%). No comparator-treated patients discontinued due to these adverse events. Respiratory adverse events of potential interest leading to discontinuation but reported in only isolated TI-treated patients included asphyxia, laryngospasm, painful respiration, and throat tightness. The patient with “asphyxia” had been treated with Afrezza for 77 days and did not die. The narrative states that the asphyxia resolved 2 days after its onset. No other details are provided. The patient with laryngospasm reported this event on the first day of dosing but continued treatment with Afrezza for 3 additional weeks. The event was reported as resolved 1 day after Afrezza was discontinued. The patient with painful respiration reported intermittent muscle soreness with inspiration leading to premature discontinuation. The patient with throat tightness reported this event in the setting of an upper respiratory tract infection.

Respiratory adverse events were more common in the Afrezza (33%) and the TP-only (25%) groups than in the comparator group (10%) with this difference driven mostly by cough (27% with TI, 18% with TP vs. 6% with comparator) (Table 11). Dr. Karimi-Shah notes that >90% of cough episodes were characterized as intermittent or single episodes and that most (75-80%) cough events occurred within 10 minutes of drug inhalation. The cough is dry and has the highest incidence during the first 3 months of therapy. DPAP notes that the incidence of cough with Afrezza is high when compared to other dry powder inhalers and have attributed this finding to airway irritation possibly due to the acidic content of the drug product.

**Table 11. Common respiratory adverse events occurring in >2% of TI-treated patients and more commonly with TI than comparator (pooled, controlled phase 2/3 database)**

	<b>TI N=2409 n (%)</b>	<b>TP N=114 n (%)</b>	<b>Comparator N=1944 n (%)</b>
Any respiratory adverse event	1088 (45)	44 (39)	606 (31)
Respiratory, Thoracic and Mediastinal	794 (33)	29 (25)	192 (10)
Cough	642 (27)	21 (18)	109 (5.6)
Pharyngolaryngeal pain	56 (2.3)	4 (3.5)	20 (1.0)
Productive cough	56 (2.3)	3 (2.6)	16 (0.8)
Throat irritation	55 (2.3)	2 (1.8)	2 (0.1)

In the controlled phase 2/3 database, there were 6 (0.25%) TI-treated patients, 2 (1.7%) TP-treated patients and 4 (0.21%) comparator-treated patients with lung nodules of unknown etiology detected incidentally on CT imaging. The nodules that had available measurements were <5 mm in diameter. After excluding lung nodules that were detected with less than 3 months of exposure to study medication, there were 5 cases among TI/TP-treated patients and 4 cases among comparator-treated patients.

There were 4 cases of hemoptysis – 3 (0.12%) with TI and 1 (0.05%) with comparator and 5 cases of interstitial lung disease – 4 (0.17%) with TI and 1 (0.05%) with comparator. Dr. Karimi-Shah questions the diagnosis of interstitial lung disease in the 4 Afrezza-treated patients because these patients did not undergo CT imaging. There were also 4 (0.17%) reported cases of laryngospasm with TI. Dr. Karimi-Shah notes that laryngospasm may be due to the irritant nature of TI.

According to Dr. Karimi-Shah, the pulmonary function test data were adequately obtained and underwent blinded central review. Ms. Joy Mele analyzed the FEV<sub>1</sub> data in the two phase 2 trials in type 2 diabetes (studies 005 and 0008), in the two 1-year trials (Study 009 in type 1 diabetes and Study 102 in type 2 diabetes) and in the 2-year trial (Study 030, which had FEV<sub>1</sub> as the primary endpoint). Ms. Mele also analyzed data from extension study 126 to assess for reversibility of FEV<sub>1</sub> findings, as this trial provided 2 months of follow-up where patients from other trials were withdrawn from TI and followed on usual care. However, <25% of randomized patients from the feeder trials provided data for Study 126. Because of the extent of missing data, Ms. Mele has determined that these data are insufficient to draw definitive conclusions regarding reversibility of FEV<sub>1</sub> after TI withdrawal.

Figure 2 shows the FEV<sub>1</sub> data for the 2-year pulmonary safety trial (Study 030). This open-label trial randomized 540 patients with type 1 diabetes and 1349 patients with type 2 diabetes to TI or usual care. There was also a non-randomized treatment arm that enrolled 164 subjects without diabetes. Note that only ~50% of the TI-treated patients and ~70% of the comparator-treated patients completed the 24-month trial. This high and differential dropout rate was driven by adverse events (11.1% vs. 0.9%) and by withdrawal of consent (23% vs. 18%) – see the other Safety sections of this memorandum for details. Ms. Mele calculated the change from

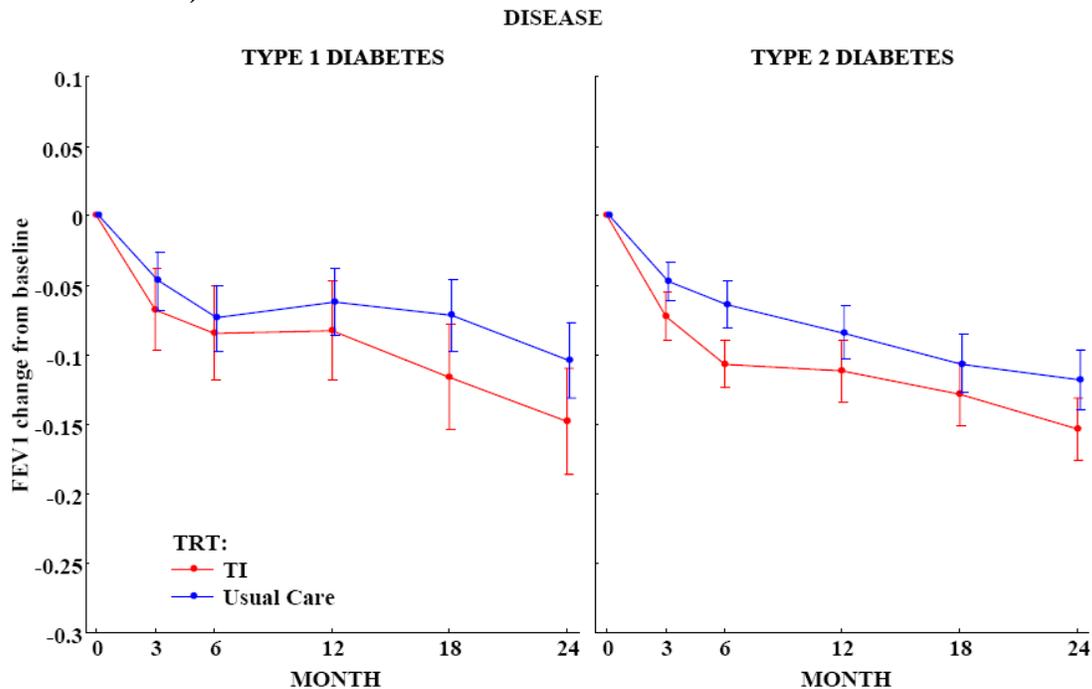
baseline using intent-to-treat and completers analyses to assess the sensitivity of the results to method used. These approaches yielded similar FEV<sub>1</sub> results.

Figure 2 shows a consistently greater lowering of FEV<sub>1</sub> with TI compared to control with both groups having a continued decrease in FEV<sub>1</sub> over time. Dr. Karimi-Shah notes that this decline in FEV<sub>1</sub> (even for the comparator arm) is somewhat larger than that described in published data for non-smoking patients without lung disease. Similar findings were seen with Exubera.

For Study 030, Ms. Mele calculated a mean treatment difference in FEV<sub>1</sub> from baseline to Month 24 of ~40 mL in both type 1 and type 2 diabetes. Ms. Mele notes that this difference is only statistically significant for type 2 diabetes but attributes the lack of statistical significance for type 1 diabetes to the lower power from the smaller sample size. Ms. Mele notes that significantly more TI-treated patients compared to usual care-treated patients had ≥20% decline in FEV<sub>1</sub> from baseline to endpoint (2.5% vs. 0% for type 1 diabetes and 1.9% vs. 0.7% for type 2 diabetes).

Ms. Mele conducted subgroup analyses for the FEV<sub>1</sub> changes from baseline based on age, gender, baseline FEV<sub>1</sub> and country (United States vs. other). Only the p-value for the treatment-by-country interaction was <0.10, with significantly more lowering of FEV<sub>1</sub> for TI compared to usual care in the United States but not in the other pooled countries. Ms. Mele was unable to identify an explanation for this finding and was unable to evaluate foreign countries individually due to smaller sample sizes.

**Figure 2. Mean change (±2SE) from baseline FEV<sub>1</sub> in Study 030 (adapted from Ms. Mele’s review)**



Across the other phase 2/3 trials, the mean treatment difference in FEV<sub>1</sub> between TI and comparator at Month 3 ranged from ~10 mL to ~60 mL, with the larger decline seen with TI. Ms. Mele found a mean treatment difference in FEV<sub>1</sub> of 60 mL (p<0.001) in Study 102 and 40 mL in Study 009 (p=0.03) (Table 12).

Dr. Karimi-Shah also reviewed the DL<sub>CO</sub> data and noted small treatment differences between TI and comparator. DPAP does not consider these differences to be clinically meaningful and places greater emphasis on FEV<sub>1</sub>, which is more reproducible than DL<sub>CO</sub>.

Chest CT imaging (magnetic resonance imaging in Germany) was obtained in a total of 667 patients, representing a subset of patients in Study 030 (55 TI-treated patients and 72 comparator-treated patients) and all patients who participated in studies 0008, 005, and their uncontrolled extension study 010. Imaging was obtained at baseline and study end or annually, depending on the duration of the study. All images were blindly reviewed by a central, independent third party. These images underwent secondary review if there was a suspected abnormality on first review. Dr. Karimi-Shah notes that 29/494 (5.9%) TI-treated patients, 8/101 (7.9%) TP-treated patients, and 3/72 (4.2%) comparator-treated patients had “abnormal, clinically significant” findings on chest CT/MRI imaging. She reviewed the narratives for all patients with an “abnormal, clinically significant” finding on chest imaging and concluded that imaging did not identify a particular safety signal with up to 2 years of treatment with Afrezza.

As noted by Dr. Yanoff, blacks were under-represented in the NDA. Dr. Karimi-Shah recommends that the required postmarketing studies adequately study this demographic subset.

<b>Table 12. FEV<sub>1</sub> (mL) change from baseline to endpoint (intent-to-treat population) (adapted from Ms. Mele’s review)</b>				
	<b>TI</b>	<b>Comparator</b>	<b>Treatment difference LS mean (95% CI)</b>	<b>p-value</b>
<b>Type 1 diabetes</b>				
<b>Study 009 (1-year)</b>	N=235	N=244		
Baseline	3,450±800	3,460±800	-40 (-80, -5)	0.03
Change	-70±200	-40±200		
% with ≥20% drop	0.8%	0.8%	-	0.06
<b>Study 030 (2-year)</b>	N=200	N=246		
Baseline	3,540±700	3,650±800	-40 (-80, -1)	0.04
Change	-130±200	-100±200		
% with ≥20% drop	2.5%	0%	-	0.03
<b>Type 2 diabetes</b>				
<b>Study 102 (1-year)</b>	N=266	N=283		
Baseline	2,860±700	2,770±700	-60 (-100, -30)	<0.001
Change	-139±200	-70±200		
% with ≥20% drop	2.6%	1.8%	-	<0.001
<b>Study 030 (2-year)</b>	N=530	N=578		
Baseline	3,090±700	3,150±700	-40 (-60, -10)	<0.01
Change	-140±200	-100±200		
% with ≥20% drop	1.9%	0.7%	-	0.003

Diabetic ketoacidosis: Among patients with type 2 diabetes, there were 3 reports of ketoacidosis (1 with TI and 2 with comparator) in the pooled, controlled phase 2/3 trials. In all 3 cases, metabolic acidosis was confirmed, supporting the diagnosis of ketoacidosis and raising questions about whether these patients truly had type 2 diabetes, given that ketoacidosis is predominantly a feature of type 1 diabetes. The TI-treated patient was diagnosed with ketoacidosis on Day 339 while prescribed detemir 64 units daily and TI 90 units with meals. The investigator reported that the patient had worsening depression that triggered neglect of anti-diabetic care.

Among patients with type 1 diabetes, there were 16 reports of ketoacidosis – 13 with TI (2.1%; 2.4 per 100 patient-years) and 3 (0.5%; 0.4 per 100 patient-years) with comparator. Four of the 13 cases with TI did not have confirmed metabolic acidosis (e.g., laboratory data not available) and, therefore, may not have had a definitive diagnosis of ketoacidosis (Table 13). The duration of treatment until the onset of ketoacidosis among TI-treated patients ranged from 1-525 days. Two of these TI-treated patients had ketoacidosis <1 month into the treatment period, with one having a buttock abscess and urinary tract infection and the other inappropriately using the inhaler. Most (8/13) of the TI-treated patients who developed ketoacidosis resumed TI and only one of these patients had a second episode of ketoacidosis (occurred approximately 3 months after the first episode and attributed to pancreatitis). Many of the episodes in the TI-treated patients had an identifiable precipitant, such as missed insulin dose(s) or infection. It is possible that the lower glycemic efficacy with TI+glargine compared to subcutaneous aspart+glargine results in less protection against diabetic ketoacidosis, particularly in times of stress. Another potential explanation for this imbalance may be variations in user flow rates.

At least 3 events of ketoacidosis appear to be related to missed doses of insulin and 1 event was attributed to inappropriate use of the inhaler. Patients who are prescribed Afrezza should be informed that Afrezza does not replace basal insulin and there should be appropriate patient education on how to correctly use the inhaler. Patients should also be informed to closely monitor glucoses during infections and to switch exclusively to subcutaneous insulin if glucoses are becoming uncontrolled.

**Table 13. Characteristics of the 14 TI-treated patients with type 1 diabetes who developed treatment-emergent ketoacidosis**

<b>Time to Onset (days)</b>	<b>Metabolic Acidosis Confirmed?</b>	<b>TI Resumed?</b>	<b>Recurrent Ketoacidosis on TI?</b>	<b>Precipitant</b>	<b>Other Comments</b>
56	Yes	Yes	No	Stopped taking basal insulin regularly	-
33	Yes	No	-	Influenza	-
421	Yes	Yes	Yes	?	Presented with nausea/vomiting/dyspepsia Recurrent ketoacidosis ~90 days after the first episode and attributed to pancreatitis
523	Yes	Yes	No	Upper respiratory tract infection	-
205	Yes	Yes	No	?Food poisoning	Nausea/vomiting after eating fish
260	Yes	Yes	No	“Dietary issues”	-
362	Yes	Yes	No	Excess food and 1 missed dose of insulin	-
3	Yes	No	-	Buttock abscess, urinary tract infection	-
254	Yes	Yes	No	?Acute cholecystitis	Cholecystitis diagnosed 2 weeks later
138	No	No	-	Unknown	Presented with headache, nausea, vomiting
348	No	Yes	No	Missed insulin during a flu-like illness	Glucose 700 mg/dL The sponsor states there were no labs reported in the discharge summary in support of a diagnosis of ketoacidosis
1	No	Yes	No	?Inappropriate use of the inhaler	Glucose 380 mg/dL on Day 1 with ketonuria but no metabolic acidosis No arterial blood gas results reported Subsequently completed the trial
266	Borderline pH	Yes	No	Gastroenteritis	Ketonemia present

Hypoglycemia: In the phase 2 trials (studies 101, 005, and 0008), patients who met any of the following criteria were classified as having hypoglycemia:

- Blood glucose <63 mg/dL OR
- Hypoglycemic symptoms that resolved with caloric intake

In the phase 3 trials (studies 009, 102, and 103), patients who met any of the following criteria were classified as having non-severe hypoglycemia:

- Hypoglycemic symptoms and blood glucose <64 mg/dL OR
- Hypoglycemic symptoms that resolved with treatment (if no blood glucose available) OR
- Blood glucose 37-50 mg/dL regardless of symptoms (patients with blood glucose <37 mg/dL were classified as having severe hypoglycemia)

Table 14, adapted from Ms. Mele’s review shows the protocol-defined criteria for classifying a hypoglycemic event as severe. Note that some of these criteria (e.g., in studies 009, 102 and 103) are not typical definitions for severe hypoglycemia. A better definition would have been an event requiring assistance of another person to treat without requiring that the blood glucose be below a certain threshold (e.g., <37 or <50 mg/dL).

<b>Table 14. Criteria for classifying hypoglycemia as severe (adapted from Ms. Mele’s review)</b>					
	<b>Needed assistance</b>	<b>≥1 cognitive/neuro symptom</b>	<b>Blood glucose &lt;50 mg/dL or symptoms reversed by carbohydrates</b>	<b>Blood glucose &lt;37 mg/dL regardless of symptoms</b>	<b>Required glucagon injection or glucose infusion</b>
<b>Type 1 diabetes</b>					
101	A	A			B
009	A	A	A	B	
<b>Type 2 diabetes</b>					
005	A	A			B
0008	B				B
014	A	A			B
102	A	A	A	B	
103	A	A	A	B	
In a given trial, “A” signs and symptoms needed to be seen together to classify hypoglycemia as severe whereas “B” signs and symptoms alone were sufficient to classify hypoglycemia as severe					

Ms. Mele has analyzed the hypoglycemia data (with a focus on severe hypoglycemia) to determine whether there is sufficient evidence to support the sponsor’s assertion that fewer hypoglycemic events are seen with TI compared to insulin controls. Note that Ms. Mele used the sponsor’s definitions of severe hypoglycemia (Table 14) for her analyses. I concur with Ms. Mele’s approach to evaluate hypoglycemia in the individual trials and not to pool the data given that the trials had different comparators and used somewhat different definitions of hypoglycemia.

Table 15 summarizes the incidence for overall hypoglycemia and severe hypoglycemia in the key phase 2/3 clinical trials. In the type 1 diabetes trials, the incidence of hypoglycemia with

Afrezza+glargine is lower than that with aspart+glargine. However, these data are confounded by the better glycemic control achieved in the aspart+glargine group. Therefore, it is not possible to conclude that Afrezza is less likely to cause hypoglycemia in this setting. Note the drastic difference in the overall incidence of severe hypoglycemia in the two type 1 diabetes trials (0% in Study 101 vs. ~35% in Study 009), which is, at least in part, due to the different definitions of severe hypoglycemia.

The incidence of hypoglycemia was numerically higher with Afrezza than placebo in studies 005 and 0008, which is expected based on Afrezza’s mechanism of action (an insulin) and the better glycemic control achieved in the Afrezza group (the placebo group was not randomized to active anti-diabetic therapy). In Study 014, the incidence of hypoglycemia and severe hypoglycemia was lower with Afrezza+glargine compared to aspart+glargine. However, as seen in the type 1 diabetes trials, the aspart comparator group had better glycemic efficacy than the Afrezza group. Thus, conclusions regarding hypoglycemia in this setting are confounded.

Ms. Mele notes that Study 102 is the only study that convincingly shows a lower incidence of protocol-defined severe hypoglycemia (14/323 or 4.3% in the TI group vs. 33/331 or 10% in the NovoLog Mix 70/30 group; p<0.01). In this study, TI+glargine was shown to be non-inferior to NovoLog Mix 70/30; therefore, differences in glycemic control do not explain these findings. However, cases of hypoglycemia with a blood glucose <37 mg/dL were classified as severe (regardless of symptoms). As explained above, this is not a typical definition for severe hypoglycemia. In fact, most of the patients classified as having severe hypoglycemia (12/14 for TI and 30/33 for comparator) had a blood glucose <37 mg/dL and did not require the assistance of another person and did not have accompanying cognitive neurological symptoms. When severe hypoglycemia is more typically defined, the incidence is low and comparable between treatment groups – only 3 TI+glargine-treated patients and 5 NovoLog Mix 70/30-treated patients required the assistance of another person to treat and had at least 1 cognitive neurological symptom.

	<b>≥1 event of hypoglycemia</b>		<b>≥1 event of severe hypoglycemia (as defined by the sponsor)</b>	
	<b>TI Group n/N (%)</b>	<b>Comparator<sup>1</sup> n/N (%)</b>	<b>TI Group n/N (%)</b>	<b>Comparator<sup>1</sup> n/N (%)</b>
<b>Type 1 diabetes</b>				
101	48/54 (89)	52/56 (93)	0	0
009	252/293 (86) <sup>2</sup>	252/272 (93)	96/293 (33)	102/272 (38)
<b>Type 2 diabetes</b>				
005	50/181 (28)	7/46 (15)	0	0
0008	26/61 (43)	22/62 (36)	0	0
014	56/151 (37)	83/158 (53)	11/151 (7.3)	14/158 (8.9)
102	155/323 (48) <sup>2</sup>	228/331 (69)	14/323 (4.3) <sup>2</sup>	33/331 (10)
103	31/177 (18) <sup>2</sup>	15/166 (9)	0	0

<sup>1</sup>Insulin secretagogue+metformin for Study 103  
<sup>2</sup>p≤0.05

Hypersensitivity reactions: Insulins, including Humulin R and Novolin R are labeled for allergic reactions, including severe, life-threatening, generalized allergy (e.g., anaphylaxis). Although human insulin and the insulin in Humulin R, Novolin R and Afrezza have identical amino acid sequences, expression systems in bacteria or yeast likely alter other characteristics of these products that predispose to allergy. Based on our knowledge of allergic reactions with currently available insulins, Afrezza is expected to have potential for hypersensitivity reactions and should be labeled as such, if/when approved. Findings of hypersensitivity reactions with Afrezza are supported by some events in the NDA, such as the patient who developed facial edema and respiratory difficulties after the second dose of TI (see Serious Adverse Events). Table 16 summarizes other adverse events potentially related to allergic reactions. Event rates were low and generally comparable between Afrezza and comparator (which mostly included other insulin therapies). Some of these adverse events (e.g., laryngospasm, throat tightness) may be related to a non-allergic mechanism (e.g., irritation) from inhalation of Afrezza.

**Table 16. Adverse events potentially related to hypersensitivity reactions**

	<b>TI N=2409 1814 PY n (%)</b>		<b>Comparator N=1944 2051 PY n (%)</b>	
	n (%)	Per 100 PY	n (%)	Per 100 PY
Hypersensitivity	15 (0.6)	0.8	8 (0.4)	0.4
Drug hypersensitivity	4 (0.2)	0.2	1 (0.1)	<0.1
Throat tightness	4 (0.2)	0.2	0	0
Laryngospasm	3 (0.1)	0.2	0	0
Rash	12 (0.5)	0.7	18 (0.9)	0.9
Urticaria	5 (0.2)	0.3	2 (0.1)	0.1
Angioneurotic edema	3 (0.1)	0.2	0	0
Pruritis generalized	3 (0.1)	0.2	0	0
Rash macular	2 (0.1)	0.1	1 (0.1)	<0.1
Rash papular	2 (0.1)	0.1	0	0
Face edema	1 (<0.1)	0.1	1 (0.1)	<0.1
Rash generalized	0	0	2 (0.1)	0.1

Major adverse cardiovascular events: In December 2008 FDA published a Guidance for Industry entitled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. This guidance document requests that sponsors of new pharmacologic therapies for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. Note that this recommendation generally does not apply to insulin products because insulin is the only life-saving treatment available for patients with type 1 diabetes and is the last-line treatment for patients with type 2 diabetes who have failed all other available therapies. Although the Afrezza program was not prospectively designed to evaluate cardiovascular safety, investigator-reported cardiovascular adverse events have been carefully analyzed by Dr. Yanoff. As shown in her review, these events were infrequent and were balanced between treatment groups.

**Neoplasms:** In the controlled phase 2/3 database, there were 40 (1.7%) TI-treated patients and 30 (1.5%) comparator-treated patients with reported neoplasms. Based on an analysis of malignant tumors, there were 12 (0.5%) events with TI and 7 (0.4%) events with comparator. In this analysis, breast cancer (n=4 with TI vs. n=2 with comparator) and prostate cancer (n=3 with TI vs. n=1 with comparator) were the only malignant tumors reported in more than one TI-treated patient. I concur with Dr. Yanoff that there are very few events and that the available data do not support an association between TI and malignancies.

**Insulin antibody formation:** The sponsor reports using a validated insulin antibody assay for their phase 2/3 trials. Study 0008 used a qualitative assay only and is not discussed in this section. The radioimmunoassay for the other trials measured IgG antibodies and was validated from a lower limit of quantification of 1.6 Kronus units/mL to an upper limit of quantification of 1,000 Kronus units/mL.

Table 17 summarizes the insulin antibody data for the main phase 3 trials. Antibody data are presented for individual trials because of different comparators (insulin vs. non-insulin) and because the trials had varying durations. Analyses focus on median values because the mean values are less reliable due to outliers.

<b>Table 17. Median insulin antibody concentrations (unit/mL) for the main phase 3 trials (Safety Population)</b>					
	Baseline	Change from Baseline			
		Month 3	Month 6	Month 12	Month 24
<b>TYPE 1 DIABETES</b>					
<b>Study 009</b>					
TI+glargine	7 (n=280)	14 (n=226)	34 (n=195)	36 (n=164)	-
Aspart+glargine	7 (n=259)	0 (n=243)	1 (n=227)	1 (n=193)	-
<b>Study 030</b>					
TI	6 (n=262)	8 (n=188)	20 (n=164)	17 (n=144)	14 (n=44)
Usual care	7 (n=268)	-1 (n=240)	-2 (n=237)	-1 (n=220)	3 (n=191)
<b>TYPE 2 DIABETES</b>					
<b>Study 103</b>					
TI alone	3 (n=131)	4 (n=131)	-	-	-
TI+metformin	3 (n=121)	0 (n=121)	-	-	-
Metformin+secretagogue	3 (n=147)	0 (n=147)	-	-	-
<b>Study 014</b>					
TI+glargine	10 (n=148)	-	22 (n=128) <sup>1</sup>	-	-
Aspart+glargine	10 (n=157)	-	11 (n=152) <sup>1</sup>	-	-
<b>Study 102</b>					
TI+glargine	6 (n=300)	4 (n=245)	7 (n=217)	7 (n=179)	-
NovoLog Mix 70/30	6 (n=309)	2 (n=282)	3 (n=254)	3 (n=213)	-
<b>Study 030</b>					
TI	4 (n=652)	0 (n=527)	0 (n=473)	2 (n=414)	5 (n=133)
Usual care	6 (n=671)	0 (n=573)	-1 (n=546)	0 (n=505)	2 (n=454)

<sup>1</sup>Actual data (sponsor did not calculate change from baseline)

As shown in the table above, the greatest median increase in insulin antibodies with TI occurred in the type 1 diabetes trials, particularly from Month 6 onwards. Patients with type 2 diabetes had numerically larger median increases in insulin antibodies with TI compared to control, although the magnitude of the increase in insulin antibodies with TI was considerably smaller than that seen in the type 1 diabetes trials. Dr. Yanoff did not identify a relationship between insulin antibody concentrations and efficacy or selected safety (e.g., hypoglycemia, allergic reactions) findings. Of note, Exubera was also associated with higher antibody concentrations compared to controls in patients with type 1 and type 2 diabetes with greater increases seen in patients with type 1 diabetes. Similarly, the higher antibody concentrations with Exubera did not have a clinical correlate.

**Laboratory data:** Dr. Yanoff has reviewed the mean changes, shift analyses, and outlier analyses for hematology and chemistry data (including liver and renal parameters) for the controlled phase 2/3 trials in patients with type 1 diabetes and type 2 diabetes. I concur that there were no clinically meaningful changes in these parameters with Afrezza compared to control. In the phase 2/3 program, elevations in ALT were balanced between Afrezza and comparator groups. There were no Afrezza-treated patients who met the biochemical criteria for Hy's Law except for the patient who also presented with pancreatitis and who had a hospital discharge diagnosis of gallstone pancreatitis (see Serious Adverse Events).

**Vital signs:** I concur with Dr. Yanoff that there were no clinically meaningful changes in heart rate or blood pressure with Afrezza or comparators in the controlled phase 2/3 trials in patients with type 1 and type 2 diabetes.

**Body weight:** Table 18 summarizes changes in body weight with Afrezza and comparators in the main phase 3 trials in patients with type 1 and type 2 diabetes. The body weight data are presented by individual trial because the comparators and glycemic efficacy conclusions differed between trials.

Afrezza is an insulin and would, therefore, be expected to cause some weight gain. Therefore, the mean reduction from baseline in body weight with TI in most of the phase 3 trials is unusual.

Across the trials shown in Table 17, there was a statistically significant ( $p < 0.05$ ) net reduction in body weight with TI relative to comparator except for the comparison of TI alone vs. metformin+insulin secretagogue. However, mean differences in body weight were small ( $< 2$  kg) and were confounded in two of the trials by the inferior glycemic control with TI. In addition, some of the body weight changes in the TI+metformin arm in Study 103 might be attributable to the changes in the metformin dose early during the treatment period (median dose increase from ~1700 mg from Weeks 1-4 to 2000 mg from Weeks 4-12). The body weight findings are likely least confounded in Study 102 (52-week comparison of TI+glargine vs. twice daily NovoLog Mix 70/30), where efficacy with TI+glargine was non-inferior to that with NovoLog Mix 70/30.

**Table 18. Change from baseline in body weight (kg)  
(Adapted from Dr. Yanoff's review)  
(intent-to-treat population with last-observation-carried-forward)**

	N	Baseline±SD	Adjusted mean change±SE	Change with TI vs. Comparator	
				Mean difference (95% CI)	p-value
<b>TYPE 1 DIABETES</b>					
<b>Study 009 (52 weeks)</b>					
TI+glargine	260	76.5±15.4	-0.6±0.3	-1.8 (-2.5, -1.1)	<0.0001
Aspart+glargine	257	76.9±15.0	1.2±0.3		
<b>TYPE 2 DIABETES</b>					
<b>Study 014 (24-weeks)</b>					
TI+glargine	143	83.4±13.8	-0.6±0.2	-0.7 (-1.2, -0.1)	0.02
Aspart+glargine	155	80.7±13.2	0.1±0.2		
<b>Study 102 (52 weeks)</b>					
TI+glargine	279	88.0±17.1	0.4±0.3	-1.5 (-2.1, -0.8)	<0.0001
NovoLog Mix 70/30	308	85.7±18.0	1.9±0.2		
<b>Study 103 (12 weeks)</b>					
TI alone	177	86.1±15.6	-0.6±0.2	-0.2 (-0.7, 0.3) <sup>1</sup>	0.53
TI+metformin	169	83.9±13.9	-1.1±0.2	-0.7 (-1.2, -0.2) <sup>1</sup>	<0.01
Secretagogue+met	162	84.2±16.2	-0.4±0.2		

<sup>1</sup>vs. secretagogue+metformin

**Electrocardiograms:** Standard 12-lead electrocardiograms were obtained in the controlled phase 2 and 3 trials. The electrocardiograms were reviewed by investigators and were not read centrally by cardiologists, which limits conclusions. The investigators classified the electrocardiogram as “normal”, “abnormal not clinically significant” or “abnormal clinically significant”. These categories are broad and somewhat subjective (e.g., criteria for assessing clinical significance likely varies from one investigator to the next). Therefore, the electrocardiogram analyses have limited utility. The sponsor could be asked to have the electrocardiograms reanalyzed centrally by cardiologists; however, there is no basis for doing so based on the currently available data - there were no concerning findings in the non-clinical trials, the Thorough QT Study, or based on reported cardiovascular adverse events. In addition, there is extensive history with insulin products administered via other routes of administration (including intravenously), which have higher bioavailability than that achieved with Afrezza.

## 9. Advisory Committee Meeting

Afrezza is not a new molecular entity and is the second NDA for an inhaled insulin product. Exubera was discussed at a public advisory committee meeting. Review of the Afrezza NDA with a comparison to the Exubera findings did not identify new efficacy or safety issues that

rose to the level of needing input from an advisory panel. Based on all the above considerations, it was determined that an advisory committee meeting for Afrezza was not needed during this review cycle.

## 10. Pediatrics

The sponsor's pediatric plan has been discussed with the Pediatric Review Committee (PeRC).

[REDACTED] (b) (4)

PeRC has instead recommended that the waiver be for children <4 years of age (which is the cutoff age used for waivers for subcutaneous insulins) so that the sponsor is required to study whether children in the 4-6 year-old age group can feasibly use Afrezza. PeRC's rationale is that if these younger children cannot properly use the device, this information will be labeled and the sponsor will be released from further studying this age group. The sponsor has agreed to this request.

After the initial feasibility study, the sponsor proposes a clinical pharmacology study, a safety study of dose-titration in children with type 1 diabetes, and a safety and efficacy trial involving patients with type 1 and type 2 diabetes. [REDACTED] (b) (4)

[REDACTED] The sponsor has agreed to all of these requests. New timelines for the pediatric studies should be submitted with the complete response.

## 11. Other Relevant Regulatory Issues

**Tradename:** The sponsor initially proposed the Tradename "Afresa" but this name was found to be unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA) because of potential confusion with Apidra, which is another prandial insulin (although Apidra is not an inhaled insulin). The sponsor subsequently proposed the Tradename "Afrezza", which DMEPA has found to be acceptable because of adequate orthographic differences from Apidra. The Afrezza tradename will need to undergo re-review by DMEPA during the next review cycle within 90 days prior to approval. Please see the review by Dr. Laura Pincock for further details.

**Financial disclosures:** Dr. Yanoff reviewed the financial disclosure statements for investigators participating in the Afrezza program. I concur with Dr. Yanoff that data from the one investigator who reported significant payments from MannKind does not adversely impact conclusions, given that he enrolled only 8 patients in the phase 2/3 program.

**Division of Scientific Investigations (DSI):** DSI inspected five clinical sites (3 domestic sites and 2 Russian sites) and [REDACTED] (b) (4) (the Contract Research Organization that interpreted the pulmonary function test results). The clinical sites were selected based on numbers of enrolled patients as well as numbers of Investigational New Drug applications (INDs) in the DSI database. DSI noted some regulatory violations but concluded that these violations were isolated occurrences that are not likely to impact overall data integrity. Examples include isolated under-reporting of non-severe hypoglycemia at 2 clinical sites. All but one of the 7 affected patients had other hypoglycemic events that were reported to the NDA. Therefore, this type of under-reporting is unlikely to impact the overall reported incidence of hypoglycemia (patients are counted for this analysis as long as they have at least 1 reported hypoglycemic episode so that under-reporting of a few events belonging to the same patient will not impact inclusion of the patient in the analysis as long as at least 1 of the events is reported). However, the incidence rate (number of hypoglycemic events adjusted by patient-year exposure) could be underestimated.

In addition, DSI noted that a total of 5 adverse events reported by the 2 Russian sites were not included in line listings in the NDA. The sponsor clarified that 3 of these adverse events were not treatment-emergent (occurred >30 days after the last dose of study medication), that one event was not reported to the sponsor, and that the remaining event was deleted via a data clarification form. I concur with DSI that these findings are not expected to impact overall data integrity.

DSI found important deficiencies upon inspection of the clinical and analytical sites for the pivotal bioequivalence study comparing the Model C inhaler (phase 2/3 product) with Model D (the to-be-marketed product). Problems identified include [REDACTED] (b) (4)

[REDACTED] Based on these deficiencies, the clinical pharmacology reviewers have concluded that the NDA is not acceptable because the to-be-marketed inhaler has not been reliably bridged to the clinical trial inhaler. The clinical pharmacology reviewers are recommending that the sponsor either conduct a new bioequivalence study or attempt to salvage the data from the completed study by reanalyzing the insulin data. These deficiencies and the items needed to resolve these deficiencies will be communicated to the sponsor in the action letter. Please see the reviews by Drs. Sean Kassim and Sang Chung for details.

## 12. Labeling

All labeling is deferred because the NDA cannot be approved at this time (see Section 13).

DMEPA noted several limitations [REDACTED] (b) (4)

(b) (4) DMEPA is concerned that these design issues may lead to confusion and medication errors. DMEPA notes that these concerns related to the design of the device are best addressed before and during the device design process. Because the design is finalized, DMEPA proposes to use labeling to address their concerns. Their recommendations include having the labeled strength and inhaled doses together on all Afrezza labels and adding the trade name Afrezza to the individual cartridges. Based on additional discussions, DMEPA is also requesting a usability study of the Model D inhaler and the corresponding instructions for use to show that the above concerns can be adequately mitigated.

Further review of labeling will be deferred until the next review cycle given that the NDA will not be approved on this cycle.

### 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

#### Complete Response.

The deficiencies of this application that do not permit approval at this time include:

1. Unreliable data submitted for the pivotal bioequivalence study comparing the Model C inhaler used in the phase 3 trials with the to-be-marketed Model D inhaler
2. (b) (4)
3. The need for a human factors study and usability study with the to-be-marketed Model D inhaler. (b) (4) and changes from Model C that affect usability have not been characterized. In addition, proper use of the device is critical for ensuring adequate dosing.

Ideally, facility inspections by the Office of Compliance should be completed before an action is taken so that the sponsor can be informed of any relevant manufacturing deficiencies in the action letter. If this is not possible, the action letter should state that completion of facility inspections are still ongoing.

The sponsor has agreed to fulfill several CMC postmarketing commitments that are fully described in Dr. Carver's and Dr. Schroeder's reviews. These post-approval agreements should be included in the action letter when Afrezza is ready for approval.

- Risk Benefit Assessment

Probably the most important limitation of the phase 3 trials is inadequate titration of insulin doses in the treatment arms (for both Afrezza and comparator). The trials also permitted adjustments in doses of background anti-diabetic medications but these doses remained generally balanced between treatment groups, limiting confounding. Other limitations of the phase 3 trials include the open-label design (which is standard for insulin development programs) and the fact that the only phase 3 efficacy trial in patients with type 1 diabetes failed to meet its primary objective of showing statistical non-inferiority to comparator.

Based on placebo-controlled data from an 11-week, forced-titration trial in patients with type 2 diabetes, pre-meal TI in combination with glargine results in significantly greater reductions in HbA1c compared to placebo in combination with glargine, with mean placebo-corrected reductions in HbA1c of -0.7% to -0.8% for pre-meal TI doses of 28-56 units. Both treatment groups in this 11-week trial had comparable increases in the glargine dose. Therefore, changes in the glargine dose are not expected to confound the between-group change from baseline in HbA1c. An important limitation of this trial includes different durations of exposure to the doses of TI (e.g., 8 weeks for 56 units vs. 11 weeks for 14 units), which may have impacted the ability to observe a dose-response relationship with the higher TI doses. It is conceivable that the mechanism by which insulin is systemically absorbed from the lung becomes saturated at some point so that higher doses of TI are not fully absorbed but this is unlikely with pre-meal doses up to 90 units (the maximum recommended TI dose) because the sponsor has shown that systemic insulin exposures increase proportionally with TI doses ranging from 25 to 100 units based on data from a clinical pharmacology study. Another important limitation of the 11-week trial is that there has been no direct bridge between the TI formulation used in this trial and the TI formulation used in the phase 3 trials. For this reason, the data from this 11-week trial can be viewed as supportive, at best.

In the phase 3 trials, pre-meal Afrezza in combination with glargine was statistically inferior to pre-meal aspart in combination with glargine in both patients with type 1 and type 2 diabetes. In patients with type 2 diabetes, Afrezza in combination with glargine was non-inferior to twice-daily NovoLog Mix 70/30. Clearly, Afrezza is not as good as the gold standard treatment (basal-bolus therapy) for patients with type 1 diabetes as well as for patients with type 2 diabetes who require multiple daily injections of insulin. However, it appears that Afrezza is somewhat comparable to an insulin mix for the treatment of type 2 diabetes. Insulin mixes are generally not as good as basal-bolus therapy for treating diabetes because titration of the mixes is limited by the fixed amount of short-acting and intermediate-acting insulin contained in the mixture. Nonetheless, insulin mixes are appropriate for some patients, such as those who resist or are unable to use more than 2 daily insulin injections, and, therefore, fill an important niche in the treatment of diabetes. A similar approach can be applied to Afrezza. There were some patients with type 1 and type 2 diabetes treated for up to 1 year with Afrezza in combination with glargine who were able to achieve adequate glycemic control (HbA1c  $\leq 7\%$ ) with Afrezza accounting for approximately 50% of the total daily insulin dose. Although a majority of patients treated with Afrezza will not achieve optimal glycemic control, these patients as well as those who are dissatisfied with Afrezza for whatever reason can return to

subcutaneous pre-meal insulin, if needed. For patients who can achieve adequate glycemic control with Afrezza, inhaled insulin offers a unique advantage (no pre-meal injections) over subcutaneous insulins, which is of value for those patients who resist or want to limit the number of daily subcutaneous doses of insulin.

In the type 2 diabetes trial comparing TI in combination with glargine to twice daily NovoLog Mix 70/30, non-inferiority was established in the setting of a higher prandial insulin dose in the TI group together with a lower dose of glargine compared to the dose of the intermediate-acting component of NovoLog Mix 70/30. The fact that TI comprised a significant proportion of the total daily insulin dose provides reassurance that the non-inferiority finding is driven by TI and not by glargine.

One question is whether any of the trials should be repeated with better titration of insulin in the treatment groups. In my opinion, this is unnecessary. The data from the current trials adequately show that Afrezza has some efficacy and that Afrezza can achieve glycemic control in some patients with type 1 and type 2 diabetes. Therefore, with its novel route of administration, Afrezza is a reasonable treatment option for some patients with diabetes.

Although there is only 1 main efficacy trial in patients with type 1 diabetes, I concur with Dr. Yanoff that efficacy for type 1 diabetes is supported, in part, by efficacy in the type 2 diabetes trials (which, if anything, reflects a patient population with a greater degree of insulin resistance than the type 1 population) and from the natural history of type 1 diabetes. Patients in Study 009 who were randomized to TI replaced all of their pre-treatment prandial insulin with TI. These patients had only a 5-unit mean increase in the glargine dose over the course of the 1-year trial and had a mean change from baseline in HbA1c of -0.1%. This finding would not be expected if TI contributed no or minimal efficacy.

From a safety perspective, it appears that Afrezza is a pulmonary irritant, causing cough in about one-fourth of treated patients. In the clinical trials, ~3% of Afrezza-treated patients discontinued treatment due to cough. This appears generally to be a tolerability issue except in patients who have underlying lung disease (e.g., asthma) who may have clinically significant declines in FEV<sub>1</sub> after inhalation and acute bronchospasm that may be life-threatening. This safety issue will be addressed with REMS (see below) that should be designed to assure that the correct patient population receives Afrezza (e.g., requiring pulmonary function testing before starting Afrezza to exclude undiagnosed lung disease). Afrezza-treated patients have greater declines in FEV<sub>1</sub> compared to non-Afrezza-treated patients, with a mean treatment difference of ~40 mL that persists in trials up to 2-years in duration. There are no controlled pulmonary data after 2-years of treatment with Afrezza and DPAP is, therefore, recommending a large (>5,000 patients per treatment arm), long-term (≥5 years) post-approval trial to further characterize the safety of Afrezza. The magnitude of decline in FEV<sub>1</sub> is comparable to that seen with Exubera and the post-approval long-term trial is also consistent with the approach used for Exubera. As with Exubera, DPAP is recommending periodic monitoring of pulmonary function in Afrezza-treated patients, which is reasonable.

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Because this application will not be approved on this cycle, it is reasonable to ask the sponsor to address this concern with the complete response.

Other safety issues include the potential for allergic reactions, including severe events (as is seen with any insulin product). For example, one patient in the Afrezza trials developed angioneurotic edema characterized as facial edema and respiratory difficulties after the second dose of TI. There did not appear to be a relationship between allergic reactions and increases in insulin antibodies although small numbers of events limits conclusions. Allergic reactions should be an adverse event of interest in the postmarketing trials.

The event rate for diabetic ketoacidosis in type 1 diabetes was 2.4 per 100 patient-years with Afrezza+glargine compared to 0.4 per 100 patient-years with aspart+glargine. This imbalance may be related to Afrezza's statistically inferior efficacy in this setting or potentially due to variations in user flow rate. Most of the episodes with Afrezza were triggered by known precipitants (e.g., infections, missing of insulin doses). One event was attributed to inappropriate use of the inhaler. Patients who are prescribed Afrezza should be informed that Afrezza does not replace basal insulin and there should be appropriate patient education on how to correctly use the inhaler. Patients should also be informed to closely monitor glucoses, particularly during infections or times of stress and to switch exclusively to subcutaneous insulin if glucoses are becoming uncontrolled.

There were 5 cases of retinal detachment with Afrezza and no cases with comparator in the controlled phase 2/3 program. These small numbers limit conclusions. Note that there was no imbalance in cases of retinal detachment in the Exubera program. However, there was a numerical imbalance in cases of retinal hemorrhage with Exubera (0.84% or 0.42 per 1000 patient-months) vs. control (0.34% or 0.29 per 1000 patient-months). Eye events should be an adverse event of interest in the postmarketing Afrezza trials.

Based on limitations of the available data, it is not possible to conclude that Afrezza is associated with lower rates of hypoglycemia compared to subcutaneous insulins and such a claim should not be permitted by the sponsor. The overall incidence of hypoglycemia (but not severe hypoglycemia) with Afrezza appears to be reduced relative to controls in only one of the phase 2/3 trials. This 1-year trial compared Afrezza to NovoLog Mix 70/30 in patients with type 2 diabetes and reported an incidence of hypoglycemia of 48% with Afrezza vs. 69% with control in the setting of non-inferior glycemic control. However, it is unclear what proportion of hypoglycemia in this trial is attributed to the basal profile of glargine in the TI arm vs. the peak in insulin concentrations seen with the intermediate-acting component of NovoLog Mix 70/30.

- Recommendation for Postmarketing Risk Management Activities

When the NDA can be approved, there should be a REMS consisting of a Medication Guide and Communication Plan. I concur with the following recommendations from DPAP:

- The need to address use by inappropriate patient populations (e.g., smokers, those with known lung disease) and to warn of the risk of acute respiratory difficulty after inhalation of Afrezza (particularly in those with undiagnosed lung disease).
- The need for patients to have an evaluation of pulmonary function prior to initiating Afrezza to exclude asthma and chronic obstructive pulmonary disease because of the concern for acute life-threatening respiratory difficulty if used in patients with undiagnosed lung disease.
- The need for periodic monitoring of pulmonary function tests (with recommendations on when to discontinue Afrezza) given that there was a greater decline in lung function with Afrezza compared to controls in trials of up to 2 years duration.
- That patients be aware of the need to inhale Afrezza at a consistent air flow rate. This pertains to particle size distribution being dependent on the air flow rate generated by the user, as discussed above.

DPAP is suggesting that the first dose of Afrezza be given in the clinic to ensure that bronchospasm does not occur and that the patient understands how to correctly use the device. In my opinion, this is unnecessary provided that the human factors study and usability study (see deficiencies above) show that patients can correctly use the device. We are requiring patients to undergo pulmonary function testing before initiating Afrezza, which will exclude patients with undiagnosed lung disease who are expected to have the greatest risk for bronchospasm after inhalation of Afrezza. In addition, there are practical issues with giving Afrezza in the clinic because of the need to eat after inhalation.

DPAP is concerned that device failure could pose a significant risk to patients who continue to use the inhaler as if it were functioning normally and recommends that the durability of Model D be formally tested over the proposed 1-year life of the device. Note that the sponsor has conducted *in vitro* testing to support the proposed 1-year in-use life of Model D but clinical testing of Model D durability over this proposed in-use life is lacking. Based on the *in vitro* data for Model D and the clinical data from Model C (the Model D predecessor), one option is to require durability testing of Model D in the 5-year required postmarketing trial (see below and the Recommendations section of this memorandum). With this approach it would be reasonable to reduce the in-use life of Model D to less than 1 year until the clinical durability data are available. Another option is to list the lack of clinical data with Model D as a deficiency in the Complete Response letter and require pre-approval trials with Model D. As recently as the Pre-NDA meeting, we did not state that it was a requirement to do so. Therefore, I favor the option of obtaining the Model D clinical durability data in the

postmarketing setting. However, if there is a determination that additional pre-approval trials are needed to support efficacy then testing of Model D should be incorporated into those trials. Alternatively, if the sponsor will anyhow have clinical data on Model D durability based on trials that are currently ongoing, those data should be required with the sponsor's complete response. The action letter should ask the sponsor to address the lack of clinical data with the Model D inhaler.

Lastly, patients who are prescribed Afrezza should be informed that Afrezza does not replace basal insulin and there should be appropriate patient education on how to correctly use of the inhaler. Patients should also be informed to closely monitor glucoses during infections or times of stress and to switch exclusively to subcutaneous insulin if glucoses are becoming uncontrolled.

The Communication Plan for the REMS should consist of a Dear Health Care Provider Letter explaining the safety concerns described above.

- Recommendation for other Postmarketing Study Commitments

I concur with the postmarketing required studies recommended by DPAP, which are summarized below and are generally in line with what had been requested for Exubera:

- A large ( $\geq 5,000$  patients per treatment arm), long-term ( $\geq 5$  years) controlled trial to further assess the long-term safety of Afrezza, including effects on FEV<sub>1</sub>. Other adverse events of interest should include retinal detachment and allergic/immune reactions. This trial should further evaluate whether there is reversibility of FEV<sub>1</sub> upon discontinuation of Afrezza as there are inconclusive data due to small sample sizes from completed trials. The trial must also test durability of the Model D inhaler over the proposed life of the device. The sponsor should collect reports of device problems and collect the problem devices for evaluation. Towards the end of the life of the device, a subset of functioning devices should be returned for *in vitro* analyses to confirm that these devices are still functioning correctly.
- A long-term epidemiologic study to evaluate the risk of malignant lung tumors in Afrezza-treated patients. I concur with Dr. Yanoff that this trial should also assess allergic/immune reactions with Afrezza.
- Completion of Study 134 (the ongoing phase 3 trial in patients with type 1 diabetes and mild obstructive pulmonary disease) to provide additional data in patients with underlying lung disease.

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As noted by Dr. Yanoff, blacks were under-represented in the Afrezza NDA. I concur with DPAP that the long-term postmarketing studies must adequately study this demographic subset.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	Afrezza (insulin) inhalation powder

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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HYLTON V JOFFE  
03/11/2010

MARY H PARKS  
03/12/2010  
Concur with overall recommendations. Please see DD memo.

**Division Director's Memo**

<b>NDA #</b>	22-472
<b>Drug Product</b>	Afrezza (insulin human [rDNA origin]) Inhalation Powder and Inhaler
<b>Sponsor</b>	Mannkind Corporation
<b>Date of Submission</b>	March 16, 2009
<b>Indication</b>	Treatment of hyperglycemia in adults with type 1 or 2 diabetes mellitus
<b>Action</b>	Complete Response

**Introduction**

NDA 22,472 was submitted by Mannkind Corporation in support of Afrezza, an inhaled insulin product for the treatment of hyperglycemia in adults with type 1 or 2 diabetes mellitus. The drug product is comprised of recombinant human insulin formulated with a novel excipient (fumaryl diketopiperazine or FDKP) which enables the delivery of insulin via inhalation (referred to as Technosphere insulin or T1) with the use of a reusable device. Afrezza is intended for use as prandial insulin therapy only.

This memo accompanies Dr. Hylton Joffe's Cross-Discipline Team Leader (CDTL) Review. Please see his review and other primary reviews for detailed discussions of multiple disciplinary issues. This application will be receiving a *complete response* action primarily due to deficiencies noted on inspection by the Division of Scientific Investigations (DSI) of a pivotal clinical bioequivalence trial bridging the to-be-marketed device (Model D) to the clinically tested device (Model C). The findings from this inspection have been summarized by Drs. Sean Kassim and Sang Chung in their reviews. Other deficiencies involving the device have been identified by reviewers from Center for Devices and Radiologic Health (CDRH – Dr. Melanie Choe) and the Division of Pulmonary and Allergy Products (DPAP – Drs. Banu Karimi-Shah, Sally Seymour, and Alan Schroeder). In addition, the Division of Medication Errors and Prevention Analysis (DMEPA – Dr. Laura Pincock) has concerns regarding the labeling. These issues have been summarized in Dr. Joffe's review and I will not reiterate them in this memo. My memo will focus only on the clinical efficacy findings because the suboptimal glycemic control observed across several trials in Type 1 and 2 diabetes populations has led me to recommend the presentation of this NDA to the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) after the applicant has submitted its complete response to this action letter. I would also note that I have read the safety reviews written by medical reviewers in DPAP and DMEP (Dr. Lisa Yanoff). Although no safety concern *per se* was identified as a deficiency precluding approval, I note the absence of long-term safety data to address lung cancer risk, the limited data in patients with underlying lung disease, and the higher rate of diabetic ketoacidosis in Afrezza-treated patients. These safety concerns will be revisited with the review of the applicant's complete response.

**Clinical Issues**

There were 6 trials evaluating efficacy of T1 in the T2DM patient population. Efficacy data were not pooled as the study designs, choice of comparator, and duration of studies were different across these

trials. The following table summarizes selected characteristics of the trial and patient population. Please note that all these trials employed the Model C device for which the applicant has not been able to establish adequate bridging to the to-be-marketed device based on DSI inspection.

**Table 1 Summary of Phase 2/3 T2DM Trials**

<b>Trial</b>	<b>Study Design</b>	<b>Treatment groups</b>	<b>Background therapy allowed</b>	<b>Duration</b>	<b>Mean Baseline HbA1c (range across treatment groups)</b>
008	DB, PC, rand	T1 vs pbo	OADs	12 weeks	7.78-7.87
005	DB, PC, rand	T1 vs pbo	Insulin glargine	24 weeks	8.59-8.91
026	OL, UC, rand	T1 vs no-treatment control	OADs	12 weeks	9.33-9.58
014	OL, AC, rand	T1 + glargine vs insulin aspart + glargine	Insulin glargine	24 weeks	8.85-9.00
102	OL, AC, rand	T1 + Lantus vs Novolog 70/30	OADs	52 weeks	8.68-8.69
103	OL, AC, rand	T1 + metformin vs metformin + oral secretagogue	Metformin + SU or meglitinide	12 weeks	8.90-8.95

**Placebo-controlled Trials**

Study 0008

This was one of two double-blind, randomized, placebo-controlled trials in patients with T2DM submitted with this NDA. Patients in this trial had sub-optimal glycemic control on monotherapy or combination therapy of oral anti-diabetics (metformin, SU, or TZD). Sub-optimal was defined as per an inclusion criterion of HbA1c 6.6 – 10.5%, the lowest range of all the trials conducted.

After screening, patients were randomized to T1 or placebo for 12 weeks; patients could continue previous OADs throughout this trial. Patients assigned to T1 were initiated on therapy at 6 U prandially before meals. There were no pre-specified titration algorithms. Investigators could increase T1 dose in 6U increments up to a maximum of 48 U with meals to maintain fasting blood glucose < 200 mg/dL.

There were 123 patients randomized to T1 (n=61) or placebo (n=62). Overall completion rate was 87% and comparable between the two treatment groups (88.5% vs 85.5%). The mean Baseline HbA1c in this trial was the lowest of all the Phase 2/3 trials (see Table 7.2). T1 treatment resulted in significantly greater HbA1c reduction from Baseline compared to placebo as analyzed in both the ITT population (LOCF) and completers. The treatment difference was approximately -0.4% (See Table 10 in Dr. Liu’s review).

Study 005

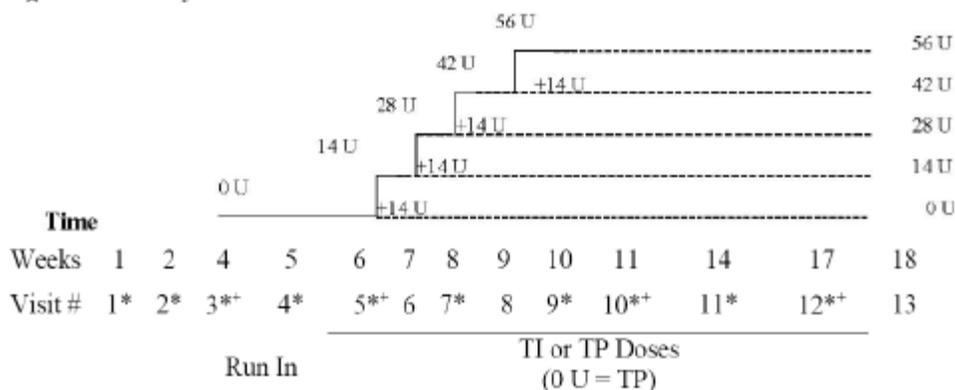
This other placebo-controlled trial differed from Trial 0008 in that it was a forced dose-titration study and had a 24-week treatment period. Patients with suboptimal glycemic control despite treatment with one or more OADs (SUs, alpha glucosidase inhibitors, metformin, meglitinides, TZDs, and/or glargine) who qualified for enrollment were randomized to 5 different treatment groups:

- Placebo
- TI – 14U
- TI – 28 U
- TI – 42 U
- TI – 56 U

After randomization, patient received placebo for 2 weeks and then prior OADs were discontinued at Week 5. Insulin glargine was initiated (if patient not already receiving this) in all patients at differing doses depending on current glargine status. At Week 6, double-blind treatment was initiated. All T1-

treated patients were to initiate treatment at the 14U dosing with upward titration by 14U every week to the assigned treatment. Upward titration was complete by Week 9 wherein patients would all be at their assigned T1 dose group. The following figure illustrates this titration scheme.

**Figure 5.2 - Study 005 schematic**



\*Indicates in-clinic visit  
 + Indicates a meal challenge

Source: Figure 3 Trial 005 CSR.

There were 227 patient randomized in this trial: placebo (n=46); T1 14U (n=45); T1 28U (n=46); T1 42U (n=45); and T1 56U (n=45). Completion rate across all the treatment groups were comparable (87%-97.8%). Discontinuation rates were highest in the placebo group with the predominant reason being ‘patient withdrew consent’. Table 6.10 in Dr. Yanoff’s review discusses the reasons provided for consent withdrawal in this trial. It does not appear that there was any predominant reason to suggest a serious problem with misclassification in this trial.

The following table from Dr. Liu’s review summarizes the efficacy findings from Study 005.

**Table 9 – Study 005 – Efficacy Results for HbA1c**

Trt Group ITT/LOCF	N	Chg from Baseline Raw Mean (SD)	Chg from Baseline LS Mean (SE)	Treatment Diff LS Mean (SE)	95% CI *	p-value *
T (placebo)	41	0.24 (0.91)	0.23 (0.15)	---	---	---
TI 14 U	43	-0.35 (1.15)	-0.29 (0.14)	-0.52 (0.21)	(-1.03, -0.01)	0.0439
TI 28 U	43	-0.54 (1.15)	-0.59 (0.14)	-0.82 (0.21)	(-1.33, -0.31)	0.0004
TI 42 U	41	-0.47 (0.91)	-0.49 (0.15)	-0.72 (0.21)	(-1.24, -0.21)	0.0026
TI 56 U	42	-0.62 (1.11)	-0.59 (0.15)	-0.82 (0.21)	(-1.33, -0.31)	0.0004

The ANCOVA model included treatment as a fixed factor and baseline HbA1c as a covariate.  
 \* Results were based on Dunnett’s t-test and similar to the sponsor’s unadjusted t-test (with site included in the statistical model).

Statistically significant reductions in HbA1c were achieved with all doses of T1 relative to placebo. No dose-response was observed across the 4 T1 doses; however, as noted by Dr. Yanoff, the titration scheme may have contributed to the inability to demonstrate a dose response with T1.

**Active-controlled Trials**

Insulin is rarely used as initial therapy in T2DM except in the setting of severe hyperglycemia, which often represents previously undiagnosed diabetes that has presented in a decompensated state secondary to some other inciting event (e.g., infection). Consequently, insulin is typically considered in T2DM patients currently treated with other anti-diabetic therapies who have sub-optimal glycemic control. Continuation of the current diabetic regimen is not an option in this clinical situation and a decision regarding what therapy to initiate is best evaluated in active-controlled trials.

In this development program, the applicant conducted three active-controlled trials which inform us on the comparative effectiveness of T1 to other approved therapies for T2DM.

*Study 102 (Comparing T1 plus glargine to NovoLog Mix 70/30 in patients previously treated with insulin ± metformin or TZD)*

Patients who had T2DM for a mean duration of 13 years and were receiving 2-3 times daily injection of insulin with or without metformin or a TZD were randomized to T1 plus a basal insulin (insulin glargine) or a premix insulin (NovoLog Mix 70/30) for 52 weeks. Prior use of metformin or TZD could be continued throughout the trial in both treatment groups. The dosing and titration of insulin in both treatment groups are discussed in Dr. Yanoff's review (page 53-55).

677 patients were randomized: 334 to T1 + glargine and 343 to premix insulin. Fewer patients in the T1 + glargine group completed the trial (64.7%) compared to the premix group (71.7%). The predominant reason for discontinuation was 'subject withdrew consent' (15% vs 9.3%) followed by 'adverse event' (8.7% vs 3.5%). Dr. Yanoff requested additional information for the withdrawals due to consent withdrawal and it would appear that some of these discontinuations may have been due to inadequate efficacy. Discontinuations recorded as due to 'hyperglycemia' or 'diabetes mellitus inadequate control' were low and all occurred in T1 + glargine group (n=3; 0.9%).

This trial was designed as a non-inferiority (NI) trial with a pre-specified NI margin of 0.4% wherein NI of T1 to premix insulin would be established if the upper bound of the 95% CI of the treatment difference in mean change from Baseline in HbA1c at Week 52 was < 0.4%.

In this trial, patients with suboptimal glycemic control on their current sc insulin regimen ± metformin or a TZD had significant reductions in HbA1c with initiation of T1 + glargine (mean chg from Baseline -0.59%) or premix insulin (-0.71%). The treatment difference between the two groups was not statistically significant (+0.12%; p=0.16) but was numerically less with T1+glargine. However, since the upper bound of the 95% CI was 0.29, the applicant was able to establish NI between the two treatment regimens. The following table from Dr. Liu's review summarizes the primary efficacy results in this trial. Other analyses support the conclusion that T1 is non-inferior to premix insulin.

Table 15 – Study 102 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	302	8.69 (1.12)	8.11 (1.26)	-0.58 (1.22)	-0.59 (0.06)
Premixed 70/30 analog	316	8.68 (1.08)	7.98 (1.16)	-0.70 (1.16)	-0.71 (0.06)
Treatment Comparison	Treatment Difference			95% CI	p-value
	LS Mean (SE)				
TI + Lantus vs. Premixed 70/30 analog (ITT w/ LOCF)		0.12 (0.09)		(-0.05, <b>0.29</b> )	0.16
TI + Lantus vs. Premixed 70/30 analog (Completers)		0.06 (0.10)		(-0.14, <b>0.26</b> )	0.55
TI + Lantus vs. Premixed 70/30 analog (Dropouts)		0.30 (0.19)		(-0.07, 0.68)	0.11
TI + Lantus vs. Premixed 70/30 analog (ITT using MMRM with AR(1) for variance-covariance structure)		0.09 (0.09)		(-0.09, <b>0.27</b> )	0.31
The ANCOVA model included treatment and pooled site as fixed factors and baseline HbA1c as the covariate. Similar results were observed when pooled site factor was excluded from the model. In addition, similar results were observed when the disqualified sites (Nos. 286 and 325) were excluded from the analysis.					

Study 014 (Comparing T1+glargine to insulin aspart+glargine in patients previously treated with an insulin regimen)

Patients with T2DM for a mean duration of 12 years and who were treated with insulin were enrolled in this trial. After screening, patients were discontinued from their previous anti-diabetic regimens and randomized to T1+glargine or insulin aspart + glargine for 24 weeks. Dosing and titration of insulin in both treatment groups are discussed on page 57 of Dr. Yanoff's review.

A total of 309 patients were randomized, 151 to T1+glargine and 158 to aspart+glargine. There were 123 (81.5%) completers in the T1+glargine group compared to 153 (96.8%) in the aspart+glargine group. The predominant reason for study discontinuation was 'adverse event' followed by 'subject withdrew consent'. All discontinuations due to an AE (n=15) occurred in the T1+glargine group with 8 of these due to cough of mild to moderate severity. There were two T1-treated patients who discontinued due to hyperglycemia.

The trial was designed as an equivalency trial which was defined as the lower and upper bound of the 95% CI of the treatment difference in mean change from Baseline HbA1c at Week 24 of > -0.4% and < +0.4%, respectively.

In this trial, patients with suboptimal glycemic control on their current insulin regimen who were then switched to T1+glargine or aspart+glargine had significant reductions in HbA1c from baseline. However, the HbA1c reduction in the T1+glargine group was inferior to that of aspart+glargine (+0.36%; p=0.002). The following table from Dr. Liu's review summarizes the efficacy findings from this trial.

Table 12 – Study 014 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 24 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	150	8.85 (1.10)	7.96 (1.34)	-0.89 (1.14)	-0.92 (0.08)
Insulin aspart + Lantus	155	9.00 (1.31)	7.69 (1.09)	-1.31 (1.08)	-1.28 (0.08)
Treatment Comparison	Treatment Difference				
	LS Mean (SE)	95% CI	p-value		
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF)	0.36 (0.11)	(0.14, 0.58)	0.002		
TI + Lantus vs. Insulin aspart + Lantus (Completers)	0.23 (0.12)	(-0.00, 0.47)	0.052		
The ANCOVA model included treatment as a fixed factor and baseline HbA1c as the covariate. Similar results were observed when the disqualified sites (Nos. 517 and 518) were excluded from the analysis.					

*Study 103 (Comparing the substitution of an insulin secretagogue with T1 added to metformin versus continuation of metformin and the insulin secretagogue)*

Patients who had T2DM for a mean duration of 10.5-11 years and were treated with metformin and an insulin secretagogue (SU or meglitinide) but still had suboptimal glycemic control were enrolled. Patients were randomized to T1 alone, T1+metformin, or metformin+secretagogue for a 12-week treatment period which was followed by a 12-week observational period. The primary efficacy analysis was performed at Week 12.

There were 528 patients randomized in a 1:1:1 fashion to T1 (n=183), metformin+secretagogue (n=170) or T1+metformin (n=175). Discontinuation rates were higher in the T1-treatment groups with ~73% completers in the T1-only group and 68% in the T1+metformin compared to ~89% completers in the metformin+secretagogue group. The predominant reason for study discontinuation was ‘subject withdrew consent’ which upon further review there were some cases which may have represented inadequate glycemic control. In Table 6.17 of Dr. Yanoff’s review, the sponsor’s adjudication of discontinuations reveals lack of efficacy as a reason in 11.5% of the T1-only group and 17.7% in the T1+metformin group versus 1.2% in the metformin + secretagogue group.

This trial was designed to demonstrate superiority of T1+metformin over metformin+secretagogue. The trial failed to meet this study objective. Although both the T1+metformin and metformin+secretagogue groups had mean reductions from Baseline in HbA1c, the treatment difference favored metformin+secretagogue. However, Dr. Liu’s analysis reveals that the 95% CI around this treatment difference suggests that T1+metformin is noninferior to metformin+secretagogue since the upper bound of the 95% CI is below 0.4%, an acceptable NI margin specified in other trials.

Table 17 – Study 103 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 12 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI alone	176	8.92 (0.95)	9.15 (1.27)	0.23 (1.19)	0.21 (0.07)
Metformin + Secretagogue	162	8.90 (0.94)	8.15 (1.04)	-0.75 (0.90)	-0.78 (0.08)
TI + Metformin	169	8.95 (0.97)	8.25 (1.09)	-0.70 (1.01)	-0.67 (0.07)
Treatment Comparison	Treatment Difference			95% CI *	p-value *
	LS Mean (SE)				
TI + Met. vs. Met. + Secretagogue (ITT w/ LOCF)		0.10 (0.10)		(-0.13, 0.33)	0.51
TI + Met. vs. Met + Secretagogue (Completers)		-0.06 (0.12)		(-0.33, 0.20)	0.81
TI + Met. vs. Met. + Secretagogue (Dropouts)		0.33 (0.26)		(-0.24, 0.90)	0.29
The ANCOVA model included treatment and pooled site as fixed factors and baseline HbA1c as the covariate. Similar results were observed when pooled site factor was excluded from the model. In addition, similar results were observed when the disqualified site (No. 286) was excluded from the analysis.					
* Results were based on Dunnett's t-test and similar to the sponsor's unadjusted t-test.					

Although this trial is considered an active-controlled trial, the metformin+secretagogue arm is similar to a no control, usual care arm. In fact, one might consider this more to be a no control arm since additional therapies were not allowed, as might be appropriate in a usual care arm. These patients have suboptimal glycemic control but are not randomized to any additional therapy. Instead they are randomized to remain on their current regimen, which is not what one would expect in clinical practice. In clinical practice, changes to the patient's treatment regimen would likely occur with the intent of achieving better glycemic control. Presumably, this formed the basis for superiority trial design since there is no clinical benefit to establishing non-inferiority to a sub-optimal regimen. In my opinion, the significant HbA1c reductions in both the T1+metformin and metformin+secretagogue arms do not negate the fact that this trial failed its primary objective. Since T1+metformin was not able to demonstrate superiority over metformin+secretagogue and was numerically worse, the applicant has not provided a basis for why patients should discontinue the secretagogue and replace it with T1.

Since this trial was designed to be a superiority trial with no pre-specification that should this objective fail, a demonstration of non-inferiority is a secondary efficacy analysis, I would conclude that trial failed to meet its primary objective and additional analyses to describe efficacy is not only exploratory but not appropriate for labeling considerations.

I note that patients who were randomized to treatment with T1 only showed worsening glycemic control. Although the primary efficacy comparisons were between T1+ metformin and metformin+secretagogue, this trial clearly shows that patients failing an oral anti-diabetic regimen should not be transitioned entirely to insulin provided as T1.

### Uncontrolled Study

#### Study 026

This was a 12-week study which enrolled patients with T2DM suboptimally treated on diet and exercise and one or more OADs. For the most part, the OADs used in this trial were metformin and SUs (see page 81 of Dr. Yanoff's review). Patients previously treated with insulin were excluded. After a 2-week screening period, patients were randomized in a 5:1 fashion to T1 or to remain on their current regimen. There was no primary hypothesis test pre-specified for this trial, therefore the objectives of this trial are unclear and results are considered exploratory.

The majority of patients in both treatment groups completed this trial and 100% of patients randomized contributed to the ITT analysis. After 12 weeks of treatment, both treatment groups had significant mean reductions in HbA1c from Baseline but the treatment difference was not statistically significant (-0.03%; p=0.90).

Table 11 – Study 026 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 2) Mean (SD)	Week 14 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI	75	9.58 (1.39)	8.18 (1.12)	-1.40 (1.15)	-1.38 (0.10)
No Treatment Control	15	9.33 (1.50)	8.09 (1.06)	-1.24 (0.93)	-1.35 (0.23)
Treatment Comparison			Treatment Difference		
			LS Mean (SE)	95% CI	p-value
TI vs. No Treatment Control (ITT w/ LOCF)			-0.03 (0.25)	(-0.52, 0.46)	0.90
The ANCOVA model included treatment as a fixed factor and baseline HbA1c as the covariate. Similar results were observed when the disqualified site (No. 518) was excluded from the analysis.					

No conclusions can be made regarding the results of this trial given the unbalanced randomization scheme, lack of prespecified statistical plan, and other design issues. The efficacy data should be considered exploratory and not included in any labeling.

### Type 1 Diabetes Program

Unlike T2DM, exogenous insulin in T1DM is a necessity, not a consideration after diet, exercise, and other oral anti-diabetics have failed to achieve adequate glycemic control. There were only two trials conducted in the T1DM patient population evaluating efficacy (and safety) of T1. Neither of these trials evaluated T1 in the newly-diagnosed T1DM patient but rather, T1 was evaluated for its potential utility as an alternative to prandial subcutaneous insulin injections. As a result, a question that must be asked of these trials is whether a patient with T1DM will achieve a benefit when switching from his/her current regimen of insulin injections to a regimen containing T1. Benefit can be defined as improved glycemic control (i.e., superiority of T1 over current regimen) or maintenance of glycemic control (i.e., non-inferiority of T1 over current regimen). In the latter setting, one might accept the non-injectable route as a benefit to the patient.

#### Study 009

This was a 52-week, randomized, active-controlled, open-label trial comparing T1+ glargine to insulin aspart+glargine. The trial was designed as a non-inferiority study with a prespecified NI margin of 0.4%. The patient population included patients with T1DM between the ages of 18 and 80 years, inclusive, with HbA1c > 7% but ≤ 11%. After a 2-week screening period, 589 patients were randomized 1:1 to the aforementioned treatment groups. Completion rate was low in both treatment groups (71% overall completers) with the primary reason for discontinuation being ‘subject withdrew consent’ (15.6% in T1 group vs. 6.6% in control) followed by physician decision and adverse events.

The patient population was comprised of patients whose mean duration of T1DM was approximately 18 years. Mean baseline HbA1c was 8.4%.

Both T1+glargine and insulin aspart+glargine had statistically significant but clinically modest reductions in HbA1c at Week 52; however, the treatment difference clearly favored the aspart+glargine treatment group. T1+glargine failed to demonstrate non-inferiority to aspart+glargine and was also inferior to this

regimen, as noted in the following table from Dr. Liu’s review, which shows a consistency in results regardless of population analyzed.

Table 19 – Study 009 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	277	8.41 (0.92)	8.28 (1.19)	-0.14 (1.03)	-0.13 (0.06)
Insulin aspart + Lantus	262	8.48 (0.97)	8.09 (1.13)	-0.39 (0.93)	-0.37 (0.06)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF)			0.24 (0.08)	(0.08, 0.404)	0.003
TI + Lantus vs. Insulin aspart + Lantus (Completers)			0.26 (0.10)	(0.07, 0.45)	0.008
TI + Lantus vs. Insulin aspart + Lantus (Dropouts)			0.06 (0.17)	(-0.28, 0.40)	0.731
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF, but including Subjects 1109 and 5029)			0.25 (0.08)	(0.09, 0.42)	0.002
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF, but excluding Sites 286 and 325)			0.26 (0.08)	(0.09, 0.42)	0.003
TI + Lantus vs. Insulin aspart + Lantus (ITT using MMRM with AR(1) for variance-covariance structure)			0.27 (0.09)	(0.10, 0.44)	0.002
The ANCOVA model included treatment and pooled site as fixed factors and baseline HbA1c as the covariate. Similar results were observed when pooled site factor was excluded from the model.					

Dr. Yanoff notes that for T1DM patients, the necessary requirement for exogenous insulin to prevent worsening hyperglycemia is a consideration in the interpretation of these trial results. The fact that there was a mean reduction of -0.14 and no worsening over time of glycemic control is evidence of effectiveness. However, it is not appropriate to disregard the control group results in order to conclude effectiveness of an investigational drug in an active-controlled study. Although there is no doubt that T1 is insulin based on chemical characterization and a plethora of clinical pharmacology studies and other clinical trials, the results from this trial reveal that this recombinant insulin delivered via inhalation was less effective than a standard regimen of prandial + basal insulin injections in T1DM.

I acknowledge that neither groups achieved a mean HbA1c level that was below the ADA (<7%) or AACE (<6.5%) treatment goals which may reflect a variety of speculative factors (e.g., reluctance of investigators for intensive insulin treatment, non-adherence to titration instructions). On pages 128-130 of Dr. Yanoff’s review, she discusses T1, aspart, and glargine dosing during the trial. There was little difference between treatment groups for median daily doses of glargine. Figure 6.8 in Dr. Yanoff’s review suggests continued upward titration of T1 whereas insulin aspart doses remained fairly stable throughout the trial after the initial 12-week titration period. It appears that more intensive dosing of insulin to achieve pre-meal BG < 110 mg/dL, 2-hr PPG < 140 mg/dL, or ADA/AACE HbA1c targets could have been utilized in this trial and successfully met these targets (albeit with a risk of hypoglycemia).

Regardless of the explanation for the less-than-adequate glycemic control in both treatment groups, when patients in this trial replaced their regimen of insulin injections to one that replaced prandial injection with prandial T1 inhalation, they were not able to achieve better or maintain glycemic control as the standard injection regimen. As noted above, such a switch should provide either improved glycemic control or

maintenance of glycemic control that could have been achieved if the patient were to have remained on standard injection therapies. This trial failed to demonstrate either one of these scenarios.

### Study 101

This trial evaluated the efficacy of T1 replacement of sc prandial insulin in patients with T1DM on a stable regimen of prandial+basal insulin. The 12-week treatment period was preceded by a 7-day screening period and a 3-week substitution period in which patients randomized to the T1 group had a step-wise replacement of their sc prandial insulin with T1. Basal insulin (glargine) was administered in both treatment groups. The sc prandial insulin in the control group was insulin aspart.

A total of 111 patients were randomized 1:1 to the two treatment groups. Patients had T1DM for a mean duration of 10.9 (T1 group) and 14.1 years (control) and mean baseline HbA1c was approximately 9.0% in both groups. Overall completion rate was 96%. No patients in the control group discontinued whereas 5 patients in the T1 group discontinued with 3 withdrawing consent.

The primary efficacy endpoint was not a change from baseline in HbA1c but rather, it was the change in blood glucose following a standard meal defined as the AUC<sub>0-300min</sub> and AUC<sub>0-420min</sub> glucose concentration. Mean change from Baseline in HbA1c was a secondary endpoint and is summarized below from Dr. Liu's efficacy analysis.

Table 21 – Study 101 – Efficacy Results for HbA1c

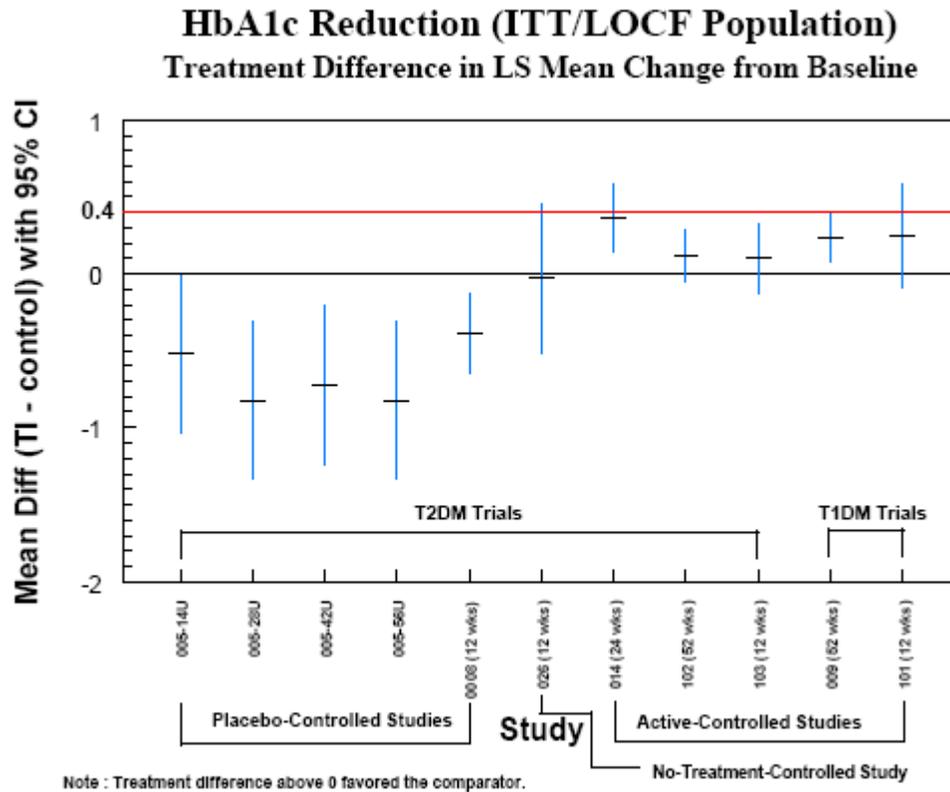
Treatment Group (ITT with LOCF)	N	Baseline (Week -4) Mean (SD)	Week 12 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	51	9.01 (1.22)	8.19 (1.10)	-0.81 (1.10)	-0.78 (0.12)
Insulin aspart + Lantus	56	8.88 (1.18)	7.89 (0.95)	-0.99 (1.07)	-1.02 (0.12)
Treatment Comparison	Treatment Difference				
	LS Mean (SE)	95% CI	p-value		
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF)	0.25 (0.17)	(-0.09, 0.58)	0.15		
TI + Lantus vs. Insulin aspart + Lantus (completers)	0.21 (0.17)	(-0.13, 0.54)	0.22		
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF, but including Subjects 162, 236, and 650)	0.24 (0.16)	(-0.08, 0.57)	0.14		
The ANCOVA model included treatment as a fixed factor and baseline HbA1c as the covariate. Subjects 162, 236, and 650 were excluded from the sponsor's ITT population because they did not have post-baseline measurement of primary efficacy endpoint which was post-prandial glucose excursions AUC <sub>0-300 minutes</sub> .					

Both treatment groups had statistically significant lowering of HbA1c at Week 12 from Baseline; however, the treatment difference was not statistically different from one another with a numerically lower mean reduction in the T1 group. This trial was not designed based on assessment of HbA1c reduction and no non-inferiority margin was pre-specified for this endpoint. However, based on other NI trials in this program, Dr. Liu's calculation of the 95% CI around the treatment difference in a variety of populations suggest that the T1 substitution was not non-inferior to continued sc prandial insulin. I agree with both Drs. Liu and Yanoff that this trial was not designed to adequately assess HbA1c reduction, although the results align with the 52-week pivotal T1DM trial which failed to meet its primary objective of demonstrating NI between T1 and prandial sc insulin.

### **Conclusions on Clinical Efficacy**

From the results of all Phase 2/3 trials summarized above, one can conclude that T1 is behaving as exogenous insulin in that it reduced HbA1c reduction and the change from Baseline is statistically

significant. However, when one considers its efficacy compared to active controls, the efficacy results are inconsistent with respect to achieving the studies' primary objectives, all studies reveal numerically less efficacy of T1 over the comparator, and in some studies T1 is worse than the comparator. The following figure created by Dr. Liu is an excellent graphical presentation of the efficacy of T1 relative to controls across these Phase 2/3 trials.



The placebo-controlled trials in the T2DM population clearly met their study objectives of demonstrating superiority and effectiveness of T1 over placebo (see left side of above figure). However, this is not surprising since it should be fully expected that when patients with suboptimal glycemic control are randomized to placebo or the addition of an insulin, greater efficacy will be achieved with the latter treatment. These two trials support the conclusion that T1 is biologically active exogenous insulin and that its delivery system allows for systemic absorption of the insulin resulting in HbA1c reduction. However, the decision facing clinicians is not to treat a patient with T1 or placebo. Rather, the decision is whether to initiate T1 or some other available therapy. In this setting, one would need to carefully consider the active-controlled trials to determine whether T1 plays a role in the armamentarium of anti-diabetic therapies.

**Overall Recommendation**

As noted in the *Introduction*, this application will receive a *complete response* action. The applicant has been encouraged to meet with the division in an End-of-Review meeting as corrective actions of the deficiencies in this application are complicated and failure to adequately address one deficiency may greatly impact another (e.g., inability to bridge Model C to Model D inhaler device).

Despite the multiple deficiencies in this application precluding its approval, I believe the applicant has demonstrated that systemic absorption of Technosphere insulin does lower blood glucose levels making it a viable candidate for the treatment of type 1 and 2 diabetes. In addition, the non-injectable route of

administration might make it more acceptable to patients than subcutaneous administration of prandial insulins. However, its inferior efficacy to other available anti-diabetic therapies and complexity in device use require a broader discussion among a panel of experts in endocrinology/diabetology before a final regulatory decision is rendered. It should be anticipated that this application will be discussed before a public advisory committee after receipt of the applicant's complete response to the action letter.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	Afrezza (insulin) inhalation powder

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/s/

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MARY H PARKS  
03/12/2010

**MEDICAL OFFICER REVIEW**  
**Division Of Pulmonary and Allergy Drug Products (HFD-570)**

<b>APPLICATION:</b> NDA # 22-472	<b>TRADE NAME:</b> Afresa
<b>APPLICANT:</b> MannKind Corporation	<b>USAN NAME:</b> Technosphere Insulin Inhalation System
<b>MEDICAL OFFICER:</b> Banu Karimi-Shah, MD	<b>CATEGORY:</b> Inhaled Insulin
<b>TEAM LEADER:</b> Sally Seymour, MD	<b>ROUTE:</b> Oral inhalation
<b>REVIEW DATE:</b> April 21, 2009	

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
March 16, 2009		NDA	eCTD

**REVIEW SUMMARY:**

This is a medical officer 45-day Filing Review of NDA 22-472, Technosphere Insulin Inhalation System (TI). MannKind Corporation is developing TI for the treatment of Type 1 and Type 2 diabetes mellitus. Given that the drug product is to be delivered via inhalation, the Division of Pulmonary and Allergy Products (DPAP) has been consulted throughout the development program and will now review the pulmonary safety portion of this NDA submission.

The pulmonary safety of TI Inhalation Powder has been evaluated in 10 controlled Phase 2 and 3 trials: 2 studies in subjects with type 1 diabetes (MKC-TI-009 and MKC-TI-101); 6 studies in subjects with type 2 diabetes (PDC-INS-0008, MCK-TI-005, -014, -026, -102, and -103); 1 study with subjects with type 1 or type 2 diabetes (MKC-TI-030), and 1 study in diabetic subjects with bronchial asthma that was ended after only 3 subjects had enrolled because of difficulty recruiting subjects (MKC-TI-105). One uncontrolled and one observational trial have also been conducted (MKC-TI-010 and MKC-TI-126, respectively).

Pulmonary safety monitoring included assessments of respiratory adverse events, including characterization of cough, serious respiratory adverse events, and discontinuations due to respiratory events. Pulmonary function testing was performed in ten Phase 2/Phase 3 studies, with centrally blinded reading of these PFTs. The program also included chest radiographs and high resolution computed tomography (HRCT) in a subset of patients. All HRCT images were subject to independent central review. HRCT of the chest (or MRIs in Germany) were obtained in a subset of subjects in MCK-TI-030, and all subjects who participated in PDC-INS0008, MKC-TI-005, and MKC-TI-010 (N=667). Respiratory events of special interest are also reported, and these include: asthma, emphysema, dyspnea, laryngospasm, asphyxia, hemoptysis, interstitial lung disease, pulmonary fibrosis, sarcoidosis, and lung neoplasm.

Of note, the current NDA submission does not adequately address the pulmonary effects of TI inhalation powder in patients with underlying lung disease, namely asthma and COPD. Study MKC-134 is currently ongoing and aims to address this issue. Because the Applicant has not conducted thorough investigation of this inhaled insulin drug product in patients with underlying lung disease or smokers, (b) (4)

The Applicant submitted the PFT, HRCT, and AE data requested by the Agency to evaluate the pulmonary safety of Afresa. The supplement is provided in eCTD format and was found to be easily navigated by this reviewer. The submitted pulmonary safety data appear adequate for review, and the application is therefore fileable from a pulmonary safety standpoint. The final regulatory decision regarding filing will be made by DMEP.

**OUTSTANDING ISSUES:** None

**RECOMMENDED REGULATORY ACTION**

<b>IND/NEW STUDIES:</b>	<input type="checkbox"/> SAFE TO PROCEED	<input type="checkbox"/> CLINICAL HOLD
<b>NDA:</b>	<input checked="" type="checkbox"/> FILEABLE	<input type="checkbox"/> NOT FILEABLE
	<b>APPROVAL</b>	<b>APPROVABLE</b> <b>NOT APPROVABLE</b>

**Medical Reviewer:** Banu A. Karimi-Shah, MD

**Medical Team Leader:** Sally Seymour, MD

## I. General Information

Technosphere Insulin (TI) is being proposed as an ultra-rapid acting prandial insulin for the treatment of type 1 and type 2 diabetes mellitus. The drug product consists of Technosphere insulin inhalation powder pre-metered into unit dose cartridges and the MedTone Inhaler. TI is a dry powder formulation of insulin that is delivered via inhalation. It is comprised primarily of insulin and a novel excipient, fumaryl diketopiperazine (FDKP). TI is formed by adsorbing insulin onto the surfaces of Technosphere® particles. The particles are highly porous and have a large specific surface area that is compatible with insulin adsorption.

This review will be limited to the analysis of the pulmonary safety of TI. Non-pulmonary safety and efficacy will not be addressed in this review. This clinical efficacy and overall safety of TI will be reviewed by Dr. Lisa Yanoff in the Division of Metabolic and Endocrine Products (DMEP). Because of the novel method of delivery of insulin in this application, the Division of Pulmonary and Allergy Products (DPAP) has provided input regarding assessment of the pulmonary safety of TI during clinical development. The focus of this review will be the pulmonary safety of TI, which will supplement Dr. Yanoff's clinical review of the efficacy and non-pulmonary safety of TI.

## II. Regulatory History

IND 61,729 was submitted on January 3, 2001, for the TI Inhalation System. The Agency held an End of Phase 2 (EOP2) meeting on October 12, 2004 with MannKind to discuss their plans to pursue Phase 3 trials and conduct a 2 year carcinogenicity study. On July 14, 2008, the Agency held a pre-NDA meeting with the Applicant. The regulatory history pertinent to the pulmonary safety review of this application is outlined below.

### Pre-NDA Meeting

The Applicant's plans to prepare a separate comprehensive integrated evaluation of pulmonary safety were noted. We provided the following comments to the Applicant regarding pulmonary function testing, imaging, underlying lung disease, and pulmonary adverse events:

#### *1. Pulmonary Function Testing*

*Clarify the data you plan to submit with the NDA (e.g. number of patients, duration of exposure, etc). The PFT data you submit in your NDA should include the following:*

- A discussion of patients with significant decline in pulmonary function (i.e. outliers) categorized by degree of deterioration from baseline (e.g. >5%, >10%, >15%, >20% etc.). Provide narratives for patients with significant decline in pulmonary function.*
- Narratives for patients who discontinued participation in the study secondary to a decline in lung function or a pulmonary adverse event.*
- A subgroup analysis by age, sex, race, presence of insulin antibodies, insulin exposure, Type 1 and Type 2 diabetes as these relate to a change in pulmonary function.*
- A discussion of reversibility (if applicable).*
- Cumulative distribution plots of decline in pulmonary function measured as percent change from baseline.*

## 2. Imaging – X-Ray and High Resolution CT (HRCT)

Clarify the data you plan to submit with the NDA (e.g. number of patients undergoing x-ray and HRCT, duration of exposure, etc.). Additionally, clarify whether the imaging studies were read in a blinded fashion in a central location. Provide the details as to how you will present the data from HRCT in your NDA.

## 3. Underlying Lung Disease (ULD)

We note your planned study MKC-TI-134 in response to our request at the End of Phase 2 meeting that you study the long-term safety of your drug product in patients with asthma and chronic obstructive pulmonary disease (COPD). Typically, in clinical trials in asthma or COPD patients, the diagnoses of these disease is based upon established criteria, e.g. Global Initiative for Chronic Obstructive Lung Disease (GOLD), Global Initiative for Asthma (GINA), or National Asthma Education and Prevention Program (NAEPP). The validity of (b) (4) in establishing these diagnoses is unknown and, therefore, we find this inclusion criterion to be unacceptable. Modify the inclusion criteria to utilize widely accepted criteria.

## 4. Pulmonary Adverse Events

A discussion of pulmonary safety should include notable pulmonary adverse events, including, but not limited to:

- Neoplasm
- Interstitial Lung Disease (i.e. sarcoidosis, pulmonary fibrosis, etc.)
- Pleural Effusions

Provide narratives for all notable pulmonary adverse events.

With regard to the population of patients with underlying lung disease, the Applicant resubmitted protocol MKC-134 for our review after amending per our recommendations. This study is currently ongoing.

### III. Clinical Studies

The safety of TI Inhalation Powder and T inhalation Powder has been evaluated in 10 controlled Phase 2 and 3 trials: 2 studies in subjects with type 1 diabetes (MKC-TI-009 and MKC-TI-101); 6 studies in subjects with type 2 diabetes (PDC-INS-0008, MKC-TI-005, MKC-TI-014, MKC-TI-026, MKC-TI-102, and MKC-TI-103); 1 study with subjects with type 1 or type 2 diabetes (MKC-TI-030), and 1 study in diabetic subjects with bronchial asthma that was ended after only 3 subjects had enrolled because of difficulty recruiting subjects (MKC-TI-105). Finally, 1 uncontrolled trial and 1 observational trial have been conducted (MKC-TI-010 and MKC-TI-126, respectively). These studies are depicted in Table 1 below. The pulmonary safety parameters that were assessed in each study are denoted with check marks.

*Reviewer's comment: TI denotes the drug product (Technosphere + Insulin) while T denotes the excipient (FDKP only).*

<b>Table 1: TI clinical studies with Pulmonary Safety Assessments</b>							
Study #	Design	Duration	Number of Subjects	Pulmonary Safety Assessment			
				Adverse Events	Chest X-Rays	PFTS	HRCT
<b>TYPE 1 DIABETES</b>							
<b>MKC-TI-101</b>	R, OL, Multi-site substitution study	12 weeks	120	✓	✓	✓	
<b>MKC-TI-009</b>	R, C, OL	52 weeks	589	✓	✓	✓	
<b>TYPE 2 DIABETES</b>							
<b>MKC-TI-005</b>	MC, R, DB, PC	13 weeks	227	✓	✓	✓	✓
<b>PDC-INS-0008</b>	R, DB, PC, PG	12 weeks	126	✓	✓	✓	✓
<b>MKC-TI-026</b>	R, C, OL	12 weeks	90	✓	✓	✓	
<b>MKC-TI-014</b>	R, OL	24 weeks	309	✓	✓	✓	
<b>MKC-TI-103</b>	R, C, OL	24 weeks	528	✓	✓	✓	
<b>MKC-TI-102</b>	R, C, OL	52 weeks	677	✓	✓	✓	
<b>MKC-TI-010</b>	OL, UC, extension (from MKC-005, PDC-INS-0008)	48 months	229			✓	✓
<b>TYPE 1 AND 2 DIABETES</b>							
<b>MKC-TI-030</b>	MC, R, OL	24 months	2053	✓	✓	✓	✓ (subset of US patients)
<b>MKC-TI-126</b>	Safety follow-up study (from MKC-TI-009, 102, 103, 030)	8 weeks	649			✓	

MC: multicenter, R: randomized, C: controlled, OL: open-label, PC: placebo-controlled, PG: parallel group, UC: uncontrolled, DB: double-blind, PFTS: pulmonary function tests, HRCT: high resolution computed tomography  
 \*\* MKC-TI-105: study not included in table as study terminated prematurely due to difficulty recruiting patients

#### IV. Statistical Analysis Plan for Integrated Review of Pulmonary Safety

The statistical objectives of the comprehensive integrated review of pulmonary safety were to evaluate the pulmonary safety of TI Inhalation powder by assessing pulmonary AEs, cough events, x-ray and HRCT results, and PFTs. The data were either pooled or non-pooled. For pooled data, 2 pooling strategies were adopted, one for AES, cough and CXRs, and another

for pulmonary function tests (see below). Data that were not pooled included HRCT results and results of 2 follow-up safety studies (MKC-TI-010, a long-term uncontrolled trial and MKC-TI-126, a 2 month safety follow-up study).

## **V. Pulmonary Safety Assessments**

*Reviewer's comment: The Applicant's methodology for pulmonary safety assessment is reviewed below. A brief statement regarding the safety findings is also included, but it should be noted that these are the results as reported by the applicant, and are thus, still subject to review.*

### **A. Pulmonary Function Tests (PFTS)**

Pulmonary function testing was performed according to criteria set forth by the American Thoracic Society (ATS). For the Phase 3 clinical trials, PFTs were performed in only those laboratories that were certified by the Applicant. Certification was based on successful completion of the initial on-site equipment verification and training, an ongoing quality control of the precision and accuracy of test procedures. Blinded, central review of all PFTs was conducted at the certified laboratories by registered pulmonary function technologists in real-time to evaluate the test for adherence to ATS standards.

The specific PFTs evaluated were: FEV1, FVC, FEF 25%-75%, DLCO, RV, and TLC. A total of 21,451 spirometry tests were performed. Per the Applicant, 94% of these tests met ATS/ERS recommendations for quality testing.

*Reviewer's comment: From the pulmonary safety standpoint, the review of FEV1 and DLCO will be emphasized, as these are the most robust and reproducible measures of lung function.*

For analysis of PFTs, data were pooled for controlled efficacy and safety studies lasting at least 12 months. The PFT results were pooled for type 1 diabetes, type 2 diabetes, and the combined population. Studies for which PFT data were pooled were:

- Type 1 DM: MKC-TI-009, MKC-TI-030
- Type 2 DM: MKC-TI-102, MKC-TI-030

The remainder of the studies were not pooled as they had shorter treatment periods, key PFT inclusion criteria were not uniform, and the comparator arms differed. These studies also had different PFT measurements and were not always conducted at certified pulmonary function test laboratories. Summaries of the pulmonary safety in these trials are provided by individual trial.

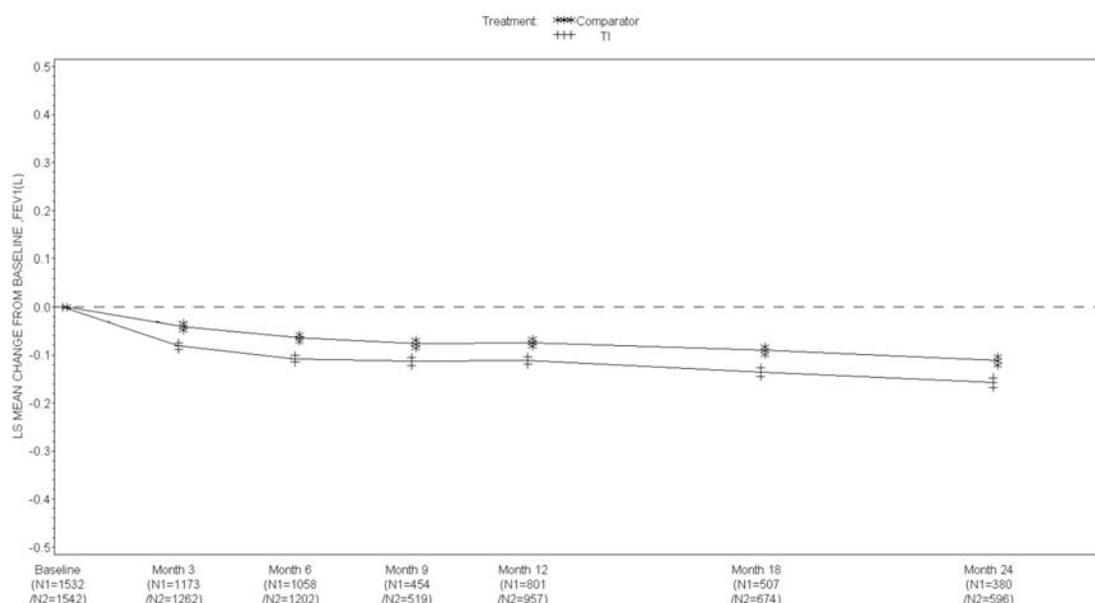
The Phase 3 protocol designs included a pre-defined "PFT finding," defined as a decrease of  $\geq 15\%$  from baseline in FVC, FEV1, TLC, or DLCO. This definition was meant to assist the investigators in noting changes from baseline that should be investigated further.

#### **1. Summary of PFT Safety Findings (per Applicant)**

Small declines from baseline in mean FEV1 and DLCO were observed between subjects treated with TI inhalation powder and comparator, and also in subjects without diabetes. The initial decline was greater for subjects who received TI inhalation powder. The observed

differences in mean change from baseline in FEV1 and DLCO between subjects treated with TI inhalation powder and subjects treated with comparator manifested fully at the first post-baseline time point, were non-progressive for up to 2 years, and disappeared upon cessation of TI inhalation powder irrespective of duration of exposure. The LS Mean difference (TI group- comparator) was -40 mL at 3 months, -43 mL at 6 months, -36 mL at 9 months, -38 mL at 12 months, -45 mL at 18 months, and -45 mL at 24 months. There were no consistent patterns in mean changes from baseline in pulmonary function testing in any subgroup analysis. See Figure 1 for a representative graph of the effect of TI powder on pulmonary function (FEV1).

**Figure 1 LS Mean (SE) of Change from Baseline in FEV<sub>1</sub> (L) by Visit, MMRM Model, Type 1 and Type 2 Diabetes (Safety Population)**



The incidence of PFT Findings (> 15% decrease relative to baseline values) over the course of 2 years of continued therapy was similar between TI Inhalation Powder-treated and comparator-treated subjects. PFT findings leading to early discontinuation of TI Inhalation Powder therapy were rare and occurred in only 3 out of 530 TI Inhalation Powder-treated subjects with PFT findings (2 subjects with type 2 diabetes and 1 subject

with type 1 diabetes).

*Reviewer's comment: The 2 year PFT data are adequate.*

### **B. High Resolution Computed Tomography (HRCT)**

Chest HRCTs (or MRIs in Germany) were obtained in a subset of patients in MKC-TI-030 and all subjects who participated in PDC-INS0008, MKC-TI-005, and MKC-TI-0010. HRCT data are presented separately for each study as study design, duration of study drug exposure, and the comparator treatment arms were different. HRCTs were conducted at baseline and at the end of the study, or annually, depending on the duration of the study. A total of 677 subjects were evaluated by HRCT or MRI.

*Reviewer's comment: This is an adequate number of HRCTs for review purposes.*

All images were collected and centrally reviewed by an independent third party. During the reviews, the independent radiologist was blinded to subject identity, sequence of examinations, and reason for imaging. The reviewer prepared one electronic analysis form per imaging time point. An algorithm was provided to all radiologists in which they had to assess the presence of: interlobular septal thickening, ground glass opacities, tree-in-bud opacities, parenchymal abnormalities, bronchial abnormalities, pleural abnormalities, or pleural effusion. For interlobular septal thickening, ground glass opacities, and tree-in-bud opacities, the radiologist was to assess whether these were absent, present in 50% of the lung, 50-100% of the lung, 100% of the lung, or uncertain. For parenchymal, bronchial, and pleural abnormalities, the radiologist was to assess whether these were absent, present, or uncertain. Subjects found to have "absent" in all categories for both lungs in each image were deemed "normal". Any subject with a response other than "absent" was submitted for secondary review. The second review was conducted by an independent board-certified radiologist (different from the primary reviewer) and an independent board-certified pulmonologist. The second review included presentation of all relevant imaging and the analysis forms of the first reviewer. Subjects were re-queued and blinding of the image data was conducted as for the first review. In addition, the second reviewers were supplied with the following clinical data: subject demographics, smoking history, diabetes treatment history, exposure to pulmonary toxins or chronic irritants, family pulmonary disease history, drug and environmental allergies, medical and surgical history, respiratory infection history, abnormal central laboratory assessments, physical examination findings abnormal vital signs, electrocardiogram results, thoracic radiography reports, pulmonary function testing, self-reported health assessments, pulmonary status update, interim visits, unscheduled visits, concomitant medications and herbal therapies, adverse events, cough reports, subject summary including reason for withdrawal, but were blind to the clinical trial treatment arm. Based upon the data, the secondary reviewers wrote a joint brief narrative for each subject to provide a final interpretation of the radiology imaging. This joint interpretation includes a statement of finding whether the subjects' images were "normal, "abnormal, not clinically significant", or abnormal, clinically significant."

### 1. Summary of HRCT Findings (per Applicant)

**Table 96. High Resolution Computed Tomography Findings (N = 667)**

Finding	TI Inhalation Powder (n = 494)		T Inhalation Powder (n = 101)		Usual Care (n = 72)	
	n	%	n	%	n	%
Normal	140	28.3	40	39.6	14	19.4
Abnormal, not clinically significant	325	65.8	53	52.5	55	76.4
Abnormal, clinically significant	29	5.9	8	7.9	3	4.2

The radiology assessment was included in 4 clinical trials leading to a total of 677 subjects being evaluated by HRCT or MRI. Of all subjects evaluated, 494 were treated with TI Inhalation Powder, 101 were exposed to T Inhalation Powder, and, 72 were in the usual care treatment group with no exposure to Technosphere®. In the TI Inhalation Powder group, 140 subjects (28.3%) were characterized as normal during the independent review, 325 subjects (65.8%) had abnormalities that were not clinically significant, and 29 subjects (5.9%) had findings deemed to be abnormal and clinically significant. The number of subjects and their findings in the Technosphere® Inhalation Powder group were 40 normal (39.6%), 53 abnormal not clinically significant (52.5%), and 8 abnormal clinically significant (7.9%). The corresponding numbers in the usual care group were normal, 14 subjects (19.4%), abnormal not clinically significant, 55 subjects (76.4%), and abnormal clinically significant, 3 subjects (4.2%). Per the Applicant, HRCT and MRI data suggest that there were no clinically significant changes from Baseline. Observed radiologic findings were not suggestive of a safety signal with long term use of TI Inhalation Powder.

### C. Respiratory AEs, Cough, and Chest X-rays

For analysis of respiratory AEs, cough, and chest x-rays, data were pooled for controlled phase 2/3 efficacy and safety studies lasting longer than 14 days. The results were pooled for type 1 diabetes, type 2 diabetes, and the combined population. Studies for which this data were pooled were:

- Type 1 DM: MKC-TI-009, MKC-TI-030, MKC-TI-101
- Type 2 DM: PDC-INS0008, MKC-TI-005, MKC-TI-014, MKC-TI-026, MKC-TI-102, MKC-TI-030, MKC-TI-103

Cough was evaluated as an AE in some studies and with a cough case report form in other studies.

#### 1. Summary of AE findings (per Applicant)

Overall, in controlled clinical studies, reported treatment-emergent respiratory AEs were more common in the TI Inhalation Powder group (43%) followed by the T Inhalation Powder group (38.6%), and the comparator group (28.3%). Cough was reported more commonly in the TI Inhalation Powder group (25.8%) than in the T Inhalation Powder group (18.4%) or

the comparator group (5.4%).

## VI. Brief Review of Proposed Labeling

Draft labeling in the new structured product label format is included in the electronic submission. A brief review of the proposed labeling from a pulmonary safety standpoint is notable for the following points:

- 



(b) (4)

*Reviewer's comment: The product label does not include*

(b) (4)

*It also does not include*

(b) (4)

*These issues will be addressed by this reviewer throughout the course of this review. The language in the label and recommendations for PFT monitoring on drug will need to be addressed.*

## VII. Timeline for Review

Milestone	Target Date for Completion
Stamp Date	March 16, 2009
Filing Date	
74 <sup>th</sup> Day	May 30, 2009
Mid-Cycle Meeting	August 18, 2009
Label Review	October 27, 2009
Wrap-up Meeting	September 29, 2009
Primary Reviews	October 16, 2009
Draft CDTL Memo	November 16, 2009
Labeling Tcon with Applicant	
Secondary Reviews	November 18, 2009
PDUFA Due Date	January 16, 2010

### VIII. Decision

The submission appears adequate from a pulmonary safety standpoint to allow for further review, and is therefore fileable. The final regulatory decision will be made by DMEP.

### IX. Summary

This is a medical officer 45-day Filing Review of NDA 22-472, Technosphere Insulin Inhalation System (TI). MannKind Corporation is developing TI for the treatment of Type 1 and Type 2 diabetes mellitus. Given that the drug product is to be delivered via inhalation, the Division of Pulmonary and Allergy Products (DPAP) has been consulted throughout the development program and will now review the pulmonary safety portion of this NDA submission.

The pulmonary safety of TI Inhalation Powder has been evaluated in 10 controlled Phase 2 and 3 trials: 2 studies in subjects with type 1 diabetes (MKC-TI-009 and MKC-TI-101); 6 studies in subjects with type 2 diabetes (PDC-INS-0008, MCK-TI-005, -014, -026, -102, and -103); 1 study with subjects with type 1 or type 2 diabetes (MKC-TI-030), and 1 study in diabetic subjects with bronchial asthma that was ended after only 3 subjects had enrolled because of difficulty recruiting subjects (MKC-TI-105). One uncontrolled and one observational trial have also been conducted (MKC-TI-010 and MKC-TI-126, respectively).

Pulmonary safety monitoring included assessments of respiratory adverse events, including characterization of cough, serious respiratory adverse events, and discontinuations due to respiratory events. Pulmonary function testing was performed in ten Phase 2/Phase 3 studies, with centrally blinded reading of these PFTs. The program also included chest radiographs and high resolution computed tomography (HRCT) in a subset of patients. All HRCT images were subject to independent central review. HRCT of the chest (or MRIs in Germany) were obtained in a subset of subjects in MCK-TI-030, and all subjects who participated in PDC-INS0008, MKC-TI-005, and MKC-TI-010 (N=667). Respiratory events of special interest are also reported, and these include: asthma, emphysema, dyspnea, laryngospasm, asphyxia, hemoptysis, interstitial lung disease, pulmonary fibrosis, sarcoidosis, and lung neoplasm.

Of note, the current NDA submission does not adequately address the pulmonary effects of TI inhalation powder in patients with underlying lung disease, namely asthma and COPD. Study MKC-134 is currently ongoing and aims to address this issue. Because the Applicant has not conducted thorough investigation of this inhaled insulin drug product in patients with underlying lung disease or smokers, (b) (4)

The Applicant submitted the PFT, HRCT, and AE data requested by the Agency to evaluate the pulmonary safety of Afresa. The supplement is provided in eCTD format and was found to be easily navigated by this reviewer. The submitted pulmonary safety data appear adequate for review, and the application is therefore fileable from a pulmonary safety standpoint. The final regulatory decision regarding filing will be made by DMEP.

Reviewed by:

Banu Karimi-Shah, M.D.

Medical Officer, Division of Pulmonary and Allergy Products

Sally Seymour, M.D.

Medical Team Leader, Division of Pulmonary and Allergy Products

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Banu Karimi-Shah  
5/20/2009 12:34:12 PM  
MEDICAL OFFICER

Sally Seymour  
5/20/2009 01:12:13 PM  
MEDICAL OFFICER  
I concur.

**DIVISION OF PULMONARY AND ALLERGY PRODUCTS MEDICAL  
OFFICER CONSULTATION**

Date: December 28, 2009  
To: Lisa Yanoff, Medical Officer, DMEP  
From: Banu Karimi-Shah, M.D., Medical Officer, DPAP  
Through: Sally Seymour, M.D., Deputy Director for Safety, DPAP  
Subject: Pulmonary Safety of Afrezza (insulin monomer human [rDNA origin]) Inhalation Powder)

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**General Information**

NDA/IND#: NDA 22-472  
Sponsor: MannKind Corporation  
Drug Product: Technosphere Insulin/Afrezza  
Request From: Lisa Yanoff, Medical Officer, DMEP  
Date of Request: March 24, 2009  
Date Received: March 27, 2009  
Materials: Phase 2 and 3 Clinical Trials, Comprehensive Integrated Review of  
Reviewed: Pulmonary Safety, and the Integrated Summary of Safety

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This document is the response from the Division of Pulmonary and Allergy Products (DPAP) to the request for consultation issued by the Division of Metabolic and Endocrine Products (DMEP), requesting analysis of the pulmonary safety of insulin monomer human [rDNA origin]) Inhalation Powder (previously known as Technosphere Insulin Inhalation Powder), or Afrezza (NDA 22-472).

The clinical efficacy and overall safety of Afrezza were reviewed by Dr. Lisa Yanoff, Medical Officer in DMEP. Because of the inhalation method of delivery of insulin in this application, DPAP has been asked to provide input regarding the assessment of the pulmonary safety, which will supplement Dr. Yanoff's clinical review of the efficacy and non-pulmonary safety of Afrezza.

There were no specific questions for response with the consultation. This consult addresses the pulmonary safety of Afrezza, specifically the respiratory adverse events, pulmonary function tests, radiologic imaging, and events of special interest in subjects with type 1 and type 2 diabetes mellitus. In addition, this consult addresses some general issues with inhalation products. This consult does not address the pulmonary safety of Afrezza in subjects with underlying lung disease, as this population has not been studied in the current application. A summary of the pulmonary safety, including analysis of respiratory adverse events, pulmonary function tests, chest x-rays, and high resolution computed tomography of the chest is located in Sections 1.5 Summary of Clinical Findings. A more detailed evaluation of pulmonary safety is

described in Section 5 Review of Safety. The review of pulmonary safety by individual study can be found in Section 6 Appendices. From a pulmonary safety standpoint, there are several issues which the Division of Metabolic and Endocrine Products should consider in making their decision regarding approval of Afrezza.

### **Nomenclature**

Throughout this document, TI (Technosphere Insulin) refers to the drug product, Afrezza; TP or T Inhalation Powder refers to the Technosphere Particles (excipient only); CXR: chest x-ray, HRCT: high resolution computed tomography, PFTs: pulmonary function tests, FEV1: forced expiratory volume in 1 second, DLco: diffusion capacity of carbon monoxide.

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-472
Priority or Standard	Standard
Submit Date(s)	March 16, 2009
Received Date(s)	March 16, 2009
PDUFA Goal Date	January 16, 2010
Division / Office	Pulmonary and Allergy Products Office of Drug Evaluation 2
Reviewer Name(s)	Banu A. Karimi-Shah
Review Completion Date	December 28, 2009
Established Name	Technosphere Insulin
(Proposed) Trade Name	Afrezza
Therapeutic Class	Inhaled Insulin
Applicant	MannKind Corporation
Formulation(s)	Dry Powder for Inhalation
Dosing Regimen	Prandial based on blood glucose
Indication(s)	Type 1 and Type 2 Diabetes
Intended Population(s)	18 years and older

Template Version: [March 6, 2009](#)

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## 1 Executive Summary

### 1.1 General Information

In NDA 22-472, MannKind Corporation has developed Afrezza, insulin monomer human [rDNA origin] Inhalation Powder (previously referred to as Technosphere® Insulin), as an ultra-rapid acting prandial insulin for the treatment of Type 1 and Type 2 Diabetes Mellitus in adults 18 years of age and older. Afrezza is to be administered prior to meals in medication regimens including a long-acting insulin. Afrezza consists of Technosphere® Insulin Inhalation Powder pre-metered into unit dose cartridges and the MedTone® Inhaler.

Technosphere® Insulin (TI) Inhalation Powder is a dry powder formulation of recombinant human insulin and contains a novel proprietary excipient, fumaric acid dihydrate (FDKP). The MedTone Inhaler was designed for exclusive use with Afrezza-filled cartridges. The inhaler is breath-powered, re-usable for 12 months, (b) (4)

The applicant conducted the pivotal phase 2 and 3 clinical trials with a Model C inhaler; however, the Applicant plans to market the Model D inhaler, which has modifications to address some of the issues noted with the Model C inhaler.

This review is limited to the analysis of the pulmonary safety of Afrezza, specifically the respiratory adverse events, pulmonary function tests, radiologic imaging, and pulmonary events of special interest in subjects with type 1 and type 2 diabetes mellitus. In addition, this consult addresses some general issues with inhalation products. Non-pulmonary safety and efficacy are deferred to Dr. Lisa Yanoff, in the DMEP.

There has been one previous inhaled insulin marketed for the treated of type 1 and type 2 diabetes, Exubera Inhalation Powder. Where appropriate throughout this review, the pulmonary safety data from the Exubera clinical program will be noted.

### 1.2 Recommendation on Regulatory Action

The ultimate regulatory action taken on this application is deferred to the Division of Metabolic and Endocrine Products. This review noted several issues which the Division of Metabolic and Endocrine Products should consider in making its decision regarding approval of Afrezza. These are summarized briefly below:

#### 1) *Bronchospasm and cough*

Afrezza appears to cause irritation of the upper respiratory tract, as manifested by cough and occasional bronchospasm, particularly in patients with underlying lung disease, such as asthma. Cough was the most common adverse event noted in the clinical program (25-30% incidence) with Afrezza. Although cough was generally mild, dry, intermittent, and tended to decrease over

time, cough was the reason for discontinuation in approximately 3% of patients treated with Afrezza. There were a number of other respiratory adverse events reported that suggested irritation of the upper respiratory tract including, asthma, bronchial hyperreactivity, bronchospasm, dyspnea, laryngospasm, throat irritation, throat tightness, and wheezing. This raises concern if there is a decline in FEV1 following inhalation of Afrezza.

The Applicant has characterized serial pulmonary function (spirometry, FEV1) immediately post-inhalation of Afrezza, up to 2 hours in asthmatic patients (n=22), and up 4 hours in patients with COPD (n=8) and in patients without asthma or COPD in three small phase 1 studies (see 1.5.3.1 Serial Post-Dose Spirometry). In patients without asthma, a mean decline in FEV1 up to 90mL-138mL post Afrezza was noted in two of the trials. Thus, there is a decline in FEV1 noted post inhalation, albeit likely not large enough to cause symptoms in someone with normal FEV1. In asthmatic patients, FEV1 declined approximately 400 mL when measured 15 minutes after administering Afrezza. This decline recovered towards baseline (to within 20 mL) at 2 hours. In addition, the Applicant has noted difficulties with bronchospasm in the ongoing clinical trial (MKC-TI-134) in patients with asthma. Patients with COPD had a smaller decline (200 mL) and a slower recovery over 4 hours towards baseline. Although Afrezza is not proposed to be labeled for patients with asthma or COPD, there is significant concern that a patient with undiagnosed underlying lung disease may receive the drug and experience respiratory difficulty post-inhalation. Due to this concern, it is DPAP's recommendation to DMEP that if Afrezza is to be approved, labeling should include specific guidance to prescribing physicians that patients should have an evaluation of pulmonary function and exclude the diagnosis of lung disease (asthma and COPD) prior to initiating therapy with Afrezza. Other labeling considerations would be to have the first dose of Afrezza administered in the clinic to ensure bronchospasm does not occur and that patients understand how to use the device.

2)

(b) (4)

(b) (4)

3) *Device durability and patient use data*

This review focuses on pulmonary safety and does not address other issues pertinent to inhalation products, such as device durability and patient use data. However, DPAP has concerns regarding both of these issues as briefly summarized below.

a) *Device durability/ruggedness:*

DPAP typically recommends that device durability be evaluated with the to be marketed device in the phase 3 clinical trials to obtain data over the life of the device. The MedTone Inhaler has a proposed one year life span. It is noted that all the devices evaluated in the clinical program were Model C and not the to-be-marketed Model D inhalers. (b) (4)

(b) (4)  
However, it is unclear if the improvements made to the inhaler achieved their goal, as the durability and ruggedness of the Model D device have not been evaluated. Device failure could pose a significant risk to patients who continue to use the device as if it were functioning normally. Given that the Model C device had identified defects and there is no clinical device durability data with the Model D device, the DMEP needs to consider if the device durability data submitted in this application are adequate. DPAP suggests that the durability of the Model D inhaler be formally tested over its proposed one-year life to ensure that the improvements made to the Model C inhaler did in fact improve device durability and ruggedness.

b) *Patient-use data*

(b) (4) Due to the novel delivery of insulin in Afrezza, patients with diabetes who are accustomed to subcutaneous and/or oral therapies may not be familiar with inhalation devices. Further, physicians who will prescribe Afrezza may not be familiar with inhalation products. Because of these issues, (b) (4) we recommend that the Applicant obtain patient-use data to demonstrate that patients are able to use the device appropriately. While the Applicant has provided some patient use data, it is unclear that this is sufficient to ensure patients are able to use the device appropriately. DPAP recommends DMEP to consider a label comprehension and use study to ensure that patients are able to read, comprehend, and use the device in the manner specified in the labeling. The study should test, for example, whether the written instructions provide clear instructions for patients to open, use, and close the device appropriately. Such a study may identify any problems with the device handling and use, and identify the need to modify the Patient Instructions for Use.

4) Pulmonary Safety

A summary of pulmonary safety is located in Section 1.5 with detailed discussion in Section 5. A high level summary is provided here. The submitted data were adequate to assess pulmonary safety over 2 years. Respiratory adverse events were more common with Afrezza. Concerns regarding cough and bronchospasm were mentioned above. Malignancy is an event of special interest. While a pulmonary malignancy signal was not noted, the database is likely too small to

identify such a signal. If Afrezza is approved, additional data post-marketing is recommended to evaluate for malignancy, similar to what was requested with the Exubera program.

In terms of pulmonary function, patients with type 1 or type 2 DM treated with Afrezza had a greater decline in FEV1 over time than patients treated with comparators. The decline was noted during the first 3 months of therapy. The treatment differences were small (on average about 40-50 mL) and the results from the long-term studies show that the early difference persists and that the endpoint results are statistically significantly different when Afrezza is compared against a non-inhaled anti-diabetic product. There was insufficient data to draw definitive conclusions regarding reversal of the FEV1 effects. Categorical analysis showed that more patients treated with Afrezza had a significant decline in FEV1 ( $\geq 15\%$ ) than in the comparator groups. Overall, a treatment group difference of 40-50mL is not likely to be clinically significant if the treatment groups do not continue to separate over time. The FEV1 data is generally consistent with the effects seen in the Exubera program. Based upon the two year data it is unclear if the groups will separate more with longer treatment, thus, additional long term data is recommended as a post-marketing requirement, similar to what was requested with the Exubera program. The product label should include information about the effects on FEV1 and recommendation for periodic monitoring of FEV1.

### 1.3 Recommendation on Postmarketing Actions

#### 1.3.1 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

MannKind Corporation (MKC) voluntarily submitted a Risk Evaluation Mitigation Strategy (REMS) for Afrezza on July 22, 2009. The REMS proposal consists of a Medication Guide and a Communication Plan. MKC describes the purpose of the Afrezza REMS to (b) (4)



MKC characterizes the risk with Afrezza in their Pharmacovigilance Plan document as those generally associated with insulin treatment and with the inhalation of a dry powder. The identified risks include hypoglycemia and cough. Additionally, there is the potential risk of hypo- and hyperglycemia during treatment initiation (i.e. titration of Afrezza and changes in subcutaneous insulin dosing). Other potential risks include using Afrezza in patients, in whom the safety has not been established, including patients with underlying lung disease, smokers, pediatrics, pregnancy and lactating women, and patients with hepatic or renal impairment.

If Afrezza is approved, DPAP recommends a REMS to include a Medication Guide for patients and possibly a communication plan for healthcare providers. The Medication Guide is recommended because Afrezza has effects on pulmonary function and should not be used in patients with asthma or COPD. Patients should be made aware of this information as this could affect patients' decision to use Afrezza. A communication plan should be considered for

healthcare providers regarding the appropriate patient population for Afrezza, baseline screening spirometry, and periodic monitoring of spirometry.

Per discussion between the Office of Surveillance and Epidemiology (OSE) and the review divisions, the "serious risk" will be the possibility of harm due to use by inappropriate patient populations and the risk of respiratory difficulty immediately post-inhalation and the risk of pulmonary function decline over time.

### 1.3.2 Recommendation for Post-market Requirements and Commitments

If this application is to be approved, the following are recommended post-marketing requirements regarding pulmonary safety:

- The Applicant should conduct a large controlled study designed to further assess the long-term pulmonary safety of Afrezza. In the absence of a safety signal, the most appropriate duration and size of the study are uncertain. We suggest a minimum of 5,000 patients in each treatment arm for a duration of at least 5 years. Ideally, the study will include an assessment of FEV1.
- The Applicant should design and conduct a long-term epidemiologic lung cancer study in order to collect more data regarding the risk of malignant lung neoplasm in patients that use Afrezza.
- The Applicant should complete study MKC-TI-134 to provide more data regarding the safety and efficacy of Afrezza in patients with underlying lung disease, such as asthma and COPD.

## 1.4 Labeling Recommendations

*Reviewer's comment: Although no longer marketed, the Exubera product label was used as a guide to review the proposed label for Afrezza.*

A detailed line-by-line labeling review is pending at the time of this consult response. However, initial review of the proposed product label has revealed some notable omissions. (b) (4)  
High-level labeling comments pertaining to the inclusion of pulmonary safety data include:

### Section 2: Dosage and Administration

- A recommendation for baseline and periodic monitoring of PFTs should be included.

### Section 4: Contraindications

(b) (4). The following contraindications should be included:

- Patients with hypersensitivity to Afrezza or its ingredients

- Smokers
- Unstable or poorly controlled lung disease

#### Section 5: Warnings and Precautions

- (b) (4)  
This statement should be corrected to read that Afrezza is not recommended for patients with any concomitant or underlying lung disease, as it has not been studied in this patient population. In addition, the concern for bronchospasm in patients with asthma should be noted.
- A warning and precaution regarding the decline in pulmonary function should also be included. More detailed information regarding the change in pulmonary function can be presented in Section 6.
- A recommendation that patients have baseline spirometry and periodic monitoring of spirometry. In addition, underlying lung disease should be ruled out.

#### Section 6: Adverse Reactions

- A section entitled “Respiratory Adverse Events” and “Pulmonary Function” should be added to this section. A full explanation of change in PFTs, including figures, in both Type 1 and Type 2 diabetics, as well as a table of common respiratory adverse reactions should be included.

## 1.5 Summary of Clinical Findings

### 1.5.1 Brief Overview of Clinical Program for Pulmonary Safety

The Applicant’s clinical program to evaluate pulmonary safety consisted of 9 controlled phase 2/3 clinical trials, as well as 2 uncontrolled, open label, extension trials (see Table 4, trials grouped by diabetes type). In addition, the Applicant has conducted 31 clinical pharmacology trials to support this NDA. It is of note, that trial MKC-TI-105, which was to evaluate the use of Afrezza in asthma patients, was terminated early due to difficulty in enrolling patients.

The pulmonary safety data were analyzed utilizing the controlled phase 2 and 3 studies in type 1 and type 2 diabetes presented in Table 4. The pulmonary safety data was examined for respiratory adverse events, respiratory SAEs, pulmonary events of special interest (including lung neoplasm), pulmonary function tests, chest x-rays, and HRCT data. Although both forced expiratory volume in 1 second (FEV1) and diffusion capacity (DLco) are discussed in the pulmonary function test section of this review (see 5.3.6 Pulmonary Function Tests) the summary below will focus on the FEV1 findings, as this is thought to be the most clinically reproducible parameter.

The number of subjects exposed to Afrezza in the controlled clinical trials (>600 type 1 diabetics and > 1700 type 2 diabetics) is adequate to assess the pre-marketing pulmonary safety of Afrezza

in subjects without underlying lung disease. In addition, the duration of exposure of up to two years in 538 type 1 diabetics and 1334 type 2 diabetics, is reasonable to assess the pulmonary safety of subjects without underlying lung disease. It should be noted that there are limited data on non-Caucasian subjects.

### 1.5.2 Respiratory Adverse Events

In the controlled phase 2 and 3 trials, there were more respiratory serious adverse events (SAES), respiratory adverse events (AEs), and discontinuations due to respiratory AEs, reported in patients treated with TI than in those subjects who were treated with comparator therapies. There were no deaths due to primary respiratory events in subjects with type 1 or type 2 diabetes in the controlled phase 2 and 3 trials.

Serious adverse events reported in type 1 diabetes included bronchial obstruction, cough, and hemoptysis. Serious adverse events reported in type 2 diabetes included asthma, atelectasis, dyspnea, pulmonary edema, respiratory failure, pneumonia, and pulmonary tuberculosis (Table 10). Overall, however, there were no SAEs that were reported in more than one subject in the Afrezza group and more commonly than in the comparator group. Analysis of the respiratory SAEs does not demonstrate a particular safety signal with use of Afrezza.

More subjects with type 1 or type 2 diabetes discontinued due to respiratory AEs in the Afrezza group than in the comparator groups. The respiratory AEs leading to discontinuation were divided into 3 system organ classes (SOC): Respiratory, Infections, and Investigations. The majority of the AEs were reported in the Respiratory SOC (n = 101, 4.2%). Overall, the most common AE leading to discontinuation was cough, seen only in TI-treated patients, with an overall incidence of 2.7% in TI-treated subjects versus none in the comparator group. In the Respiratory SOC, other AEs leading to discontinuation and reported by more than one subject were dyspnea, asthma, throat irritation, bronchial hyperreactivity, bronchospasm, respiratory tract congestion, and wheezing. In the Infections SOC, the most common AEs leading to discontinuation were bronchitis (0.2%) and upper respiratory tract infection (0.2%). Pneumonia was also reported in 2 subjects in the TI group. Other than cough, other respiratory AEs accounted for the discontinuation of  $\leq 0.4\%$  of subjects. There were 3 subjects who had pulmonary function test abnormalities reported as a reason for discontinuation. When adverse events leading to discontinuation were examined by diabetes type (Table 13), there were no major differences noted.

Respiratory AEs were more common in the Afrezza (33%) and TP-excipient only (25%) groups than in the comparator groups (10%) [Table 18]. Cough was the respiratory AE with the largest difference in incidence between treatment groups (18-27% in TI/TP groups vs. 6% in comparator groups). Other respiratory AEs that were reported in  $\geq 1\%$  of patients and more commonly than in the comparator group for the pooled type 1 and type 2 safety population were: dyspnea, lung infiltration, pharyngolaryngeal pain, productive cough, throat irritation, bronchitis, nasopharyngitis, rhinitis, and pulmonary function test decreased. When adverse events leading to

discontinuation were examined by diabetes type (Table 17), there were no major differences noted. The similarity in both the type and incidence of adverse events in both the TI and TP groups suggests that the AEs are due not only to the active drug substance (insulin), but rather to the excipient as well, however, the number of patients treated with TP-excipient only were small, and therefore this conclusion cannot be definitively drawn.

Cough was further assessed in all phase 2 and 3 controlled clinical trials. In the pooled safety population of type 1 and type 2 diabetes (Table 20), approximately 27% and 20% of patients treated with TI or TP, respectively, reported cough compared to 5.5% of subjects in the comparator group. Greater than 90% of cough episodes in the treatment groups were categorized as intermittent or single-defined. Most cough events in the TI and TP groups occurred within 10 minutes of inhalation of study drug. Although the data collected regarding sputum production is incomplete, it appears that from the data that is present, that TI treatment is not associated with a productive cough. The incidence of cough was highest during the first 3 months of therapy, and then declined as the study treatment continued. Similarly, the cough event rate was highest early in treatment and similar for patients with type 1 or type 2 diabetes. This pooled analysis of cough is consistent with what was seen in each of the individual studies and in type 1 and type 2 diabetes patients. The Applicant also examined the FEV1 decline from baseline to various time points in patients who reported cough versus those who did not report cough (p.167, Pulmonary CIR). In the TI group, mean changes in FEV1 were generally larger in subjects who coughed (by about 20-50 mL at any given time point) compared to those who did not cough up to Month 12 (particularly in the initial 6 months, the same time when the occurrence of cough was also more common.) For subjects who reported no cough over the course of 24 months of continued treatment, change from baseline in mean FEV1 was comparable between the TI and comparator groups. The high percentage of patients experiencing cough within 10 minutes of inhalation is concerning from a pulmonary safety standpoint. Patients are likely to be experiencing airway irritation from the drug product.

*Reviewer's comment: Per the Applicant, the cough was simply due to the dry powder formulation and was an expected adverse event. However, in the experience of DPAP, this cough rate is quite high, even in the clinical development program for a dry powder inhaler. It has been noted by Dr. Ted Carver, CMC reviewer, that the novel excipient, FKDP contains a significant amount of* (b) (4)

*The FKDP particles dissolve at the higher pH in lung and mucosal fluid.* (b) (4) *. Although it is unclear how much* (b) (4) *is required to induce bronchial irritation, this may provide a mechanism for the high incidence of cough observed in this clinical development program and the irritant nature of this drug product.*

Some uncommon respiratory adverse events are worth noting. There was one definitive case of malignant lung neoplasm reported in the controlled clinical studies. This case involved a 62 year-old Caucasian male who developed a small cell carcinoma of the lung approximately 3 months into therapy. Given the short duration of exposure to the drug, this case was unlikely to be due to Afrezza. In addition to the one definitive case of lung malignancy, there were 6 TI-treated, 2

TP-treated, and 4 comparator-treated subjects with lung nodules of unknown etiology (Table 15). These nodules were found on HRCT only and did not otherwise present clinically. The Applicant has not provided any further follow-up on these patients. There were four cases of hemoptysis, 3 in the TI group, 1 in the comparator group. There were 4 cases of interstitial lung disease, including pulmonary fibrosis, reported in the TI group, and one in the comparator group. However, in all four of the cases, HRCT was not performed, which calls the diagnosis into question. There were also 4 cases of laryngospasm reported with inhalation of TI.

### 1.5.3 Pulmonary Function

#### 1.5.3.1 Serial Post-Dose Spirometry

Serial assessment of FEV<sub>1</sub> immediately post-dosing of Afrezza was evaluated in three studies: MKC-TI-027, MKC-TI-113, and MKC-TI-015. Results of the serial FEV<sub>1</sub> assessments are summarized for each trial.

##### MKC-TI-027

The immediate effect of inhalation of TI on pulmonary function in asthmatic subjects and non-asthmatic subjects was measured as the change in spirometry test results (FEV<sub>1</sub> and FVC) over the course of 120 minutes after administration of TI. Mean changes in FEV<sub>1</sub> and FVC at all time points after administration of TI Inhalation Powder are presented in Table 1 below.

**Table 1: Mean Change in FEV<sub>1</sub> and FVC from Pre to Post Dosing with TI Inhalation Powder - Safety Population (MKC-TI-027)**

Parameter/ Statistic/ Time Point	Asthmatic Subjects n = 5	Non-asthmatic Subjects n = 15
<b>FEV<sub>1</sub>, Actual (L)</b>		
Predose: Mean (SD)	2.97 (0.894)	3.15 (0.745)
Post-dose: Mean Change (SD)		
5 minutes	-0.09 (0.040)	-0.07 (0.103)
15 minutes	-0.10 (0.081)	-0.08 (0.138)
30 minutes	-0.04 (0.137)	-0.05 (0.112)
60 minutes	-0.09 (0.108)	-0.04 (0.078)
120 minutes	-0.04 (0.163)	-0.09 (0.085)
<b>FVC, Actual (L)</b>		
Predose: Mean (SD)	3.75 (1.033)	3.95 (0.957)
Post-dose: Mean Change (SD)		
5 minutes	-0.07 (0.080)	-0.10 (0.124)
15 minutes	-0.11 (0.128)	-0.07 (0.135)
30 minutes	-0.06 (0.142)	-0.03 (0.072)
60 minutes	-0.02 (0.227)	-0.04 (0.102)
120 minutes	-0.05 (0.201)	-0.06 (0.104)

Although, the baseline values for FEV<sub>1</sub> and FVC were lower in the asthmatic group, mean decreases from predose levels in FEV<sub>1</sub> and FVC were small in both study groups, with no clear pattern of difference in the mean change from pre to post-TI Inhalation Powder spirometry measurements. The mean change in FEV<sub>1</sub> during the 120-minute post-dosing period ranged from -0.04 L to -0.10 L in the asthmatics group and from -0.04 L to -0.09 L in the non-asthmatics group. The mean change in FVC ranged from -0.02 L to -0.11 L in the asthmatics group and from -0.03 L to -0.10 L in the non-asthmatics group. The largest decrease in FVC was observed at 15 minutes post-dose in the asthmatics group (-0.11 L) and at 5 minutes post-dose in the non-asthmatics group (-0.10 L). No clinically meaningful mean change occurred at any time point in either study group. In addition, review of the individual subject data revealed no clinically significant decrease ( $\geq 15\%$ ) in any asthmatic or non-asthmatic subject at any time point after administration of TI Inhalation Powder. No decrease exceeded 9%.

#### MKC-TI-113

The immediate effect of inhalation of TI on pulmonary function in asthmatic subjects and non-asthmatic subjects was measured as the change in FEV<sub>1</sub> over the course of 120 minutes after administration of TI alone and after administration of TI following pre-treatment with salbutamol (short-acting beta-agonist bronchodilator). Mean changes in FEV<sub>1</sub> at time points up to 120 minutes after administration of TI Inhalation Powder are presented in Table 2 below.

**Table 2: Mean Change in FEV<sub>1</sub> (L) from Pre to Post Dosing with TI Inhalation Powder at Visit 2, Visit 3 and Visit 4- Safety Population (MKC-TI-113)**

Table 1 Scheduled Time Point	Non-asthmatic Subjects (n = 13)		Asthmatic Subjects (n = 17)	
	Absolute Value Mean (SD) L	Change from Baseline Mean (SD) L	Absolute Value Mean (SD) L	Change from Baseline Mean(SD) L
<b>Visit 2 (TI Inhalation Powder administered Alone)</b>				
-15 min	4.085 (0.5548)	NA	3.289(0.678)	NA
15 min post	3.947(0.5998)	-0.138(0.1923)	2.809(0.5967)	-0.396(0.3773)
30 min post	3.937(0.5995)	-0.129(0.1808)	3.022(0.6315)	-0.201(0.2766)
60 min post	4.005(0.5450)	-0.112(0.0820)	3.154(0.6383)	-0.105(0.2514)
120 min post	4.023(0.5887)	-0.042(0.0778)	3.292(0.6334)	-0.020(0.2397)
<b>Visit 3 (TI Inhalation Powder administered after pre-treatment with salbutamol)</b>				
-15 min	4.018(0.6232)	NA	3.332(0.5067)	NA
15 min post	4.167(0.6451)	0.148(0.1112)	3.691(0.65840)	0.487(0.42940)
30 min post	4.157(0.6387)	0.138(0.1055)	3.893(0.7502)	0.563(0.4179)
60 min post	4.151(0.6388)	0.132(0.1311)	3.876(0.7225)	0.566(0.4853)
120 min post	4.068(0.6294)	0.050(0.1216)	3.870(0.7398)	0.487(0.4418)

Data source MKC-113 Table 14.4.13

These data indicate that asthmatic subjects had a clinically significant decline in FEV<sub>1</sub> 15 minutes post-dose (~400 mL), with a return towards baseline FEV<sub>1</sub> by 120 minutes. When TI Inhalation Powder was given after pretreatment with salbutamol, mean FEV<sub>1</sub> was higher at all time points after dosing than before dosing.

*Reviewer's comment: Although no adverse events were reported in this trial in conjunction with these FEV<sub>1</sub> declines, the magnitude of the declines may be clinically significant for patients outside a clinical trial setting.*

#### MKC-TI-015

The immediate effect of inhalation of TI on pulmonary function in COPD subjects and non-COPD subjects was measured as the change in FEV<sub>1</sub> over the course of 485 minutes after administration of TI. Mean changes in FEV<sub>1</sub> at time points up to 120 minutes after administration of TI Inhalation Powder are presented in Table 4 below.

**Table 3: Mean Change in FEV<sub>1</sub> (L) from Pre to Post Dosing with TI Inhalation Powder at Visit 2 (MKC-TI-015)**

Scheduled Time Point	COPD Subjects (n = 8)		Non-COPD subjects (n = 8)	
	Absolute Value Mean(SD)	Change from Baseline Mean(SD)	Absolute Value Mean(SD)	Change from Baseline Mean(SD)
<b>Visit 2 (TI Inhalation Powder administered Alone)</b>				
-15 min	2.480 (0.7713)	NA	3.429(0.7617)	NA
18 min post	2.275 (0.8282)	-0.205 (0.2002)	3.297(0.7306)	0.036 (0.1253)
35 min post	2.315(0.8145)	-0.165 (0.1483)	3.484 (0.8322)	0.055 (0.1110)
65 min post	2.305(0.7940)	-0.175 (0.1472)	3.461(0.7830)	0.033 (0.1459)
125 min post	2.341(0.7718)	-0.139 (0.1880)	3.478 (0.7944)	0.049 (0.1253)
485 min post	2.427(0.8057)	-0.096 (0.1182)	3.353(0.8217)	0.017 (0.1816)

Data source MKC 015 Table 14.4.4.3D

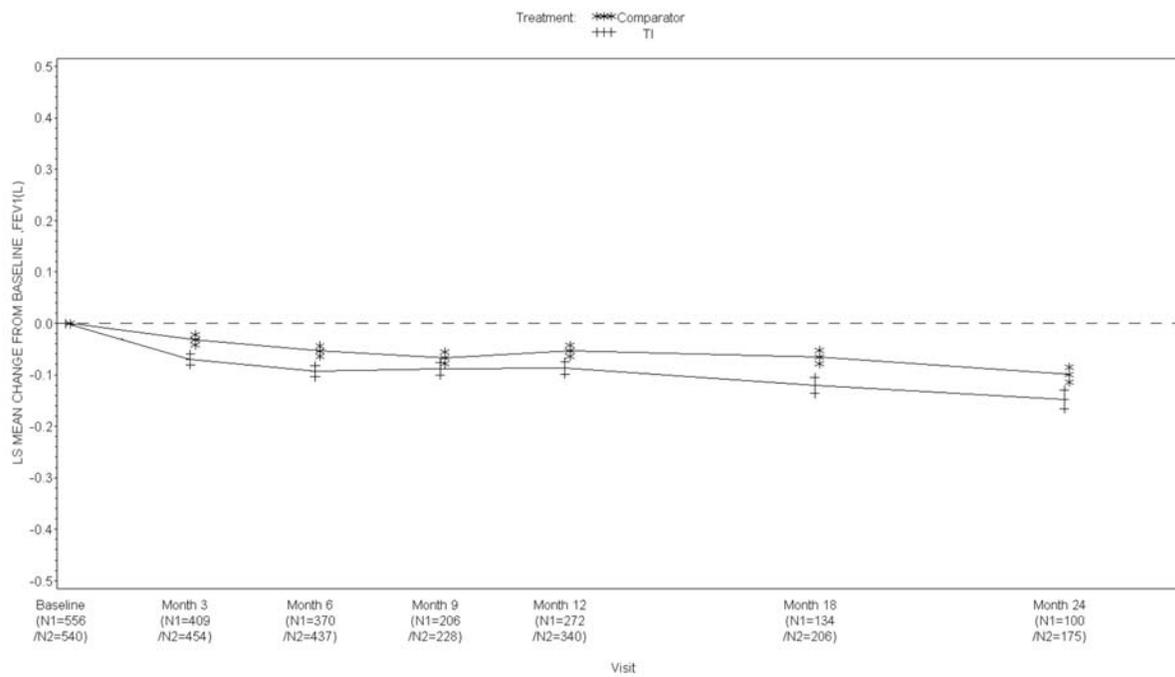
Subjects with COPD had a slightly lower mean FEV<sub>1</sub> before dosing than subjects without COPD. This difference was maintained throughout the 480 minute measurement period. In both groups, the mean changes were small at all time points. In subjects with COPD, the mean decline in FEV<sub>1</sub> was -8.27% at 18 minutes after dosing, -6.65% at 35 minutes, -7.06% at 65 minutes, -5.6% at 125 minutes, and -3.8% at 485 minutes. In Subjects without COPD, the corresponding values were 1.75% improvement at 18 minutes, 1.6% at 35 minutes, 1% at 65 minutes, 1.43% at 125 minutes, 0.5% at 425 minutes.

These data demonstrate that subjects with COPD had an acute, small decline in FEV<sub>1</sub> by 18 minutes and gradually recovered by 485 minutes, whereas subjects without COPD had no meaningful change or minimal improvement in FEV<sub>1</sub> acutely after inhalation of a single dose of TI Inhalation Powder.

### 1.5.3.2 Effect on Pulmonary Function Type 1 Diabetes

The individual phase 2 and 3 trials as well as the pooled controlled studies showed that subjects with type 1 diabetes treated with Afrezza had greater mean decline from baseline FEV<sub>1</sub> over time versus the comparator group. The greatest decline in FEV<sub>1</sub> occurred within the first three months, and then the two treatment groups declined in a parallel fashion. Given the lack of controlled data beyond 2 years, no conclusion can be drawn regarding whether the decline is stable after that time point (See Figure 1).

**Figure 1 LS Mean (SE) Change from Baseline in FEV1 (L) by Visit, MMRM Model, Type 1 Diabetes**



N1=TI; N2 = Comparator; SE=standard error

Source: Figure 35, p. 159, Pulmonary CIR, ISS, Module 5.

For the pooled type 1 diabetes population, after 2 years of treatment, subjects in the Afrezza group had a mean decline from baseline in FEV1 of 150 mL, while subjects in the comparator group had a mean decline from baseline of approximately 100 mL. Both treatment groups demonstrated a larger mean decline than what would be expected in non-smoking subjects without significant lung disease.

*Reviewer’s Comment: To interpret the clinical significance of the change from baseline FEV1 noted in the Applicant’s studies, the following should be noted:*

- *The Lung Health Study was a randomized trial of smoking cessation in middle-aged smokers who had airway obstruction. One of the main outcome variables was the annual change in lung function as measured by the FEV1. Long term (11 year) follow up data was published. Subjects who continued to smoke had an annual change in FEV1 of approximately -60mL/year. Subject who stopped smoking had an annual change in FEV1 of approximately- 30 mL/year.(1)*
- *In a longitudinal epidemiologic study, the Copenhagen City Heart Study, which was conducted between 1976 and 1994, subjects with and without self reported asthma were identified. The annual change in FEV1 was determined from 15 years of data.*

*In nonsmoking subjects without asthma, the annual change in FEV1 was +5 to -5mL/year in subjects age 20-39 years, -17 to -24mL/year in subjects age 40-59 years and -31 to -37mL/year in subjects age 60-79 years.(2)*

*• The Lung Health Study Research Group examined the effect of inhaled corticosteroids on pulmonary function in subjects with COPD. In a randomized, placebo-controlled trial investigating the use of inhaled triamcinolone in 1116 subjects with COPD, the rate of decline in FEV1 in both the placebo and triamcinolone groups was approximately 45cc per year.(3)*

Per the Applicant' analysis, the 2-year mean treatment group difference between Afrezza and the comparator group was -48 mL (a negative difference denotes a greater decline in the TI group) [95% CI: -91, -5], which was statistically significant. In fact the treatment group difference was statistically significant at all time points examined, with the greatest mean treatment group difference observed at 18 months (-56 mL). The Applicant's analysis was consistent with the Agency's statistical analysis which demonstrated a mean treatment difference of -40 mL at 2 years. The Applicant also presented an annual rate of change (slope) in FEV1 between Month 3 (first post-baseline measurement) and Month 24 (last post-baseline measurement) for each treatment group. The annualized change in FEV1 was numerically greater in the TI group, but not statistically different between the two groups from Month 3 to Month 24. The TI group declined approximately 45 mL/year while the comparator group declined approximately 32 mL/year. No data (controlled or uncontrolled) are available to assess the effect of Afrezza on pulmonary function decline in type 1 diabetes after 2 years of exposure.

*Reviewer's comment: Although the lung function decline of patients with diabetes has yet to be fully characterized, the similarities of the Afrezza program to the Exubera program, with respect to the unexpected magnitude of decline in FEV1 in the comparator therapy groups, lends some credence to the notion that there may be an entity of the "diabetic lung".*

A small number of patients from the one-year trial in type 1 diabetes were followed up 8 weeks after TI discontinuation, to examine the effect on FEV1 post-TI discontinuation. Although the number of patients is small, it appears as if only 37% of TI-treated patients returned to their baseline FEV1 as measured at the beginning of the one-year trial. These results suggest that declines in FEV1 that occurred during the course of 1 year treatment did not return to baseline at 2 months of follow-up in the majority of TI-treated patients. Given that both groups' FEV1 are simultaneously declining, return to baseline FEV1 may not be a plausible measure of reversibility. Ideally, the comparison between the treatment difference at randomization baseline and then extension follow-up would have provided the most useful data. However, Dr. Mele completed the analysis in this manner, due to the very small number of patients contributing data at the end time point, which precluded a meaningful comparison of treatment differences. Thus, with the data that are present, one cannot definitively conclude that the change in FEV1 noted with Afrezza is reversible off-treatment, at least at 2 months of follow-up (*Biometrics Review, Dr. Joy Mele*).

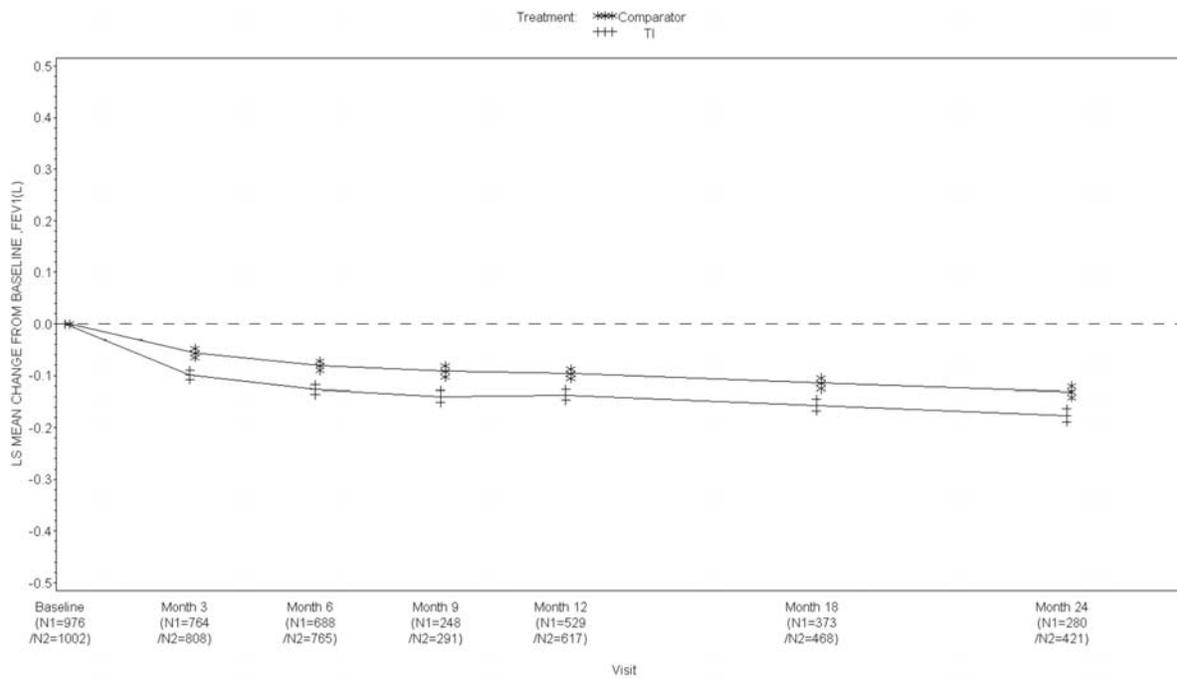
The Agency performed a categorical response analysis to assess the proportion of subjects with a decrease in FEV1 from baseline of various magnitudes. At 1 year, 2.5% of TI subjects and 1.2% of comparator group subjects had  $\geq 15\%$  decline from baseline FEV1. At 1 year, the percentage of subjects with  $\geq 20\%$  drop was the same (0.8%) in the TI and comparator groups. At 2 years, 5.5% of TI subjects and 0.8% of comparator subjects had a  $\geq 15\%$  decline in FEV1. More subjects in the TI group (2.5%) also experienced a  $\geq 20\%$  decline in FEV1 at 2 years than in the comparator group (0%). The differences in subjects experiencing FEV1 declines of both 15% and 20% were statistically significant at 2 years, but not at 1 year (*data courtesy of Dr. Joy Mele, Biometrics Reviewer*).

In summary, FEV1 results for the individual trials in type 1 diabetics generally showed greater decreases in FEV1 during the first 3 months of therapy for TI versus a variety of comparators. These treatment differences were small (on average about 40-50 mL) and no statistically significant, particularly in trials of short duration. However, the results from the long-term studies show that the early differences persist and that the endpoint results are statistically significantly different when TI is compared against a non-inhaled anti-diabetic product. There was insufficient data to draw definitive conclusions regarding reversal of the FEV1 effects with few patients (<25% of randomized patients) proving follow-up data after withdrawal of treatment (from the Biometrics review of Dr. Joy Mele).

#### 1.5.3.3 Effect on Pulmonary Function in Type 2 Diabetes

The individual phase 2 and 3 trials as well as the pooled controlled studies showed that subjects with type 2 diabetes treated with Afrezza had greater mean decline from baseline FEV1 over time versus the comparator group. The greatest decline in FEV1 occurred within the first three months, and then the two treatment groups declined in a parallel fashion. Given the lack of controlled data beyond 2 years, no conclusion can be drawn regarding whether the decline is stable after that time point (See Figure 2).

**Figure 2 LS Mean (SE) of Change from Baseline in FEV1 (L) by Visit, MMRM Model, Type 2 Diabetes**



N1=TI; N2=Comparator; SE=standard error

Source: Figure 66, p. 229, Pulmonary CIR, ISS, Module 5.

For the pooled type 2 diabetes population, after 2 years of treatment, subjects in the Afrezza group had a mean decline from baseline in FEV1 of 180 mL, while subjects in the comparator group had a mean decline from baseline of approximately 130 mL. Both treatment groups demonstrated a larger mean decline than what would be expected in non-smoking subjects without significant lung disease. Per the Applicant's analysis, the 2-year mean treatment group difference between Afrezza and the comparator group was -46 mL (a negative difference denotes a greater decline in the TI group) [95% CI: -73, -18], which was statistically significant. In fact the treatment group difference was statistically significant at all time points examined, with the greatest mean treatment group difference observed at 9 months (-48 mL). The Applicant's analysis was consistent with the Agency's statistical analysis which demonstrated a mean treatment difference of -40 mL at 2 years. The Applicant also presented an annual rate of change (slope) in FEV1 between Month 3 (first post-baseline measurement) and Month 24 (last post-baseline measurement) for each treatment group. The annualized change in FEV1 was numerically greater in the TI group, but not statistically different between the two groups from Month 3 to Month 24. The TI group declined approximately 49 mL/year while the comparator group declined approximately 44 mL/year.

Controlled data are not available to assess the effect of Afrezza on FEV1 after 2 years of exposure. However, in one uncontrolled extension study, some subjects had been exposed to

Afrezza for up to 4 years. The uncontrolled study data suggest that the mean decline from baseline FEV1 continues with continued exposure to Afrezza. However, without a comparator group, it is unknown if the treatment group difference changes with time. The Applicant computed a mean annual rate of decline of -48 mL/year over the 48 month study period, which is of similar magnitude to what was seen in the controlled phase 2/3 trials up to 2 years.

A small number of patients from the one-year trial in type 2 diabetes were followed up 8 weeks after TI discontinuation, to examine the effect on FEV1 post-TI discontinuation. Although the number of patients is small, it appears as if only 32% of TI-treated patients returned to their baseline FEV1 as measured in the one-year trial. Given that both groups' FEV1 are simultaneously declining, return to baseline FEV1 may not be a plausible measure of reversibility. Ideally, the comparison between the treatment difference at randomization baseline and then extension follow-up would have provided the most useful data. However, Dr. Mele completed the analysis in this manner, due to the very small number of patients contributing data at the end time point, which precluded a meaningful comparison of treatment differences. Thus, with the data that are present, one cannot definitively conclude that the change in FEV1 noted with Afrezza is reversible off-treatment, at least at 2 months of follow-up (*data from Biometrics Review, Dr. Joy Mele*).

The Agency performed a categorical response analysis to assess the proportion of subjects with a decrease in FEV1 from baseline of various magnitudes. At 1 year, 9% of TI subjects and 2.8% of comparator group subjects had  $\geq 15\%$  decline from baseline FEV1. At 1 year, the percentage of subjects with  $\geq 20\%$  drop was 2.6% in the TI group and 1.8% in the comparator group. At 2 years, 5.9% of TI subjects and 4.3% of comparator subjects had a  $\geq 15\%$  decline in FEV1. More subjects in the TI group (1.9%) also experienced a  $\geq 20\%$  decline in FEV1 at 2 years than in the comparator group (0.7%). The differences in subjects experiencing FEV1 decline of 15% was statistically significant at 1 year (*data courtesy of Dr. Joy Mele, Biometrics Reviewer*).

#### 1.5.4 Chest X-Ray

Chest x-rays were performed by standard imaging using 1 frontal exposure and 1 lateral exposure at baseline at the end of the treatment period. For studies longer than 52 weeks, chest x-rays were performed annually. Investigators were asked to review the reports by the local radiologist and determine the clinical significance of the finding. For analysis of chest x-rays, data were pooled for controlled phase 2/3 efficacy and safety studies lasting longer than 14 days. The results were evaluated for diabetes by type and the combined population. The pooling strategy for chest x-ray data is presented in Table 42. CXR results were categorized and recorded as: normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). Shift tables presenting change from baseline to end of the study in the above category were provided by treatment group. The percentage was calculated based on the total number of subjects in the treatment group who had non-missing values for both visits in the comparison. Narratives of subjects with clinically significant findings on CXR were reviewed. Overall, the incidence of significant changes in CXR findings was low in both TI and comparator groups.

In summary, the observed chest x-ray findings in type 1 and type 2 diabetes patients treated from 3 months to 2 years were not suggestive of a particular safety signal with the use of Afrezza during this time period.

### 1.5.5 High Resolution Computed Tomography

Chest HRCTs (or MRIs in Germany) were obtained in a subset of patients in MKC-TI-030 and all subjects who participated in PDC-INS0008, MKC-TI-005, and MKC-TI-0010 (Table 45). HRCTs were conducted at baseline and at the end of the study, or annually, depending on the duration of the study. The duration of the controlled studies ranged from 3 months to 2 years. All images were collected and centrally reviewed by an independent third party. During the reviews, the independent radiologist was blinded to subject identity, sequence of examinations, and reason for imaging. Any subject with a suspected abnormality on first review was submitted for secondary review. Based upon the data, the secondary reviewers wrote a joint brief narrative for each subject to provide a final interpretation of the radiology imaging. This joint interpretation includes a statement of finding whether the subjects' images were normal, abnormal, not clinically significant (NCS), or abnormal, clinically significant (CS). The blinded independent central readings are discussed in this review.

A total of 667 subjects were evaluated by HRCT or MRI. Of all the subjects evaluated, 29 (5.9%), 8 (7.9%), and 3(4.2%) had findings that were deemed to be abnormal, clinically significant in the TI (Afrezza), TP (excipient only), and Usual Care groups respectively. The narratives of each of the abnormal imaging studies in the controlled phase 2/3 studies are reviewed in Table 47.

Overall, the methodology of obtaining and interpreting HRCTs in this clinical development program was adequate. Based on the 667 HRCTs/MRIs, the observed radiologic findings in type 1 and type 2 diabetes patients treated from 3 months to 2 years were not suggestive of a particular safety signal with the use of Afrezza during this time period. However, evaluation after periods of longer exposure will be necessary to gain a full understanding of airway and lung parenchyma changes in patients who use Afrezza.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Afrezza, insulin monomer human [rDNA origin] Inhalation Powder (previously referred to as Technosphere® Insulin), is being proposed as an ultra-rapid acting prandial insulin for the treatment of Type 1 and Type 2 Diabetes Mellitus in adults 18 years of age and older. Afrezza is to be administered prior to meals in medication regimens including a long-acting insulin. Afrezza consists of Technosphere® Insulin Inhalation Powder pre-metered into unit dose cartridges and the MedTone® Inhaler.

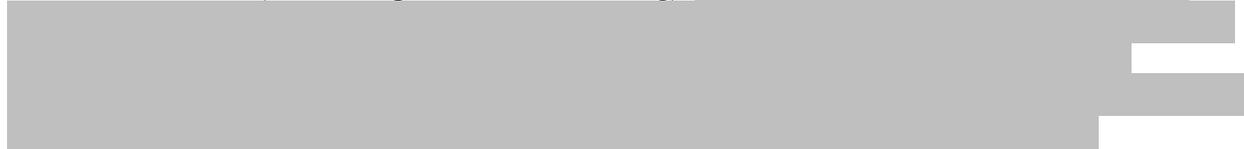
Technosphere Insulin Inhalation Powder [Figure 3]

Technosphere® Insulin (TI) Inhalation Powder is a dry powder formulation of insulin. Insulin consists of two polypeptide chains, A and B. The A chain has 21 amino acids and the B chain has 30 amino acids. The chains are linked together through the sulfur atoms of cysteine. Afrezza consists of recombinant human insulin, fumaryl diketopiperazine (FDKP) and polysorbate 80. FDKP is a proprietary, novel excipient which self-assembles into Technosphere particles. Afrezza is formed by adsorbing insulin onto pre-formed Technosphere® particles. Afrezza is targeted to contain 3U insulin/mg and is filled into unit-dose cartridges at nominal strengths of 15U/ and 30U/cartridge. The 15U and 30U product presentations have nominal fill weights of 5 mg and 10 mg respectively.

FDKP was chosen as the particle matrix because it crystallizes under acidic conditions and the crystals self-assemble to form particles. Technosphere and Technosphere Insulin particles are sized for inhalation, with a typical median particle diameter ~ 2-2.5 µm. The particles dissolve under physiological conditions where the pH is neutral. Per the Applicant, FDKP is not metabolized and is excreted intact, primarily in the urine.

MedTone Inhaler (Model D) [Figure 3]

The Model D MedTone Inhaler has been designed and developed by the Applicant for exclusive use with Afrezza-filled cartridges. It is an inhaler that is intended to deliver the dry powder formulation of Afrezza to the pulmonary tract. The inhaler is breath-powered, re-usable for 12 months, (b) (4). The design is comprised of two subassemblies (the mouthpiece and the housing), (b) (4)



**Figure 3 Model D MedTone Inhaler and Insulin Cartridges**



The Applicant employed the Model C inhaler device in the phase 2 and the majority of the phase 3 clinical studies. A review of the device led to development of the Model D device which contains improvements. The modifications to the Model C inhaler to result in the Model D inhaler are summarized in Dr. Melanie Choe's (CDRH) review (page 9). A listing of these modifications is as follows:

[REDACTED] (b) (4)

*Reviewer's comment: Dr. Choe notes that the sponsor was requested to validate each of the improvements noted above in a side-by-side comparison test of Model C and D. However several of the improvements, such as [REDACTED] (b) (4) [REDACTED] were not compared side-by-side.*

The Applicant claims [REDACTED] (b) (4). Per the review of Dr. Melanie Choe from CDRH, the sponsor has provided adequate validation to demonstrate the equivalence of the improved Model D inhaler to the Model C inhaler in performance. Per Dr. Choe's review, over 10,000 Model C inhalers were issued to patients in the Phase 2 and Phase 3 clinical trials. Information from the Model C inhaler device returns established the need for the Model D improvements. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)  
This also led to the Model D improvements.

*Reviewer's comment: The durability/ruggedness of the Model D inhaler has not been evaluated by the Applicant so it is uncertain if the changes made to the Model C actually achieved the goal of improving the device.*

## 2.2 Important Pulmonary Safety Issues With Consideration to Related Drugs

Exubera (NDA 21-868, approved January 27, 2006), a powdered form of inhaled insulin, was the first formulation of inhalable insulin to receive FDA approval. Exubera was available in the United States from September 2006 to October 2007. In October 2007, Pfizer announced that it

would be discontinuing the production and sale of Exubera due to poor sales and because Exubera failed to gain acceptance among patients and physicians.

Although Exubera is no longer marketed, safety concerns raised with Exubera are relevant to Afrezza. On April 9, 2008, Pfizer announced in a “Dear Doctor” letter that Exubera may have been associated with lung cancer: of the 4,740 patients who used Exubera in clinical trials, 6 had developed lung cancer as of April 2008, compared to only 1 of the 4,292 patients in the placebo group. The Agency had asked Pfizer, as part of a Phase 4 Commitment to conduct a 12 year epidemiologic lung cancer cohort study utilizing The Health Improvement Network records in the United Kingdom. However, Exubera was removed from the market before this study could be conducted and completed.

*Reviewer’s Comment: As a result of the findings with Exubera, DPAP suggests that DMEP institute a similar epidemiologic study as post-marketing requirement if Afrezza is to be approved.*

### **2.3 Summary of Pre-submission Regulatory Activity Related to Pulmonary Safety**

The following is a list of key regulatory meetings in which the Agency provided guidance and answered questions regarding the evaluation of pulmonary safety in the Afrezza clinical development program.

#### **A) October 12, 2004 – End of Phase 2 Meeting**

At the EOP2 meeting, the following general guidance was provided by the Agency to the Applicant regarding establishment of a long-term pulmonary safety database:

- To evaluate the long-term safety profile of Technosphere Insulin, the Agency requested adequate long-term controlled pulmonary safety data in patients with type 1 and type 2 diabetes studied for at least 2 years, in a controlled fashion.
- The Agency noted the Applicant’s plans to conduct a (b) (4) and advised that (b) (4) was not appropriate. A single study with randomization to drug or placebo/control is preferable.
- For the long-term pulmonary safety database, assessments should include:
  - Pulmonary function tests (PFTs) – spirometry, lung volumes, and diffusing capacity – in a post-meeting comment the Agency recommended serial spirometry before and after inhaled insulin dosing to evaluate the effect of inhaled insulin both on acute bronchospasm and with chronic use.
  - High resolution computed tomography (HRCTs) – approximately 50 patients on drug and 50 patients on standard therapy should undergo HRCT at 0 and 24 months.
  - Pulmonary safety parameters (e.g., PFTs, HRCTs, AEs) should be assessed in the patient population that develops antibodies.
- For those patients with underlying lung disease, the Agency requested long-term controlled pulmonary safety data in at least 100 patients with COPD and 100 patients with asthma for  $\geq$

1 year. The safety of use in those with underlying pulmonary disease will not be satisfied with a small number of study patients.

*Reviewer's comment: The study to examine the effects of Afrezza in patients with asthma and COPD has not been submitted with this application. The Applicant is still in the plenary stages with the study proposed above (MKC-TI-134).*

- The PK/PD of upper respiratory infection, other inhaled medications, smoking, and smoking cessation will need to be addressed.
- The Phase 3 protocols should be conducted with the to-be-marketed drug and device formulation. Device performance data should be collected for the life of the device.

B) April 21, 2005 – Response to Special Protocol Assessment: MKC-TI-030

- Pulmonary function tests should be included in the inclusion/exclusion criteria. Further, subjects with any underlying lung disease should be excluded even in the face of normal lung function.
- Corrected alveolar volume should not be used to estimate TLC. Lung volumes should be measured using multiple breath helium dilution technique or body plethysmography. Single breath helium dilution methods may underestimate the TLC, especially in the presence of airway obstruction.
- A 15% change in FEV1 was considered acceptable to define a PFT event. The Applicant was reminded, however, that the pulmonary safety assessment would be based on the entire pulmonary safety database, and changes in FEV1 less than 15% could be clinically meaningful. As a result, any treatment effect would be considered and described.
- PFTs need not be corrected for age, as the primary comparison is between TI and usual care comparators.
- A non-inferiority analysis can be employed, however we cannot agree that a claim of “non-inferiority” can be justified, even if the statistical analyses exclude the specified margins. If there is a treatment effect, even if it falls within your proposed margins, the clinical significance will need to be considered.
- Measure DLCO more frequently than at baseline, 3, 12, and 24 months.
- The protocol should include more details regarding the handling of PFT and HRCT data. For example, PFTs should be interpreted by blinded personnel at a central location. A process for analyzing the HRCT data should also be included.

C) October 14, 2005 – Response to Special Protocol Assessment: MKC-TI-102

MKC-TI-102 was initially proposed as the only study to examine pulmonary function after treatment had been discontinued. The Agency felt that this strategy had inherent limitations as stated below:

- The program will not assess reversal of the effects of TI on pulmonary function in type 1 diabetics, nor will it assess reversal in patients who have been treated for over 1 year, nor those with underlying lung disease.
- A PA and lateral chest x-ray should be performed rather than an AP. CXRs should be interpreted by radiologists who are blinded to treatment allocation and sequence of the films.
- FEV1 inclusion criteria should be included in the protocol.
- Details regarding PFT data handling and interpretation should be included in the protocol.

D) April 10, 2006 - Agency Comments on MKC-TI-105 Protocol

*Reviewer's comment: This study was prematurely terminated as the Applicant had difficulty enrolling patients. As a result, this study is not reviewed in this consult response, and the comments made regarding the protocol are not relevant.*

E) July 14, 2008 - Pre-NDA Meeting

- The Applicant was asked to provide all safety data (including pulmonary data) separately for both type 1 and type 2 diabetes, and then for the combined population, in the NDA submission.
- The Applicant was asked to provide details of their pooling strategies in the NDA submission
- The Applicant was asked to provide the following PFT information in the NDA:
  - A discussion of patients with significant decline in pulmonary function (i.e. outliers) categorized by degree of deterioration from baseline (>5%, >10%, >15%, >20%, etc.)
  - Narratives for those patients who experienced a significant decline in pulmonary function.
  - A discussion of reversibility off-treatment (if applicable).
  - Cumulative distribution plots of decline in pulmonary function measured as percent change from baseline.
  - A discussion of pulmonary special events of interest, including but not limited to:
    - Neoplasm
    - Interstitial Lung Disease (sarcoidosis, pulmonary fibrosis, etc)
    - Pleural effusions
- Input regarding the design of study MKC-TI-134 in diabetic patients with underlying lung disease was also provided. Specifically, the use of an unvalidated questionnaire to establish the diagnosis of either asthma or COPD was discouraged.

### 3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

#### 3.1 Chemistry Manufacturing and Controls

The drug product consists of particles of the novel excipient fumaryl diketopiperazine (FDKP) coated with recombinant human insulin, as well as trace amounts of polysorbate 80 (b) (4). The drug product is contained within cartridges that are intended for use in the MedTone Inhaler (See 2.1 Product Information). Two issues pertinent to the clinical program arise from the CMC review: 1) (b) (4) 2) (b) (4) the novel excipient FDKP as a potential mechanism for airway irritation and cough.

(b) (4)

(b) (4)

(b) (4)

(b) (4) FDKP  
Per the review of Dr. Ted Carver, there is a significant amount of (b) (4) present in the excipient, FDKP (b) (4)

(b) (4) may be a potential mechanism for the high incidence of cough noted post-inhalation.

*Reviewer's comment:*

(b) (4)  
*but this may provide a potential mechanism as to why there was such a high incidence of coughing in this clinical development program.*

Both CMC and CDRH are recommending approval pending satisfactory recommendations from other disciplines.

### 3.2 Clinical Microbiology

Because Exubera was approved with a drug product specification for endotoxins, the issue was raised whether Afrezza should have the same specifications. Afrezza does not have endotoxin specifications for the drug product, but does have these specifications for the drug substance. (b) (4)

(b) (4)  
this approach is acceptable.

### 3.3 Preclinical Pharmacology/Toxicology

The Applicant conducted inhalation toxicology studies in rats and dogs, for 6 and 9 months duration, respectively. No effects on cell proliferation indices were observed in lung tissue in dogs after 9 months of daily inhalation administration. There was a slight numerical imbalance in the proliferation indices recorded across groups in the 6-month rat inhalation toxicology study. This imbalance was not considered biologically significant since the labeling index was within the range frequently reported as background for controls and the magnitude of change was not considered clinically meaningful. There were no histological changes of epithelial hyperplasia or metaplasia noted in any of the respiratory tissues that were examined. No differences in proliferation were observed in alveolar cells for any species or treatment interval. Cell proliferation changes were not observed in lung tissue after 2-years of dosing in a rat carcinogenicity study. No effects on pulmonary function were observed in rats that received Afrezza by intratracheal administration. No change was observed in airway resistance or dynamic lung compliance when Afrezza was administered at doses 15-fold greater on a mg/kg basis in rats compared to humans.

Following intratracheal instillation or insufflations of <sup>14</sup>C-FDKP, the highest tissue radioactivity concentrations and largest AUC<sub>0-tlast</sub> were generally observed in the site of administration, namely lung and trachea, and to some extent the primary excretory organ, the

kidney. Based on lung histopathology data and corresponding serum PK data in rats and dogs, there was no evidence of systemic or pulmonary accumulation of FDKP or insulin. [Refer to the Nonclinical Review of NDA 22-472 for further details]. Based on their review, the pharmacology/toxicology reviewer recommends approval of the application.

### 3.4 Clinical Pharmacology

The Applicant has conducted 32 clinical pharmacology studies. Several of the clinical pharmacology studies assessed the effects of smoking, asthma, COPD, and upper respiratory tract infection on the bioavailability of Afrezza. These studies are of interest and will be briefly discussed in this section (ISS, appendix 2).

*Reviewer's comment: Although the results of these studies are briefly discussed in this section, it should be noted that this reviewer is not interpreting the significance of these findings, as these studies are not intended to provide information regarding the pulmonary safety of Afrezza. In fact, the Applicant has not studied Afrezza in these patient populations, and therefore, no safety conclusions can be drawn for patients with underlying lung disease from this clinical development program.*

Study MKC-TI-016 was a clinical pharmacology study to assess the effect of smoking on the bioavailability of TI inhalation powder in Type 2 diabetics after a single dose. The study was conducted in 24 subjects (12 smokers, 12 non-smokers). Relative bioavailability was the ratio of mean baseline-adjusted insulin  $AUC_{0-480}$  in smokers (2092 min· $\mu$ IU/mL) over that of non-smokers (1677 min· $\mu$ IU/mL). Similarly, there was no difference in exposure to FDKP (novel excipient) between smokers and non-smokers. (2.7.2 Summary of Clinical Pharmacology Studies, pp. 139-142)

*Reviewer's comment: Numerically, bioavailability of Afrezza was higher in smokers. However, the results were not statistically different in this single dose study.*

Study MKC-TI-027 was a clinical pharmacology study to assess the effect of asthma on the bioavailability of TI in patients with Type 2 diabetes. The study consisted of 20 subjects, of which only 5 were asthmatic. PK parameters were compared after a single dose, and thrice daily dosing for 7 days. There were no differences in  $AUC_{0-6h}$ ,  $C_{max}$ , or  $t_{max}$  between asthmatics and non-asthmatics. (2.7.2 Summary of Clinical Pharmacology Studies, pp. 143-145)

*Reviewer's comment: The number of asthmatics studied in this trial are too small to draw any meaningful conclusions.*

Study MKC-TI-112 was a clinical pharmacology study designed to assess the PK profile of FDKP and TI after a meal challenge, during active symptomatic URI compared with post-resolution. The study was conducted in 20 subjects. The PK profiles of FDKP and insulin measured by  $AUC_{0-4h}$  after dosing with TI Inhalation Powder following a meal challenge was similar during an active symptomatic URI compared with after URI resolution. The ratio of  $AUC_{0-4h}$  during a URI to after resolution was 1.1 for FDKP and 0.9 for insulin. For FDKP, no

statistically significant difference was noted for  $AUC_{0-4h}$ ,  $t_{max}$ , or  $t_{1/2}$  during and after a URI. For insulin, no statistically significant difference was noted for  $AUC_{0-4h}$  or  $t_{max}$  ( $t_{1/2}$  was not calculated because insulin is an endogenous compound). (2.7.2 Summary of Clinical Pharmacology Studies, pp. 152-154).

Study MKC-TI-015 was a clinical pharmacology study designed to assess the bioavailability of TI and FDKP in 20 non-diabetic COPD subjects compared with 20 non-diabetics without COPD after a single dose of TI. The mean insulin  $AUC_{0-240}$  was slightly higher for subjects without COPD (2279  $mU \cdot min/L$ ) compared with subjects with COPD (2037  $mU \cdot min/L$ ). The C-peptide corrected insulin  $C_{max}$  was also comparable in subjects with and without COPD (34.7  $mU/L$  vs. 39.5  $mU/L$ ). Similar exposures and  $C_{max}$  were also demonstrated for FDKP. (Module 2.7.2 Summary of Clinical Pharmacology Studies, pp. 156-159).

*Reviewer's comment:*

(b) (4)

## 4 Sources of Clinical Data

### 4.1 Tables of Studies/Clinical Trials

The primary sources of clinical data for this NDA are the clinical trials conducted by the Applicant and submitted with the NDA in March 2009. Several abbreviations are commonly used throughout the review: TI: Technosphere Insulin (Afrezza), TP: Technosphere Particles (excipient only), CXR: chest x-ray, HRCT: high resolution computed tomography, PFTs: pulmonary function tests, FEV1: forced expiratory volume in 1 second, DLco: diffusion capacity of carbon monoxide.

The Applicant's clinical program consists of 9 controlled phase 2/3 clinical trials, as well as 2 uncontrolled, open label, extension trials (see Table 4, trials grouped by diabetes type). In addition, the Applicant has conducted 31 clinical pharmacology trials to support this NDA. It is of note, that trial MKC-TI-105, which was to evaluate the use of Afrezza in asthma patients, was terminated early due to difficulty in enrolling patients. This study is not included below as no meaningful data was gathered for analysis.

Table 4: TI clinical studies with Pulmonary Safety Assessments								
Study # (N=safety pop)	Design	Duration	TI Group NR, NC (%)	Comparator NR, NC (%)	Pulmonary Safety Assessment			
					AE	CXR	PFTS	CT
<b>TYPE 1 DIABETES</b>								
<b>MKC-TI-101</b> N = 110	R, OL	12 weeks	NR=54 NC=49 (91)	NR=56 NC=56 (100)	✓	✓	✓	
<b>MKC-TI-009</b> N = 565 <sup>a</sup>	R, C, OL	1 year	NR=301 NC=198 (66)	NR=288 NC=220 (76)	✓	✓	✓	
<b>TYPE 2 DIABETES</b>								
<b>MKC-TI-005</b> N = 227	MC, R, DB, PC	11 weeks	NR=181 NC=165 (91)	NR=46 NC=40 (87)	✓	✓	✓	✓
<b>PDC-INS-0008</b> N = 123	R, DB, PC, PG	12 weeks	NR=61 NC=54 (93)	NR=62 NC=53 (87)	✓	✓	✓	✓
<b>MKC-TI-026</b> N = 90	R, C, OL	12 weeks	NR=75 NC=69 (92)	NR=15 NC=14 (93)	✓	✓	✓	
<b>MKC-TI-014</b> N = 309	R, OL	24 weeks	NR=151 NC=123 (82)	NR=158 NC=153 (97)	✓	✓	✓	
<b>MKC-TI-103<sup>b</sup></b> N = 528	R, C, OL	24 weeks	NR=358 NC=252 (70)	NR= 170 NC 152 (89)	✓	✓	✓	
<b>MKC-TI-102</b> N = 677	R, C, OL	1 year	NR = 334 NC= 216 (65)	NR= 343 NC 246 (72)	✓	✓	✓	
<b>MKC-TI-010<sup>c</sup></b> N = 229	OL, UC, extension (005, 0008)	4 years	All patients treated with TI				✓	✓
<b>TYPE 1 AND 2 DIABETES</b>								
			<b>Type 1 DM</b>					
<b>MKC-TI-030</b> N = 2035 <sup>d</sup>	MC, R, OL	2 years	NR=267 NC=126 (47)	NR=271 NC=199 (73)	✓	✓	✓	✓
			<b>Type 2 DM</b>					
			NR=656 NC=349 (52)	NR=678 NC=463 (68)				
<b>MKC-TI-126<sup>c</sup></b> N = 649	Safety follow-up study (009, 102, 103, 030)	8 weeks	8 weeks untreated f/u				✓	

MC: multicenter, R: randomized, C: controlled, OL: open-label, PC: placebo-controlled, PG: parallel group, UC: uncontrolled, DB: double-blind, PFTS: pulmonary function tests, HRCT: high resolution computed tomography; CXR: chest x-ray, AEs: adverse events, f/u: follow-up; NR: number randomized; NC: number of completers; TI: Technosphere Insulin, Afrezza

\*\* MKC-TI-105: study not included in table as study terminated prematurely due to difficulty recruiting patients

a: discrepancy between number randomized and safety population is 24 subjects who were randomized but discontinued prior to 1<sup>st</sup> dose

b: Study MKC-TI-103 was not reviewed in any detail by this reviewer because of a complicated crossover design that made results difficult to analyze

c: 2 uncontrolled extension studies

## 4.2 Review Strategy

The pulmonary safety data were analyzed utilizing the controlled phase 2 and 3 studies in type 1 and type 2 diabetes presented in Table 4. Each study was individually reviewed (see 6 Appendices), except for those studies which were uncontrolled extensions in which subjects from controlled studies were simply continued, as a means of collecting long-term pulmonary function data. The uncontrolled data will be presented in summary fashion in the review of safety below. The pulmonary safety data was examined for respiratory adverse events, respiratory SAEs, pulmonary events of special interest (including neoplasm), pulmonary function tests, chest x-rays, and HRCT data. The safety information is generally presented by diabetes type and then for the pooled controlled phase 2/3 safety population. The pooling/analysis strategy was different for evaluation of pulmonary function tests than for adverse events, and this is therefore discussed in Section 5.3.6.2 PFT Review Strategy. The pooling strategy for AEs, cough, and chest x-rays is presented in Section 5.1.2 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.

## 5 Review of Safety

### 5.1 General Methods

Safety monitoring in the controlled phase 2 and 3 trials pertinent to the pulmonary safety database included adverse events (including cough), pulmonary function tests, chest x-rays, and high resolution chest tomography (in a subset of patients). The Applicant's monitoring for pulmonary safety in this clinical development program was adequate for pre-marketing assessment.

The Safety Population was the analysis population for the ISS. The Safety Population was defined as all randomized subjects who received at least one dose of study drug. This population definition was consistently used across all pooled and non-pooled trials.

*Reviewer's comment: Specific details regarding the methods used to collect and analyze pulmonary function tests, chest x-rays, and HRCTs will be presented in the individual sections [see 5.3.6.1 PFT Methods, 5.3.7.1 CXR Methods, and 5.3.8.1 HRCT Methods]*

#### 5.1.1 Categorization of Adverse Events

An adverse event was defined as any untoward medical occurrence or change of an existing condition in a trial subject that occurred during the trial period (from the time the informed consent was signed to 30 days following the last trial visit or trial-related procedure) whether or not it was considered treatment-related. A serious adverse event (SAE) was defined as any AE with an outcome that: was fatal or life-threatening, required inpatient hospitalization, resulted in

a persistent or significant disability/incapacity, or was an important medical event. All AEs were coded using the MedDRA dictionary (version 7.1). This review focuses on the adverse events in the Respiratory, Thoracic, and Mediastinal Disorders SOC. In addition, some events relevant to the respiratory system were coded under the Infections and Infestations SOC (e.g. pneumonia, bronchitis, URTI) and the Investigations SOC (PFT decreased). Pertinent to pulmonary safety, cough was considered of special interest during the clinical development program. Categorization of cough is discussed in more detail in Section 5.3.5.1 Cough.

### 5.1.2 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

A brief summary of the pooling strategy unique to pulmonary safety (AEs, cough, and CXR) is provided here. Pooling/analysis strategy for PFTs is presented in 5.3.6.1 PFT Methods.

For analysis of respiratory AEs, cough, and chest x-rays, data were pooled for controlled phase 2 and 3 efficacy and safety studies with a duration of  $\geq 14$  days. Pooled studies for subjects with Type 1 and Type 2 diabetes is shown in Table 5. Data was pooled for type 1 and type 2 diabetes separately and together as the pooled safety population. Data that were not pooled included HRCT results and the results of the two follow up extension trials, MKC-TI-010 and MKC-TI-126.

<b>Table 5: Pooling Strategy for Respiratory AEs, Cough, and Chest X-Ray Data</b>				
Study Pooling Group	DM Type	Trials	Safety Population	
			# Subjects TI	# Subjects Comparator
Controlled Phase 2/3 Trials	Type 1	MKC-TI-009, MKC-TI-030, MKC-TI-101	614	599
	Type 2	PDC-INS-0008, MKC-TI-005, MKC-TI-014, MKC-TI-026, MKC-TI-030, MKC-TI-102, MKC-TI-103	1795	1345
			2409	1944
**Safety population and Randomized Subject numbers differ because some subjects were randomized, but did not receive treatment **An additional 114 subjects were treated with TP (excipient only) Source: Table 2, pg. 33, Pulmonary CIR, ISS, Module 5.				

## 5.2 Adequacy of Safety Assessments

### 5.2.1 Overall Exposure and Demographics of Target Populations

A total of 2409, 1945, and 114 type 1 or type 2 subjects in the TI, comparator, and TP groups were exposed to study medication, respectively, in controlled phase 2/3 TI clinical trials.

Exposure data is presented by diabetes type and for the pooled safety population in Table 6 and Table 7, respectively.

<b>Table 6: Duration of Exposure (by Diabetes Type) – Phase 2/3 Controlled Clinical Trials</b>					
<b>Exposure</b>	<b>Type 1</b>		<b>Type 2</b>		
	<b>TI n = 614 n (%)</b>	<b>Comparator n = 599 n (%)</b>	<b>TI n = 1795 n (%)</b>	<b>Comparator n = 1345 n (%)</b>	<b>TP n = 114 n (%)</b>
0-3 months	128 (20.8)	39 (6.5)	676 (37.7)	257 (19.1)	62 (54.4)
> 3-6 months	93 (15.1)	77 (12.9)	392 (21.8)	254 (18.9)	52 (45.6)
> 6-12 months	155 (25.2)	149 (24.9)	241 (13.4)	236 (17.5)	0
> 12-24 months	236 (38.4)	331 (55.3)	482 (26.9)	582 (43.3)	0
> 24 months	2 (0.3)	3 (0.5)	4 (0.2)	15 (1.1)	0
At least 6 months	395 (64.3)	483 (80.6)	731 (40.7)	835 (62.1)	0
At least 12 months	296 (48.2)	386 (64.4)	535 (29.8)	658 (48.9)	0
At least 18 months	131 (21.3)	210 (35.1)	373 (20.8)	480 (35.7)	0
At least 24 months	2 (0.3)	3 (0.5)	5 (0.3)	15 (1.1)	0
	<b># days (SD)</b>	<b># days (SD)</b>	<b># days (SD)</b>	<b># days (SD)</b>	<b># days (SD)</b>
Mean exposure	321.2 (229.8)	415.7 (219.2)	259.2 (237.9)	372 (251.9)	81.4 (27.4)

Source: Tables 12, 13, 15, 16, p. 62-65, ISS, Module 5.

A total of 614 and 599 subjects with type 1 diabetes were exposed to TI or comparator, respectively. Mean duration of exposure was  $321 \pm 229.8$  days in the TI group and  $415 \pm 219.2$  days in the comparator group. Mean duration of exposure to TI was comparable in the type 2 diabetes population at  $259.2 \pm 237.9$  days.

The majority (51.8%) of subjects with type 1 diabetes were exposed to TI for up to 12 months. The number of type 1 subjects exposed to TI for greater than 12 months was 296/614 or 48.2%. Approximately 70% of type 2 diabetics were exposed to TI for up to 12 months with 30% being exposed for greater than 12 months.

Overall, approximately 60% of subjects received TI for more than 3 months. The number of subjects with either type 1 or type 2 diabetes exposed to TI for greater than 1 year was 831/2409 (34%). Data for the duration of exposure pooled for Type 1 and Type 2 diabetes is presented in Table 7 below.

<b>Table 7: Duration of Exposure – Pooled Safety Population</b>			
<b>Exposure</b>	<b>TI (n = 2409)</b>	<b>Comparator (n = 1944)</b>	<b>TP (n = 114)</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
0-3 months	804 (33.4)	296 (15.2)	62 (54.4)
> 3-6 months	485 (20.1)	331 (17.0)	52 (45.6)
> 6-12 months	396 (16.4)	385 (19.8)	0
> 12-24 months	718 (29.8)	913 (47.0)	0
> 24 months	6 (0.2)	18 (0.9)	0
At least 6 months	1126 (46.7)	1318 (67.8)	0
At least 12 months	831 (34.5)	1044 (53.7)	0
At least 18 months	504 (20.9)	690 (35.5)	0
At least 24 months	7 (0.3)	18 (0.9)	0
	<b># days (SD)</b>	<b># days (SD)</b>	<b># days (SD)</b>
Mean exposure	275.01 (237.4)	385.5 (243.1)	81.4 (27.4)

Source: Tables 11, 14, p. 62-65, ISS, Module 5.

The number of subjects exposed to Afrezza and the duration of exposure to Afrezza are adequate to initially assess the routine pulmonary safety of Afrezza in patients without underlying lung disease.

*Reviewer’s comment: Further studies with larger numbers of subjects followed for longer periods of time will be necessary to assess for rare events, such as malignancy.*

#### *Demographics*

The demographic characteristics of the safety population, divided by type of diabetes and for the pooled safety population, are presented in Table 8 and Table 9, respectively. Pertinent to the pulmonary safety evaluation, smoking history of the subjects is presented as well.

<b>Table 8: Demographic Characteristics of Safety Population by Diabetes Type</b>					
<b>Characteristic</b>	<b>Type 1</b>		<b>Type 2</b>		
	<b>TI n = 614</b>	<b>Comparator n = 599</b>	<b>TI n = 1795</b>	<b>Comparator n = 1345</b>	<b>TP n = 114</b>
Gender					
Male	321 (52.3)	320 (53.4)	921 (51.3)	682 (50.7)	65 (57.0)
Race					
Caucasian	557 (90.7)	547 (91.3)	1457 (81.2)	1080 (80.3)	91 (79.8)
Black	23 (3.7)	20 (3.3)	88 (4.9)	62 (4.6)	3 (2.6)
Hispanic	23 (3.7)	25 (4.2)	183 (10.2)	143 (10.6)	14 (12.3)
Asian	7 (1.1)	3 (0.5)	43 (2.4)	35 (2.6)	5 (4.4)
Other	4 (0.7)	4 (0.7)	24 (1.3)	25 (1.9)	1 (0.9)
Age					
Mean	38.4	38.5	56.2	55.7	56.0
SD	12.6	12.5	8.7	8.8	9.8
Range	18,69	18,76	19,82	18,78	26,76
Age Group					
18-64	603 (98.2)	589 (98.3)	1486 (82.8)	1135 (84.4)	90 (78.9)
65-74	11 (1.8)	9 (1.5)	291 (16.2)	197 (14.6)	22 (19.3)
≥75	0	1 (0.2)	18 (1.0)	13 (1.0)	2 (1.8)
Past smoker					
Yes	149 (24.3)	138 (23.0)	540 (30.1)	396 (29.4)	43 (37.7)
No	465 (75.7)	461 (77.0)	1255 (69.9)	949 (70.6)	71 (62.3)
# of Pack-Years					
n	142	128	502	375	38
Mean	9.10	10.05	19.21	19.75	21.69
SD	11.01	13.09	22.79	22.69	20.76
Range	0,58	0, 78	0,144	0, 138	0.1, 93

Source: Tables 21, 22, 24, 25, p. 71-74, ISS, Module 5.

<b>Table 9: Demographic Characteristics – Pooled Safety Population</b>			
<b>Characteristic</b>	<b>TI n = 2409</b>	<b>TP n = 114</b>	<b>Comparator n = 1944</b>
Gender			
Male	1246 (51.6)	65 (57.0)	1002 (51.5)
Race			
Caucasian	2014 (83.6)	91 (79.8)	1628 (83.7)
Black	111 (4.6)	3 (2.6)	82 (4.2)
Hispanic	206 (8.6)	14 (12.3)	168 (8.6)
Asian	50 (2.1)	5 (4.4)	38 (2.0)
Other	28 (1.2)	1 (0.9)	29 (1.5)
Age			
Mean	51.6	56.0	50.4
SD	12.5	9.8	12.9
Range	18,82	26,76	18,78
Age Group			
18-64	2089 (86.7)	90 (78.9)	1725 (88.7)
65-74	302 (12.5)	22 (19.3)	206 (10.6)
≥75	18 (0.7)	2 (1.8)	14 (0.7)
Past smoker			
Yes	689 (28.6)	43 (37.7)	534 (27.5)
No	1720 (71.4)	71 (62.3)	1410 (72.5)
# of Pack-Years			
n	644	38	503
Mean	16.99	21.69	17.28
SD	21.19	20.76	21.09
Range	0,144	0.1, 93	0, 138

Source: Tables 20, 23, p. 70, 73, ISS, Module 5.

The majority of subjects in the safety population were Caucasian males in all treatment groups. As expected, the mean age of the subjects with type 2 diabetes was higher than those with type 1 diabetes, and there were a higher percentage of patients age 65 to 74 in the type 2 diabetes safety population. Although smoking up to 6 months prior to study entry was an exclusion criterion for all clinical trials, former smokers were enrolled. The majority of subjects in both type 1 and type 2 diabetes safety populations were never-smokers. The type 2 diabetics had a higher pack-year smoking history than the type 1 diabetes subjects.

### 5.3 Major Safety Results

#### 5.3.1 Deaths

There were no deaths due to primary respiratory events in subjects with type 1 or type 2 diabetes in the controlled phase 2/phase 3 studies.

### 5.3.2 Nonfatal Serious Pulmonary Adverse Events

Overall, there were 12 respiratory SAEs in the TI (Afrezza) group versus 9 in the usual care group. A small number of subjects in Trials PDC-INS-008 and MKC-TI-005 (n = 114) were exposed to Technosphere inhalation powder without the insulin (excipient only, not shown in table), and this treatment group did not report any respiratory SAEs. SAEs by diabetes type are presented in Table 10 and in Table 11 for the pooled safety population.

<b>Table 10: Serious Respiratory Adverse Events for Safety Population - by Diabetes Type</b>					
<b>System Organ Class/Preferred Term</b>	<b>Type 1</b>		<b>Type 2</b>		
	<b>TI n = 614</b>	<b>Comparator n = 599</b>	<b>TI n = 1795</b>	<b>Comparator n = 1345</b>	<b>TP n = 114</b>
Subjects with any SAE	2 (0.3)	2 (0.3)	10 (0.6)	7 (0.5)	0
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	2 (0.3)	0	6 (0.3)	2 (0.1)	0
Asthma	0	0	1 (0.1)	0	0
Atelectasis	0	0	1 (0.1)	0	0
Bronchial obstruction	1 (0.2)	0	0	0	0
Cough	1 (0.2)	0	0	0	0
Dyspnea	0	0	1 (0.1)	0	0
Hemoptysis	1 (0.2)	0	0	0	0
Orthopnea	0	0	1 (0.1)	0	0
Pulmonary edema	0	0	1 (0.1)	1 (0.1)	0
Respiratory Failure	0	0	1 (0.1)	0	0
Hydrothorax	0	0	0	1 (0.1)	0
<b>INFECTIONS AND INFESTATIONS</b>	0	2 (0.3)	4 (0.2)	5 (0.4)	0
Pneumonia	0	1 (0.2)	2 (0.1)	4 (0.3)	0
Pulmonary tuberculosis	0	1 (0.2)	1 (0.1)	0	0
Upper resp tract infection	0	0	1 (0.1)	0	0
Bronchitis	0	0	0	1 (0.1)	0

Source: Tables 42,69, p. 140, 208 , Pulmonary CIR, ISS, Module 5.

<b>Table 11: Serious Respiratory Adverse Events for All Subjects – Safety Population</b>		
System Organ Class Preferred Term	Treatment Group	
	TI n = 2409	Comparator n = 1944
Subjects with any SAE	12 (0.5)	9 (0.5)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	8 (0.3)	2 (0.1)
Asthma	1	0
Atelectasis	1	0
Bronchial obstruction	1	0
Cough	1	0
Dyspnea	1	0
Hemoptysis	1	0
Orthopnea	1	0
Pulmonary edema	1	1
Respiratory Failure	1	0
Hydrothorax	0	1
<b>INFECTIONS AND INFESTATIONS</b>	4 (0.2)	7 (0.4)
Pneumonia	2 (0.1)	5 (0.3)
Pulmonary tuberculosis	1	1 (0.1)
Upper resp tract infection	1	0
Bronchitis	0	1

Source: Table 10, page 49, Pulmonary CIR, ISS, Module 5.

The respiratory SAEs were divided into two system organ classes: Respiratory, Thoracic, and Mediastinal Disorders, or Infections and Infestations. Of the respiratory SAEs reports, pneumonia was the only SAE that was reported by more than one subject in any treatment group. There were 2 cases of pneumonia in the TI group compared to 5 in the usual care comparator group. Analysis of the respiratory SAEs, both pooled (Table 11), and by diabetes type (Table 10), does not demonstrate a particular safety signal associated with the use of Afrezza.

### 5.3.3 Dropouts and/or Discontinuations

Pooled subject disposition for the phase 2/3 clinical trials is displayed in Table 12. A total of 2409 patients with type 1 or type 2 diabetes received treatment with TI (Afrezza). A total of 1944 patients received comparator treatment with either a different insulin product or an oral agent. An additional 114 patients with type 2 diabetes received only Technosphere powder (excipient only, no insulin attached).

<b>Table 12: Subject Disposition – Total Safety Population in Phase 2/3 Trials</b>					
			<b>Comparators</b>		
	<b>TI</b>	<b>TP</b>	<b>Other insulin</b>	<b>Non-insulin</b>	<b>All</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Safety population	2409	114	1541	403	1944
Completed	1539 (63.9)	83 (81.6)	1208 (78.4)	281 (69.7)	1489 (76.6)
Prematurely discontinued	870 (36.1)	21 (18.4)	333 (21.6)	122 (30.3)	455 (23.4)
<b>Reason for discontinuation from study</b>					
Adverse events	185 (7.7)	2 (1.8)	22 (1.4)	5 (1.2)	27 (1.4)
Protocol violation	50 (2.1)	3 (2.6)	24 (1.6)	5 (1.2)	29 (1.5)
Withdrew consent	380 (15.8)	11 (9.6)	162 (10.5)	69 (17.1)	231 (11.9)
Death	8 (0.3)	0	5 (0.3)	0	5 (0.3)
Invest. decision	64 (2.7)	1 (0.9)	16 (1.0)	6 (1.5)	22 (1.1)
Lost to follow-up	69 (2.9)	0	78 (5.1)	33 (8.2)	111 (5.7)
Other	113 (4.7)	4 (3.5)	26 (1.7)	4 (1.0)	30 (1.5)
Unknown	1 (0.0)	0	0	0	0
Source: Table 8, p. 57, ISS, Module 5. TI: Afrezza; TP: Technosphere powder (excipient only); invest.: investigator					

The incidence of discontinuation for any reason from the trials was 36.1% in the Afrezza group versus 23.4% in all the comparator groups combined. The most common reason for discontinuation in all the treatment groups was withdrawal of consent.

When disposition was analyzed by type of diabetes, the discontinuation rate was similar to what was seen for the pooled population of type 1 and type 2 diabetics (Table 12). A total of 614 TI-treated subjects and 599 comparator-treated subjects were included in the type 1 diabetes safety population. For patients with type 1 diabetes, the incidence of discontinuation in the TI group was about 39% (241/614) versus 21% (124/599) for the comparator group (Table 9, p. 60, ISS, Module 5). The most common reason for discontinuation in type 1 diabetes was withdrawal of consent: 21% (129/614) and 9.7% (58/599) in the TI and comparator groups, respectively. The incidence of discontinuations due to adverse events was 7% (43/614) and 0.5% (3/599) in the TI and comparator groups, respectively (Table 9, p. 60, ISS, Module 5).

A total of 1795 TI-treated subjects and 1345 comparator-treated subjects were included in the type 2 diabetes safety population. An additional 114 subjects received TP only. In patients with type 2 diabetes, the incidence of discontinuation was 35% (629/1795) in the TI group and 25% (331/1345) in the comparator group. The most common reason for discontinuation in type 2 diabetes, just as in type 1 diabetes, was withdrawal of consent: 14% (251/1795), 13% (173/1345), and 10% (11/114) in the TI, comparator, and TP groups, respectively. The incidence of discontinuations due to adverse events was 8% (142/1795), 2% (24/1345), and 2% (2/114) in the TI, comparator, and TP groups, respectively.

#### 5.3.3.1 Discontinuations due to Respiratory Adverse Events

Overall, adverse events accounted for 7.7% of discontinuations in the Afrezza group versus 1.2-1.4% of discontinuations in the TP (excipient only) and other comparator treatment groups. Of the 185 patients treated with TI that discontinued secondary to an adverse event, 114 patients discontinued secondary to a respiratory adverse event as compared with 3 patients in the comparator groups. There were no discontinuations secondary to respiratory AEs in the excipient only group (not shown in table). The respiratory AEs leading to discontinuation are displayed in Table 13 by diabetes type and in Table 14 for the pooled safety population.

<b>Table 13: Respiratory Adverse Events Leading to Discontinuation – by Diabetes Type</b>					
<b>System Organ Class/Preferred Term</b>	<b>Type 1</b>		<b>Type 2</b>		
	<b>TI n = 614</b>	<b>Comparator n = 599</b>	<b>TI n = 1795</b>	<b>Comparator n = 1345</b>	<b>TP n = 114</b>
Subjects with Respiratory AE leading to Discontinuation	28 (4.6)	1 (0.2)	86 (4.8)	2 (0.1)	0
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	26 (4.2)	0	73 (4.1)	0	0
Allergic pharyngitis	0	0	1 (0.1)	0	0
Asphyxia	0	0	1 (0.1)	0	0
Asthma	1 (0.2)	0	3 (0.2)	0	0
Bronchial Hyperreactivity	0	0	2 (0.1)	0	0
Bronchial obstruction	1 (0.2)	0	0	0	0
Bronchospasm	2 (0.1)	0	0	0	0
Cough	19 (3.1)	0	47(2.6)	0	0
Dyspnea	2 (0.3)	0	8 (0.4)	0	0
Hemoptysis	1 (0.2)	0	0	0	0
Hydrothorax	0	0	0	1 (0.1)	0
Increased upper airway secretion	0	0	1 (0.1)	0	0
Laryngospasm	0	0	1 (0.1)	0	0
Lung disorder	0	0	1 (0.1)	0	0
Painful respiration	0	0	1 (0.1)	0	0
Pharyngolaryngeal pain	0	0	1 (0.1)	0	0
Productive cough	1 (0.2)	0	0	0	0
Pulmonary edema	0	0	1 (0.1)	0	0
Pulmonary congestion	0	0	1 (0.1)	0	0
Respiratory disorder	1 (0.2)	0	0	0	0
Respiratory tract congestion	1 (0.2)	0	0	0	0
Respiratory tract irritation	0	0	1 (0.1)	0	0
Rhonchi	0	0	1 (0.1)	0	0
Throat irritation	0	0	4 (0.2)	0	0
Throat tightness	0	0	1 (0.1)	0	0
Upper respiratory tract congestion	1 (0.2)	0	0	0	0
Wheezing	0	0	2 (0.1)	0	0
<b>INFECTIONS AND INFESTATIONS</b>	3 (0.5)	1 (0.2)	13 (0.7)	1 (0.1)	0
Bronchitis	1 (0.2)	0	4 (0.2)	0	0
Bronchitis acute	0	0	2 (0.1)	0	0
Bronchitis chronic	0	0	1 (0.1)	0	0
Pharyngitis	0	0	1 (0.1)	0	0
Pneumonia	0	0	2 (0.1)	1 (0.1)	0
Pulmonary tuberculosis	0	1 (0.2)	1 (0.1)	0	0
Upper respiratory tract congestion	1 (0.2)	0	0	0	0
Upper Respiratory Tract Infection	0	0	3 (0.2)	0	0
Sinusitis	1 (0.2)	0	0	0	0
<b>INVESTIGATIONS</b>	1 (0.2)	0	2 (0.1)	0	0
Pulmonary function test abnormal	0	0	1 (0.1)	0	0
Pulmonary function test decreased	1 (0.2)	0	1 (0.1)	0	0

Source: Tables 43,70, p. 141, 209 , Pulmonary CIR, ISS, Module 5.

<b>Table 14: Respiratory Adverse Events Leading to Discontinuation – Safety Population</b>		
<b>System Organ Class/PT</b>	<b>TI n= 2409</b>	<b>Comparator n = 1944</b>
Subjects with Respiratory AE leading to Discontinuation	114 (4.7)	3 (0.2)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	101 (4.2)	1 (0.1)
Cough	66 (2.7)	0
Dyspnea	10 (0.4)	0
Asthma	4 (0.2)	0
Throat irritation	4 (0.2)	0
Bronchial hyperactivity	2 (0.1)	0
Bronchospasm	2 (0.1)	0
Respiratory tract congestion	2 (0.1)	0
Wheezing	2 (0.1)	0
Allergic pharyngitis	1 (0)	0
Asphyxia	1 (0)	0
Bronchial obstruction	1 (0)	0
Hemoptysis	1 (0)	0
Increased upper airway secretion	1 (0)	0
Laryngospasm	1 (0)	0
Lung cyst benign	1 (0)	0
Lung disorder	1 (0)	0
Painful respiration	1 (0)	0
Pharyngolaryngeal pain	1 (0)	0
Productive cough	1 (0)	0
Pulmonary congestion	1 (0)	0
Pulmonary edema	1 (0)	0
Respiratory disorder	1 (0)	0
Respiratory tract irritation	1 (0)	0
Rhonchi	1 (0)	0
Throat tightness	1 (0)	0
Upper respiratory tract congestion	1 (0)	0
Hydrothorax	0	1 (0.1)
<b>INFECTIONS AND INFESTATIONS</b>	16 (0.7)	2 (0.1)
Bronchitis	5 (0.2)	0
Upper respiratory tract infection	4 (0.2)	0
Pneumonia	2 (0.1)	1 (0.1)
Bronchitis acute	1 (0)	0
Bronchitis chronic	1 (0)	0
Pharyngitis	1 (0)	0
Pulmonary tuberculosis	1 (0)	1 (0.1)
Sinusitis	1 (0)	0
<b>INVESTIGATIONS</b>	3 (0.1)	0
Pulmonary function test decreased	2 (0.1)	0
Pulmonary function test abnormal	1 (0)	0

Source: Table 11, p. 50-51, Pulmonary CIR, ISS, Module 5.

The respiratory AEs leading to discontinuation were divided into 3 system organ classes (SOC): Respiratory, Infections, and Investigations. The majority of the AEs were reported in the Respiratory SOC (n = 101, 4.2%). Overall, the most common AE leading to discontinuation was cough, seen only in TI-treated patients, with an overall incidence of 2.7%. In the Respiratory SOC, other AEs leading to discontinuation and reported by more than one subject were dyspnea, asthma, throat irritation, bronchial hyperreactivity, bronchospasm, respiratory tract congestion, and wheezing. In the Infections SOC, the most common AEs leading to discontinuation were bronchitis (0.2%) and upper respiratory tract infection (0.2%). Pneumonia was also reported in 2 subjects in the TI group. Other than cough, other respiratory AEs accounted for the discontinuation of  $\leq 0.4\%$  of subjects. There were 3 subjects who had pulmonary function test abnormalities reported as a reason for discontinuation, which are accounted for in the categorical response analysis (see 5.3.6.3.1.1 and 5.3.6.3.1.2). When adverse events leading to discontinuation were examined by diabetes type (Table 13), there were no major differences noted.

*Reviewer's comment: Although the AEs of dyspnea, asthma, bronchial hyper-reactivity, bronchospasm, wheezing are listed as separate preferred terms, review of the narratives revealed that these are all likely to be describing the same type of adverse event. If these are combined into one category (asthma or asthma-like AEs), they form the second most common reason for discontinuation.*

Analysis of the adverse events leading to discontinuation demonstrates that cough and asthma-like AEs are likely treatment-related adverse events, based on the event rates in the treatment and comparator groups. A full analysis of cough as an adverse event in the Afrezza development program is presented in 5.3.5 Common Pulmonary Adverse Events.

### 5.3.4 Pulmonary Adverse Events of Special Interest

#### 5.3.4.1 Lung Neoplasm

No definitive association between Afrezza and lung neoplasm can be made based upon the 1 definitive case of lung malignancy that was reported in the Applicant's clinical studies. However, there are a number of patients who were identified to have new nodules by imaging, whose final diagnosis is not known. These subjects are described in Table 15. Given the overall number of patients in the clinical program and the small number of cases, it is difficult to draw any conclusion regarding malignancy risk with Afrezza. The following section contains a brief discussion of lung neoplasms reported in this clinical development program: malignant, benign, and undetermined lung nodules.

#### Malignant Neoplasms

In the controlled phase 2/3 trials, there was one definite case of lung malignancy identified in a subject treated with TI and Lantus who developed a neuroendocrine tumor with lung

involvement after 120 days of treatment, in trial MCK-TI-102. A summary of the case is provided:

- Subject 067/2909 – 62 year-old Caucasian male receiving TI for 137 days. While in routine follow-up of a previously resected colon cancer (1999), a CEA level was noted to be elevated, and physical exam revealed an enlarged neck lymph node. CT of the thorax without contrast revealed nodules in the mediastinum and right lung hilum with lymph node enlargement in the right mediastinum. There was a 3 x 2 cm nodule with irregular borders in the peribronchial parenchyma in the right superior lobe. These findings were not seen in a CT scan done 7 months prior. The patient was withdrawn from the study. After failure to make diagnosis by needle aspiration, the patient went on to open cervical ganglion biopsy in the supraclavicular area, which led to the diagnosis of neuroendocrine carcinoma. This was identified as a lesion separate from this subject's previous colon cancer, and was identified as a small cell carcinoma, neuroendocrine type. The patient went on to palliative treatment.

*Reviewer's comment: Given the short duration of exposure, this case of small cell carcinoma is unlikely to be related to TI therapy.*

There was also one case of reported primary lung malignancy in a patient enrolled in the uncontrolled extension trial 010. The patient was a 66 year old Czech man, former 40 pack-year smoker, family history significant for father who died of lung cancer in his sixties, who was found to have a non-small cell lung cancer on work-up for microcytic anemia, after having been on TI for a little over one year.

*Reviewer's comment: Although this patient was exposed to TI for longer than the subject 067/2909, he also has other significant risk factors for lung cancer.*

#### Benign Neoplasms

There were two cases of a lung nodule seen on HRCT in the TI-treatment group that were labeled as "benign lung neoplasms". The two cases are described below:

- Subject 2973 in trial MKC-TI-030: 55 year old male with Type 2 diabetes was noted to have a 4 mm nodule in the lateral left lower lobe which occurred after 115 days of TI treatment.
- Subject 8472 in trial MKC-TI-005: 72 year old female noted to have an 8 mm pleural tumor which occurred after 115 days of TI treatment.

In review of the narratives, neither of these was proven by biopsy to be benign, just labeled as such by the respective investigators. In the opinion of this reviewer, these diagnoses remain uncertain, but given the short duration of exposure to TI in both cases, whatever the outcome, it would be unlikely that they were related to TI exposure.

### Lung Nodules of Unknown Etiology

Table 15 includes those cases of lung nodules which were identified based on the findings of HRCT, but for which no further information is available in this NDA submission. At the time of this review, these cases (except that which is discussed below) have not been further characterized.

- Subject 112/1751 in trial MKC-TI-009 was reported to have an enlarged pulmonary nodule shown on CXR at the end of the treatment period (1 year). He was a 22 year old non-smoking, Caucasian male in the United States who began TI therapy on February 2007 with a 9 mm x 6 mm nodule in the LUL. Chest X-ray performed at Week 52 indicated enlargement of this mass to 13 x 11x 14 mm. In addition, there were new, smaller satellite nodules. 5 mm in diameter, in the same segment. Infection work-up and PET scan were negative. The patient was referred for pulmonary consultation. A repeat imaging study was pending at the time of the study report.

<b>Table 15: Lung Nodules (NOS) by HRCT – Safety Population</b>				
<b>Finding</b>	<b>Description</b>	<b>Age/Sex</b>	<b>Latency (days)</b>	<b>Trial/Subject Number</b>
<b>TI –Treated Patients (N=6 cases)</b>				
Lung nodule	Enlarging lung nodule per CXR at end of study	22M Type 1	378	MKC-TI-009/1751
Lung Nodule	2 mm nodular infiltrate inferior right lobe (never biopsied)	54F Type 2	678	MKC-TI-030/0108
Lung Nodule	Nodules in right lung (etiology unknown)	55F Type 2	364	MKC-TI-102/1906
Lung Nodule	4 mm nodule posterior right base of lung	57M Type 2	93	PDC-INS-0008/157
Lung Nodule	3 mm nodular density RML	54M Type 2	88	PDC-INS-0008/323
Lung Nodule	Nodular density in the RLL at the cardiophrenic recess	37M Type 2	82	PDC-INS-0008/399
<b>TP-Treated Patients (N=2 cases)</b>				
Lung Nodule	2 mm subpleural nodular density LUL; 5 mm nodular density in RUL	49M Type 2	92	PDC-INS-0008/154
Lung Nodule	3 mm pulmonary nodule posterior aspect RLL	62M Type 2	88	PDC-INS-0008/403
<b>Comparator (N=4 cases)</b>				
Lung Neoplasm	Abnormal CXR, 4 mm non-calcified nodule in RML	43M Type 1	376	MKC-TI-009/1200
Lung Nodule	Multiple micronodules in lung	73F Type 2	365	MKC-TI-102/2221
Lung Nodule	Lung nodule LUL	58M Type 2	708	MKC-TI-030/1764
Lung Nodule	4.5 mm soft tissue nodules in RML	70M Type 2	336	MKC-TI-030/3543
Source: Table 59, p.179-180, ISS, Module 5. RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; CXR: chest x-ray				

There were 6 (0.25%) cases of lung nodules in patients treated with TI and 2 (1.7%) in the TP group, compared with 4 (0.21%) in the comparator group. If the TI and TP groups are combined, the incidence of lung nodule is n = 8 (0.30%). These nodules of unknown etiology occur somewhat more frequently in the TI/TP group, but no definitive conclusions can be drawn regarding causality without the definitive diagnosis. There is no additional follow-up information available for these cases in the current submission.

*Reviewer’s comment: Given the small size of most of these nodules, it is unlikely that any diagnosis was arrived at in most cases. These nodules are too small to biopsy. Clinically, subcentimeter nodules warrant HRCT follow-up to ensure that they are not growing.*

#### 5.3.4.2 Other Adverse Events of Interest

Other respiratory events of special interest are described Table 16 below.

<b>Table 16: Summary of Pulmonary Adverse Events of Special Interest</b>		
Adverse Event	Trial/Subject #	Description
Laryngospasm	MKC-TI-030 0948	67M with multiple episodes of laryngospasm after first and subsequent TI inhalation/discontinued secondary to events
	MKC-TI-102 2105	50M with multiple episodes of laryngospasm with onset 30 days after initiation of therapy with TI
	MKC-TI-026 504/489	55F with laryngospasm, flushing, and hypotension – continued TI therapy.
	PDC-INS-0008 001/165	55M with h/o laryngospasm on TI experienced one episode of moderate laryngospasm/completed trial
Hemoptysis	MKC-TI-009 186/1064	66F with moderate hemoptysis 230 days after initiation of TI therapy. CXR normal. Discontinued from trial.
	MKC-TI-009 237/1207	44F with episodes of coughing up blood, 4 months after initiation of TI therapy. Continued post-discontinuation of TI. CXR, PFTs, sinus CT unremarkable. Pulmonary consult obtained, but no further information gleaned.
	MKC-TI-030 080/0101	46M with blood-tinged sputum 1 month after starting TI therapy. Subject withdrawn from study.
	MKC-TI-102 2888	59M with sinusitis and hemoptysis 2 months after starting TI therapy. Patient not discontinued, hemoptysis attributed to sinusitis.
Interstitial Lung Disease	MKC-TI-102 056/2790	50M prior smoker, on TI therapy, no other exposures, diagnosis circumspect as based solely on a mildly reduced DLCO.
	MKC-TI-103 190/1730	54F with reported ILD, on TI therapy, however no HRCT or reduction in PFTs to support diagnosis
Pulmonary Fibrosis	MKC-TI-103 523/1348	57F treated with TI with “root of lung fibrosis” on chest x-ray 6 months after starting therapy. No symptoms, no change in PFTs.
Sarcoidosis	PCD-INS-0008 023/0376	42M with mediastinal Lymphadenopathy diagnosed as sarcoid. Stable at all visits. Had at baseline before initiation of TI.
Source: Section 3.1.3.3 Respiratory Events of Special Interest, Pulmonary CIR, P. 58, ISS.		

Significant events such as laryngospasm, interstitial lung disease, pulmonary fibrosis, and sarcoidosis are reported above. Although these events are significant, review of the narratives makes their relatedness to TI therapy circumspect, and in fact, the diagnoses, especially those of ILD, are also questionable. Multiple events of ILD were reported, however, there were not HRCT or pulmonary function findings to support these diagnoses which makes the diagnoses unreliable. Laryngospasm appears to be a rare event which occurred in TI-treated patients right after inhalation of study medication, and therefore may be a safety signal associated with the use of Afrezza.

*Reviewer’s comment: Given the irritant nature of this formulation (inducing cough and air flow obstruction), it is plausible that Afrezza could be inducing laryngospasm.*

### 5.3.5 Common Pulmonary Adverse Events

Table 17 and Table 18 show the respiratory AEs that occurred in  $\geq 1\%$  of patients and also occurred more commonly in the TI or TP groups than in the comparator group, by diabetes type, and in the pooled safety population (Type 1 and Type 2 Diabetes), respectively.

*Reviewer’s comment: The Applicant had compiled a table that included AEs that occurred with a frequency of  $>5\%$ . It was the opinion of this reviewer that by making the cutoff 5%, many AEs which would be important to note were being omitted. If this product is to be approved, a version of Table 17 should be included in Section 6 Adverse Reactions.*

<b>Table 17: Common Adverse Events Occurring at <math>\geq 1\%</math> and More Commonly with Active Treatment (TI or TP) than Comparator – by Diabetes Type</b>					
System Organ Class/PT	Type 1		Type 2		
	TI n = 614	Comparator n = 599	TI n = 1795	Comparator n = 1345	TP n = 114
Subjects with Respiratory AE	317 (51.6)	226 (37.7)	771 (43.0)	380 (28.3)	44 (38.6)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL</b>	231 (37.6)	63 (10.5)	563 (31.4)	73 (5.4)	29 (25.4)
Cough	179 (29.2)	36 (6.0)	463 (25.8)	73 (5.4)	21 (18.4)
Crackles lung	0	0	1 (0.1)	0	2 (1.8)
Dyspnea	9 (1.5)	1 (0.2)	23 (1.3)	4 (0.3)	0
Lung Infiltration	0	0	1 (0.1)	0	2 (1.8)
Pharyngolaryngeal Pain	23 (3.7)	9 (1.5)	33 (1.8)	11 (0.8)	4 (3.5)
Productive Cough	14 (2.3)	5 (0.8)	42 (2.3)	1 (0.1)	2 (1.8)
Throat irritation	12 (2)	1 (0.2)	43 (2.4)	1 (0.1)	2 (1.8)
<b>INFECTIONS AND INFESTATIONS</b>	177 (28.8)	190 (31.7)	397 (22.1)	307 (22.8)	29 (25.4)
Bronchitis	8 (1.3)	5 (0.8)	37 (2.1)	19 (1.4)	2 (1.8)
Bronchitis acute	10 (1.6)	8 (1.3)	22 (1.2)	22 (1.6)	1 (0.9)
Nasopharyngitis	61 (9.9)	70 (11.7)	123 (6.9)	85 (6.3)	16 (14.0)
Pharyngitis	11 (1.8)	8 (1.3)	19 (1.1)	15 (1.1)	0
Rhinitis	10 (1.6)	6 (1.0)	16 (0.9)	13 (1.0)	1 (0.9)
<b>INVESTIGATIONS</b>	30 (4.9)	10 (1.7)	21 (1.2)	14 (1.0)	1 (0.9)
Pulmonary function test decreased	27 (4.4)	8 (1.3)	17 (0.9)	14 (1.0)	0

Source: Tables 44, 71 p. 142, 211, Pulmonary CIR, ISS, Module 5.

<b>Table 18: Common Adverse Events Occurring at <math>\geq 1\%</math> and More Commonly with Active Treatment (TI or TP) than Comparator – Safety Population</b>			
<b>System Organ Class/PT</b>	<b>TI n = 2409</b>	<b>TP n = 114</b>	<b>Comparator n = 1944</b>
Subjects with Respiratory AE	1088 (45.2)	44 (38.6)	606 (31.2)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL</b>	794 (33)	29 (25.4)	192 (9.9)
Cough	642 (26.7)	21 (18.4)	109 (5.6)
Crackles Lung	1 (0)	2 (1.8)	0
Dyspnea	32 (1.3)	0	5 (0.3)
Lung Infiltration	1 (0)	2 (1.8)	0
Pharyngolaryngeal Pain	56 (2.3)	4 (3.5)	20 (1)
Productive Cough	56 (2.3)	3 (2.6)	16 (0.8)
Throat irritation	55 (2.3)	2 (1.8)	2 (0.1)
<b>INFECTIONS AND INFESTATIONS</b>	574 (23.8)	29 (25.4)	497 (25.6)
Bronchitis	45 (1.9)	2 (1.8)	24 (1.2)
Nasopharyngitis	184 (7.6)	16 (14)	155 (8)
Rhinitis	26 (1.1)	1 (0.9)	19 (1)
<b>INVESTIGATIONS</b>	51 (2.1)	1 (0.9)	24 (1.2)
Pulmonary function test decreased	44 (1.8)	0	22 (1.1)

Source: Table 12, p. 53-57, Pulmonary CIR, ISS, Module 5.  
 TI: Afrezza; TP: Technosphere powder, excipient only

When evaluated by diabetes type (Table 17), the AEs that occurred in  $\geq 1\%$  of type 1 diabetes subjects in the TI group and more frequently than in the comparator in type 1 diabetes were: dyspnea, pharyngolaryngeal pain, productive cough, throat irritation, bronchitis, acute bronchitis, pharyngitis, rhinitis, and pulmonary function test decreased. For the type 2 diabetes population, the AEs that occurred in  $\geq 1\%$  of TI or TP treated subjects, and more frequently than in the comparator group were: lung crackles (TP group), dyspnea, pharyngolaryngeal pain, productive cough, throat irritation, bronchitis, nasopharyngitis, pharyngitis, and pulmonary function test decreased. Specific AEs that occurred in  $\geq 1\%$  of TP-treated subjects and more commonly than in the comparator group were: lung crackles, pharyngolaryngeal pain, productive cough, throat irritation, bronchitis, and nasopharyngitis.

Overall, respiratory AEs occurred more commonly in the TI (33%) and TP (25%) groups, than in the comparator group (10%). Excluding cough (which will be discussed in further detail in Section 5.3.5.1 Cough), the most common AEs that were reported in  $\geq 1\%$  of patients and more commonly than in the comparator group for the pooled safety population were: dyspnea, lung infiltration, pharyngolaryngeal pain, productive cough, throat irritation, bronchitis, nasopharyngitis, rhinitis, and pulmonary function test decreased.

The similarity in both the type and incidence of adverse events in both the TI and TP groups suggests that the AEs are due not only to the active drug substance (insulin), but rather to the excipient as well.

### 5.3.5.1 Cough

Cough was pre-specified as an adverse event of interest. The number of subjects, characteristics, severity, temporal relationship to inhalation, and duration of cough were recorded on a separate cough CRF page, but also collected as an AE in some studies. Other information that was evaluated was discontinuation due to cough (see 5.3.3 Dropouts and/or Discontinuations) and relationship of cough to TI exposure duration. The cough CRF was modified as the clinical development program progressed. The cough CRF was used if cough was an isolated symptom not associated with a specific clinical condition (e.g., respiratory infection).

*Reviewer’s comment: All cough events were recorded on the cough CRF page, however, not all cough episodes were reported by the investigator as an AE (especially in cases of mild cough). As a result, the total number of cough events reported in this section may be different from the total number of cough AEs.*

The number of subjects reporting cough and the characteristics of the cough episodes are presented by diabetes type in Table 19 and for the pooled safety population in Table 20.

<b>Table 19: Characteristics of Cough - by Diabetes Type</b>						
		<b>Type 1</b>		<b>Type 2</b>		
		<b>TI n = 614</b>	<b>Comparator n = 599</b>	<b>TI n = 1795</b>	<b>Comparator n = 1345</b>	<b>TP n = 114</b>
# of subjects w/ cough		181 (29.5)	31 (5.2)	471 (26.2)	76 (5.7)	23 (20.2)
# of total episodes		308	42	985	84	124
Frequency <sup>a</sup>	Continuous	21 (6.8)	2 (4.8)	56 (5.7)	8 (9.5)	5 (4.0)
	Intermittent	159 (51.6)	36 (85.7)	559(56.8)	59 (70.2)	93 (75.0)
	Single-defined	128 (41.6)	3 (7.1)	370 (37.6)	17 (20.2)	26 (21.0)
Occurred w/i 10 min of inhalation	Yes	260 (84.4)	0	715 (72.6)	16 (19.0)	101 (81.5)
	No	47 (15.3)	30 (17.4)	268 (27.2)	48 (57.1)	23 (18.5)
	Not collected	1 (0.3)	12 (28.6)	2 (0.2)	20 (23.8)	0
Sputum Production	Yes	39 (12.7)	8 (19.0)	138 (14.0)	17 (20.2)	4 (3.2)
	No	181 (58.8)	26 (61.9)	401 (40.7)	49 (58.3)	19 (15.3)
	Not Collected	88 (28.6)	8 (19.0)	446 (45.3)	101 (81.5)	18 (21.4)

Source: Tables 46, 73 p. 146, 215 , Pulmonary CIR, ISS, Module 5.  
 a: Percentages are based on the total number of cough episodes in each treatment group

**Table 20: Characteristics of Cough – Pooled Safety Population**

	Category	TI n = 2409 n (%)	TP n = 114 n (%)	Comparator n = 1944 n (%)
Number of subject reporting cough		652 (27.1)	23 (20.2)	107 (5.5)
Number of total cough episodes		1293	124	126
Frequency of Coughing <sup>a</sup>	Continuous	77 (6.0)	5 (4.0)	10 (7.9)
	Intermittent	718 (55.5)	93 (75.0)	95 (75.4)
	Single-defined	498 (38.5)	26 (21.0)	20 (15.9)
Cough occurred w/i 10 min of inhalation	Yes	975 (75.4)	101 (81.5)	16 (12.7)
	No	315 (24.4)	23 (18.5)	78 (61.9)
	Not collected	3 (0.2)	0	32 (25.4)
Sputum Production	Yes	178 (13.8)	4 (3.2)	25 (19.8)
	No	581 (44.9)	19 (15.3)	75 (59.5)
	Not collected	534 (41.3)	101 (81.5)	26 (20.6)

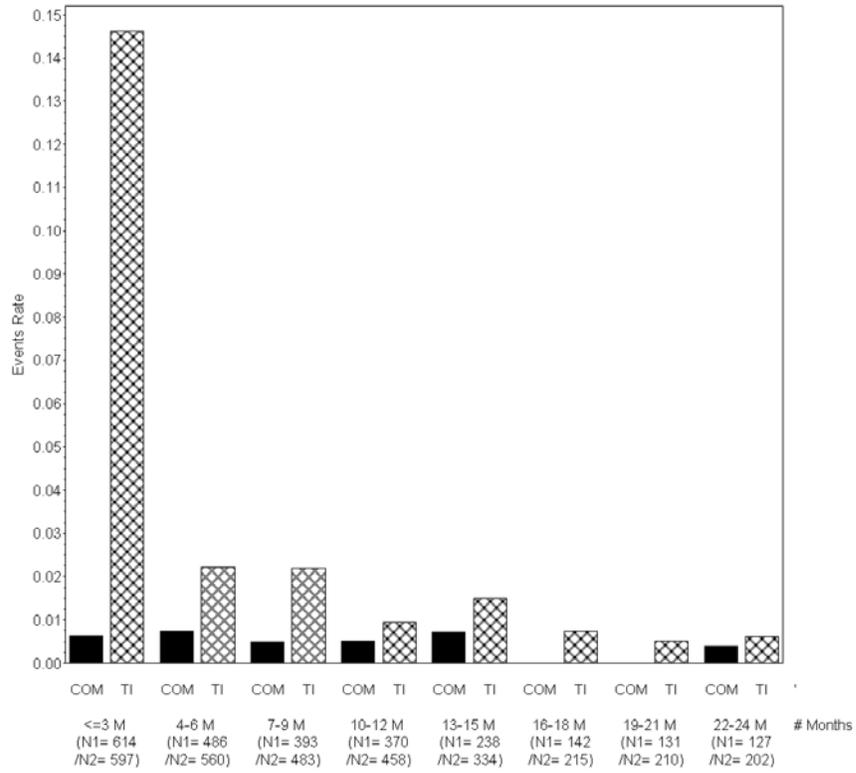
Source: Table 18, p. 76-77, Pulmonary CIR, ISS, Module 5.  
 a: Percentages are based on the total number of cough episodes in each treatment group

In the type 1 diabetes population (Table 19), approximately 30% of subjects treated with TI reported cough compared to 5% in the comparator group. Greater than 90% of cough episodes in both groups were described as single or intermittent. Most reported cough events occurred within 10 minutes of study drug inhalation. Similar results were noted for cough in type 2 diabetics Table 19.

In the pooled population (Table 20), approximately 27% and 20% of patients treated with TI or TP, respectively, reported cough compared to 5.5% of subjects in the comparator group. Greater than 90% of cough episodes in the treatment groups were categorized as intermittent or single-defined. Most cough events in the TI and TP groups occurred within 10 minutes of inhalation of study drug. Although the data collected regarding sputum production is incomplete, it appears that from the data that is present, that TI treatment is not associated with a productive cough. This pooled analysis of cough is consistent with what was seen in each of the individual studies and in type 1 and type 2 diabetes patients (See Section 6 Appendices).

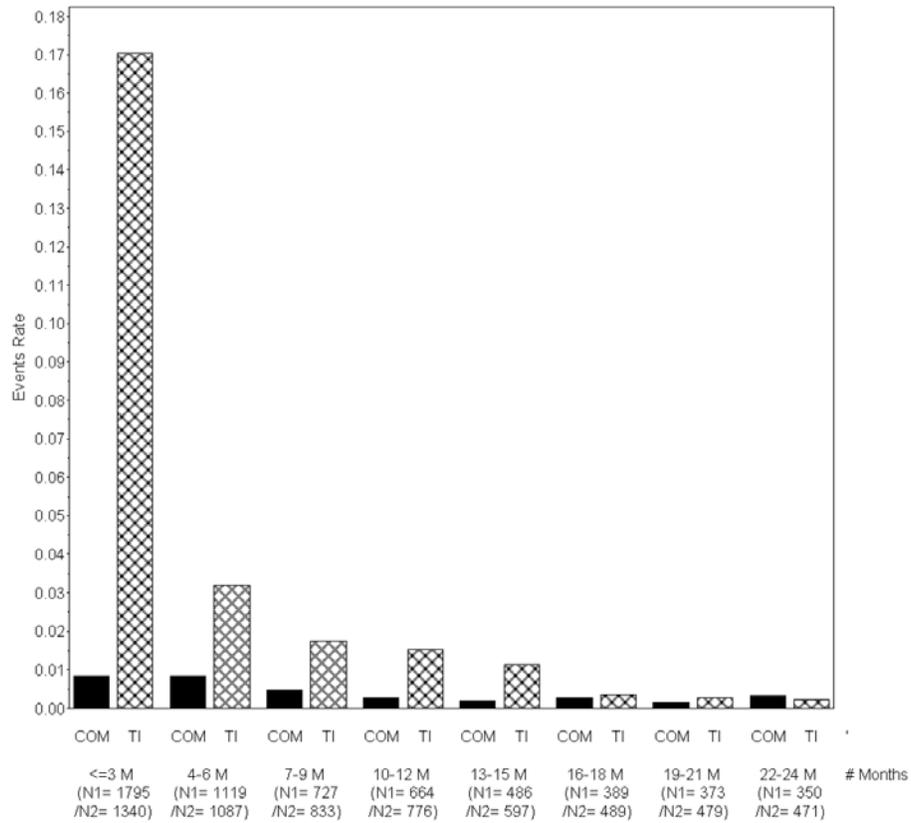
The data regarding cough in relation to exposure to TI is represented graphically in Figure 4, Figure 5, Figure 6, and Figure 7.

**Figure 4 Cough Event Rates by 3 Month Interval – Type 1 Diabetes**



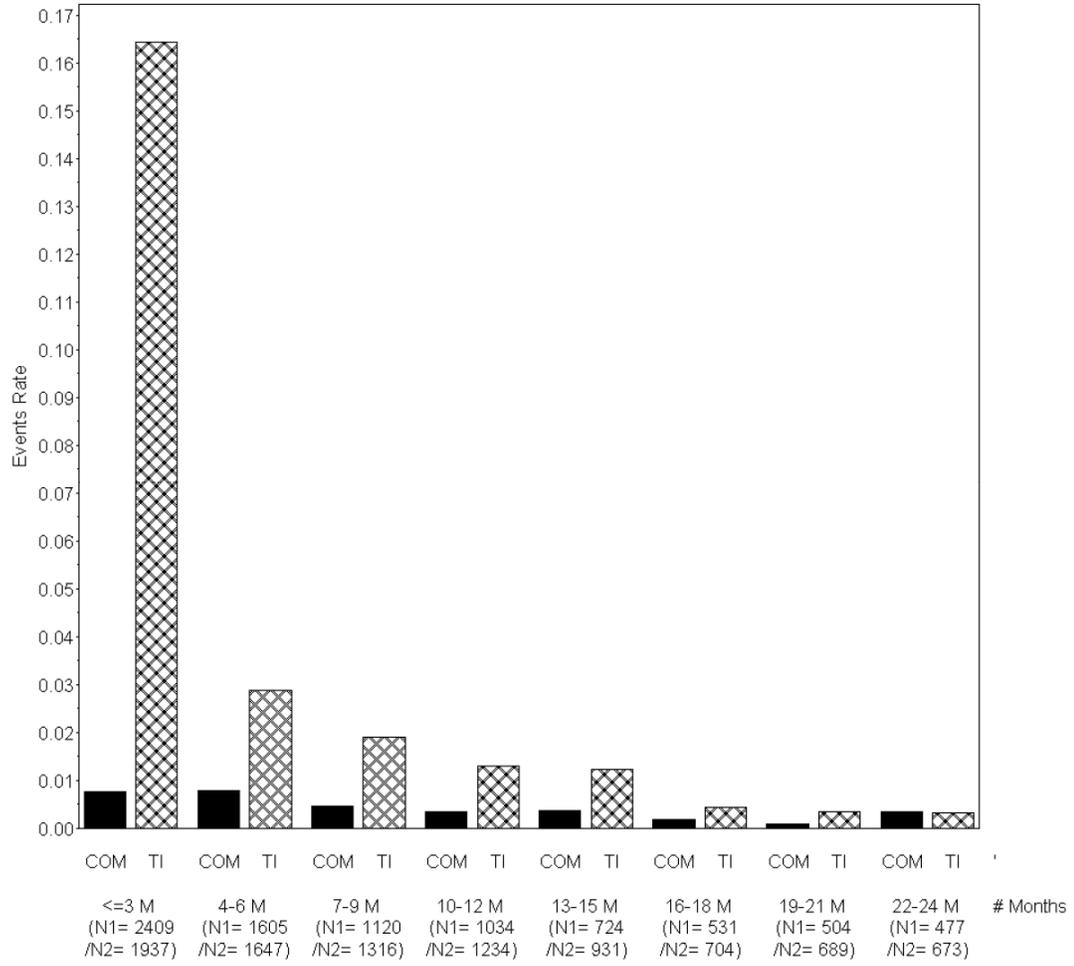
Source: Figure 30, p. 150, Pulmonary CIR, ISS, Module 5.

**Figure 5 Cough Event Rates by 3 Month Interval – Type 2 Diabetes**



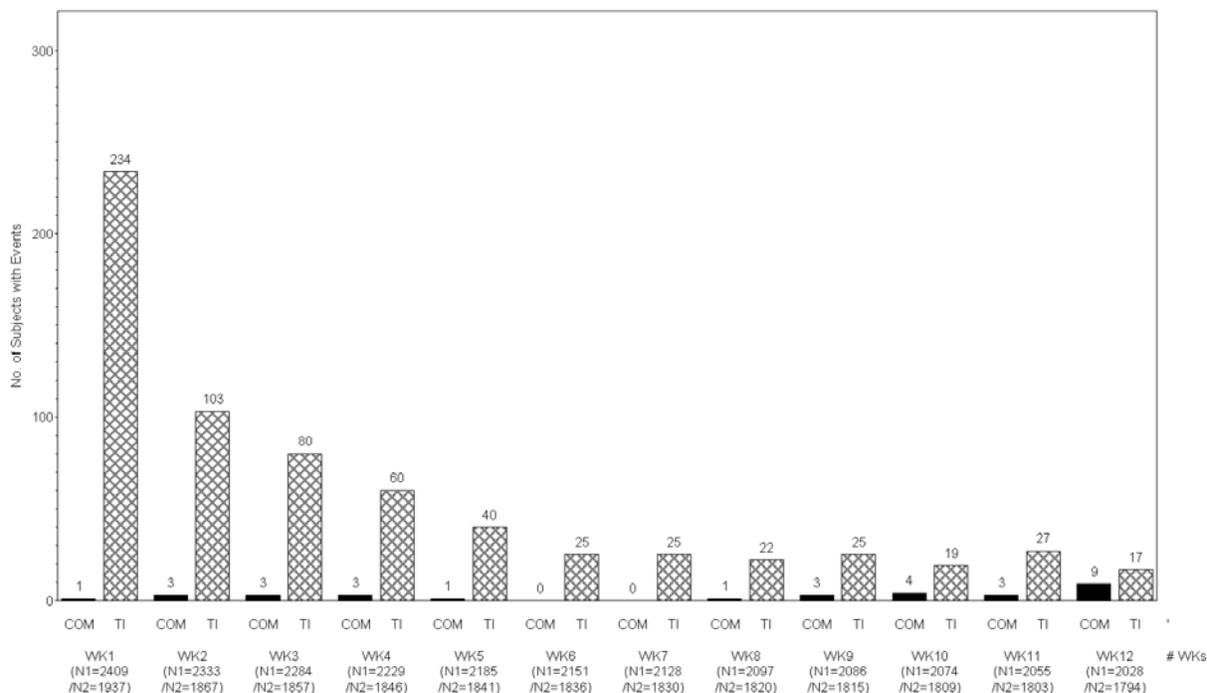
Source: Figure 61, p. 220, Pulmonary CIR, ISS, Module 5.

**Figure 6 Cough Event Rates by 3 Month Interval – Safety Population**



Source: Figure 3, p. 82, Pulmonary CIR, ISS, Module 5.

**Figure 7 Number of Subjects Experiencing Cough During First 3-Month Interval – Safety Population**



Source: Figure 2, p. 81, Pulmonary CIR, ISS, Module 5.

As is shown in the figures above, the incidence of cough was highest during the first 3 months of therapy, and then declined as the study treatment continued. Similarly, the cough event rate was highest early in treatment and similar for patients with type 1 or type 2 diabetes.

The Applicant also examined the FEV1 decline from baseline to various time points in patients who reported cough versus those who did not report cough (p.167, Pulmonary CIR). In the TI group, mean changes in FEV1 were generally larger in subjects who coughed compared to those who did not cough up to Month 12 (particularly in the initial 6 months, the same time when the occurrence of cough was also more common.) For those subjects in the TI group that reported cough, mean FEV1 change was -80 mL at 3 months, -110 mL at 6 months, -80 mL at 9 months, -90 mL at 12 months, -90 mL at 18 months, -110 mL at 24 months, and -130 mL at last measurement. For those subjects in the TI group that did not report cough, mean FEV1 change was -50 mL at 3 months, -60 mL at 6 months, -60 mL at 9 months, -70 mL at 12 months, -130 mL at 18 months, -170 mL at 24 months, and -90 mL at last measurement. From months 3 through 9, the decline in FEV1 was greater for those who reported cough than those patients who did not. For subjects who reported no cough over the course of 24 months of continued treatment, change from Baseline in mean FEV1 was comparable between the TI (-90 mL) and comparator groups (-70 mL), although numerically greater for the TI group (Table 54, p. 168, Pulmonary CIR).

The mechanistic cause of cough in the Afrezza development program is unclear. It is the Applicant's assertion that cough is an anticipated side effect of dry powder inhalation. However, in the experience of this reviewer who is familiar with dry powder inhalation formulations for pulmonary indications (asthma, COPD), the incidence of cough in the TI and TP treated patients is quite high. It is the opinion of this reviewer that the incidence of cough in this development program cannot simply be ascribed as a formulation effect of a dry powder inhaler, but rather, is specific to the ingredients of Afrezza. (See 3.1 Chemistry Manufacturing and Controls for a discussion of the potential mechanism behind cough).

The high incidence of cough, and ultimately, its effect on a patient's pulmonary function in the minutes to hours following dosing, is of concern. Given the highly irritant nature of this drug product, bronchial provocation by the drug product and subsequent life-threatening airway emergencies are of concern (see 1.2 Recommendation on Regulatory Action)..

### 5.3.6 Pulmonary Function Tests

#### 5.3.6.1 PFT Methods

Pulmonary function tests were performed to assess for a change in pulmonary function associated with study medication. PFTs were performed at baseline and at different time points during each individual study. All controlled phase 2/3 trials had PFTs measured at 3 months. See Table 21 for a summary schedule of PFT measurements.

Trial #	Time Points at Which Pulmonary Function Was Measured (month)							
	0	3	6	9	12	18	24	F/U
<b>PDC-INS-0008</b>	x	x						x
<b>MKC-TI-005</b>	x	x						x
<b>MKC-TI-009</b>	x	x	x	x	x			x
<b>MKC-TI-014</b>	x	x	x					x
<b>MKC-TI-026</b>	x	x						x
<b>MKC-TI-030</b>	x	x	x	x	x	x	x	x
<b>MKC-TI-101</b>	x	x	x					x
<b>MKC-TI-102</b>	x	x	x	x	x			x

Source: Biometrics Review of Dr. Joy Mele, NDA 22-472.

All PFTs were performed according to American Thoracic Society (ATS) standards. For Phase 3 clinical trials, PFTs were performed only in MannKind Corporation-certified pulmonary function laboratories. Certification was based on successful completion of initial on-site equipment verification and training, and on-going quality control of the precision and accuracy of test procedures. Blinded central review of all PFTs conducted was performed by registered pulmonary function technologists in real time to evaluate the test for adherence to ATS testing. All subjects were assigned a number which was used to identify the subject throughout the course of the trial. The reviewers had access to subject numeric identifiers only, and no information regarding treatment. The specific PFTs that were evaluated included:

- Spirometry: Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), and Forced Expiratory Flow (FEF) 25-75%
- Lung volumes: Total Lung Capacity (TLC), Residual Volume (RV)
- Diffusing Capacity: DLco

#### 5.3.6.2 PFT Review Strategy

*Reviewer’s comment: PFTs were reviewed for each of the individual trials (see 6 Appendices). In the individual study reviews, the Applicant’s analysis of the data is presented. For the*

*purposes of this integrated analysis of PFTs, the Agency’s analysis, as conducted by the Biometrics Reviewer, Dr. Joy Mele, will be presented.*

*Reviewer’s comment: Throughout this review, FEV1 and DLCO have been discussed because of their reproducibility and measurement of different aspects of lung function (air flow, diffusion capacity). Although the applicant has provided information on a number of other pulmonary function parameters, they will not be discussed here.*

The Applicant proposed a pooling strategy for PFTs that pooled the one and two year studies for Type 1 and Type 2 diabetics. Specifically, the Applicant presented the pulmonary function data in the Integrated Summary of Safety, with trials MKC-TI-009 and MKC-TI-030 pooled for Type 1 diabetics, and trials MKC-TI-102 and MKC-TI-030 pooled for Type 2 diabetics. However, as is noted by the Applicant, individual studies varied greatly in design, inclusion and exclusion criteria, duration, comparator, location of PFT evaluation, and type of PFTs performed. The goal of the PFT analysis was to gain an understanding as to the magnitude of pulmonary function change over time in Afrezza treated patients versus un-treated patients. As a result, this review presents the pulmonary function data as analyzed by the Division’s Biometrics Reviewer, Dr. Joy Mele. The evaluation strategy was based on the time points at which pulmonary function was measured, and the duration of the trials. Per Dr. Mele, this approach was taken for two reasons: 1) the pulmonary safety endpoints under review were measured and recorded over time for each trial so the data within trials is sufficient and pooling is not necessary or desirable for assessing this endpoints 2) the trials differ in designs and populations so assessment of safety for each study provides valuable information. Table 21 shows the schedule of PFTS performed in the controlled phase 2 and 3 clinical trials.

- In consultation and collaboration with Dr. Joy Mele, it was determined that the Agency’s statistical analysis would be conducted for FEV1 only. The review will therefore focus on the FEV1 results, however, the Applicant’s analysis of DLCO will also be presented. Dr. Mele also constructed cumulative distribution plots to examine the categorical percentage changes in FEV1 from baseline.

*Reviewer’s comment: The Agency’s statistical review has included only FEV1, as this parameter was considered to be more clinically meaningful and reproducible in its measurement. The Applicant’s analysis of DLco will be briefly discussed, however, if Afrezza is to be approved, the FEV1 information is the most relevant for the product label.*

Per the Agency’s statistical review, FEV1 was analyzed in the following manner:

Type 1 Diabetes: Trials MKC-TI-009, MKC-TI-030, and MKC-TI-101

- Since all of the clinical trials in Table 21 included an evaluation of PFTs at month 3 (see red outline in Table 21 above), change in FEV1 from baseline to month 3 was evaluated for each of the studies.
- Trials MKC-TI-009 and MKC-TI-030 were reviewed for one year pulmonary function data in Type 1 diabetes.

- Trial MKC-TI-030 was reviewed for 2-year pulmonary function data.
- Trial MKC-TI-009 also provided a limited amount of data in patients that were followed up 2 months after being off treatment (as a part of extension study MKC-TI-126). This data is also discussed.
- Categorical percentage changes in FEV1 from baseline are also presented using cumulative distribution plots.

Type 2 Diabetes: Trials PDC-INS-008, MKC-TI-105, MKC-TI-014, MKC-TI-026, MKC-TI-030, MKC-TI-102, and MKC-TI-103

- Since all of the clinical trials in Table 21 included an evaluation of PFTs at month 3 (see red outline above), change in FEV1 from baseline to month 3 was evaluated for each of the studies.
- MKC-TI-102 and MKC-TI-030 were reviewed for one year pulmonary function data in Type 2 diabetes.
- Trial MKC-TI-030 was reviewed for 2 year PFT data in Type 2 diabetics.
- Trial MKC-TI-010 was reviewed for 4 year pulmonary function data as an extension of Type 2 patients who had completed MKC-TI-005 and PDC-INS-008.
- Trial MKC-TI-102 also provided a limited amount of data in patients that were followed up 2 months after being off treatment (as a part of extension study MKC-TI-126). This data is also discussed.
- Categorical percentage changes in FEV1 from baseline are also presented using cumulative distribution plots.

Pulmonary Function in Untreated Diabetics

- MKC-TI-030 presented information regarding the FEV1 decline in patients without diabetes. This data was also reviewed and will be presented.

Results for change in pulmonary function are presented separately for subjects with type 1 and type 2 diabetes, as the baseline characteristics of these two groups are different. The FEV1 data discussed in this review is per the analyses of Dr. Joy Mele. Pulmonary function data analysis per the pooling strategy of the Applicant will be summarized for FEV1 and DLco and differences (where present) will be noted in the review of FEV1.

*Reviewer's comment: The applicant analyzed the FEV1 change from baseline data using a mixed model with repeated measures and using analysis of covariance with baseline as a covariate. The mixed model with repeated measures (MMRM) contained terms for age, height, gender, baseline PFT, time(visit), treatment and region. For analyses of both Type 1 and Type 2 patients in the same model, a term for disease was included. This model provided an overall estimate of the average treatment difference using all the data for each patient. To estimate an annual decline rate, the applicant used a random coefficients model. This model contained terms for age, height, gender and time (years). As for MMRM, a term for disease was included if both Type 1 and Type 2 patients were being analyzed. Although the protocols defined an intent-to-*

*treat population in each study, for some studies the applicant only analyzed observed cases or completers; Dr. Mele presents ITT results for long-term studies as well.*

### 5.3.6.3 Type 1 Diabetes

#### 5.3.6.3.1 FEV1

##### 5.3.6.3.1.1 FEV1 Results (Agency’s Analysis)

Change in FEV1 from baseline to 3 months, 1 year, 2 years, and follow-up off treatment will be presented as described above in 5.3.6.2 PFT Review Strategy. Those patients with a  $\geq 15\%$  decline in FEV1 (pre-specified “PFT finding”) will also be presented.

##### Change in FEV1 from Baseline to 3 months

FEV1 was evaluated for patients with type 1 diabetes in trials MKC-TI-009, -101, and -030. The change in FEV1 from baseline to month 3 was examined for each of these trials for the TI group and the comparator group. The data were analyzed for observed completers (OC) as well as by the LOCF method. By Month 3, dropout rates were relatively low in these studies, so results for OC matched LOCF results. The results are presented in Table 22 below.

<b>Table 22: Change in FEV1 (L) from Baseline to Month 3 – Type 1 Diabetes</b>			
<b>Study/Duration</b>	<b>FEV1 (L)</b>		<b>p-value TI-Comparator (95% CI)</b>
	<b>TI Group Mean (SD)</b>	<b>Comparator Mean (SD)</b>	
<b>MKC-TI-009*</b> 1 year	NR=301 NC=198	NR=288 NC= 220	<b>p&lt;0.009</b> <b>[-0.05 (-0.08, -0.01)]*</b>
	-0.06 (0.20)	-0.01 (0.16)	
<b>MKC-TI-030*</b> 2 years	NR=267 NC=126	NR= 271 NC=199	p= 0.16
	-0.07 (0.21)	-0.05 (0.16)	
<b>MKC-TI-101**</b> 12 weeks	NR=54 NC=49	NR=56 NC=56	p=0.84
	-0.07 (0.18)	-0.07 (0.19)	

Source: Biometrics Review, Dr. Joy Mele  
 NR: # randomized; NC: # completed; \* computed for Observed Completers; \*\* computed by LOCF

As is demonstrated in Table 22, only MKC-TI-009, the one-year trial in type 1 diabetics demonstrated a significant decline in FEV1 for the TI group versus the Comparator group (-0.05L, p <0.009) at month 3 [a negative difference denotes a greater decline in the TI group].

*Reviewer’s comment: When the 3 month FEV1 data was examined by the Applicant for the pooled population in MKC-TI-009 and -030, the treatment difference at 3 months was a statistically significant -38 mL. This result is of similar numerical magnitude as what is seen with the individual type 1 diabetes studies (see Table 27).*

Change in FEV1 from Baseline to 1 year (trials MKC-TI-009 and MKC-TI-030)

Change in FEV1 from baseline to 1 year was evaluated in both the one year (-009) and two year (-030) clinical trials. The results are presented individually for each trial in Table 23 and Table 24.

<b>Table 23: Change in FEV1(L) from Baseline to 1 year – Type 1 Diabetes -MKC-TI-009</b>			
Time-point	FEV1 (L)		p-value Treatment Difference TI-UC (95% CI)
	TI Mean (SD) (n=200)	Comparator Mean (SD) (n=246)	
Baseline (ITT)	3.45 (0.77)	3.46 (0.79)	p>0.5
Month 12 (Observed)	-0.07 (0.22) (n=134)	-0.04 (0.19) (n=138)	-0.02 (-0.07, +0.02) p=0.33
Month 12 (Applicant’s analysis)	-0.06 (0.21) (n=161)	-0.06 (0.20) (n=173)	NR p=0.72
Month 12 (LOCF)	-0.07 (0.22) (n=235)	-0.04 (0.17) (n=244)	<b>-0.04 (-0.08, -0.05)</b> <b>p=0.03*</b>

Source: Biometrics Review, Dr. Joy Mele; results are based on ANCOVA model with baseline as a covariate  
 LOCF: last observation carried forward  
 Observed: observed completers

<b>Table 24: Change in FEV1(L) from Baseline to 1 year – Type 1 Diabetes -MKC-TI-030</b>			
Time-point	FEV1 (L)		p-value Treatment Difference TI-UC (95% CI)
	TI Mean (SD) (n=200)	Comparator Mean (SD) (n=246)	
Baseline (ITT)	3.54 (0.72)	3.65 (0.84)	-0.10 (-0.25, 0.05) p=0.19
Month 12 (Observed)	-0.07 (0.21) (n=148)	-0.06 (0.18) (n=217)	-0.02 (-0.06, 0.02) p=0.30

Source: Biometrics Review, Dr. Joy Mele  
 Observed: observed completers

*Reviewer’s comment: The applicant analyzed the FEV1 change from baseline data using a mixed model with repeated measures and using analysis of covariance with baseline as a covariate. The mixed model with repeated measures (MMRM) contained terms for age, height, gender, baseline PFT, time(visit), treatment and region. For analyses of both Type 1 and Type 2 patients in the same model, a term for disease was included. This model provided an overall estimate of the average treatment difference using all the data for each patient. To estimate an annual decline rate, the applicant used a random coefficients model. This model contained terms for age, height, gender and time (years). As for MMRM, a term for disease was included if both*

*Type 1 and Type 2 patients were being analyzed. Although the protocols defined an intent-to-treat population in each study, for some studies the applicant only analyzed observed cases or completers; Dr. Mele presents ITT results for long-term studies as well. Dr. Mele also used the MMRM approach. In addition, Dr. Mele performed LOCF, observed cases, and completer analyses using an ANCOVA model with baseline FEV1 as a covariate. These analyses apply to all Dr. Mele's results as presented in the tables that follow for both Type 1 and Type 2 DM..*

In trial MKC-TI-009, the one-year trial in type 1 diabetes, baseline FEV1 was similar between the TI and comparator groups. Per the Agency's analysis of the data, the difference in FEV1 change from baseline at month 12 between the two groups was not statistically significant when analyzed for observed completers. If LOCF was used, the difference in the change from baseline FEV1 was about -40 mL (a negative difference denotes a greater decline in the TI group) at 1 year, which did achieve statistical significance. The Applicant's analysis showed no difference between the TI and comparator groups at 1 year in trial MKC-TI-009. Regardless of the statistical method used to analyze the data, the differences between TI and comparator-treated patients are small (20-40cc) at 1 year (see Table 23).

In trial MKC-TI-030, the two-year trial in type 1 diabetes, baseline FEV1 was similar between the TI and comparator groups. Per the Agency's analysis, the difference in FEV1 change from baseline at month 12 was not statistically significant when analyzed for observed completers (Table 24).

*Reviewer's comment: When the 1 year FEV1 data from MKC-TI-009 and -030 are pooled in the Applicant's analysis, the treatment difference is significant, with a value of -34 mL, which is in the same numerical range as what was observed for the individual studies in the Agency's analysis (see Table 27).*

Change in FEV1 from Baseline to 2 years (MKC-TI-030)

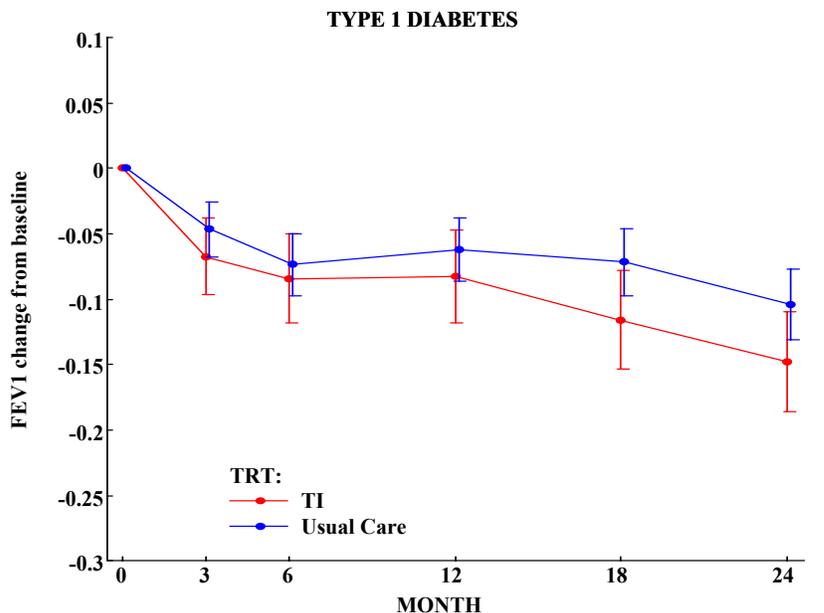
<b>Table 25: Change in FEV1(L) from Baseline to 2 years – Type 1 Diabetes – MKC-TI-030</b>				
	<b>FEV1 (L)</b>		<b>p-value</b>	<b>Treatment Difference TI-UC (95% CI)</b>
	<b>TI Mean (SD) (n=200)</b>	<b>Comparator Mean (SD) (n=246)</b>		
<b>Baseline (ITT)</b>	3.54 (0.72)	3.65 (0.84)	0.19	-0.10 (-0.25, 0.05)
<b>Month 24 (Observed)</b>	-0.15 (0.21) (n=115)	-0.10 (0.18) (n=182)	0.04	-0.05 (-0.09, -0.002)
<b>Month 24 (ITT) (LOCF)</b>	-0.13 (0.22) (n=200)	-0.10 (0.19) (n=246)	0.04	<b>-0.04 (-0.08, -0.001)*</b>
<b>MMRM (ITT)</b>				<b>-0.04 (-0.08, -0.002)*</b>
<b>Month 24 LSM (SE) Average difference over 24 months</b>	-0.15 (0.01)	-0.11 (0.01)	0.04	<b>-0.03 (-0.05, -0.01)*</b>

Source: Biometrics Review, Dr. Joy Mele.  
 ITT: Intent-to-Treat Population; LOCF: Last Observation Carried Forward; MMRM: Mixed Model Repeated Measures; LSM: Least Squares mean; SE: Standard Error; \*: Statistically Significant

In trial MKC-TI-030, the 2-year trial in type 1 diabetes, baseline FEV1 was similar between the TI and comparator groups. Per the Agency’s analysis of the data, the difference in FEV1 change from baseline at month 24 was statistically significant (by both LOCF and MMRM analysis models). The treatment difference in mean change from baseline in FEV1 between the treatment groups was approximately - 40 mL at 2 years. (See Table 25). These results are demonstrated graphically in Figure 8 (UC denotes “usual care”).

*Reviewer’s comment: This value is consistent with the Applicant’s analysis (see Table 27) which demonstrated a statistically significant -48mL treatment difference at 2 years.*

**Figure 8 Change in FEV1 (L) from Baseline to 2 years – Type 1 DM- MKC-TI-030 (MMRM results)**



T1/Mth	0	3	6	12	18	24
TI	266	197	167	149	134	115
UC	268	236	230	217	207	182

Source: Biometrics Review, Dr. Joy Mele.

In summary, the individual phase 2 and 3 trials as well as the pooled controlled studies showed that subjects with type 1 diabetes treated with Afrezza had greater mean decline from baseline FEV1 over time versus the comparator group. The greatest decline in FEV1 occurred within the first three months, and then the two treatment groups declined in a parallel fashion. The treatment difference was generally small, and similar to what was seen in the Exubera program. If the treatment difference was to remain stable over time, it would be unlikely to be of clinical significance. However, given the lack of controlled data beyond 2 years, progression of the treatment difference cannot be definitively ruled out.

#### FEV1 Off-Treatment

A small number of patients from the one-year trial, MKC-TI-009, were followed up 8 weeks after TI discontinuation, as part of the extension trial MKC-TI-126, to examine the effect on FEV1 post-TI discontinuation. The results of this analysis are presented in Table 26.

**Table 26: FEV1(L) Results Off Treatment – Type 1 Diabetes - MKC-TI-126 (extension of MKC-TI-009)**

	<b>TI (n=81) Mean (SD)</b>	<b>Comparator (n=83) Mean (SD)</b>
<b>Last FEV1 on 009</b>		
<b>Observed</b>	3.54 (0.7)	3.53 (0.8)
<b>Change from baseline</b>	-0.07 (0.21)	-0.02 (0.19)
<b>Last FEV1 on 126</b>		
<b>Observed</b>	3.48 (0.7)	3.50 (0.8)
<b>Change from last 009</b>	+0.01 (0.14)	-0.02 (0.14)
<b>% patients with increase in FEV1 during 126</b>	42/81 51%	35/83 42%
<b>% patients returning to 009 baseline FEV1 or higher</b>	30/81 37%	43/83 52%

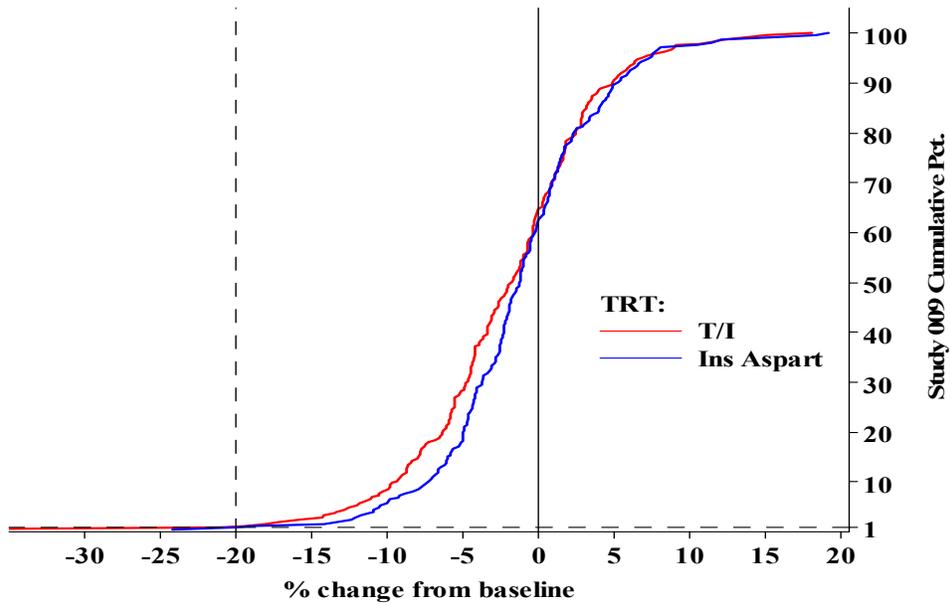
Source: Biometrics Review, Dr. Joy Mele

Eighty-one (81) patients in the TI group and 83 patients in the comparator group were followed up 2 months after discontinuing TI treatment in trial MKC-TI-009. Although the numbers are small, it appears as if only 37% of TI-treated patients returned to their baseline FEV1 as measured in MKC-TI-009. Given that both groups' FEV1 are simultaneously declining, return to baseline FEV1 may not be a plausible measure of reversibility. Ideally, the comparison between the treatment difference at randomization baseline and then extension follow-up would have provided the most useful data. However, Dr. Mele completed the analysis in this manner, due to the very small number of patients contributing data at the end time point, which precluded a meaningful comparison of treatment differences. Thus, with the data that are present, one cannot definitively conclude that the change in FEV1 noted with Afrezza is reversible off-treatment, at least at 2 months of follow-up (*Biometrics Review, Dr. Joy Mele*).

Proportion of Subjects with Categorical Percentage Changes in FEV1 from Baseline

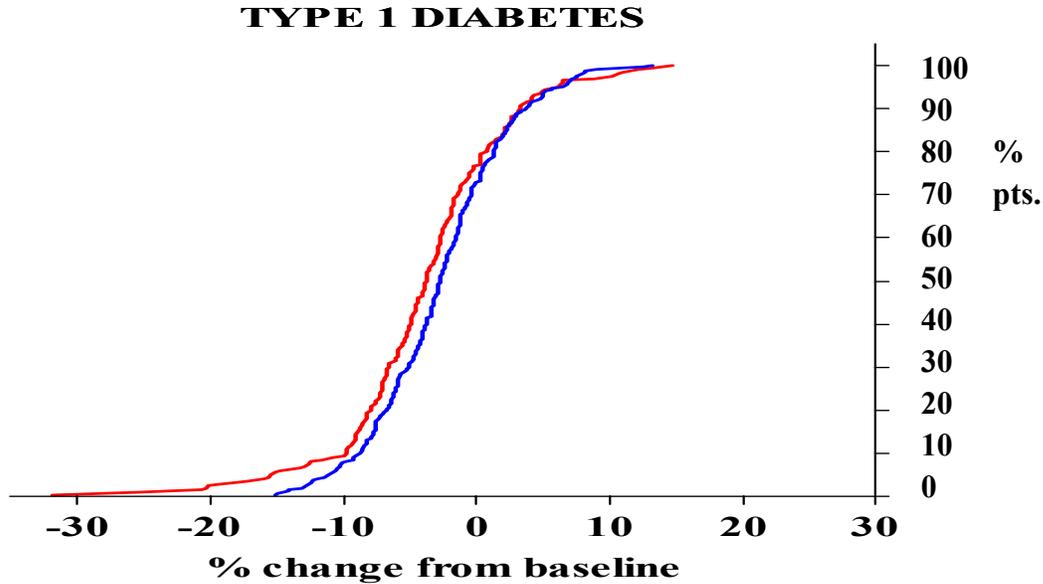
The Biometrics reviewer performed a categorical response analysis to assess the proportion of subjects with a decrease in FEV1 from baseline of various magnitudes. The proportion of subjects with a decrease in FEV1 was analyzed at 1 year in trials MKC-TI-009 and at 2 years in trial MKC-TI-030 (Figure 9 and Figure 10). At 1 year, 2.5% of TI subjects and 1.2% of comparator group subjects had  $\geq 15\%$  decline from baseline FEV1 in MKC-TI-009. At 1 year, the percentage of subjects with  $\geq 20\%$  drop was the same (0.8%) in the TI and comparator groups in MKC-TI-109. At 2 years, 5.5% of TI subjects and 0.8% of comparator subjects had a  $\geq 15\%$  decline in FEV1. More subjects in the TI group (2.5%) also experienced a  $\geq 20\%$  decline in FEV1 at 2 years than in the comparator group (0%) in MKC-TI-030. The difference in subjects experiencing FEV1 decline (both 15% and 20%) were statistically significant at 2 years, but not at 1 year (data courtesy of Dr. Joy Mele, Biometrics Reviewer).

**Figure 9 Cumulative distribution plot FEV1 % change from baseline to 1 year – Type 1 Diabetes (MKC-TI-009) - LOCF**



Source: Biometrics Review, Dr. Joy Mele

**Figure 10 Cumulative distribution plot FEV1 % change from baseline to 2 years – Type 1 Diabetes (MKC-TI-030) - LOCF**



----- TI    ----- Comparator

Source: Biometrics Review, Dr. Joy Mele

#### 5.3.6.3.1.2 FEV1 Results (Applicant's Analysis )

##### Change in FEV1 from Baseline to Various Time Points

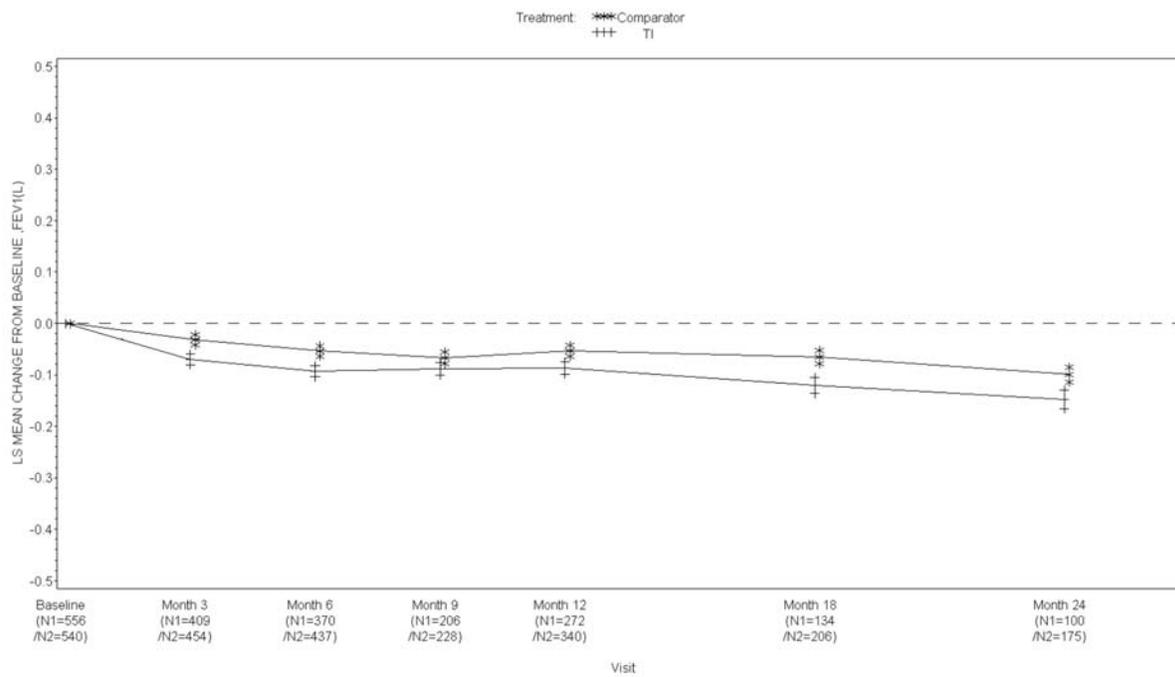
The Applicant examined the change in FEV1 from baseline over time in the type 1 diabetes patient population pooled from trials MKC-TI-009 and MKC-TI-030. Mean baseline, mean (absolute mean and LS mean) change from baseline, and the adjusted mean treatment group difference in mean change from baseline in FEV1 between the TI and comparator treatment group by time was summarized. These results are presented in Table 27 and Figure 11 below.

**Table 27: Treatment Group Difference in LS Mean Change from Baseline in FEV1(L) – Type 1 Diabetes**

Visit Statistics	Absolute Values		MMRM Model		
	TI	Comparator	TI	Comparator	Treatment-Diff TI-comparator
<b>Baseline</b>					
n	556	540			
mean	3.51	3.54			
SD	0.77	0.809			
<b>Month 3</b>					
n	409	454	409	454	
mean/LS mean	-0.06	-0.03	-0.07	-0.03	<b>-0.038*</b>
SD/SE <sup>a</sup>	0.200	0.162	0.011	0.010	<b>0.0128</b>
95% CI			(-0.09, -0.05)	(-0.05, -0.01)	<b>(-0.063, -0.013)</b>
<b>Month 6</b>					
n	370	437	370	437	
mean/LS mean	-0.08	-0.05	-0.09	-0.05	<b>-0.040*</b>
SD/SE <sup>a</sup>	0.220	0.177	0.011	0.010	<b>0.0130</b>
95% CI			(-0.11, -0.07)	(-0.07, -0.03)	<b>(-0.065, -0.014)</b>
<b>Month 9</b>					
n	370	228	206	228	
mean/LS mean	-0.08	-0.05	-0.09	-0.07	<b>-0.021*</b>
SD/SE <sup>a</sup>	0.220	0.185	0.012	0.012	<b>0.0156</b>
95% CI			(-0.11, -0.06)	(-0.09, -0.04)	<b>(-0.051, -0.010)</b>
<b>Month 12</b>					
n	272	340	272	340	
mean/LS mean	-0.07	-0.05	-0.09	-0.05	<b>-0.034*</b>
SD/SE <sup>a</sup>	0.220	0.179	0.012	0.011	<b>0.0146</b>
95% CI			(-0.11, -0.06)	(-0.07, -0.03)	<b>(-0.062, -0.005)</b>
<b>Month 18</b>					
n	134	206	134	206	
mean/LS mean	-0.12	-0.07	-0.12	-0.06	<b>-0.056*</b>
SD/SE <sup>a</sup>	0.217	0.183	0.015	0.013	<b>0.0186</b>
95% CI			(-0.15, -0.09)	(-0.09, -0.04)	<b>(-0.092, -0.019)</b>
<b>Month 24</b>					
n	100	175	100	175	
mean/LS mean	-0.15	-0.11	-0.15	-0.10	<b>-0.048*</b>
SD/SE <sup>a</sup>	0.213	0.185	0.018	0.014	<b>0.0217</b>
95% CI			(-0.18, -0.11)	(-0.13, -0.07)	<b>(-0.091, -0.005)</b>

Source: Table 51, p. 159-160, Pulmonary CIR, ISS, Module 5.  
a: Mean and SD are for absolute values, LS Mean and SE are for adjust values  
LS Mean, SE, adjusted mean differences, and 95% CI are derived from MMRM analysis with disease type, region, treatment, age, gender, height, visit, and baseline PFT values in the model.  
\*: Statistically significant

**Figure 11 LS Mean (SE) of Change from Baseline in FEV1 (L) by Visit, MMRM Model, Type 1 Diabetes**



N1=TI; N2 = Comparator; SE=standard error

Source: Figure 35, p. 159, Pulmonary CIR, ISS, Module 5.

As is shown in Table 27 and Figure 11, over the course of 24 months, subjects in both the TI and comparator treatment groups showed declines from baseline in mean FEV1 at each assessment time point with a greater initial decline in FEV1 for subjects in the TI group. The results were similar when absolute mean change and adjusted LS mean change from baseline in FEV1 values were compared. The LS mean difference (TI-comparator) in the change in FEV1 from baseline was -38 mL at 3 months, -40 mL at 6 months, -21 mL at 9 months, -34 mL at 12 months, -56 mL at 18 months, and -48 mL at 24 months. The difference at each time point, though numerically small, demonstrated statistical significance when examined for the pooled type 1 patient population in MKC-TI-009 and MKC-TI-030.

The Applicant also presented an annual rate of change (slope) in FEV1 between Month 3 (first post-baseline measurement) and Month 24 (last post-baseline measurement) for each treatment group using a random coefficient model for the observed longitudinal FEV1 data. The treatment group difference in the annual rate of change in FEV1 and the corresponding 95% CI was determined (See Table 28).

**Table 28: Mean Annual Rate of Change in FEV1(L) Between Month 3 and Month 24 – Type 1 Diabetes**

	<b>TI n=432</b>	<b>Comparator n = 493</b>	<b>Treatment Diff. TI-Comparator</b>
<b>LS Mean</b>	-0.045	-0.032	-0.0130
<b>SE</b>	0.0084	0.0070	0.0109
<b>95% CI</b>	(-0.062, -0.029)	(-0.046, -0.019)	(-0.034, 0.008)

Source: Table 52, p. 160, Pulmonary CIR, ISS, Module 5.

As shown in Table 28, the annualized change in FEV1 was numerically greater in the TI group, but not statistically different between the two groups from Month 3 to Month 24. The TI group declined approximately 45 mL/year while the comparator group declined approximately 32 mL/year.

*Reviewer’s comment: The Applicant states that this finding in annual rate of decline further demonstrates that the effect on FEV1 associated with TI is non-progressive. In the opinion of this reviewer, this conclusion cannot be drawn without data at later time points.*

#### 5.3.6.3.2 DLco

*Reviewer’s comment: The analysis of DLco was not repeated by the statistical reviewer, as clinically, we felt that the emphasis should be on FEV1 as there may be more variability with DLCO. Because of this, the clinical interpretation and relevancy of the DLCO data is more uncertain. In addition, statistical review of the FEV1 data was consistent with the Applicant’s analysis; therefore, the Applicant’s results will be summarized here for the pooled Type 1 Diabetes Population.*

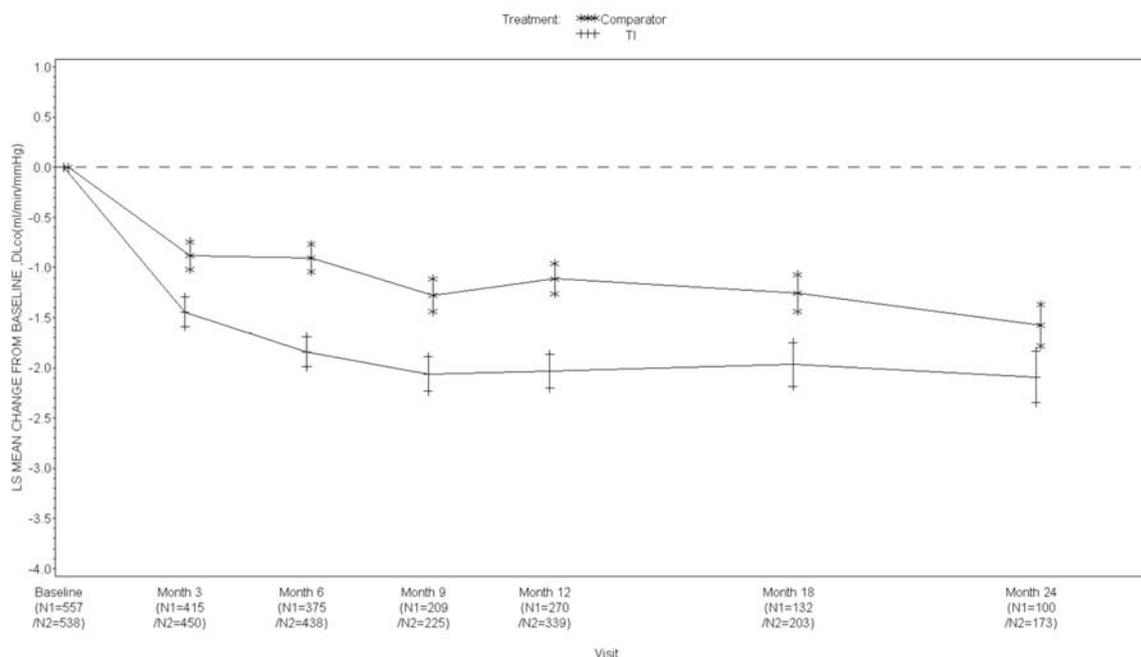
The Applicant examined the change in DLco from baseline over time in the type 1 diabetes patient population pooled from trials MKC-TI-009 and MKC-TI-030. Mean baseline, mean (absolute mean and LS mean) change from baseline, and the adjusted mean treatment group difference in mean change from baseline in DLco between the TI and comparator treatment group by time was summarized. These results are presented in Table 29 and Figure 12.

**Table 29: Treatment Group Difference in LS Mean Change from Baseline in DLco (mL/min/mm Hg) – Type 1 Diabetes**

Visit Statistics	Absolute Values		MMRM Model		
	TI	Comparator	TI	Comparator	Treatment-Diff TI-comparator
<b>Baseline</b>					
n	557	538			
mean	27.97	28.24			
SD	6.337	6.702			
<b>Month 3</b>					
n	415	450	415	450	
mean/LS mean	-1.34	-0.82	-1.44	-0.88	<b>-0.564*</b>
SD/SE <sup>a</sup>	2.895	2.545	0.145	0.138	<b>0.1774</b>
95% CI			(-1.73,-1.16)	(-1.15,-0.61)	<b>(-0.912, -0.216)</b>
<b>Month 6</b>					
n	375	438	375	438	
mean/LS mean	-1.69	-0.79	-1.84	-0.90	<b>-0.939*</b>
SD/SE <sup>a</sup>	2.858	2.802	0.149	0.138	<b>0.1806</b>
95% CI			(-2.13,-1.55)	(-1.17,-0.63)	<b>(-1.293, -0.585)</b>
<b>Month 9</b>					
n	209	225	209	225	
mean/LS mean	-1.96	-1.11	-2.06	-1.28	<b>-0.786*</b>
SD/SE <sup>a</sup>	3.077	2.785	0.173	0.163	<b>0.2203</b>
95% CI			(-2.40,-1.72)	(-1.60,-0.96)	<b>(-1.218, -0.354)</b>
<b>Month 12</b>					
n	270	339	270	339	
mean/LS mean	-1.93	-1.10	-2.03	-1.11	<b>-0.922*</b>
SD/SE <sup>a</sup>	2.866	3.058	0.167	0.151	<b>0.2051</b>
95% CI			(-2.36,-1.71)	(-1.41,-0.82)	<b>(-1.324,-0.520)</b>
<b>Month 18</b>					
n	132	203	132	203	
mean/LS mean	-1.88	-1.26	-1.97	-1.25	<b>-0.714*</b>
SD/SE <sup>a</sup>	2.605	2.859	0.218	0.183	<b>0.2650</b>
95% CI			(-2.39, -1.54)	(-1.61, -0.89)	<b>(-1.233, -0.194)</b>
<b>Month 24</b>					
n	100	173	100	173	
mean/LS mean	-1.88	-1.62	-2.09	-1.57	-0.519
SD/SE <sup>a</sup>	2.809	3.061	0.256	0.205	0.3082
95% CI			(-2.60,-1.59)	(-1.98, -1.17)	(-1.123, 0.085)

Source: Table 61, p. 190-191, Pulmonary CIR, ISS, Module 5.  
 a: Mean and SD are for absolute values, LS Mean and SE are for adjusted values  
 LS Mean, SE, adjusted mean differences, and 95% CI are derived from MMRM analysis with disease type, region, treatment, age, gender, height, visit, and baseline PFT values in the model.  
 \*: Statistically significant

**Figure 12 LS Mean (SE) of Change from Baseline in DLCO (mL/min/mm Hg) by Visit, MMRM Model, Type 1 Diabetes**



N1=TI; N2=Comparator; SE=standard error

Source: Figure 54, p. 190, Pulmonary CIR, ISS, Module 5.

As is shown in Table 29 and Figure 12, over the course of 24 months, subjects in both the TI and comparator treatment groups showed declines in baseline in mean DLco at each assessment time point, with a greater initial decline in DLco for subjects in the TI group. The results were similar when absolute mean change and adjusted LS mean change from baseline in DLco values were compared.

The difference in the LS mean change from baseline in DLco between the TI group and the comparator treatment groups was small, noted at the first post-baseline assessment time point (Month 3), and then remained relatively constant with small fluctuations until the last assessment time point at Month 24, where the observed difference became smaller and not statistically significant. The LS mean difference (TI group –Comparator group) was -0.564 mL/min/mm Hg at 3 months, -0.939 mL/min/mm Hg at 6 months, -0.786 mL/min/mm Hg at 9 months, -0.922 mL/min/mm Hg at 12 months, - 0.714mL/min/mm Hg at 18 months and -0.519 mL/min/mm Hg at 24 months. The difference at each time point (except at 24 months), though numerically small, demonstrated statistical significance when examined for the pooled type 1 patient population in MKC-TI-009 and MKC-TI-030.

The Applicant also presented an annual rate of change (slope) in DLco between Month 3 (first post-baseline measurement) and Month 24 (last post-baseline measurement) for each treatment group using a random coefficient model for the observed longitudinal DLco data. The treatment group difference in the annual rate of change in DLco and the corresponding 95% CI was determined (See Table 30).

<b>Table 30: Mean Annual Rate of Change in DLco (ml/min/mm Hg) Between Month 3 and Month 24 – Type 1 Diabetes</b>			
	<b>TI n=432</b>	<b>Comparator n = 493</b>	<b>Treatment Diff. TI-Comparator</b>
<b>LS Mean</b>	-0.604	-0.392	-0.2127
<b>SE</b>	0.1194	0.0998	0.1555
<b>95% CI</b>	(-0.839,-0.370)	(-0.587, -0.196)	(-0.518,0.092)
Source: Table 62, p. 191, Pulmonary CIR, ISS, Module 5.			

As shown in Table 30, the annual rate of change in DLCO was numerically higher in the TI group, but not statistically different between the two groups from months 3 to 24. The TI group declined approximately 0.6 ml/min/mm Hg per year while the comparator group declined approximately 0.4 ml/min/mm Hg per year.

*Reviewer’s comment: The Applicant states that this finding in annual rate of decline with the data at various time points, further demonstrates that the effect on DLco associated with TI is non-progressive. In the opinion of this reviewer, this conclusion cannot be drawn without data at later time points.*

#### 5.3.6.4 Type 2 Diabetes

##### 5.3.6.4.1 FEV1

###### 5.3.6.4.1.1 FEV1 Results (Agency’s Analysis)

Change in FEV1 from baseline to 3 months, 1 year, 2 years, 4 years, and follow-up off treatment will be presented as described above in 5.3.6.2 PFT Review Strategy. Those patients with a ≥ 15% decline in FEV1 (pre-specified “PFT finding”) will also be presented.

###### Change in FEV1 from Baseline to 3 Months

FEV1 was evaluated for patients with type 2 diabetes in trials PDC-INS-0008, MKC-TI-005, -014, -026, -030, -102, and -103. The change in FEV1 from baseline to month 3 was examined for each of these trials for the TI group and the comparator group. The data were analyzed for observed completers (OC) as well as by the LOCF method. By Month 3, dropout rates were relatively low in these studies, so results for OC matched LOCF results. The results are presented in Table 31 below.

<b>Table 31: Change in FEV1(L) from Baseline to Month 3 – Type 2 Diabetes</b>			
Study/Duration	FEV1 (L)		p-value TI-Comparator (95% CI)
	TI Group Mean (SD)	Comparator Mean (SD)	
<b>PDC-INS-0008**</b> 12 weeks	NR=61 NC=54	NR=62 NC= 53	p = 0.42
	-0.04 (0.20)	-0.01 (0.20)	
<b>MKC-TI-005**</b> 12 weeks	NR=181 NC=165	NR= 46 NC=40	p = 0.34
	-0.04 (0.26)	-0.09 (0.20)	
<b>MKC-TI-014**</b> 24 weeks	NR=151 NC=123	NR=158 NC=153	p = 0.19
	-0.02 (0.22)	-0.01 (0.16)	
<b>MKC-TI-026**</b> 12 weeks	NR=75 NC=69	NR=15 NC=14	p = 0.98
	-0.05 (0.34)	-0.05 (0.33)	
<b>MKC-TI-030</b> 2 years	NR= 656 NC=349	NR=678 NC=463	<b>p = 0.02*</b> <b>[-0.03 (-0.05, -0.005)]</b>
	-0.07 (0.20)	-0.05 (0.17)	
<b>MKC-TI-102</b> 1 year	NR=334 NC=216	NR=343 NC=246	<b>p&lt;0.001*</b> <b>[-0.06 (-0.09, -0.03)]</b>
	-0.09 (0.20)	-0.03 (0.17)	
<b>MKC-TI-103</b> 12 weeks	NR=358 NC=252	NR=170 NC=152	p = 0.6
	-0.04 (0.19)	-0.02 (0.14)	

Source: Biometrics Review, Dr. Joy Mele, NR: # randomized; NC: # completed; \* computed for Observed Completers; \*\* LOCF

As is demonstrated in Table 31, only trails MKC-TI-102 and -030, the one and two-year trials in type 2 diabetes, respectively, demonstrated a significant decline in FEV1 for the TI group versus the comparator group (-30 mL to -60 mL, p = 0.02 and p < 0.001, respectively).

*Reviewer’s comment: When the 3 month FEV1 data was examined by the Applicant for the pooled population of MKC-TI-102 and MKC-TI-030, the treatment difference at 3 months was a statistically significant -42 mL. This is similar to what was noted for Type 1 diabetics (-38 mL).*

Change in FEV1 from Baseline to 1 year (trials MKC-TI-102 and MKC-TI-030)

Change in FEV1 from baseline to 1 year was evaluated in both the one year (-102) and two year (-030) clinical trials. The results are presented individually for each trial in Table 32 and Table 33.

<b>Table 32: Change in FEV1(L) from Baseline to 1 year – Type 2 Diabetes -MKC-TI-102</b>			
Time-point	FEV1 (L)		p-value Treatment Difference TI-UC (95% CI)
	TI Mean (SD) (n=266)	Comparator Mean (SD) (n=283)	
Baseline (ITT)	2.86 (0.69)	2.77 (0.69)	0.14
Month 12 (Observed)	-0.13 (0.22) (n=141)	-0.09 (0.20) (n=139)	0.22 -0.03 (-0.08, +0.02)
Month 12 (Applicant's Analysis)	-0.13 (0.22) (n=175)	-0.09 (0.20) (n=199)	0.22
Month 12 (LOCF)	-0.13 (0.23) (n=266)	-0.07 (0.19) (n=283)	<b>&lt;0.001*</b> <b>-0.06 (-0.10, -0.03)</b>

Source: Biometrics Review, Dr. Joy Mele; results are based on ANCOVA model with baseline as a covariate  
 LOCF: last observation carried forward

<b>Table 33: Change in FEV1(L) from Baseline to 1 year – Type 2 Diabetes -MKC-TI-030</b>			
Time-point	FEV1 (L)		p-value Treatment Difference TI-UC (95% CI)
	TI Mean (SD) (n=530)	Comparator Mean (SD) (n=578)	
Baseline (ITT)	3.09 (0.66)	3.15 (0.74)	p=0.13 -0.06 (-0.15, 0.02)
Month 12 (Observed)	-0.07 (0.20) n=414	-0.05 (0.17) n=504	<b>p=0.04*</b> <b>-0.03 (-0.06, -0.002)</b>

Source: Biometrics Review, Dr. Joy Mele

In trial MKC-TI-102, the one-year trial in type 2 diabetes, baseline FEV1 was similar between the TI and comparator groups. Per the Agency's analysis of the data, the difference in FEV1 change from baseline at month 12 between the two groups was not statistically significant when analyzed for observed completers. If LOCF was used, the difference in the change from baseline FEV1 was about -60 mL (a negative difference denotes a greater decline in the TI group) at 1 year, which did achieve statistical significance. The Applicant's analysis showed no difference between the TI and comparator groups at 1 year in trial MKC-TI-009. Regardless of the statistical method used to analyze the data, the differences between TI and comparator-treated patients are small (30-60 cc) at 1 year, and likely of little clinical significance (Table 32).

*Reviewer's comment: The decline (30-60cc) in type 2 diabetics is slightly greater than type 1 diabetics (20-40cc). Although this might be disease specific, it may also have to do with the older subjects in the type 2 population.*

In trial MKC-TI-030, the two-year trial in type 1 diabetes, baseline FEV1 was similar between the TI and comparator groups. Per the Agency's analysis, the difference in FEV1 change from

baseline at month 12 was -30 mL and statistically significant when analyzed for observed completers (Table 33).

*Reviewer’s comment: When the 1 year FEV1 data from MKC-TI-102 and -030 are pooled in the Applicant’s analysis, the treatment difference is significant, with a value of -40 mL, which is in the same numerical range as what was observed for the individual studies in the Agency’s analysis. This decline is also similar to that experienced by Type 1 diabetics at 1 year (-34 mL).*

Change in FEV1 from Baseline to 2 years (MKC-TI-030)

<b>Table 34: Change in FEV1(L) from Baseline to 2 years – Type 2 Diabetes – MKC-TI-030</b>				
	<b>FEV1 (L)</b>		<b>p-value</b>	<b>Treatment Difference TI-UC (95% CI)</b>
	<b>TI Mean (SD) (n=530)</b>	<b>Comparator Mean (SD) (n=578)</b>		
<b>Baseline (ITT)</b>	3.09 (0.66)	3.15 (0.74)	0.13	-0.06 (-0.15, 0.02)
<b>Month 24 (Observed)</b>	-0.15 (0.20) n=319	-0.12 (0.22) n=436	<b>&lt;0.01</b>	<b>-0.04 (-0.07, -0.01)*</b>
<b>Last Value (ITT)</b>	-0.14 (0.21) n=530	-0.10 (0.22) n=578	<b>&lt;0.01</b>	<b>-0.04 (-0.06, -0.01)*</b>
<b>MMRM (ITT)</b>				
<b>Month 24 LSM (SE)</b>	-0.15 (0.01)	-0.12 (0.01)	<b>&lt;0.01</b>	<b>-0.04 (-0.06, -0.01)*</b>
<b>Average difference over 24 months</b>				<b>-0.03 (-0.04, -0.01)*</b>

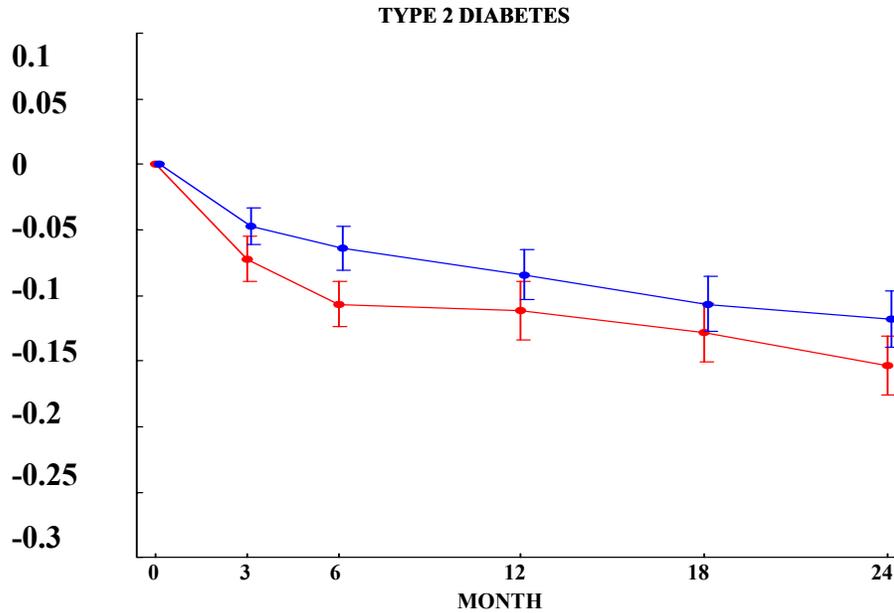
Source: Biometrics Review, Dr. Joy Mele.  
 \*: Statistically Significant; ITT: intent to treat; MMRM: mixed model repeated measures; LSM: least squares mean; SE (standard error)

In trial MKC-TI-030, the 2-year trial in type 1 diabetes, baseline FEV1 was similar between the TI and comparator groups. Per the Agency’s analysis of the data, the difference in FEV1 change from baseline at month 24 was statistically significant (by both LOCF and MMRM analysis models). FEV1 declined in both groups (150 cc for TI, 120 cc for comparator). The treatment difference in mean change from baseline in FEV1 between the treatment groups was approximately - 40 mL at 2 years. (See Table 50). These results are demonstrated graphically in Figure 13 (UC denotes “usual care”).

*Reviewer’s comment: This value is consistent with the Applicant’s analysis (see) which demonstrated a statistically significant -46 mL treatment difference at 2 years. This is similar to what was noted in type 1 diabetes (-48 mL) at 2 years.*

*Reviewer’s comment: It is curious that lung function is declining in both groups to this degree over a 2 year period, especially since those patients with lung disease have been excluded. The same degree of decline occurred in both the TI and comparator groups in the type 1 population as well.*

**Figure 13 Change in FEV1 (L) from Baseline to 2 years – Type 2 DM MKC-TI-030 (MMRM results)**



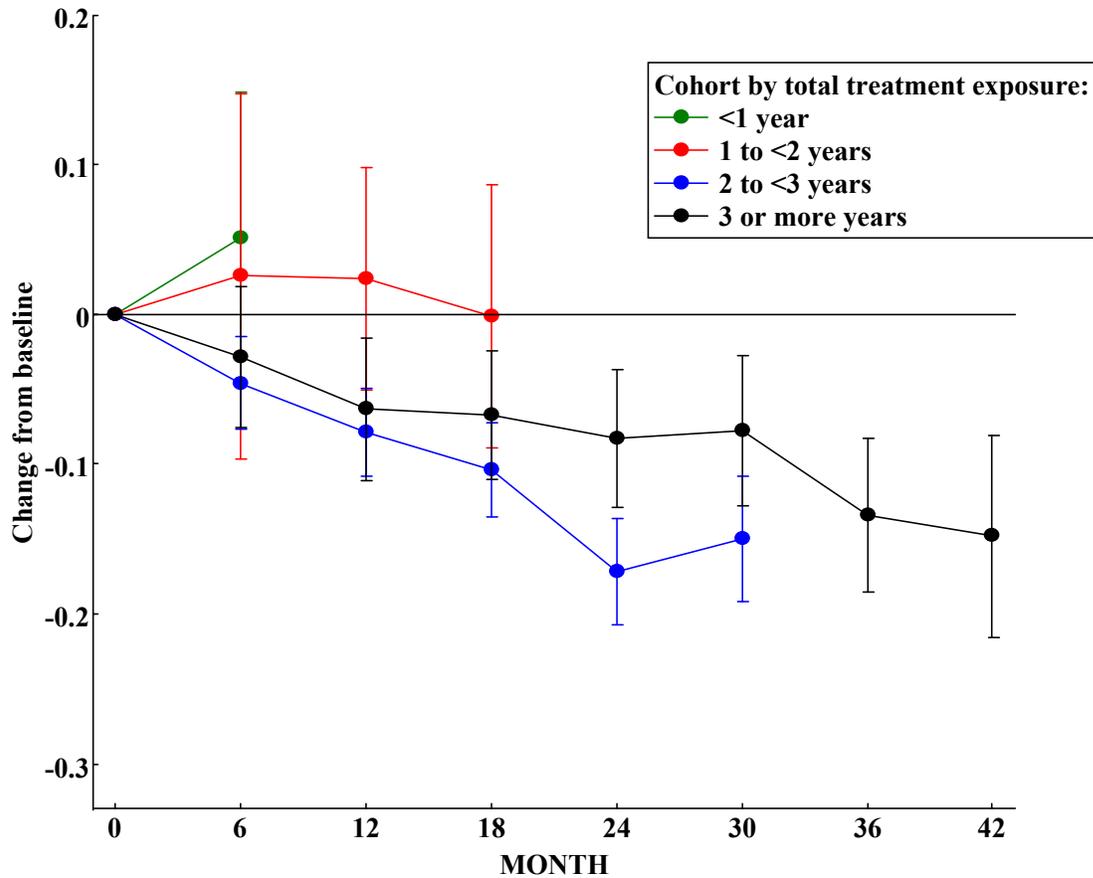
T2/Mth	0	3	6	12	18	24
TI	654	523	468	414	375	319
UC	673	560	535	504	468	436

Source: Biometrics Review, Dr. Joy Mele.

Change in FEV1 from Baseline to 4 Years (trial MKC-TI-010)

MKC-TI-010 was an open-label extension trial for subjects with type 2 diabetes who had completed either PDC-INS-0008 or MKC-TI-005. This trial provided additional long-term pulmonary safety data. A total of 229 subjects participated in the trial and all received active treatment with TI. Because it was an uncontrolled study, it is of limited use in providing information regarding the incidence of adverse events. However, it does provide a means for looking at the effect on pulmonary function in patients treated for 4 years. The data was analyzed by Dr. Joy Mele, and the results are presented in Figure 14 and Table 35 below.

**Figure 14 Mean Change from Baseline FEV1 in MKC-TI-030 (Defined by Time on Study)**



Source: Biometrics Review, Dr. Joy Mele

Month	N	Change from Baseline
		Mean (SD)
0 (end of DB)	229	Baseline
		2.99 (0.7)
6	195	-0.03 (0.2)
12	205	-0.05 (0.2)
24	170	-0.15 (0.2)
36	56	-0.13 (0.2)
42	39	-0.15 (0.2)

Source: Biometrics Review, Dr. Joy Mele

As is shown in Figure 14 and Table 35, those patients that remained on TI continued to show a decline in FEV1, although it is difficult to interpret, because very few patients contributed to the measurements at the end of 4 years (n=39), and there is no comparator group to assess if the

treatment difference is changing over time. The Applicant’s computed a mean annual rate of decline of -48 mL/year over the 48 month study period, which is of similar magnitude to what was seen in the controlled phase 2/3 trials up to 2 years.

In summary, the individual phase 2 and 3 trials as well as the pooled controlled studies showed that subjects with type 2 diabetes treated with Afrezza had greater mean decline from baseline FEV1 over time versus the comparator group. The greatest decline in FEV1 occurred within the first three months, and then the two treatment groups declined in a parallel fashion. The treatment difference was generally small, and similar to what was seen in the Exubera program. If the treatment difference was to remain stable over time, it would be unlikely to be of clinical significance. However, given the lack of controlled data beyond 2 years, progression of the treatment difference cannot be definitively ruled out.

FEV1 Off-Treatment

A small number of patients from the one-year trial, MKC-TI-102, were followed up 8 weeks after TI discontinuation, as a part of extension trial MKC-TI-126, to examine the effect on FEV1 post-TI discontinuation. The results of the analysis are presented in Table 36.

<b>Table 36: FEV1(L) Results Off Treatment – Type 2 Diabetes -MKC-TI-126 (extension of MKC-TI-102)</b>		
	<b>TI (n=69) Mean (SD)</b>	<b>Comparator (n=67) Mean (SD)</b>
<b>Last FEV1 on 102</b>		
<b>Observed</b>	2.89 (0.7)	2.80 (0.7)
<b>Change from baseline</b>	-0.11 (0.19)	-0.08 (0.17)
<b>Last FEV1 on 126</b>		
<b>Observed</b>	2.93 (0.7)	2.78 (0.7)
<b>Change from 102</b>	+0.04 (0.18)	-0.02 (0.15)
<b>% patients with increase in FEV1 during 126</b>	45/69 65%	29/67 43%
<b>% patients returning to 102 baseline FEV1 or higher</b>	22/69 32%	21/67 31%

Source: Biometrics Review, Dr. Joy Mele

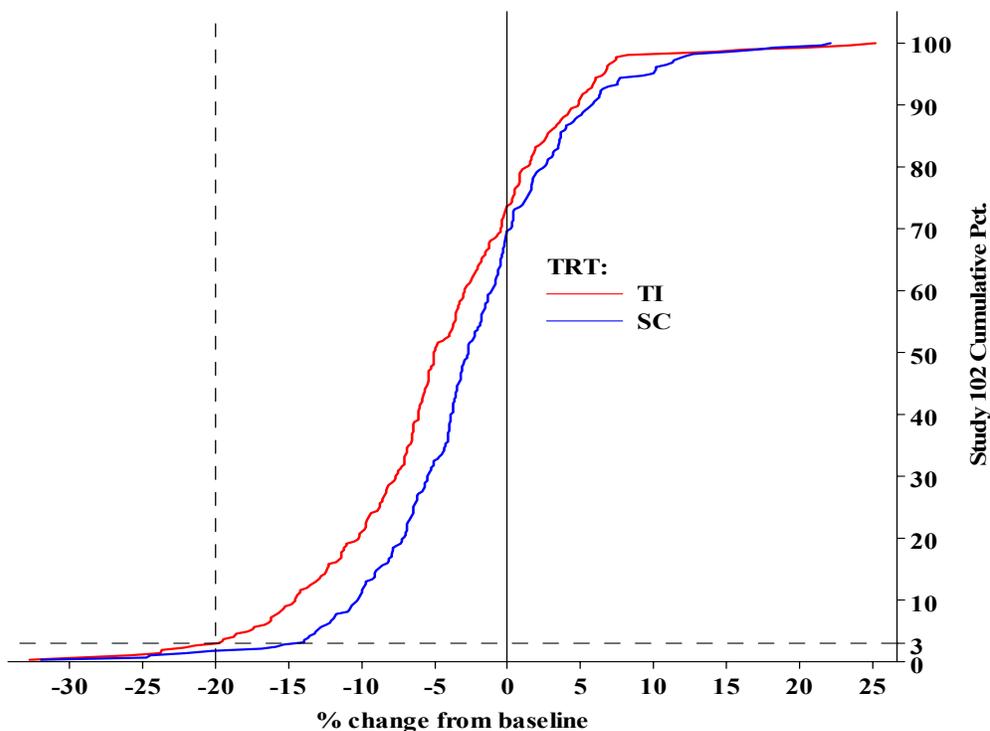
Sixty-nine (69) patients in the TI group and 67 patients in the comparator group were followed up 2 months after discontinuing TI treatment in trial MKC-TI-102. Although the numbers are small, it appears as if only 32% of TI-treated patients returned to their baseline FEV1 as measured in MKC-TI-102. Given that both groups’ FEV1 are simultaneously declining, return to baseline FEV1 may not be a plausible measure of reversibility. Ideally, the comparison between the treatment difference at randomization baseline and then extension follow-up would have provided the most useful data. However, Dr. Mele completed the analysis in this manner, due to the very small number of patients contributing data at the end time point, which precluded

a meaningful comparison of treatment differences. Thus, with the data that are present, one cannot definitively conclude that the change in FEV1 noted with Afrezza is reversible off-treatment, at least at 2 months of follow-up (*Biometrics Review, Dr. Joy Mele*).

Proportion of Subjects with Categorical Percentage Changes in FEV1 from Baseline

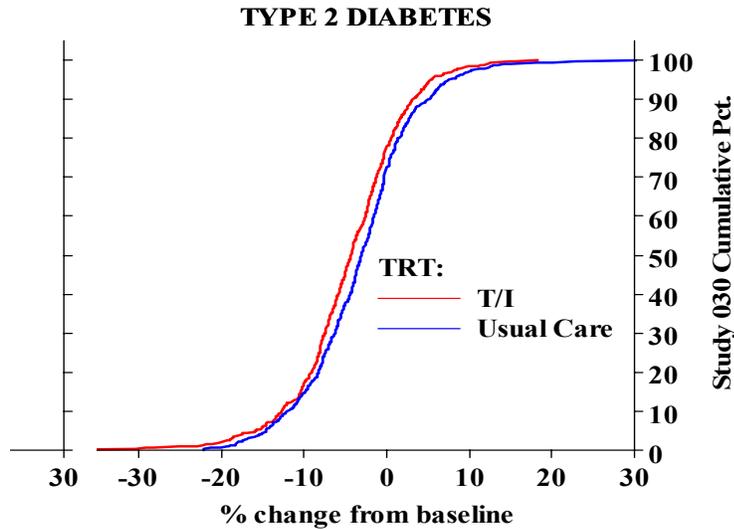
The Biometrics reviewer performed a categorical response analysis to assess the proportion of subjects with a decrease in FEV1 from baseline of various magnitudes. The proportion of subjects with a decrease in FEV1 was analyzed at 1 year in trial MKC-TI-102 and at 2 years in trial MKC-TI-030 (Figure 15 and Figure 16). At 1 year, 9.0% of TI subjects and 2.8% of comparator group subjects had  $\geq 15\%$  decline from baseline FEV1 in MKC-TI-009. At 1 year, the percentage of subjects with  $\geq 20\%$  drop was 2.6% in the TI group and 1.8% in the comparator group in trial MKC-TI-109. At 2 years, 5.9% of TI subjects and 4.3% of comparator subjects had a  $\geq 15\%$  decline in FEV1. More subjects in the TI group (1.9%) also experienced a  $\geq 20\%$  decline in FEV1 at 2 years than in the comparator group (0.7%) in MKC-TI-030. The difference in subjects experiencing  $\geq 15\%$  FEV1 decline at 1 year (MKC-TI-102) was statistically significant (data courtesy of Dr. Joy Mele, Biometrics Reviewer).

**Figure 15 Cumulative distribution plot FEV1 % change from baseline to 1 year – Type 2 Diabetes (MKC-TI-102) - LOCF**



Source: Biometrics Review, Dr. Joy Mele

**Figure 16 Cumulative distribution plot FEV1 % change from baseline to 2 years – Type 2 Diabetes (MKC-TI-030) - LOCF**



Source: Biometric Review, Dr. Joy Mele

#### 5.3.6.4.1.2 FEV1 Results (Applicant's Analysis)

##### Change in FEV1 from Baseline to Various Time Points

The Applicant examined the change in FEV1 from baseline over time in the type 2 diabetes patient population pooled from trials MKC-TI-102 and MKC-TI-030. Mean baseline, mean (absolute mean and LS mean) change from baseline, and the adjusted mean treatment group difference in mean change from baseline in FEV1 between the TI and comparator treatment group by time was summarized. These results are presented in Table 34 and Figure 17 below.

**Table 37: Treatment Group Difference in LS Mean Change from Baseline in FEV1(L) – Type 2 Diabetes**

Visit Statistics	Absolute Values		MMRM Model		
	TI	Comparator	TI	Comparator	Treatment-Diff TI-comparator
<b>Baseline</b>					
n	976	1002			
mean	3.02	3.04			
SD	0.699	0.746			
<b>Month 3</b>					
n	764	808	764	808	
mean/LS mean	-0.08	-0.04	-0.10	-0.06	<b>-0.042*</b>
SD/SE <sup>a</sup>	0.201	0.170	0.009	0.009	<b>0.0100</b>
95% CI			(-0.12, -0.08)	(-0.07, -0.04)	<b>(-0.062, -0.023)</b>
<b>Month 6</b>					
n	688	765	688	765	
mean/LS mean	-0.11	-0.07	-0.13	-0.08	<b>-0.046*</b>
SD/SE <sup>a</sup>	0.196	0.195	0.009	0.009	<b>0.0102</b>
95% CI			(-0.15, -0.11)	(-0.10, -0.06)	<b>(-0.066, -0.026)</b>
<b>Month 9</b>					
n	248	291	249	291	
mean/LS mean	-0.14	-0.08	-0.14	-0.09	<b>-0.048*</b>
SD/SE <sup>a</sup>	0.244	0.190	0.011	0.011	<b>0.0136</b>
95% CI			(-0.16, -0.12)	(-0.11, -0.07)	<b>(-0.075, -0.022)</b>
<b>Month 12</b>					
n	529	617	529	617	
mean/LS mean	-0.11	-0.09	-0.14	-0.10	<b>-0.040*</b>
SD/SE <sup>a</sup>	0.219	0.214	0.010	0.009	<b>0.0112</b>
95% CI			(-0.16, -0.12)	(-0.11, -0.08)	<b>(-0.062, -0.018)</b>
<b>Month 18</b>					
n	373	468	373	468	
mean/LS mean	-0.13	-0.11	-0.16	-0.11	<b>-0.042*</b>
SD/SE <sup>a</sup>	0.213	0.225	0.011	0.010	<b>0.0126</b>
95% CI			(-0.18, -0.13)	(-0.13, -0.09)	<b>(-0.066, -0.017)</b>
<b>Month 24</b>					
n	280	421	280	421	
mean/LS mean	-0.16	-0.12	-0.18	-0.13	<b>-0.046*</b>
SD/SE <sup>a</sup>	0.207	0.222	0.012	0.011	<b>0.0141</b>
95% CI			(-0.20, -0.15)	(-0.15, -0.11)	<b>(-0.073, -0.018)</b>

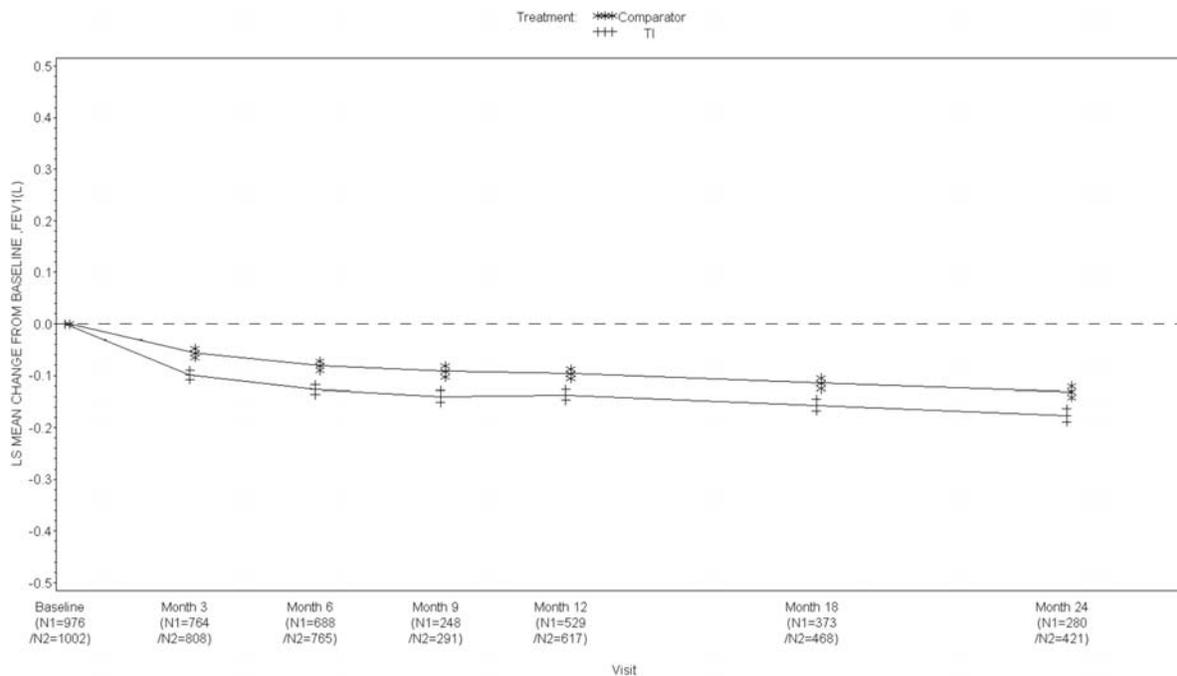
Source: Table 78, p. 229-30, Pulmonary CIR, ISS, Module 5.

a: Mean and SD are for absolute values, LS Mean and SE are for adjust values

LS Mean, SE, adjusted mean differences, and 95% CI are derived from MMRM analysis with disease type, region, treatment, age, gender, height, visit, and baseline PFT values in the model.

\*: Statistically significant

**Figure 17 LS Mean (SE) Change from Baseline in FEV1 (L) by Visit, MMRM Model, Type 2 Diabetes**



N1=TI; N2=Comparator; SE=standard error

Source: Figure 66, p. 229, Pulmonary CIR, ISS, Module 5

As shown in Table 34 and Figure 17, over the course of 24 months, subjects in both the TI and comparator treatment groups showed declines from baseline in mean FEV1 at each assessment time point, with a greater initial decline for subjects in the TI group. The results were similar when absolute mean change and adjusted LS mean change from baseline in FEV1 values were compared. The LS mean difference (TI-comparator) in the mean change in FEV1 from baseline was -42 mL at 3 months, -46 mL at 6 months, -48 mL at 9 months, -40 mL at 12 months, -42 mL at 18 months, and -46 mL at 24 months. The difference at each time point, though numerically small, demonstrated statistical significance when examined for the pooled type 2 patient population in MKC-TI-102 and MKC-TI-030.

The Applicant also presented an annual rate of change (slope) in FEV1 between Month 3 (first post-baseline measurement) and Month 24 (last post-baseline measurement) for each treatment group using a random coefficient model for the observed longitudinal FEV1 data. The treatment group difference in the annual rate of change in FEV1 and the corresponding 95% CI was determined (See Table 38).

**Table 38: Mean Annual Rate of Change in FEV1(L) Between Month 3 and Month 24 – Type 2 Diabetes**

	<b>TI n=793</b>	<b>Comparator n = 863</b>	<b>Treatment Diff. TI-Comparator</b>
<b>LS Mean</b>	-0.049	-0.044	-0.0047
<b>SE</b>	0.0058	0.0051	0.0077
<b>95% CI</b>	(-0.060, -0.037)	(-0.054, -0.034)	(-0.020, 0.011)

Source: Table 79, p. 231, Pulmonary CIR, ISS, Module 5.

As shown in Table 38, the annualized change in FEV1 was numerically greater in the TI group, but not statistically different between the two groups from Month 3 to Month 24. The TI group declined approximately 49 mL/year while the comparator group declined approximately 44 mL/year.

*Reviewer’s comment: This annual rate of change in FEV1 in type 2 diabetes is similar to what was observed for type 1 diabetes treated with TI (-45 mL/year). The Applicant once again states that this finding in the annual rate of decline demonstrates that the effect on FEV1 associated with TI is non-progressive. In the opinion of this reviewer, this conclusion cannot be drawn without data or later time points.*

#### 5.3.6.4.2. DLco

*Reviewer’s comment: The analysis of DLco was not repeated by the statistical reviewer, as clinically, we felt that FEV1 was more relevant. Therefore, the Applicant’s results will be summarized here for the pooled Type 2 Diabetes Population.*

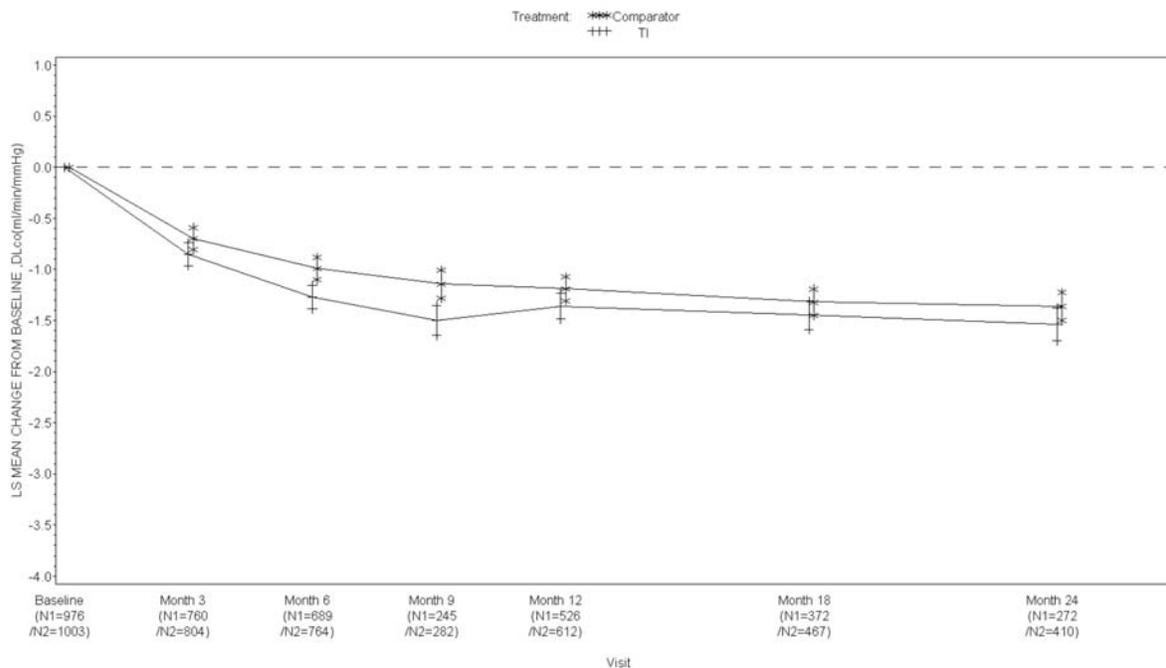
The Applicant examined the change in DLco from baseline over time in the type 2 diabetes patient population pooled from trials MKC-TI-102 and MKC-TI-030. Mean baseline, mean (absolute mean and LS mean) change from baseline, and the adjusted mean treatment group difference in mean change from baseline in DLco between the TI and comparator treatment group by time was summarized. These results are presented in Table 39 and Figure 18.

**Table 39: Treatment Group Difference in LS Mean Change from Baseline in DLco (mL/min/mm Hg) – Type 2 Diabetes**

Visit Statistics	Absolute Values		MMRM Model		
	TI	Comparator	TI	Comparator	Treatment-Diff TI-comparator
<b>Baseline</b>					
n	976	1003			
mean	25.45	25.54			
SD	5.777	6.076			
<b>Month 3</b>					
n	760	804	760	804	
mean/LS mean	-0.64	-0.56	-0.85	-0.70	-0.152
SD/SE <sup>a</sup>	2.570	2.413	0.113	0.109	0.1254
95% CI			(-1.07,-0.63)	(-0.91, -0.49)	(-0.398, 0.094)
<b>Month 6</b>					
n	689	764	689	764	
mean/LS mean	-1.02	-0.86	-1.27	-0.99	<b>-0.280*</b>
SD/SE <sup>a</sup>	2.779	2.435	0.115	0.109	<b>0.1281</b>
95% CI			(-1.50,-1.04)	(-1.20, -0.78)	<b>(-0.532, -0.029)</b>
<b>Month 9</b>					
n	245	282	245	282	
mean/LS mean	-1.13	-0.97	-1.50	-1.14	<b>-0.357*</b>
SD/SE <sup>a</sup>	2.702	2.555	0.148	0.138	<b>0.1810</b>
95% CI			(-1.79, -1.21)	(-1.41, -0.87)	<b>(-0.712, -0.002)</b>
<b>Month 12</b>					
n	526	612	526	612	
mean/LS mean	-1.16	-1.08	-1.36	-1.19	-0.171
SD/SE <sup>a</sup>	2.757	2.707	0.126	0.117	0.1430
95% CI			(-1.61,-1.11)	(-1.42, -0.96)	(-0.452, 0.109)
<b>Month 18</b>					
n	372	467	372	467	
mean/LS mean	-1.33	-1.27	-1.45	-1.32	-0.129
SD/SE <sup>a</sup>	2.957	2.847	0.141	0.129	0.1620
95% CI			(-1.73, -1.17)	(-1.57, -1.07)	(-0.446, 0.189)
<b>Month 24</b>					
n	272	410	272	410	
mean/LS mean	-1.53	-1.26	-1.54	-1.36	-0.179
SD/SE <sup>a</sup>	2.927	2.766	0.160	0.138	0.1832
95% CI			(-1.85,-1.23)	(-1.63, -1.09)	(-0.539, 0.180)

Source: Table 89, p. 262-263, Pulmonary CIR, ISS, Module 5.  
 a: Mean and SD are for absolute values, LS Mean and SE are for adjusted values  
 LS Mean, SE, adjusted mean differences, and 95% CI are derived from MMRM analysis with disease type, region, treatment, age, gender, height, visit, and baseline PFT values in the model.  
 \*: Statistically significant

**Figure 18 LS Mean (SE) of Change from Baseline in DLCO (mL/min/mm Hg) by Visit, MMRM Model, Type 2 Diabetes**



N1=TI; N2=Comparator; SE=standard error

Source: Figure 66, p. 261, Pulmonary CIR.

As is shown in Table 39 and Figure 18, over the course of 24 months, subjects in both the TI group and the comparator treatment groups showed declines from baseline in mean DLco at each assessment time point. The results were similar when absolute mean change and adjusted LS mean change from baseline in DLco values were compared.

The difference in the LS mean change from baseline in DLco between the TI group and the comparator treatment groups was small and not statistically different at the first post-baseline assessment time point (Month 3). The observed difference between the groups then fluctuated, and was statistically different at Month 6 and Month 9, and thereafter became smaller and was not statistically different at Month 12, Month 18 and at the last assessment time point at Month 24. The LS mean difference (TI group – Comparator group) was -0.152 mL/min/mm Hg at 3 months, -0.280 mL/min/mm Hg at 6 months, -0.357 mL/min/mm Hg at 9 months, -0.171 mL/min/mm Hg at 12 months, -0.129 mL/min/mm Hg at 18 months and -0.179 mL/min/mm Hg at 24 months). The difference at each time point, regardless of whether statistical differences were achieved were numerically small, and unlikely to be of clinical significance.

*Reviewer’s comment: Numerically, patients with type 1 diabetes had a greater decline in DLco at 24 months (0.519 mL/min/mm Hg), and at the other assessment points as well. However the magnitude of change is still unlikely to be of clinical significance.*

The Applicant also presented an annual rate of change (slope) in DLco between Month 3 (first post-baseline measurement) and Month 24 (last post-baseline measurement) for each treatment group using a random coefficient model for the observed longitudinal DLco data. The treatment group difference in the annual rate of change in DLco and the corresponding 95% CI was determined (See Table 40).

<b>Table 40: Mean Annual Rate of Change in DLco (ml/min/mm Hg) Between Month 3 and Month 24 – Type 2 Diabetes</b>			
	<b>TI n=790</b>	<b>Comparator n = 861</b>	<b>Treatment Diff. TI-Comparator</b>
<b>LS Mean</b>	-0.480	-0.441	-0.0387
<b>SE</b>	0.0782	0.0691	0.1043
<b>95% CI</b>	(-0.634, -0.327)	(-0.577, -0.306)	(-0.243,0.166)

Source: Table 90, p. 263, Pulmonary CIR, ISS, Module 5.

As shown in Table 40, the annual rate of change was numerically higher in the TI group, but not statistically different between the two groups from months 3 to 24. The TI group declined approximately 0.5 mL/min/mm Hg per year while the comparator group declined about 0.44 mL/min/mm Hg per year.

*Reviewer’s comment: The Applicant states that this finding in annual rate of decline with the data at various time points further demonstrates that the effect on DLco associated with TI is non-progressive. In the opinion of this reviewer, this conclusion cannot be drawn without data at later time points.*

### 5.3.6.5 Untreated non-diabetics

In trial MKC-TI-030, non-diabetics were also followed as an epidemiological or observational investigation, comparing subjects with diabetes who received usual anti-diabetes treatments with subjects without abnormalities in glycemic control, with respect to change in pulmonary function. Of the 164 non-diabetics that were randomized, 163 were included in the safety population, and 127 (77%) completed the study. The non-diabetic population had fewer males than females, were younger, and had lower BMIs than diabetic subjects.

The mean annual rate of change (slope) in FEV1 (L/year) Over 24 months and between 3 and 24 months was evaluated for TI-treated diabetics, UC diabetics, and untreated non-diabetics. See Table 41.

**Table 41: Mean Annual Rate of Change in FEV1 (L/year) Over 24 months and Between Month 3 and Month 24 (ITT Population) – Study MKC-TI-030**

	Mean Annual Rate of Change Over 24 Months		Mean Annual Rate of Change Between Months 3 and Month 24	
	Mean ± SEM	95% CI	Mean ± SEM	95% CI
TI	-0.073 ± 0.005		-0.047 ± 0.005	
UC	-0.054 ± 0.004		-0.036 ± 0.004	
Non-diabetics	-0.037 ± 0.009		-0.024 ± 0.010	
UC-TI	0.021 ± 0.006	0.010, 0.033	0.010 ± 0.006	-0.003, 0.022

Source: Table 21, p. 91, MKC-TI-030 CSR, Module 5.

After the initial slightly greater decline in the first 3 months, the annualized change in FEV1 was not statistically different in subjects treated with TI and UC between 3 and 24 months, although numerically, the non-diabetics declined the least (-24 mL/year). The TI-untreated type 2 diabetics declined 44 mL/year, and TI-untreated type 1 diabetics declined 45 mL/year.

*Reviewer’s comment: It is unclear what to make of greater decline in the TI-untreated diabetics versus the untreated non-diabetics. There is very little information regarding the rate of decline in lung function in patients with diabetes. The literature is controversial in this regard. While some studies have shown no significant differences in age, gender, and smoking status adjusted rates of longitudinal changes in lung function between subjects with and without diabetes mellitus (4,5) other studies have reported an accelerated annual rate of decline in lung function in subjects with diabetes (approximately 71 mL/yr for FEV1 and 68 mL/yr FVC) (6,7).*

### 5.3.7 Chest X-Rays (CXR)

#### 5.3.7.1 CXR Methods

Chest x-rays were performed by standard imaging using 1 frontal exposure and 1 lateral exposure at baseline at the end of the treatment period. For studies longer than 52 weeks, chest x-rays were performed annually. Investigators were asked to review the reports by the local radiologist and determine the clinical significance of the finding. For analysis of chest x-rays, data were pooled for controlled phase 2/3 efficacy and safety studies lasting longer than 14 days. The results were evaluated for diabetes by type and the combined population. The pooling strategy for chest x-ray data is presented in Table 42.

<b>Table 42: Pooling Strategy for Chest X-Ray Data</b>				
Study Pooling Group	DM Type	Trials	Safety Population	
			# Subjects TI	# Subjects Comparator
Controlled Phase 2/3 Trials	Type 1	MKC-TI-009, MKC-TI-030, MKC-TI-101	614	599
	Type 2	PDC-INS-0008, MKC-TI-005, MKC-TI-014, MKC-TI-026, MKC-TI-030, MKC-TI-102, MKC-TI-103	1795	1345
			2409	1944

\*\*Safety population and Randomized Subject numbers differ because some subjects were randomized, but did not receive treatment  
 \*\*An additional 114 subjects were treated with TP (excipient only)  
 Source: Table 2, pg. 33, Pulmonary CIR, ISS, Module 5.

CXR results were categorized and recorded as: normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS). Shift tables presenting change from baseline to end of the study in the above category were provided by treatment group. The percentage was calculated based on the total number of subjects in the treatment group who had non-missing values for both visits in the comparison. Narratives of subjects with clinically significant findings on CXR were reviewed.

### 5.3.7.2 CXR in Type 1 Diabetes

**Table 43 Chest X-ray Findings: Shift Table from Baseline to Last Measurement – Type 1 Diabetes (Safety Population)**

Treatment Group	Baseline	Normal	Abnormal NCS	Abnormal CS	Total
		n (%)	n (%)	n (%)	n (%)
TI Inhalation Powder (n = 614)	Normal	382 (85.3)	20 (4.5)	1 (0.2)	403 (90.0)
	Abnormal NCS	29 (6.5)	13 (2.9)	1 (0.2)	43 (9.6)
	Abnormal CS	1 (0.2)	0	1 (0.2)	2 (0.4)
	Total	412 (92.0)	33 (7.4)	3 (0.7)	448 (100.0)
Comparator (n = 599)	Normal	406 (84.2)	21 (4.4)	4 (0.8)	431 (89.4)
	Abnormal NCS	31 (6.4)	19 (3.9)	1 (0.2)	51 (10.6)
	Abnormal CS	0	0	0	0
	Total	437 (90.7)	40 (8.3)	5 (1.0)	482 (100.0)

NCS = not clinically significant; CS = clinically significant

Source: Table 48, p. 152, Pulmonary CIR.

Table 43 summarizes changes in the chest x-ray findings between Baseline and the final evaluation for subjects with type 1 diabetes. In the TI group, 1 subject had a normal chest x-ray at Baseline that changed to abnormal CS at the last observation. The corresponding number of subjects was 4 in the comparator group. One subject in the TI group and 1 subject in the comparator group had a shift from Baseline in chest x-ray findings from abnormal NCS to abnormal CS. The patient that shifted from normal to abnormal CS was a 48 year old, type 1 diabetic, who had airway thickening noted on his chest x-ray, read as being consistent with chronic bronchitis (MKC-TI-009, subject 052/1214). The subject did not report an adverse event and completed the trial. The one subject that had a shift from abnormal NCS to abnormal CS has already been described in 5.3.4.1 Lung Neoplasm (Subject 112/1751 in trial MKC-TI-009) with nodules of unknown etiology. The majority of the shifts in the comparator group were due to newly noted skeletal abnormalities.

*Reviewer’s comment: The narratives for the abnormal CS chest x-rays at last measurement were reviewed in detail. The pertinent information is presented above.*

Overall, it did not appear that TI was associated with an increase in abnormal CXR findings in patients with type 1 diabetes.

### 5.3.7.3 CXR in Type 2 Diabetes

**Table 44 Chest X-ray Findings: Shift Table from Baseline to Last Measurement – Type 2 Diabetes (Safety Population)**

Treatment Group	Baseline	Normal	Abnormal NCS	Abnormal CS	Total
		n (%)	n (%)	n (%)	n (%)
TI Inhalation Powder (n = 1795)	Normal	645 (61.0)	88 (8.3)	6 (0.6)	739 (69.9)
	Abnormal NCS	104 (9.8)	196 (18.5)	8 (0.8)	308 (29.1)
	Abnormal CS	4 (0.4)	4 (0.4)	2 (0.2)	10 (0.9)
	Total	753 (71.2)	288 (27.2)	16 (1.5)	1057 (100.0)
Comparator (n = 1345)	Normal	572 (57.8)	99 (10.0)	3 (0.3)	674 (68.1)
	Abnormal NCS	97 (9.8)	205 (20.7)	4 (0.4)	306 (30.9)
	Abnormal CS	0	7 (0.7)	2 (0.2)	9 (0.9)
	Total	669 (67.6)	311 (31.4)	9 (0.9)	989 (100.0)

NCS = not clinically significant; CS = clinically significant

Source: Table 75, p. 222, Pulmonary CIR, ISS, Module 5.

Significant changes in radiologic findings from Baseline to the last observation included both pulmonary and extrapulmonary changes. Overall, the incidence of significant changes in the chest x-ray findings was low in both treatment groups (Table 44). In the TI group, 1 subject had a normal chest x-ray at baseline that was reported as abnormal CS at the last observation and in 1 subject, x-ray findings changed from abnormal NCS to abnormal CS. The subject that changed from normal to abnormal CS was a 52 year old type 2 diabetic (Subject 486/1774, MKC-TI-103) who developed left hilar adenopathy, which was resolved on follow up. The subject reported only cough and completed the trial. The subject that changed from abnormal NCS to abnormal CS has already been described in 5.3.4.1 Lung Neoplasm (Subject 067/2909, MKC-TI-102) as having developed a neuroendocrine tumor.

### 5.3.8 High Resolution Computed Tomography (HRCT)

#### 5.3.8.1 HRCT Methods

Chest HRCTs (or MRIs in Germany) were obtained in a subset of patients in MKC-TI-030 and all subjects who participated in PDC-INS0008, MKC-TI-005, and MKC-TI-0010. HRCTs were conducted at baseline and at the end of the study, or annually, depending on the duration of the study. A total of 667 subjects were evaluated by HRCT or MRI. See Table 45.

<b>Table 45: Trials in Which HRCT Was Performed</b>				
Trial	# with HRCT (TI,comp)	Duration	Comparator	Schedule of HRCTs
PDC-INS-008	117 (59, 58)	3 months	TI vs. TP	Baseline, End of Study
MKC-TI-005	217 (174,43)	3 months	TI vs. Usual Care	Baseline, End of Study
MKC-TI-030	127 (55,72)	2 years	TI vs. Usual Care	Baseline, Annually
MKC-TI-010	206	Up to 4 years	TI in all subjects	Baseline, Annually

Source: Table 5, p. 37, Pulmonary CIR, ISS, Module 5.

*Reviewer’s comment: This is an adequate number of HRCTs for review purposes and consistent with the Agency’s request.*

All images were collected and centrally reviewed by an independent third party. During the reviews, the independent radiologist was blinded to subject identity, sequence of examinations, and reason for imaging. An algorithm was provided to all radiologists in which they had to assess the presence of: interlobular septal thickening, ground glass opacities, tree-in-bud opacities, parenchymal abnormalities, bronchial abnormalities, pleural abnormalities, or pleural effusion. For interlobular septal thickening, ground glass opacities, and tree-in-bud opacities, the

radiologist was to assess whether these were absent, present in 50% of the lung, 50-100% of the lung, 100% of the lung, or uncertain. For parenchymal, bronchial, and pleural abnormalities, the radiologist was to assess whether these were absent, present, or uncertain. Subjects found to have “absent” in all categories for both lungs in each image were deemed “normal”. Any subject with a response other than “absent” was submitted for secondary review. The second review was conducted by an independent board-certified radiologist (different from the primary reviewer) and an independent board-certified pulmonologist. The second review included presentation of all relevant imaging and the analysis forms of the first reviewer. Based upon the data, the secondary reviewers wrote a joint brief narrative for each subject to provide a final interpretation of the radiology imaging. This joint interpretation includes a statement of finding whether the subjects’ images were normal, abnormal, not clinically significant (NCS), or abnormal, clinically significant (CS). The blinded independent central review is discussed in this report.

### 5.3.8.2 HRCT results

**Table 46 HRCT Findings (N=667)**

Finding	TI Inhalation Powder (n = 494)		T Inhalation Powder (n = 101)		Usual Care (n = 72)	
	n	%	n	%	n	%
Normal	140	28.3	40	39.6	14	19.4
Abnormal, not clinically significant	325	65.8	53	52.5	55	76.4
Abnormal, clinically significant	29	5.9	8	7.9	3	4.2

Source: Table 96, p. 284, Pulmonary CIR.

HRCT/MRI assessment was included in 4 clinical trials leading to a total of 667 subjects being evaluated by HRCT or MRI. Of all subjects evaluated, 494 were treated with TI Inhalation Powder, 101 were exposed to T Inhalation Powder (excipient only, TP), and, 72 were in the usual care treatment group. In the TI group, 140 subjects (28.3%) were characterized as normal during the independent review, 325 subjects (65.8%) had abnormalities that were not clinically significant, and 29 subjects (5.9%) had findings deemed to be abnormal and clinically significant. The number of subjects and their findings in the TP (T Inhalation Powder) group were 40 normal (39.6%), 53 abnormal not clinically significant (52.5%), and 8 abnormal clinically significant (7.9%). The corresponding numbers in the usual care group were normal, 14 subjects (19.4%), abnormal not clinically significant, 55 subjects (76.4%), and abnormal clinically significant, 3 subjects (4.2%).

The narratives for each of the abnormal CS HRCT scans in each study were reviewed. Not all abnormalities were due to pulmonary etiologies. For those abnormal scans in which the abnormality was in the lung, in the majority of cases, the abnormality was associated with mosaic attenuation (commonly seen with air trapping or insufficient breath-hold during scan)

mild interstitial change, bronchial wall thickening, atelectasis, or new sub-centimeter nodules. Those subjects that had new nodules found by HRCT are discussed in 5.3.4.1 Lung Neoplasm. A summary of the abnormal, clinically significant HRCTs is presented in Table 47 below.

<b>Table 47: Summary of Abnormal Clinically Significant HRCTs in the Controlled Phase 2/3 Clinical Trials in Type 1 and Type 2 Diabetes</b>			
Study Number # of CTs (%)	Pt. ID	HRCT Finding	
		TI (Afrezza)	Comparator
MKC-TI-030  TI: 7 (12.7%)  C: 3 (4.2%)	0110	Mosaic attenuation/air trapping	
	0702	New lingular sub-cm nodule/air trapping	
	1363	Small, subpleural area of ground glass	
	2383	Hypersensitivity pneumonitis/air trapping	
	2950	Atelectasis/mild air trapping	
	3286	Mild air trapping/focal ground glass	
	3435	Interlobular septal thickening, ground glass	
	0063		increasing fibrosis/scarring at bases/lingula, ?ILD
	3040		subpleural ground glass/mild air trapping
	3048		focal ground glass/mild air trapping
MKC-TI-005  TI: 7 (4.0%)  C: 3 (7.0%)	3825	new 9 mm nodule in right middle lobe	
	4629	PFT abnormality/no HRCT abnormality*	
	4713	PFT abnormality/no HRCT abnormality*	
	6104	Bronchial wall thickening, focal ground glass	
	7607	Patchy ground glass	
	8472	Inspiratory crackles/5 mm nodule*	
	9729	Mild interlobular septal thickening	
	0226		Subsegmental atelectasis
	0779		Hiatal hernia
6572		Changes consistent with ILD	
PDC-INS-008	0106	Bronchial wall thickening	
TI: 5 (8.4%)  C: 3 (5.1%)	0203	Mild atelectasis, patchy ground glass	
	0285	Mild centrilobular emphysema	
	0199 <sup>a</sup>		Patchy tree in bud opacities, air trapping
	0215 <sup>a</sup>		Subcentimeter nodule increased in size
	0246 <sup>a</sup>		Scattered ground glass/bony changes from prostate mets
	0299 <sup>a</sup>		Bronchial wall thickening
	0370 <sup>a</sup>		Mild ground glass opacities

Source: Subject Narratives, Section 6.2, Pulmonary CIR, ISS, Module 5.  
 \* HRCTs performed “for-cause” as a result of PFT finding or physical exam finding; even without imaging abnormality, considered abnl CS  
 a: comparator is TP (excipient only)  
 % denotes abnormal CS HRCTs as a percent of the total HRCT performed in that group (Table 45)

## 5.4 Other Safety Explorations

### 5.4.1 Dose Dependency for Adverse Events

Based upon the Applicant's analysis, neither the change in FEV1 nor DLco from baseline to each visit showed a relationship to average daily dose of TI for the safety population in either type 1 or type 2 diabetes.

### 5.4.2 Drug-Demographic Interactions

Very few subjects (n=4) were > 65 years of age. In addition, Caucasians constituted the vast majority (90%) of the safety population. With these limitations, based upon the Applicant's analysis, no consistent patterns were observed in mean changes in FEV1 or DLco from Baseline to each visit among different categories for age, race, or gender in either treatment group for the safety population in either type 1 or type 2 diabetes.

*Reviewer's comment: African Americans were underrepresented in this dataset. Long-term post-marketing studies, if Afrezza is approved, should attempt to study this demographic subset.*

### 5.4.3 Pulmonary Function in those with Anti-Insulin Antibodies

Insulin antibodies have been a clinical observation and clinical concern from the beginning of insulin therapy. While this was first noted in relation to animal-derived insulin products insulin antibody formation has been noted to occur with both insulin analogues and surprisingly, recombinant human insulin products. The development of insulin antibodies is also a function of individual patient factors, insulin formulation and method of delivery. Despite the common immunologic response to all of these insulin products, antibody responses do not preclude the use of insulin in the therapy of diabetes. Insulin antibody development has been reported to be greater in subjects treated with an inhaled insulin product as compared to subcutaneous insulin.

Anti-insulin antibodies did develop to a greater extent in subjects treated with TI Inhalation powder. Per the Applicant's analysis, on average the antibody levels were comparable between groups at the beginning of each study but the TI group's mean increase was approximately 8-fold (median increase of 6-fold) over the course of the study as compared to a 2-fold mean increase for all comparator therapies (median 2-fold). No associations between insulin antibody levels and changes in pulmonary function tests were noted (Table 10, Figures 6,-7, p. 34-7 and Figures 14-15, p. 58-59, Comprehensive Integrated Review of Insulin Antibodies, ISS, Module 5).

## 6 Appendices

### 6.1 Study MKC-TI-101

#### A. Title

Phase 2 Randomized, Open Label, Multicenter Substitution Study of the Use of Prandial Inhaled Technosphere Insulin in Combination with Basal Subcutaneous Lantus Insulin versus Prandial Subcutaneous NovoRapid Insulin in Combination with Basal Subcutaneous Lantus Insulin in Subjects with Type 1 Diabetes

**Dates:** March 3, 2005 to December 27, 2005

**Centers:** 17 sites in Russia

#### B. Protocol

Study MKC-TI-101 was a randomized, open label, multicenter substitution and comparison study in which TI was substituted for a rapid-acting prandial subcutaneous insulin (NovoRapid) and compared with continuation of the subcutaneous insulin in the treatment of subjects with type 1 diabetes. The following subjects were excluded:

- COPD, emphysema, or asthma
- Current smokers or smoking history within the past 6 months
- Upper respiratory infection in the last 15 days or a lower respiratory tract infection in the last 30 days.
- History of malignancy in the last 5 years, except basal cell carcinoma.
- FEV1, FVC, and DLCO  $\geq 75\%$  and  $\leq 125\%$  predicted normal.

The study was comprised of 4 periods: a screening period of up to 7 days, a 3-week substitution period (Visit 2 to Visit 5), a 12-week treatment period, and a 2-week follow-up period. After the 1-week screening period, subjects were randomized to remain on NovoRapid prandially plus Lantus or to substitute TI prandially with Lantus.

Safety monitoring included AEs, discontinuations due to AEs, incidence of cough (on a special case report form), clinical laboratories, chest x-rays, and pulmonary function testing. PFTs included: FEV1, FVC, and DLCO. Pulmonary function testing was performed according to ATS guidelines. At the screening visit, spirometry was performed before and after bronchodilator administration in order to identify and exclude subjects with reversible obstructive lung disease. The screening visit (Visit 1/Week -4) pre-bronchodilator FEV1 was taken as the baseline. Subsequent PFTs were performed at Weeks 1, 8, and 12. There were no PFTs performed after cessation of study drug.

*Reviewer's Comment: A special CRF page was used for reporting cough, which was meant to differentiate between cough associated with inhalation of a dry powder and that which may be*

*caused by an illness. Cough events were therefore not to be reported on the AE page of the usual CRF and were instead to be analyzed separately.*

### C. Results

The safety analysis was based on the Safety Population, defined as all randomized subjects who took at least 1 dose of study medication. A total of 110 subjects were included in the Safety Population: 54 subjects in the TI group and 56 subjects in the NovoRapid control group.

*Reviewer’s comment: All subsequent references refer to sections within the clinical study report for MKC-TI-101 located in Module 5.3.5.1 of the eCTD.*

#### 1. Patient Disposition (Section 6.2, p. 56)

Patient disposition is summarized in Table 48. Of the 110 randomized patients in the safety population, 105 completed the study: 49 in the TI group and 56 in the NovoRapid control group. All 5 subjects who were prematurely discontinued from the study were in the TI group. The reasons for discontinuation from the study recorded in the case report forms included withdrawal of consent (1 subject), AE (3 subjects), and protocol violation (1 subject). Respiratory adverse events accounted for all 3 of the discontinuations secondary to AEs (see discussion by subject under *Respiratory Adverse Events* below).

<b>Table 48: Subject Disposition (Study MKC-TI-101)</b>			
	<b>TI</b>	<b>NovoRapid</b>	<b>Total</b>
Disposition	<b>n (%)</b>	<b>n (%)</b>	<b>N (%)</b>
Randomized	54 (100)	56 (100)	110 (100)
Completed	49 (91)	56 (100)	105 (96)
Premature Discontinuation	5 (9.3)	0	5 (4.5)
Withdrawal of Consent	1 (2)	0	1 (1)
Adverse Event	3 (6)	0	3 (3)
Respiratory AE	3 (6)	0	3 (3)
Protocol Violation	1 (2)	0	1 (1)

Source table: Table 5, Page 58, MKC-TI-101 CSR, Module 5.

*Reviewer’s comment: For 2 of the 3 subjects who were discontinued due to “withdrawal of consent”, the investigator reported that the withdrawal of consent was due to cough. These 2 subjects are included in all discussions in the study report of discontinuation of subjects due to AEs. For this reason, this reviewer has included these 2 subjects in the “Adverse Event” category as their reason for discontinuation, rather than in the “Withdrawal of Consent” category, which is the way in which the Applicant has counted them. As a result, this reviewer’s table has 3 subjects discontinuing due to adverse events and only one due to withdrawal of consent, rather than vice versa in the Applicant’s table.*

#### 2. Baseline Characteristics (Section 6.3, p. 58)

The percentage of females was greater in the TI group (76%) than in the NovoRapid control group (50%). Other baseline and demographic characteristics were similar in the two treatment groups. It is of note that all patients in the Safety Population (N=110) were of Caucasian race

### **3. Extent of Exposure** (Section 6.5.1, p. 63)

The mean exposure to TI was approximately 89 days, with the maximum exposure being 119 days, during the 12-week treatment period.

### **4. Deaths and SAEs**

There were no deaths or serious respiratory adverse events during this trial.

### **5. Discontinuation due to AEs** (Module 5, MKC-TI-101 CSR, Section 8.2.3, p. 106)

There were 3 discontinuations due to drug-related AEs:

- Subject 508/203: 31 year old Caucasian women with Type 1 DM who presented with mild tachypnea approximately 2 weeks after study drug initiation which resolved on the same day. She presented 3 days later with mild “respiratory difficulty” after inhalation of TI, which resolved on the same day but then reappeared six days later with moderate severity, at which time she elected to withdraw from the trial. Duration of treatment was 25 days.  
*Reviewer’s comment: The Applicant reports her treatment duration to be 158 days (MKC-TI-101 CSR, page 57), however in reviewing her CRF, this reviewer found the duration of treatment to actually be 25 days.*
- Subject 500/236: 33 year old Caucasian female with Type 1 DM who discontinued because of cough that occurred within 10 minutes of inhalation of TI x 7 days approximately 1 week after initiating therapy. Duration of treatment was 14 days.  
*Reviewer’s comment: The Applicant reports her treatment duration to be 30 days (MKC-TI-101 CSSR, page 57), however her CRF indicated that the duration of treatment was actually 14 days.*
- Subject 519/162: 59 year old Caucasian female discontinued because of continuous cough on one occasion within 10 minutes of inhalation of study drug. Duration of treatment was 21 days.

### **6. Respiratory Adverse Events** (Section 8.1.2, p. 96)

Respiratory adverse events were reported more frequently in the TI group as compared to the control group (29.6% vs. 17.9%). Nasopharyngitis, rhinitis, upper respiratory tract infection, and throat irritation were reported more frequently in the TI group as compared to the control group (See Table 54). Most were mild in severity.

**Table 49: Summary of Most Frequently Reported ( $\geq 2\%$ ) Respiratory Adverse Events by PT (Study MKC-TI-101)**

System Organ Class and Preferred Term	TI (n = 54)	NovoRapid (n = 56)	Total (N=110)
Total Subjects with AE	16 (29.6%)	10 (17.9%)	26 (23.6%)
Nasopharyngitis	5 (9.3%)	4 (7.1%)	9 (8.2%)
Respiratory Tract Infection	2 (3.7%)	4 (7.1%)	6 (5.5%)
Rhinitis	3 (5.6%)	1 (1.8%)	4 (3.6%)
Upper Respiratory Tract Infection	3 (5.6%)	1 (1.8%)	4 (3.6%)
Throat Irritation	3 (5.6%)	0	3 (2.7%)

Source table: Table 21, Page 98, MKC-TI-101 CSR, Module 5.

**a) Cough** (Section 8.3.3, p. 112)

Of the 54 subjects in the TI group, 26% reported at least 1 coughing episode, for a total of 39 reported episodes. Most (37 of 39) coughing episodes occurred within 10 minutes of study drug inhalation, and most (28 of 39) were classified as a single defined cough (See Table 50).

**Table 50: Incidence and Characterization of Cough (Study MKC-TI-101)**

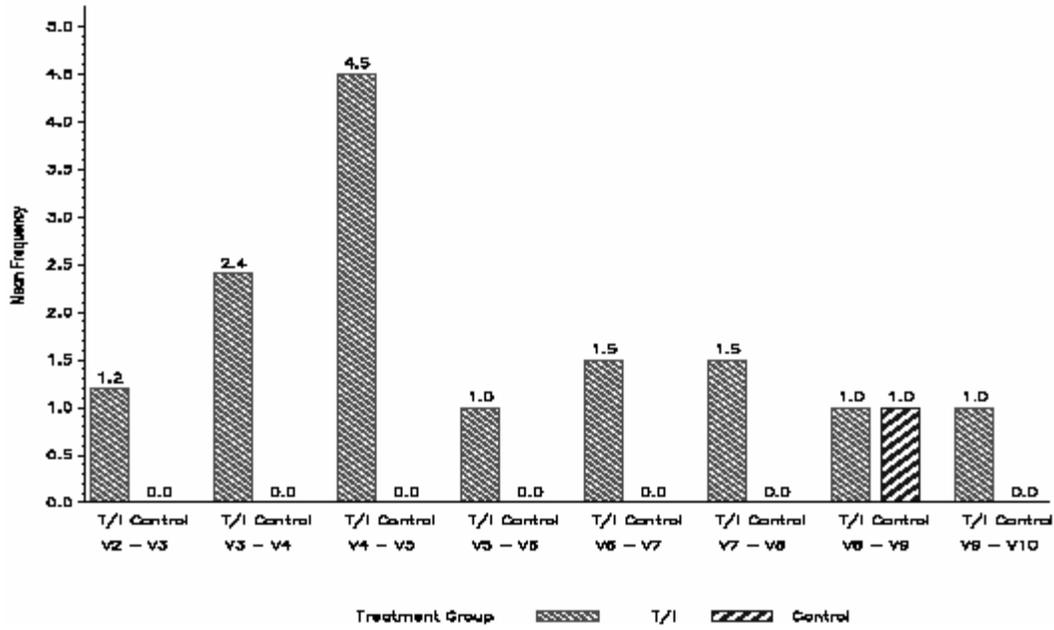
Parameter	TI	NovoRapid	p-value
Event rate of cough	14 (25.9%)	2 (3.6%)	0.0037
Frequency of cough			
Continuous	5	0	0.0463
Intermittent	6	2	
Single-Defined	28	0	
Total	39	2	
Cough within 10 minutes of treatment	37	0	0.0024
Sputum producing	2	0	1.000

Source table: Table 27, Page 114, MKC-TI-101 CSR, Module 5.

As shown in Figure 19, the mean frequency of cough decreased over time, with the greatest frequency occurring during the last week of the substitution period (Visit 4-Visit 5), which then subsequently decreased.

*Reviewer's comment: This might suggest some acclimatization to the inhaled drug.*

**Figure 19 Mean Frequency of Cough By Treatment Interval – Study MKC-TI-101**



Source Figure: Figure 6, Page 115, MKC-TI-101 CSR, Module 5.

**7. Pulmonary Function Tests** (Section 8.4, p. 115)

PFTs included spirometry and DLCO performed at Visit 1 (Baseline), and then Weeks 1 (Visit 5), 8 (Visit 9) and 12 (Visit 10). Baseline and mean changes for both treatment groups are summarized in Table 51: Pulmonary Function Tests – Summary of Mean Change – Study MKC-TI-101 below. A more detailed discussion of FEV1 and DLCO follows.

<b>Table 51: Pulmonary Function Tests – Summary of Mean Change – Study MKC-TI-101</b>						
<b>PFT</b>	<b>TI</b>			<b>NovoRapid</b>		
	<b>Baseline</b>	<b>Week 12</b>	<b>Change from BL</b>	<b>Baseline</b>	<b>Week 12</b>	<b>Change from BL</b>
FEV1						
Mean (L)	3.15	3.128	-0.06	3.398	3.325	-0.07
SD	0.69	0.705	0.19	0.691	0.687	0.19
FVC						
Mean (L)	3.87	3.883	-0.02	4.218	4.177	-0.04
SD	0.88	0.885	0.18	0.854	0.805	0.25
DLCO						
Mean (mL/min/mm Hg)	25.58	24.49	-1.18	27.21	26.57	-0.63
SD	6.09	5.056	3.18	5.264	5.489	3.10

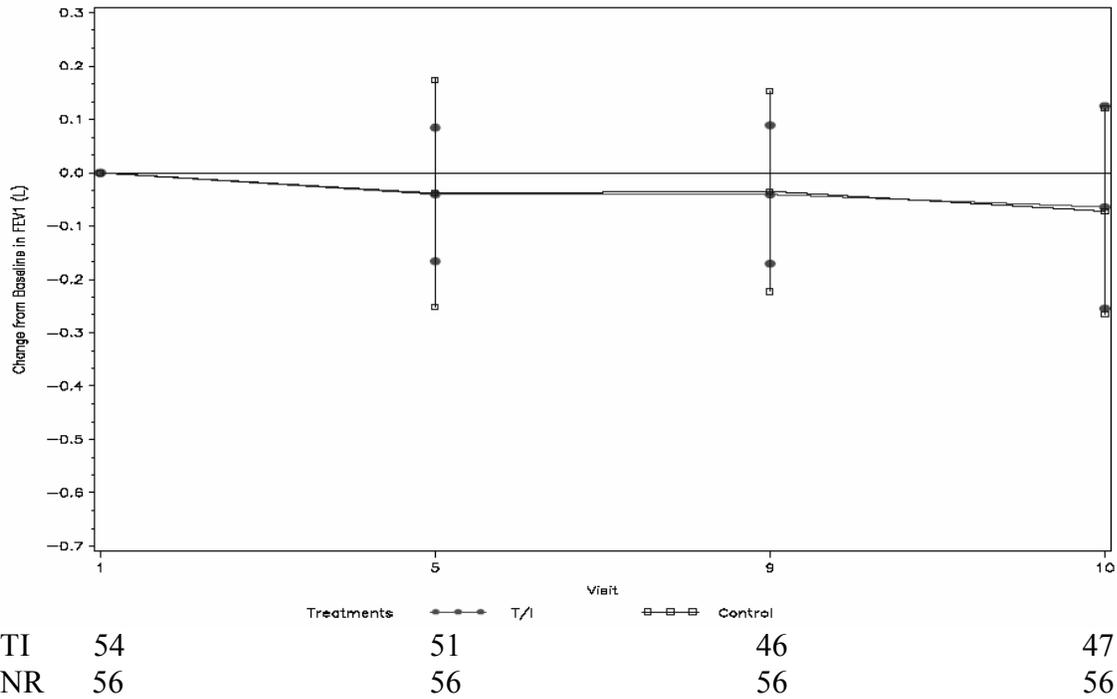
Source tables: Module 5, MKC-TI-101 CSR, Tables 28 and 29, p. 117 and 122.

**a) FEV1**

For FEV1, the mean change was -0.064 L (-2.0%) and -0.072 L (-2.1%) for TI and NovoRapid, respectively. For FEV1, the difference between the 2 groups was 0.008L.

The decline in FEV1 was most prominent during the first 3 weeks in both groups. There was no statistical or graphical difference within or between the two groups (See Figure 20). The analysis was similar when conducted using LOCF values.

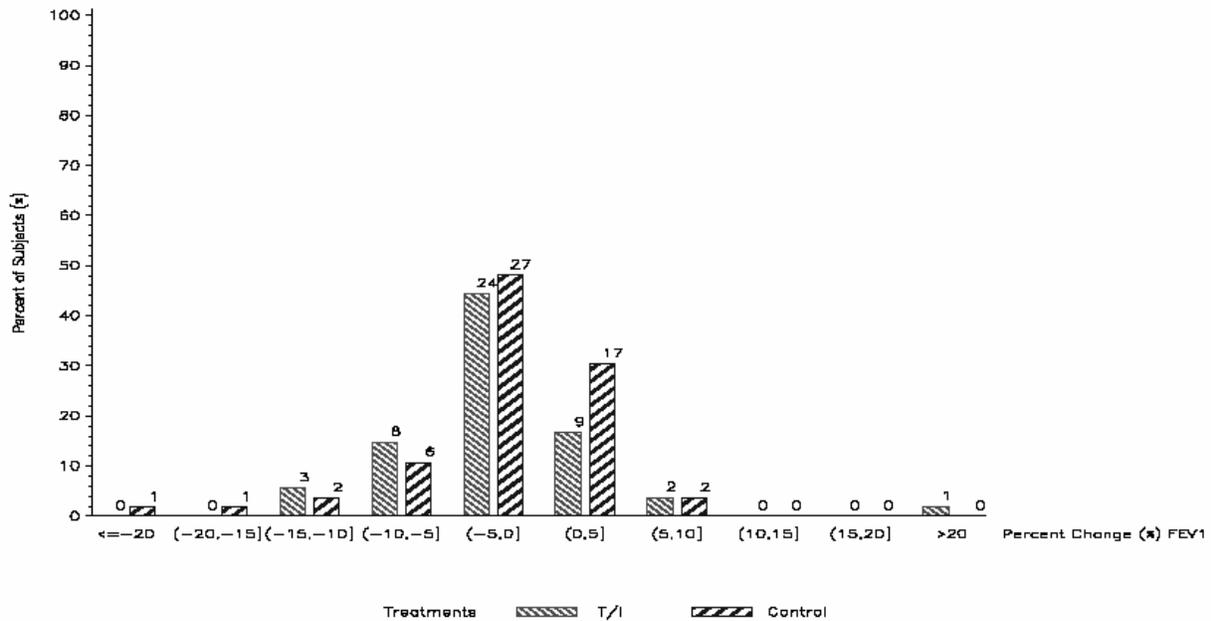
**Figure 20 Mean Change from Baseline (with SD) in FEV1 by Visit (Source: Figure 7, pg. 118)**



As shown in Figure 21 below, no subjects in the TI group experienced a greater than 15% decline in FEV1. There were 3 subjects in the TI group who experienced 10-15% declines, as compared with 2 in the control group.

*Reviewer's comment: Only 1 subject experienced a >15% decline in more than 1 PFT parameter; this subject was in the control group. Subject 318 experienced a 27.7% decrease in FEV1 and a 18.3% decrease in FVC, but only a 3% decrease in DLCO. The patient was continued in the study.*

**Figure 21 Distribution of Percent Changes in FEV1 (L) at Visit 10 (Source, Figure 8, pg. 119)**

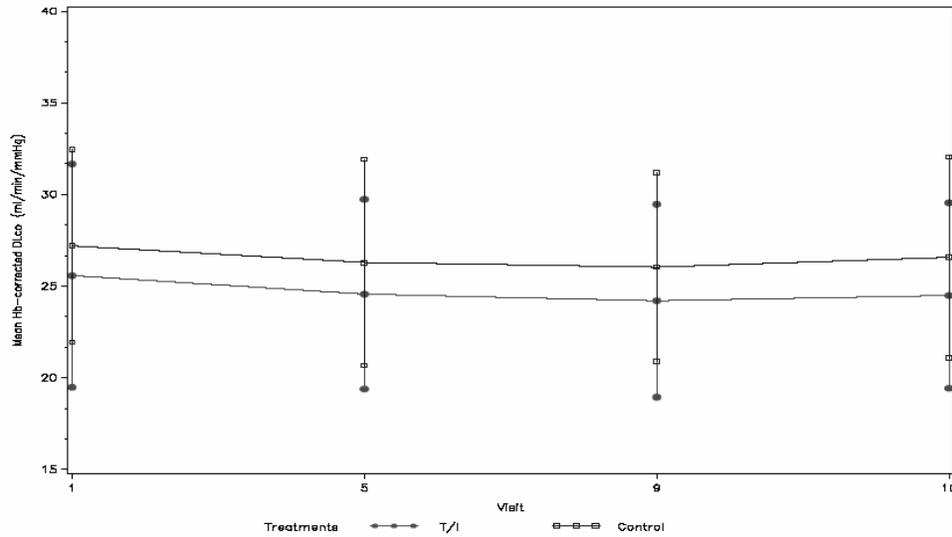


**b) DLCO (Section 8.4.2, p. 121)**

For DLCO, the mean change was -1.18 mL/min/mm Hg in the TI group and -0.63 mL/min/mm Hg in the NovoRapid group. These results were nearly identical when repeated using LOCF. There was no statistical difference between the two groups, although the decline in the TI group of -1.18 was statistically significant (P=0.012).

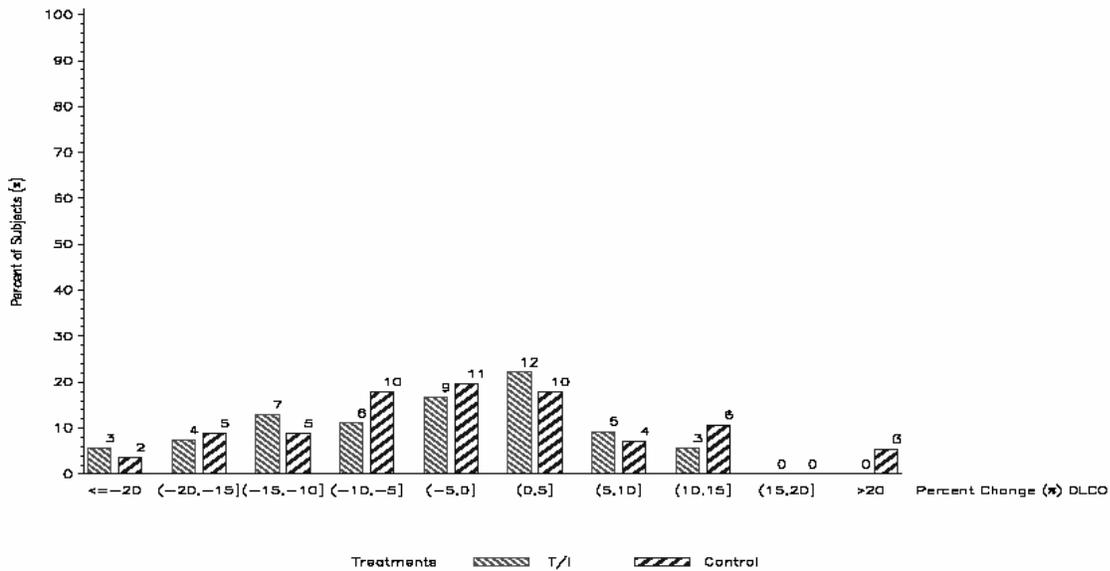
As shown in Figure 22, the TI group began with a slightly lower baseline (25 vs. 27), however the slopes of the lines are similar.

**Figure 22 Mean DLCO and SD by Visit – Study MKC-TI-101 (Source: Figure 11, p. 123)**



As shown in Figure 23, 7 subjects in both the TI and control groups experienced declines in DLCO of  $\geq 15\%$ .

**Figure 23 Distribution of Percent Changes in DLCO at Visit 10 (Source Figure 12, p. 124)**



The subjects who experienced a  $\geq 15\%$  decline in DLCO are listed below:

<b>Table 52: Subjects with a <math>\geq 15\%</math> decline in DLCO – Study MKC-TI-101</b>		
<b>Treatment group</b>	<b>Subject Number</b>	<b>DLCO change</b>
<b>TI</b>	25	-32.5%
	275	-19.9%
	530	-18.8%
	713	-21.3%
	798	-16.6%
	810	-21.0%
	821	-15.2%
<b>NovoRapid (control)</b>	326	-17.3%
	495	-16.9%
	517	-23.1%
	522	-18.8%
	840	-19.9%
	868	-17.4%
	965	-30.2%

Source: Module 5, MKC-TI-101 CSR, p. 125

Of the subjects who experienced a decline of  $\geq 15\%$  in the TI group, none of these subjects also experienced a concomitant decline in FEV1.

#### **8. Chest X-Rays** (Section 8.6.1.4, p. 134)

Chest X-rays were performed at Visit 1 and 10. Overall there were very few abnormal chest x-rays upon entry into the study. Further, there was no shift from normal to abnormal x-ray in the TI treatment group.

#### **9. Insulin Antibodies** (Section 8.6.1.5, p. 134)

The median concentration of insulin antibodies at baseline was 11.8 U/mL in the TI group and 11.4 U/mL in the control group. By Visit 10, the median concentration had increased  $> 4$  fold in the TI group to 49.3 U/mL, while remaining near baseline in the control group.

#### **D. Conclusions**

Study MKC-TI-101 was a randomized, open label, multicenter substitution and comparison study in which TI was substituted for a rapid-acting prandial subcutaneous insulin (NovoRapid) and compared with continuation of the subcutaneous insulin in the treatment of subjects with type 1 diabetes. The study was comprised of 4 periods: a screening period of up to 7 days, a 3-week substitution period (Visit 2 to Visit 5), a 12-week treatment period, and a 2-week follow-up period. After the 1-week screening period, subjects were randomized to remain on NovoRapid prandially plus Lantus or to substitute TI prandially with Lantus. Three patients withdrew from the study due to respiratory adverse events, specifically coughing. More subjects experienced

AEs in the TI group (29.6%) than in the control group (17.9%), with nasopharyngitis, respiratory tract infection, rhinitis, and throat irritation being the most commonly reported AEs. Cough was analyzed separately. Most (37 of 39) coughing episodes occurred within 10 minutes of study drug inhalation, and most (28 of 39) were classified as a single defined cough. Mean frequency of cough decreased over time. Mean changes in FEV1 and DLCO from baseline were of small magnitude and not statistically significant between groups. No patients treated with TI had a >15% decline in more than one PFT parameter.

Examination of chest x-ray data did not reveal any safety signal. Insulin antibodies increased significantly in the TI group, but correlation to clinical worsening is unclear.

## 6.2 Study MKC-TI-009

### A. Title

A Prospective, Multi-Center, Open-Label, Randomized Controlled Clinical Trial Comparing the Efficacy and Safety in Subjects with Type 1 Diabetes Receiving Subcutaneous Basal Insulin and Prandial Inhalation of Technosphere Insulin Versus Subcutaneous Basal and Prandial Insulin Over a 52-Week Treatment period and a 4-Week Follow-Up

**Dates:** February 23, 2006 to May 26, 2008

**Centers:** Multiple sites in the United States, Europe, Russia, Latin America, Canada, and Mexico

### B. Protocol

Study MKC-TI-009 was a randomized, open label, multicenter, controlled clinical trial comparing glycemic control in subjects with type 1 diabetes receiving basal insulin and prandial TI with subjects receiving basal insulin and subcutaneous rapid-acting insulin as a comparator group. The following subjects were excluded:

- COPD, emphysema, or asthma
- Current smokers or smoking history within the past 6 months
- Upper respiratory infection in the last 15 days or a lower respiratory tract infection in the last 30 days.
- History of malignancy in the last 5 years, except basal cell carcinoma.
- $FEV1 \leq 70\%$  predicted,  $TLC \leq 80\%$  predicted, and  $DLCO \leq 70\%$  predicted

The study included a 52-week treatment phase and a 4-week follow-up phase.

The study began with enrollment at Week -3 where baseline safety measurements were performed. Randomization occurred at Week -1. Subjects participated in 5 clinical assessment visits during the 52-week treatment period (Weeks 0, 14, 26, 38, and 52) and one follow-up visit at 56 weeks. Relevant pulmonary safety monitoring included: 1) PFTs: Weeks -3, 14, 26, 38, 52, 56 and ET visit (if applicable) and 2) Chest X-rays: Weeks 0 and 52. All PFTs were performed at a pulmonary function laboratory certified by the Applicant and were performed according to current American Thoracic Society guidelines. For the purposes of this trial, a PFT finding was a decrease of  $\geq 15\%$  from baseline in FVC, FEV1, TLC, or DLCO. The 15% threshold for change in PFT

parameters was selected for the purposes of requesting clinical evaluation by Investigators, AEs were also collected at each scheduled visit. A special cough CRF was used to assess this AE.

### C. Results

The safety analysis was based on the Safety Population, defined as all randomized subjects who took at least 1 dose of study medication. A total of 565 subjects were included in the Safety Population: 293 subjects in the TI group and 272 subjects in the control group.

*Reviewer’s comment: All subsequent references refer to sections within the clinical study report for MKC-TI-009 located in Module 5.3.5.1 of the eCTD.*

#### 1. Patient Disposition (Section 10.1, p. 78)

Patient disposition is summarized in Table 53. Of the 589 randomized patients, 24 subjects withdrew prior to receiving study medication, and thus the Safety Population was composed of 293 subjects in the TI group, and 272 subjects in the control group. Of these 565 patients in the safety population, 418 completed the study: 198 (65.8%) in the TI group and 220 (76.4%) in the control group. One-hundred forty-six (146) patients were discontinued from the study. The greatest number of discontinuations were due to withdrawal of consent. A greater number discontinued in the TI arm vs. the SC insulin arm. More subjects discontinued due to AEs in the TI arm than in the SC insulin arm.

Respiratory AEs leading to discontinuation are discussed below.

<b>Table 53: Subject Disposition (Study MKC-TI-009)</b>			
	<b>TI</b>	<b>SC Insulin</b>	<b>Total</b>
Disposition	<b>n (%)</b>	<b>n (%)</b>	<b>N (%)</b>
Randomized	293	272	565
Completed	198	220	418
Premature Discontinuation	94	52	146
Withdrawal of Consent	47	19	66
Adverse Event	17	2	19
Respiratory AE	13		
Investigator Decision	15	7	22
Lost-to-follow-up	5	5	10
Protocol Violation	3	14	17
Other	7	5	12

Source table: Table 6, Page 59, MKC-TI-009 CSR, Module 5.

*Reviewer’s comment: In this study, withdrawal of consent was not further categorized. Subjects who withdrew consent were further reviewed by the Applicant and misclassification were identified and reclassified as appropriate (eg. to discontinuation due to an AE) before programmatic generation of tables and files.*

#### 2. Baseline Characteristics (Section 11.2.1, p. 82, Table 6.2.1.1)

The percentage of females and males was roughly 50% in both treatment arms. Caucasians comprised the majority of both treatment arms (~85%), but African American, Hispanic, Asian, and Other ethnic groups were included. Other baseline and demographic characteristics were similar in the two treatment groups.

### 3. Extent of Exposure (Section 11.2.4, p. 87, Table 11)

The mean exposure to TI was approximately 9.5 months, with the maximum exposure being 15 months. Approximately 70% of the patients were exposed for > 9 months during the 52-week treatment period.

### 4. Deaths and SAEs (Section 12.3.1.1 and Section 12.3.1.2, p. 149, Table 8.1.2.1)

There were no deaths during this trial. There were 2 serious respiratory AEs in the TI group and none in the control arm. The 2 SAEs are as follows:

- Subject 237/1207: 45 year old woman in the US who was randomized to TI in September 2006. After 4 months of participation in the trial, she presented with episodes of coughing with hemoptysis approximately 20 minutes after inhalation of TI. Additional episodes of cough with hemoptysis were noted after discontinuation of TI. Diagnostic evaluation included hematology, chest x-ray, sinus CT, and PFTs. Pulmonary consultation was planned but not obtained since work-up was negative and symptoms resolved without intervention.
- Subject 091/1786: 39 year old female in Chile, randomized to TI in March 2007. After 3 months of participation in the trial, she presented to the hospital with signs of severe airway obstruction. TI was discontinued and she was prescribed SABA and ICS. The event was considered resolved in July 2007. The subject reported that she had experienced dyspnea and dry cough on an unknown date before the event. During the event her FEV1 dropped 200 cc (baseline 2.2 L, 2.0L during event, 2.1 L post-event). Her DLCO dropped from 101% predicted to 84% predicted, and recovered to 97% predicted. Baseline CXR was normal.

### 5. Discontinuation due to AEs (Section 12.3.1.3, p. 153)

Of the 16 subjects who discontinued secondary to AEs, 13 were due to respiratory etiologies. The most common respiratory event leading to discontinuation in the TI group was cough (n=7). Three subjects discontinued secondary to respiratory tract infections. Other respiratory AEs leading to discontinuation were : asthma (n=1, subject 229/1866) and asthma, bronchitis, and hemoptysis (n = 1, subject 186/1064). One subject discontinued secondary to bronchial obstruction (subject 091/1786). Per the clinical characterization of symptoms, three subjects were discontinued from the trial secondary to asthma.

*Reviewer's comment: I have included the preferred term of asthma as well as the subject who experienced bronchial obstruction to arrive at this n=3 discontinuations secondary to asthma.*

The narratives were reviewed (Section 14.3.3) and no additional information was extracted. The subjects with bronchial obstruction and hemoptysis are described in detail under SAEs above. The subjects with cough mainly reported cough of moderate intensity 10 minutes or less following inhalation of TI. The 2 subjects who discontinued secondary to asthma are described in more detail as follows:

- Subject 229/1866: 57 year old male in the US with no smoking history or prior history of asthma was reported to have an exacerbation of asthma of moderate severity after 6 months of treatment with TI. PFTs and CXR upon entry to the trial were unremarkable. Spirometry at time of early termination was of “unacceptable quality” and is not reported in the CSR. DLCO was 92% predicted. The patients was treated with inhaled steroids with complete resolution of the event in 1 month (See Table 55).
- Subject 186/1064: 66 year old Caucasian female in the US who had no prior history of asthma or history of smoking. Her baseline PFTs however did reveal a 200 mL improvement in FEV1 post-bronchodilator, which may suggest that she did in fact have asthma and should not have been entered into the trial (See Table 55).

#### 6. Respiratory Adverse Events (Section 12.2.3.1, p. 137, Table 37)

Respiratory adverse events were reported more frequently in the TI group as compared to the control group. Under the Respiratory SOC, cough, pharyngolaryngeal pain, nasal congestion, asthma, dyspnea, wheezing, throat irritation, bronchospasm, increased upper airway secretion, allergic rhinitis, and rhinorrhea were reported more frequently in the TI group as compared to the control group (See Table 54). Under the Infections and Infestations SOC, influenza, tonsillitis, bronchitis, and rhinitis were reported more frequently in the TI group (See Table 54).

<b>Table 54: Summary of Most Frequently Reported (<math>\geq 1\%</math>) Respiratory Adverse Events by PT occurring more frequently in TI vs. Control (Study MKC-TI-009)</b>		
Preferred Term	TI (n = 293)	SC Insulin (n = 272)
Total Subjects with AE	274 (93.5%)	261 (96%)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Cough	99 (33.8%)	21(7.7%)
Pharyngolaryngeal pain	16 (5.5%)	6 (2.2%)
Nasal congestion	7 (2.4%)	4 (1.5%)
Productive cough	6 (2.0%)	0 (0)
Asthma	5 (1.7%)	0 (0)
Dyspnea	5 (1.7%)	0
Wheezing	4 (1.4%)	0
Throat irritation	3 (1.0%)	1 (0.4%)
Bronchospasm	3 (1.0%)	0 (0)
Increased upper airway secretion	3 (1.0%)	0(0)
Allergic rhinitis	3 (1.0%)	0 (0)
Rhinorrhea	3 (1.0%)	0 (0)
<b>Infections and Infestations</b>		
Influenza	23 (7.8%)	19 (7.0%)
Tonsillitis	5 (1.7%)	3 (1.1%)
Bronchitis	5 (1.7%)	2 (0.7%)
Rhinitis	4 (1.4%)	3 (1.1%)

Source table: Table 37, Page 140, MKC-TI-009 CSR, Module 5.

*Reviewer’s comment: Of note, there were 17 cases that were split among the preferred terms of asthma, dyspnea, wheezing, and bronchospasm. When pooling the safety data, it may be more informative to group these PTs together, rather than split them apart, as they may potentially be referring to the same phenomenon.*

The 5 cases of asthma are further described in Table 38, on page 141 of the CSR. Three patients were categorized as having asthma of “mild” severity, while 2 patients were classified as moderate. Two mild subjects completed the trial, and the other mild subject discontinued the study for another reason (intermittent cough). The two patients who experienced asthma of moderate severity were both discontinued from the study and are described above under discontinuations secondary to AEs. These patients did not have a history of asthma upon trial entry, however subject 483/2401 may have had mild COPD, and should have been excluded from trial.

<b>Table 55: TI-treated Subjects with Asthma AE (Study MKC-TI-009)</b>					
<b>Subject #</b>	<b>Time to Onset (days)</b>	<b>Severity</b>	<b>Outcome</b>	<b>Clinical Description</b>	<b>PFT findings</b>
186/1064	238	Moderate	Resolved	Early Termination from trial (see DC due to AEs)	FEV1 decreased by 16%; FVC decreased by 13%; DLCO decreased by 8%
229/1866	174	Moderate	Resolved	Early Termination from trial (see DC due to AEs)	None
230/1417	102	Mild	Ongoing at end of trial	54F with “subclinical asthma”, dc’ed from trial secondary to “intermittent cough”.	None
457/2147	326	Mild	Ongoing at the end of trial	35F presented with asthma, but continued in the trial.	None
483/2401	78	Mild	Ongoing at the end of trial	42M with 35 pk-yr history of smoking and fixed airway obstruction at baseline suggestive of possible COPD, developed mild asthma. No action taken	None

**a) Cough** (Section 12.3.5, p. 176)

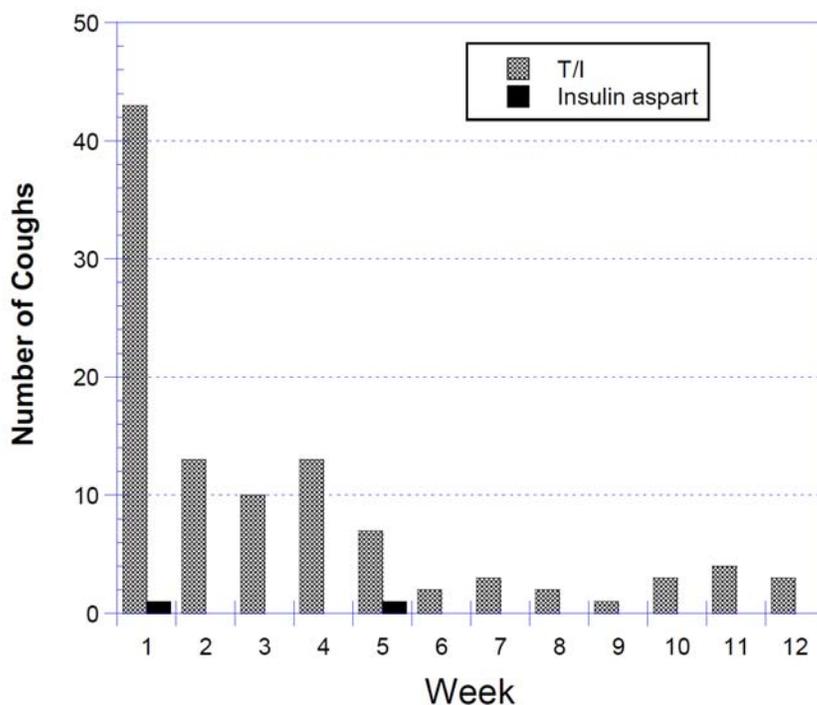
Of the 293 subjects in the TI group, 32% reported at least 1 coughing episode, for a total of 169 reported episodes. Most (143 of 169) coughing episodes occurred within 10 minutes of study drug inhalation, and most (105 of 169) were classified as a intermittent (See Table 56).

<b>Table 56: Incidence and Characterization of Cough (Study MKC-TI-101)</b>		
Parameter	TI	SC Insulin
Number of total cough episodes	169	19
Frequency of cough		
Continuous	6	1
Intermittent	105	18
Single-Defined	58	0
Cough within 10 minutes of treatment	143	0
Sputum producing	20	1

Source table: Table 61, Page 179, MKC-TI-009 CSR, Module 5.

As shown in Figure 24, the mean frequency of cough decreased over time, with the greatest frequency occurring during the first week of treatment, which then subsequently decreased. *Reviewer’s comment: This might suggest some acclimatization to the inhaled drug. Similar findings were seen in study 101 which was of shorter duration.*

**Figure 24 Mean Frequency of Cough By Treatment Interval – Study MKC-TI-101**



Source Figure: Figure 9, Page 178, MKC-TI-009 CSR, Module 5.

Cough leading to premature discontinuation of subjects from the trial was uncommon with an incidence of 2.4%. Seven subjects (Subjects 118/1053, 237/1207, 230/1417, 242/1631, 902/1824, 505/1991, and 001/2214), all in the TI group, discontinued from the study because of cough. During months 3 to 6, 6 to 9, and 9 to 12, the number of subjects who discontinued because of cough was 3 (1.2%), 4 (1.8%), and 0, respectively, in the TI group. The narrative were for these patients were reviewed. No additional information was extracted.

**7. Pulmonary Function Tests** (Section 12.3.6, p. 180)

PFTs included spirometry and DLCO performed at Baseline, Weeks 14, 26, 38, 52, and at follow-up approximately 4 weeks after stopping treatment at the end of the trial. Baseline and mean changes for both treatment groups are summarized in Table 57 below. A PFT finding was defined as a decrease of  $\geq 15\%$  from baseline in FVC, FEV1, TLC, or DLCO. During the trial, 24% of subjects in the TI group and 15% in the control group had a PFT finding. No subjects discontinued from the trial due to PFT findings. A more detailed discussion of FEV1 and DLCO follows.

**Table 57: Pulmonary Function Tests – Summary of Mean Change – Study MKC-TI-009**

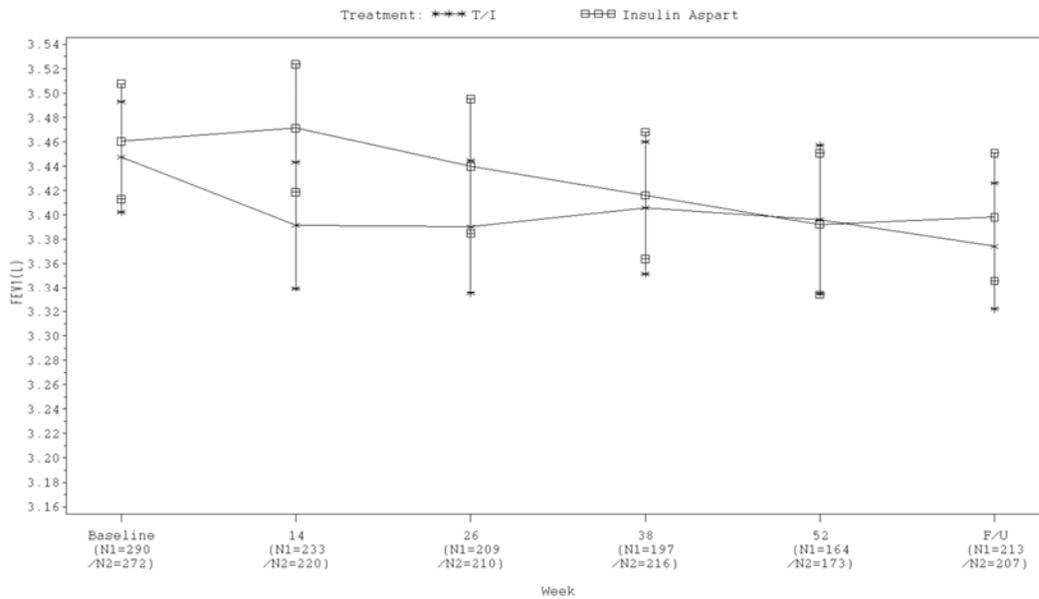
PFT	TI			NovoRapid		
	Baseline	Week 52	Change from BL	Baseline	Week 52	Change from BL
FEV1						
Mean (L)	3.45	3.40	-0.06	3.46	3.39	-0.06
SD	0.771	0.782	0.213	0.779	0.766	0.199
DLCO						
Mean (mL/min/mm Hg)	27.87	25.85	-1.97	28.00	26.54	-1.24
SD	6.68	6.79	3.21	7.143	6.46	3.28

Source tables: Module 5, MKC-TI-009 CSR, Tables 28 and 29, p. 117 and 122.

**a) FEV1**

For FEV1, the mean change from baseline for both groups was -0.06 L (-1.7%) . The decline in FEV1 was most prominent during the first 3 weeks in both groups. As shown in Figure 25, the mean FEV1 values in the TI group showed a decline of about 60 cc by Week 14, although there was no statistical difference within or between the two groups.

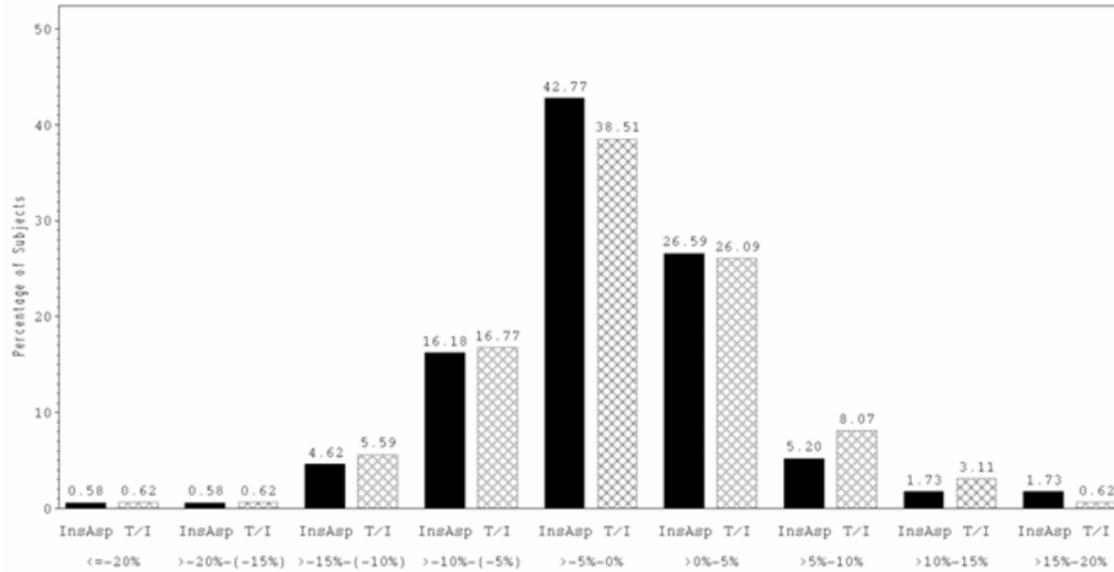
**Figure 25 Mean (SE) FEV1 Over Time (Safety Population) – Study MKC-TI-009 (Source: Figure 10, pg. 182)**



*Reviewer's comment: This graph is of absolute FEV1 over time, whereas in other study reports it is reported as mean change over time (e.g. MKC-TI-101).*

The distribution of subjects by percentage change in FEV1 is summarized by treatment group in Figure 26. Approximately 5.5% of subjects in the TI group experienced a 10-15% decline in FEV1, with only 1.2% (n=2) experiencing a >15% decline. This was not numerically different than what occurred in the control group.

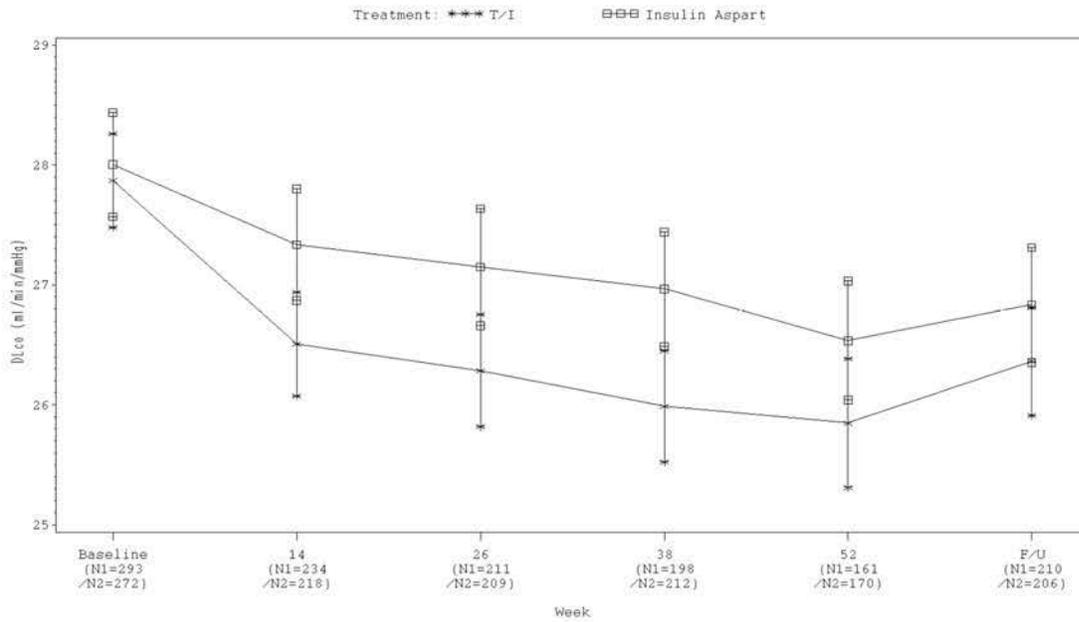
**Figure 26 Distribution of Percent Change from Baseline to Week 52 in FEV1 (L) – Safety Population, Study MCK-TI-009 (Source, Figure 14, pg. 186)**



**b) DLCO** (Section 8.4.2, p. 185)

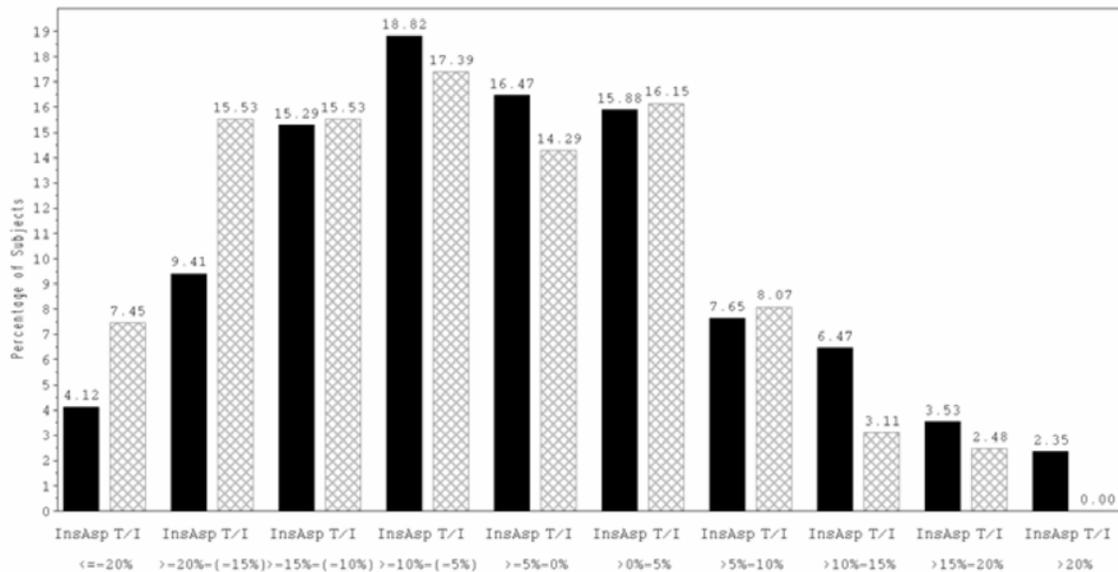
For DLCO, the mean change from baseline at 52 weeks was -1.97 mL/min/mm Hg in the TI group and -1.24 mL/min/mm Hg in the control group. The DLco decreased significantly more in the TI group than in the control group ( $p = 0.0202$ ). The greatest decline was noted by Week 14 (-1.61 mL/min/mm Hg in the TI group and -0.72 mL/min/mm Hg in the control group). Thereafter, DLco declined steadily in both groups over the remainder of trial (See Figure 27). At the follow-up visit 4 weeks after the cessation of the trial therapy, mean DLco values had returned towards baseline, but did not fully recover.

**Figure 27 Mean (SE) DLCO (ml/min/mm Hg) Over Time (Safety Population) – Study MKC-TI-009 (Source: Figure 13, p. 185)**



As shown in Figure 28, 22% of subjects in the TI versus 13% in the control group experienced declines in DLCO of  $\geq 15\%$ .

**Figure 28 Distribution of Percent Changes in DLCO from Baseline to Week 52 (Source Figure 17, p. 188)**



## 8. Chest X-Rays (Section 12.5.4, p. 200)

Chest X-rays were performed at Screening and Week 52. Overall, changes in chest x-ray findings from baseline to week 52 indicate that the shifts from baseline were similar in the 2 treatment groups. However, there is one notable case:

- Subject 112/1751: 22 year old Caucasian male in the US who began the study on February 2007 with a 9 mm x 6 mm in the LUL, which was assessed by the investigator as not clinically significant. CXR at week 52 indicated enlargement of this mass to 13 x 11 x 14 mm. In addition, there were new, smaller satellite 5 mm nodules in the same segment. Infectious work up and PET scan were negative. The patient was referred for pulmonary consultation and is being followed up.

*Reviewer's comment: Given the concern of pulmonary malignancy, I have included this case in the review. However, in the opinion of this reviewer, in a 22 year old non-smoker, it is unlikely that this represents a malignancy. We do not have the final diagnosis, so malignancy, is always a possibility.*

## 9. Insulin Antibodies (Section 12.5.5, p. 201)

The median concentration of insulin antibodies at baseline was 7.1 U/mL in the TI group and 6.6 U/mL in the control group. By week 52 the median concentration had increased > 6 fold in the TI group to 43.8 U/mL, while remaining near baseline in the control group.

## D. Conclusions

Study MKC-TI-009 was a randomized, open label, multicenter, controlled clinical trial comparing glycemic control in subjects with type 1 diabetes receiving basal insulin and prandial TI with subjects receiving basal insulin and subcutaneous rapid-acting insulin as a comparator group. The study included a 52-week treatment phase and a 4-week follow-up phase. Of the 16 subjects who discontinued secondary to AEs, 13 were due to respiratory etiologies. The most common respiratory event leading to discontinuation in the TI group was cough (n=7). Three subjects discontinued secondary to respiratory tract infections. Other respiratory AEs leading to discontinuation were : asthma (n=1) and asthma, bronchitis, and hemoptysis (n = 1). One subject discontinued secondary to bronchial obstruction.

Respiratory adverse events were reported more frequently in the TI group as compared to the control group. Under the Respiratory SOC, cough, pharyngolaryngeal pain, nasal congestion, asthma, dyspnea, wheezing, throat irritation, bronchospasm, increased upper airway secretion, allergic rhinitis, and rhinorrhea were reported more frequently in the TI group as compared to the control group. Under the Infections and Infestations SOC, influenza, tonsillitis, bronchitis, and rhinitis were reported more frequently in the TI group. Cough was analyzed separately. Of the 293 subjects in the TI group, 32% reported at least 1 coughing episode, for a total of 169 reported episodes. Most (143 of 169) coughing episodes occurred within 10 minutes of study drug inhalation, and most (105 of 169) were classified as a intermittent. The mean frequency of

cough decreased over time. For FEV1, the mean change from baseline for both groups was -0.06 L (-1.7%). The decline in FEV1 was most prominent during the first 3 weeks in both groups. As shown in Figure 25, the mean FEV1 values in the TI group showed a decline of about 60 cc by Week 14, although there was no statistical difference within or between the two groups. For DLCO, the mean change from baseline at 52 weeks was -1.97 mL/min/mm Hg in the TI group and -1.24 mL/min/mm Hg in the control group. The DLco decreased significantly more in the TI group than in the control group ( $p = 0.0202$ ). The greatest decline was noted by Week 14 (-1.61 mL/min/mm Hg in the TI group and -0.72 mL/min/mm Hg in the control group). Thereafter, DLco declined steadily in both groups over the remainder of trial (See Figure 9). At the follow-up visit 4 weeks after the cessation of the trial therapy, mean DLco values had returned towards baseline, but did not fully recover. Chest X-rays were performed at Screening and Week 52. Overall, changes in chest x-ray findings from baseline to week 52 indicate that the shifts from baseline were similar in the 2 treatment groups. Insulin antibodies increased significantly in the TI group, but correlation to clinical worsening is unclear.

### 6.3 Study MKC-TI-005

#### A. Title

A Randomized, Double-blind, Controlled, Stepwise Titration Study to Evaluate Dose Response to Prandial Administration of Inhaled Technosphere Insulin or Technosphere in Patients with Type 2 Diabetes Mellitus Who Are Sub-Optimally Treated

**Dates:** June 17, 2004 to August 30, 2005

**Centers:** 4 sites in Germany, 3 sites in the Netherlands, 10 sites in Bulgaria, 14 sites in the Czech Republic

#### B. Protocol

The purpose of this randomized, double-blind, placebo-controlled trial was to evaluate the efficacy and safety of TI plus basal insulin glargine (Lantus) versus TP plus Lantus in subjects with Type 2 diabetes. In this trial, TI was the investigational medicinal product while TP (excipient fumaryl diketopiperazine) functioned as the vehicle control. The following subjects were excluded:

- COPD, asthma, chronic lung diseases, and smokers
- History of malignancy within 5 years
- Baseline DLCO, FVC, and FEV1 < 75% predicted normal

The trial was designed to evaluate dose response to prandial administration of TI in comparison to TP in subjects with Type 2 DM who were suboptimally controlled.

The study included a 5 week run-in period and an 11-week treatment period. During the run-in period, Lantus dosing was initiated or stabilized and all patients were given inhaled TP. At Week 6, double-blind treatment with TI was initiated, with all subjects beginning with 14 U. Following Week 6, those subjected randomized to higher doses of TI (28U, 42U, and 56U) were force-titrated upwards by increases of 14U to their assigned randomization dose. Titration was completed by Week 9, and the achieved dose was continue until Week 17. Subjects were

randomized to TP (placebo/vehicle control) continued to receive this for the remainder of the trial. All subjects received Lantus during the double-blind treatment period. Relevant pulmonary safety monitoring included: 1) Spirometry at Weeks 1, 6, and 17, 2) DLCO at Weeks 1 and 17, and 3) HRCT or MRI at Weeks 2 and 17. AEs were also collected at each scheduled visit. A special cough CRF was used to assess this AE.

### C. Results

The safety analysis was based on the Safety Population, defined as all randomized subjects who took at least 1 dose of study medication (including TP). A total of 227 subjects were included in the Safety Population: 181 subjects in the TI group and 46 subjects in the TP (vehicle) control group.

*Reviewer’s comment: All subsequent references refer to sections within the clinical study report (CSR) for MKC-TI-005 located in Module 5.3.5.1 of the eCTD.*

#### 1. Patient Disposition (Section 6.2, p. 60)

Of the 227 patients in the safety population, 205 completed the study: 165 (91%) in the TI group and 40 (87%) in the control group. Twenty-two (22) patients discontinued from the study, 16 (9%) in the TI group, and 6 (13%) in the control group. Ten subjects withdrew consent, 3% in the TI group, and 11% in the TP control group (See Table 58). Withdrawal of consent was due mainly to trial conduct issues or dissatisfaction with blood sugar control (CSR Table 10, p. 63).

<b>Table 58: Subject Disposition (Study MKC-TI-005)</b>							
	<b>TP</b>	<b>TI 14</b>	<b>TI 28</b>	<b>TI 42</b>	<b>TI 56</b>	<b>TI (total)</b>	<b>Overall Total</b>
Disposition	<b>n (%)</b>	<b>n (%)</b>					
Randomized/Safety Population	46	45	46	45	45	181	227
Completed	40 (87%)	42 (93%)	41 (89%)	41 (91%)	41 (91%)	165 (91%)	205 (90%)
Premature Discontinuation	6 (13%)	3 (7%)	5 (11%)	4 (9%)	4 (9%)	16 (9%)	22 (10%)
Withdrawal of Consent	5 (11%)		2 (4%)	1 (2%)	2 (2%)	5 (3%)	10 (4%)
Adverse Event		2 (4%)	2 (4%)	2 (4%)	1 (2%)	7 (4%)	7 (3%)
Protocol Violation	1 (2%)		1 (2%)			2 (1%)	3 (1%)
Other		1 (2%)		1 (2%)	1 (2%)	3 (2%)	3 (1%)
Source table: Tables 8 and 9, Page 61-2, MKC-TI-005 CSR, Module 5.							

*Reviewer’s comment: Five subjects who discontinued due to physician decision, withdrawal of consent, and ‘other’ were subsequently reclassified as having adverse events leading to discontinuation. Table 11 above reflects this reclassification. The AEs leading to premature discontinuation were all related to blood sugar, and not a respiratory etiology (CSR, Table 11, p. 63).*

**2. Baseline Characteristics** (Section 6.3.1, p. 63, Table 12)

The percentage of females and males was roughly equal in both treatment arms. All subjects in this clinical trial were Caucasian. Other ethnic groups were not included. Other baseline and demographic characteristics were similar in the treatment groups.

**3. Extent of Exposure** (Section 6.5.1, p. 66, Table 13)

The mean exposure to TI and TP was approximately 77 days (11 weeks). No notable differences in exposure were observed between treatment groups.

**4. Deaths and SAEs** (Section 8.2.1 and Section 8.2.2, p. 91, Table 8.1.2.1)

There were no deaths during this trial. There were no respiratory SAEs in this study.

**5. Discontinuation due to AEs** (Section 8.2.3, p. 92)

No subjects were discontinued from the trial secondary to respiratory AEs. Of note. One subject was withdrawn from the trial after 7 days, due to hypersensitivity to the TP vehicle control. Painful aphthae developed on the patient's oral and laryngeal mucosa.

*Reviewer's comment: TP (FDKP) is a novel excipient and thus may be a substance to which hypersensitivity can occur. This language should be present in the label.*

**6. Respiratory Adverse Events (Section 8.1.2.1, p. 88, Table 29)**

Respiratory adverse events were reported with approximately the same frequency in the TP and the TI treatment groups. Under the Respiratory SOC, pharyngolaryngeal pain was reported in 2% of TP and TI treated subjects. Under the Infections and Infestations SOC, bronchitis and upper respiratory tract infections were reported more frequently in the TI group (8%) vs. the TP group (4%), while nasopharyngitis did not differ between treatment groups. Cough was the most frequently reported respiratory AE, and is discussed separately below.

**a) Cough** (Section 8.3.2, p. 102)

The number of subjects reporting at least one cough episode in the TP and TI treatment groups combined was 38 of 227 (16.7%); 32 of 181 (17.7%) TI-treated subjects reported at least one episode of cough. There were no statistically significant differences between any of the four TI groups and the TP group with respect to the incidence, frequency, or relatedness of cough to drug inhalation. In fact, numerically, the event rate for cough (number of cough events/total subject months) as well as the mean number of cough events per subject per month, decreased as TI dose levels increased. Additionally, the number of subjects reported cough decreased over time. No subjects were withdrawn from the trial due to cough.

**7. Pulmonary Function Tests** (Section 8.4, p. 104)

Baseline and mean changes for all treatment groups are summarized in Table 59 below. A more detailed discussion of FEV1 and DLCO follows.

<b>Table 59: Pulmonary Function Tests – Summary of Mean Change – Study MKC-TI-005</b>						
	<b>TI</b>			<b>TP</b>		
<b>FEV1</b>	<b>BL</b>	<b>Week 17</b>	<b>Change from BL</b>	<b>BL</b>	<b>Week 17</b>	<b>Change from BL</b>
	<b>TI 14 U</b>			<b>TP</b>		
Mean (L)	2.92	2.88	-0.09	2.91	2.90	-0.12
SD	0.68	0.70	0.19	0.66	0.67	0.22
	<b>TI 28 U</b>					
Mean (L)	3.06	3.04	-0.08			
SD	0.83	0.87	0.17			
	<b>TI 42 U</b>					
Mean (L)	2.97	2.93	-0.10			
SD	0.83	0.76	0.20			
	<b>TI 56 U</b>					
Mean (L)	3.14	3.04	-0.10			
SD	0.69	0.75	0.19			
	<b>BL</b>	<b>Week 17</b>	<b>Change from BL</b>	<b>BL</b>	<b>Week 17</b>	<b>Change from BL</b>
	<b>TI 14 U</b>			<b>TP</b>		
Mean (mL/min/mm Hg)	25.4	24.4	-0.99	24.4	25.6	0.55
SD	6.4	5.9	1.78	6.0	7.4	3
	<b>TI 28 U</b>					
Mean (mL/min/mm Hg)	25.51	25.7	0.09			
SD	7.2	7.4	3.0			
	<b>TI 42 U</b>					
Mean (mL/min/mm Hg)	25.6	25.5	-0.31			
SD	5.8	5.1	2.2			
	<b>TI 56 U</b>					
Mean (mL/min/mm Hg)	26.5	26.1	-0.48			
SD	6.3	6.9	3.1			

Source Table: Table 35 and 37, pg. 105 and 108, CSR MKC-TI-005, Module 5.

**a) FEV1 (Section 8.4.2.1, P. 107-109)**

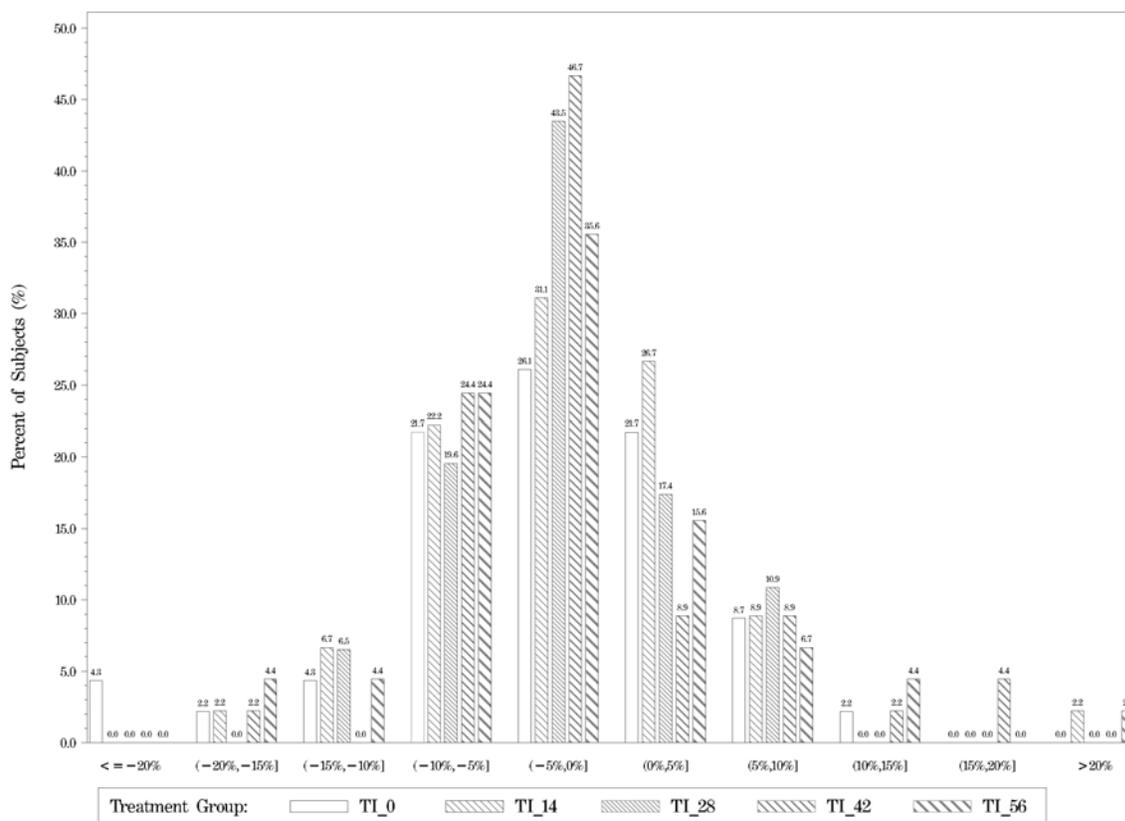
The change from baseline for FEV1 was a comparison of measurements taken at Visit 1 and Visit 2. The mean change from baseline in FEV1 ranged from a decrease of 80 to 100 cc. The change from baseline in the TP and TI 42 U treatment groups were statistically significant within each group, respectively, however there were no statistical differences between any TI group and the TP group. The mean change in FEV1 was -0.090 when all TI treatment groups were combined compared with -0.120 in the TP group.

*Reviewer’s comment: It is notable that within the TP group there was a statistically significant mean change from baseline (p = 0.0067), although this was not found in the other treatment groups. Given the fact that this is a novel excipient (FDKP), it could be the excipient that is the cause of respiratory side effect, and therefore comparison of the TP and TI groups not yielding a significant difference is not of much importance. However, the fact that FEV1 did decrease from 80-100 cc in all groups is of note.*

The distribution of subjects by percentage change in FEV1 is summarized by treatment group in Figure 29. There were 2.2% of subjects in both the TI and TP groups that had a 15-20% decline in FEV1 and 4.3% of subjects in the TP group had a > 20% decline.

*Reviewer’s comment: It is important to consider the declines individually, as again, it could be the TP excipient that causes the respiratory findings.*

**Figure 29 Distribution of Percent Change from Baseline to Week 17 in FEV1 (L) – Safety Population, Study MCK-TI-005 (Source, Figure 5, pg. 110 and Appendix 2, Figure 28)**



**b) DLCO** (Section 8.4.1, p. 104)

DLCO values were corrected for subjects’ hemoglobin and/or carboxyhemoglobin values. All treatment groups began with a similar baseline DLCO. The mean change from baseline at 17 weeks ranged from -0.99 to 0.09 ml/min/mm Hg in the TI treatment groups. The decreases in DLCO were small, clinically insignificant, and not dose-dependent (See Table 59). The mean

change from baseline in the TP control group was 0.55 ml/min/mm Hg. Analysis using LOCF yielded similar results.

#### **8. HRCT and MRI** (Section 8.6.3, p. 118)

HRCTs and MRI (in Germany) were performed at baseline and the last visit. An abnormal finding included evidence of tumor, fibrosis, infiltrate, effusion, apical scarring, and/or pleural thickening. A total of 180 imaging studies were performed at baseline in the TI-treated subjects and 44 in the TP-treated subjects. At the last visit, 162 imaging studies were acquired in the TI-treated subjects, and 39 in the TP-treated subjects. None of the HRCT/MRI films showed clinically significant abnormalities at baseline or the last visit.

#### **9. Insulin Antibodies** (Section 8.6.5, p. 121)

The median concentration of insulin antibodies at baseline were similar for all treatment groups. The highest mean levels of insulin antibodies at endpoint were seen in the TI 42U and TI56 U treatment groups, where the level of antibodies increased 3-5 fold over baseline.

#### **D. Conclusions**

Study MKC-TI-005 was a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of TI plus basal insulin glargine (Lantus) versus TP plus Lantus in subjects with Type 2 diabetes. In this trial, TI was the investigational medicinal product while TP (excipient fumaryl diketopiperazine) functioned as the vehicle control. The study included a 5 week run-in period and an 11-week treatment period. During the run-in period, Lantus dosing was initiated or stabilized and all patients were given inhaled TP. At Week 6, double-blind treatment with TI was initiated, with all subjects beginning with 14 U. Following Week 6, those subjected randomized to higher doses of TI (28U, 42U, and 56U) were force-titrated upwards by increases of 14U to their assigned randomization dose. Titration was completed by Week 9, and the achieved dose was continue until Week 17.

The mean exposure to TI and TP was approximately 77 days (11 weeks). No notable differences in exposure were observed between treatment groups. There were no deaths or respiratory SAEs in this study. No subjects discontinued from the trial secondary to respiratory AEs, although there was one case of hypersensitivity noted. Respiratory adverse events were reported with approximately the same frequency in the TP and the TI treatment groups. Under the Respiratory SOC, pharyngolaryngeal pain was reported in 2% of TP and TI treated subjects. Under the Infections and Infestations SOC, bronchitis and upper respiratory tract infections were reported more frequently in the TI group (8%) vs. the TP group (4%), while nasopharyngitis did not differ between treatment groups. Cough was the most frequently reported respiratory AE with a frequency of about 17% in both the TP and TI treatment groups. There was no dose-response in terms of cough frequency. The mean change from baseline in FEV1 ranged from a decrease of 80 to 100 cc. The change from baseline in the TP and TI 42 U treatment groups were statistically significant within each group, respectively, however there were no statistical differences between any TI group and the TP group. The mean change in FEV1 was -0.090 when all TI treatment groups were combined compared with -0.120 in the TP group. The change in

DLCO was small and clinically insignificant. HRCT or MRI did not reveal any clinically significant abnormalities over a 11 week period. Insulin antibodies increases 3-5 fold in a dose-dependent manner.

## 6.4 Study PDC-INS-0008

### A. Title

Efficacy and Safety of Inhaled Technosphere Insulin Compared to Technosphere Placebo in Patients With Type 2 Diabetes Mellitus Following Diabetes Education.

**Dates:** December 3, 2003 to November 4, 2004

**Centers:** 24 centers in the United States

### B. Protocol

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 2 study comparing treatment with prandial TI inhalation powder vs. treatment with prandial T Inhalation Powder (TP, excipient only) for approximately 12 weeks in subjects with suboptimal glucose control.

The purpose of this randomized, double-blind, placebo-controlled trial was to evaluate the efficacy and safety of TI plus basal insulin glargine (Lantus) versus TP plus Lantus in subjects with Type 2 diabetes. Subjects had to be on a stable oral anti-diabetic regimen to be enrolled. The following subjects were excluded:

- COPD, asthma, chronic lung diseases, and smokers
- History of malignancy within 5 years
- Baseline DLCO, FVC, and FEV1 < 80% predicted normal

The study included a 2 week screening period and an 12-week treatment period. Relevant pulmonary safety monitoring included: 1) Spirometry at Weeks 1, 3, 7, 11 and 15, 2) DLCO at Weeks 1 and 15, and 3) HRCT or MRI at Weeks 2 and 15. AEs were also collected at each scheduled visit. A special cough CRF was used to assess this AE.

### C. Results

The safety analysis was based on the Safety Population, defined as all randomized subjects who took at least 1 dose of study medication (including TP). A total of 123 subjects were included in the Safety Population: 61 subjects in the TI group and 62 subjects in the TP (vehicle) control group.

*Reviewer's comment: All subsequent references refer to sections within the clinical study report (CSR) for PDC-INS-0008 located in Module 5.3.5.1 of the eCTD.*

**1. Patient Disposition** (Section 10.1, p. 53)

Of the 123 patients in the safety population, 107 completed the study: 54 (89%) in the TI group and 53 (86%) in the control group. Sixteen patients (16) patients discontinued from the study, 7 (11.5%) in the TI group, and 9 (15%) in the control group. Of the listed reasons, withdrawal of consent was the most common for premature discontinuation, and occurred only in the control group (See Table 60). There were a total of 4 discontinuations secondary to AEs. Three of the four discontinuations secondary to AEs were due to pulmonary etiologies and are discussed in more detail below.

*Reviewer’s Comment: Only 3 discontinuations secondary to AEs are listed in Table 13. One subject was counted as a “withdrawal of consent”, but had cough as the reason for withdrawal of consent.*

<b>Table 60: Subject Disposition (Study PDC-INS-0008)</b>		
	<b>TI</b>	<b>TP</b>
Disposition	<b>n (%)</b>	<b>n (%)</b>
Randomized/Safety Population	61 (100%)	62 (100%)
Completed	54 (89%)	53 (86%)
Premature Discontinuation	7 (12%)	9 (14.5%)
Withdrawal of Consent	0	5 (8.1%)
Adverse Event	2 (3%)	1 (2%)
Protocol Violation	0	1 (2%)
Physician Decision	1 (2%)	0
Other	4 (7%)	2 (3.2%)
Source table: Table 9, Page 54, PDC-INS-0008 CSR, Module 5.		

**2. Baseline Characteristics** (Section 11.2.1, p. 57, Table 12)

There were 82 males and 41 females in the study group. Overall, more than 60% of the subjects were Caucasian, about 8% were Black, 21% were Hispanic, and 5% were Asian. Other baseline and demographic characteristics, including baseline pulmonary function, were similar in the treatment groups.

**3. Extent of Exposure** (Section 11.3, p. 67, Table 19)

The mean exposure to TI and TP was approximately 11.5 weeks. No notable differences in exposure were observed between treatment groups.

**4. Deaths and SAEs** (Section 12.2.1 and Section 12.2.2, p. 106)

There were no deaths during this trial. There were no respiratory SAEs in this study.

**5. Discontinuation due to AEs** (Section 12.2.3.1, p. 107)

Of the four subjects who discontinued secondary to AEs, three were due to respiratory etiologies. Two subjects withdrew from the study due to cough, and one due to an abnormal HRCT. The narratives for the patients that discontinued secondary to cough offer no further information.

Abnormality on HRCT was noted to be a 4 x 5 mm nodule in the RML and scarring in the lingula. This patient had not yet started treatment.

**6. Respiratory Adverse Events** (Section 12.1.2., p. 93, Table 33)

Respiratory AEs were reported in 42% of subjects overall, when including the respiratory, infection, and investigations SOCs. Respiratory AEs that occurred in more than 2 subjects included upper respiratory tract congestion, pharyngolaryngeal pain, throat irritation, upper respiratory tract infection, sinusitis, bronchiectasis, bronchitis, nasopharyngitis, and abnormal HRCT. The abnormal HRCTs are discussed in Section 8 below.

*Reviewer’s comment: Given that the placebo control here is the excipient, it is the opinion of this reviewer that differences between groups are less important than the overall occurrence of respiratory AEs. Nonetheless, there were no striking differences between groups.*

<b>Table 61: Summary of Most Frequently Reported (&gt; 2 subjects) Respiratory Adverse Events by PT (Study PDC-INS-0008)</b>		
Preferred Term	TI (n = 61)	TP (n = 62)
Total Subjects with AE	42 (69)	41 (66)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>	<b>8 (13.1)</b>	<b>10 (16.1)</b>
Upper respiratory tract congestion	2 (3.3)	4 (6.5)
Pharyngolaryngeal pain	1 (1.6)	2 (3.2)
Throat irritation	1 (1.6)	2 (3.2)
<b>Infections and Infestations<sup>a</sup></b>	<b>11 (18)</b>	<b>11 (17.7)</b>
Upper Respiratory Tract Infection	3 (4.9)	5 (8.1)
Sinusitis	3 (4.9)	3 (4.8)
Bronchiectasis	2 (3.3)	0 (0.0)
Bronchitis	2 (3.3)	0 (0.0)
Nasopharyngitis	1 (1.6)	3 (4.8)
<b>Investigations<sup>a</sup></b>		
HRCT abnormal	4 (6.6)	8 (12.9)

Source table: Table 33, Page 93, PDC-INS-0008, CSR, Module 5.  
 Number in ( ) = percentage of subjects in treatment group  
 a: Total and percentages include only respiratory etiologies

**a) Cough** (Section 12.4, p. 111)

A total of 18 of 61 (30%) TI subjects and 17 of 62 (27%) T subjects each experienced 1 or more coughing episodes during the study, for a total of 63 episodes in the TI group and 113 episodes in the T control group. Among subjects reporting cough, 4 subjects in the TI group and 5 subjects in the T control group experienced 5 or more cough episodes over the course of the study. One subject in the insulin group (008/108) experienced 24 episodes, which were mostly single incidents occurring within 10 minutes of study during study drug inhalation. In the T control group, 2 subjects experienced a higher number of cough episodes relative to the rest of the group: Subject 008/252 experienced 14 cough episodes, and subject 019/229 experienced 60

cough episodes. Most of these events were characterized as intermittent and occurring within 10 minutes of inhalation of study drug.

One TI subject withdrew from the study secondary to cough. The narrative of this patient was reviewed, and no additional information was noted.

*Reviewer's comment: No graphic is shown regarding frequency of cough reporting over time as it is in other studies, however, the applicant does state that most coughing episodes were reported early in the treatment period.*

#### **7. Pulmonary Function Tests** (Section 12.2.3.2, p. 107 and 12.6.1, p. 121)

A PFT finding was defined as a decrease of  $\geq 15\%$  from baseline in FVC, FEV<sub>1</sub>, TLC, or DLCO. During the trial, 3 subjects had a PFT finding as follows:

- Subject 012/100: A 46 year old Spanish man on TI, who experienced a drop in FVC from 5.97 to 4.86L and drop in FEV<sub>1</sub> from 4.55 to 3.93 L over the course of 1 month after starting TI therapy. The lower values were similar to what had been recorded at baseline and were still 100+% predicted normal. Chest x-ray was normal, and the patient was without clinical symptoms. The patient withdrew consent and discontinued prematurely from the trial.
- Subject 012/203: A 64 year old Caucasian women on TI, had a decline in FEV<sub>1</sub> and FVC from baseline to Visit 9. FEV<sub>1</sub> went from 1.9 L (92%) to 1.6 L (78%) and FVC went from 2.15 L (80%) to 1.86 L (69%). DLCO remained stable to increased slightly. CT scan of chest was normal on March 2004 at Visit 2. In June 2004, the chest CT showed mild bronchiectasis in the lower lobes. The patient was continued in study.
- Subject 012/299: A 37 year old Asian man who was on TI who had a history of intermittent wheezing and seasonal allergies, found to have an FEV<sub>1</sub> decreased from 2.53 (70%) to 1.78L (50%). Increase in DLCO from 21 to 23. No action taken with study medication. Chest CT showed bronchiectasis in lower lobes, with repeat at end showing no change.

PFTs included spirometry at Weeks 1, 3, 7, 11 and 15, and DLCO at Weeks 1 and 15. Baseline and mean changes for both treatment groups are summarized in Table 62 below.

<b>Table 62: Pulmonary Function Tests – Summary of Mean Change (Study PDC-INS-0008)</b>						
<b>PFT</b>	<b>TI</b>			<b>TP</b>		
	<b>Baseline</b>	<b>Week 15</b>	<b>Change from BL</b>	<b>Baseline</b>	<b>Week 15</b>	<b>Change from BL</b>
FEV1						
Mean (L)	3.0	2.9	-0.04	3.2	3.1	-0.01
SD	(0.67)	0.64	-0.45	0.66	0.65	.20
DLCO						
Mean (mL/min/mm Hg)	25.0	25.1	0.0	26.5	25.8	-0.7
SD	4.70	4.35	2.32	5.57	5.18	2.33

Source tables: Tables 46 and 47, p 122-3, PDC-INS-0008 CSR, Module 5.

**a) FEV1** (Section 12.6.1, p.121)

For FEV1, the mean change from baseline for the TI group was -0.04L and -0.01L for the T control group. There was no statistical difference within or between the two groups.

**b) DLCO** (Section 12.6.2, p. 122)

For DLCO, the mean change from baseline at 15 weeks was -0.023 mL/min/mm Hg in the TI group and -0.665 mL/min/mm Hg in the control group. These changes were not statistically significant within or between groups, nor were they clinically significant.

**8. HRCT** (Section 12.1.2.1, p. 95, Table 35)

HRCT was performed within 2 months of the start of the study and the patient’s final treatment visit. The HRCT scans were reviewed at the study site and any clinically significant deviations from baseline were documented as adverse event. In addition, a formal process for central and independent blinded review of the HRCTs was performed.

Four (4) subjects in the TI group and eight (8) subjects in the T control group presented with a change from normal to abnormal. The narratives and findings for each of these 12 patients were reviewed. Per my review, the majority of these changes were not clinically significant, and were notable for: atelectasis, transient ground glass which resolved on follow-up, stable sub-centimeter nodules/lymph nodes that were not initially visualized, scarring, air trapping, granulomas, and cysts.

*Reviewer’s comment: After detailed review of the narratives, even those HRCT finding that were deemed “clinically significant” were of questionable significance in the opinion of this reviewer. The imaging on HRCT is of such detailed quality, that slight differences in operator and patient technique can lead to the appearance of “ditzels” on imaging. These findings are unlikely to be of much clinical significance. There was no evidence of newly diagnosed malignancy in this short trial.*

*However, two abnormal HRCTs mentioned elsewhere in this study reported are not mentioned in this section. In the section on PFT findings, a patient who was discontinued from the trial, had an abnormal CT showing bronchiectatic changes, and this CT is not reported here. Further, the one pulmonary event of special interest also had an abnormal chest CT which is also not reported in this section. It appears that only patients who had abnormal CTs at visit 9 are reported here. An information request regarding the reporting of abnormal HRCTs will need to be sent to the Sponsor to clarify these omissions and any other potential omissions.*

#### **9. Insulin Antibodies** (Section 12.6.4, p. 125)

Insulin antibodies were detected in 10 (19.2%) of TI treated subjects and 13 (26%) of T treated subjects. The mean changes from Visit 1 to Visit 9 were small within each treatment group and not statistically significant within or between groups. Most subjects had unchanged either positive or negative insulin antibody results at both baseline and endpoint. In the TI group, 2 of 10 subjects shifted from negative to positive; in the T group, this was 3 of 13.

#### **10. Special Interest Pulmonary Event** (Section 12.2.3.3, p. 108)

Subject 023/376 was a 42 year old Asian man who was randomized to receive TI. He was diagnosed with severe sarcoidosis 1 month after initiating therapy. No action was taken with the study drug. FEV1 was noted to have declined to 2.74 L on Visit 6 from the baseline value of 2.92, but the remained stable. Other PFT parameters were stable. A spiral CT scan done 3 months after initiating therapy with TI was notable for multiple mediastinal lymph nodes that remained stable at all visits.

*Reviewer's comment: This HRCT is also not mentioned within the abnormal HRCTs. See previous Reviewer's Comment.*

#### **D. Conclusions**

Study PDC-INS-008 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 2 study comparing treatment with prandial TI inhalation powder vs. treatment with prandial T Inhalation Powder (TP, excipient only) for approximately 12 weeks in subjects with suboptimal glucose control. The study included a 52-week treatment phase and a 4-week follow-up phase. The study included a 2 week screening period and an 12-week treatment period. Relevant pulmonary safety monitoring included: 1) Spirometry at Weeks 1, 3, 7, 11 and 15, 2) DLCO at Weeks 1 and 15, and 3) HRCT or MRI at Weeks 2 and 15. AEs were also collected at each scheduled visit. A special cough CRF was used to assess this AE.

A total of 123 subjects were included in the Safety Population: 61 subjects in the TI group and 62 subjections in the TP (vehicle) control group. Of the 4 subjects who discontinued secondary to AEs, 3 were due to respiratory etiologies (cough n=2, abnormal HRCT n=1). Respiratory AEs were reported in 42% of subjects overall, when including the respiratory, infection, and investigations SOCs. Respiratory AEs that occurred in more than 2 subjects included upper respiratory tract congestion, pharyngolaryngeal pain, throat irritation, upper respiratory tract infection, sinusitis, bronchiectasis, bronchitis, nasopharyngitis, and abnormal HRCT (discussed further below). Cough was analyzed separately. A total of 18 of 61 (30%) TI subjects and 17 of

62 (27%) T subjects each experienced 1 or more coughing episodes during the study, for a total of 63 episodes in the TI group and 113 episodes in the T control group.

Three patients in the TI group had PFT findings of decrease in  $\geq 15\%$ . One subject withdrew from the trial, while the others continued on study drug. For FEV1, the mean change from baseline for the TI group was -0.04L and -0.01L for the T control group. There was no statistical difference within or between the two groups. For DLCO, the mean change from baseline at 15 weeks was -0.023 mL/min/mm Hg in the TI group and -0.665 mL/min/mm Hg in the control group. These changes were not statistically significant within or between groups, nor were they clinically significant.

Four (4) subjects in the TI group and eight (8) subjects in the T control group presented with a change from normal to abnormal. The narratives and findings for each of these 12 patients were reviewed. Per my review, the majority of these changes were not clinically significant, and were notable for: atelectasis, transient ground glass which resolved on follow-up, stable sub-centimeter nodules/lymph nodes that were not initially visualized, scarring, air trapping, granulomas, and cysts. Insulin antibodies were detected in 10 (19.2%) of TI treated subjects and 13 (26%) of T treated subjects. The mean changes from Visit 1 to Visit 9 were small within each treatment group and not statistically significant within or between groups. One subject developed sarcoidosis while on TI treatment, and this was reported as an event of interest.

Overall, the pulmonary function findings were not of clinical significance in this trial. The HRCT findings of interest are those that are not reported as AEs, and include the special event of interest (i.e. sarcoid) and bronchiectasis in the patient that discontinued secondary to a PFT finding. These will need to be taken into consideration in the overall review.

## 6.5 Study MKC-TI-026

### A. Title

A Prospective, Controlled, Multi-Center Open-label, Randomized, 12-Week Safety and Efficacy Trial of Inhaled Technosphere Insulin in Patients with Type 2 DM Who are Suboptimally Treated

**Dates:** August 2004 to January 2005

**Centers:** 10 centers in Russia

### B. Protocol

This was a Phase 2b, randomized, controlled, open-label, multicenter, 12 week efficacy and safety trial to evaluate the effect of prandial administration of inhaled TI on HbA1C levels in subjects with type 2 DM. Subjects were to be insulin-treatment naïve, and to be currently receiving treatment with diet and exercise and/or single or combination oral anti-hyperglycemic agents with suboptimal glycemic control. Subjects were randomized in a 5:1 ratio to treatment with TI, administered in an unblinded fashion, or no TI treatment (control arm).

The following subjects were excluded:

- COPD, asthma, chronic lung diseases, and smokers
- History of malignancy within 5 years
- Baseline FVC, and FEV1 < 70% predicted normal

The study included a 2 week screening period and an 12-week treatment period. Relevant pulmonary safety monitoring included spirometry at Weeks 0 and Week 14 and AEs collected at each scheduled visit. A special cough CRF was used to assess this AE.

### C. Results

The safety analysis was based on the Safety Population, defined as all randomized subjects who took at least 1 dose of study medication . A total of 90 subjects were included in the Safety Population: 75 subjects in the TI group and 15 subjections in the control group.

*Reviewer’s comment: All subsequent references refer to sections within the clinical study report (CSR) for MKC-TI-026 located in Module 5.3.5.1 of the eCTD.*

#### 1. Patient Disposition (Section 6.2, p. 39)

Of the 90 patients in the safety population, 83 completed the study: 69 (92%) in the TI group and 14 (93%) in the control group. Seven patients (7) patients discontinued from the study, 6 (8%) in the TI group, and 1 (7%) in the control group. Of the listed reasons, protocol violation was the most common for premature discontinuation in the TI group, followed by AEs (See Table 63).

There were 2 AEs that led to discontinuation in the TI group, both of which were due to pulmonary etiologies and are discussed in more detail below.

<b>Table 63: Subject Disposition (Study MKC-TI-026)</b>		
	<b>TI</b>	<b>Control</b>
Disposition	<b>n (%)</b>	<b>n (%)</b>
Randomized/Safety Population	75 (100%)	15 (100%)
Completed	69 (92%)	14 (93%)
Premature Discontinuation	6 (8%)	1 (7%)
Withdrawal of Consent	1 (1%)	0
Adverse Event	2 (3%)	1 (7%)
Protocol Violation	3 (4%)	0
Physician Decision	0	0
Other	0	0

Source table: Table 7-8, Page 40-41, MKC-TI-026, CSR, Module 5.

**2. Baseline Characteristics** (Section 6.3.1, p. 41, Table 8)

There were more females than males in both treatment groups, 75-80% females vs. 20-25% males. All patients were Caucasian. There were no substantial demographic differences between the treatment group and the control group with respect to other baseline variables.

**3. Extent of Exposure** (Section 6.5.1, p. 44, Table 10)

The mean exposure to TI was 80 days. No notable differences in exposure were observed between treatment groups. The total number of days at each prandial dose level of TI was also summarized for the Safety Population. The greatest total number of days on any single prandial TI dose was at the 15 U dose (75 days), followed by 30 U (59 days), and 45 U (29 days). Overall, in this trial, subjects used the lower prandial doses of 15 U and 30 U TI for the greatest periods of time.

**4. Deaths and SAEs** (Section 8.2.1 and Section 8.2.2, p. 56)

There were no deaths during this trial. There were no respiratory SAEs in this study.

**5. Discontinuation due to AEs** (Section 8.2.3.1, p. 56)

Of the two subjects who discontinued secondary to AEs in the TI group, both were due to respiratory etiologies. The subject who discontinued secondary to an AE in the control group discontinued secondary to thrombocytopenia. One TI subject discontinued after developing pharyngitis 1 month into TI treatment, and the other due to the development of an upper respiratory infection. The narratives for the patients that discontinued were reviewed and offer no additional information.

**6. Respiratory Adverse Events** (Section 8.1.2, p. 54, Table 16)

Respiratory AEs were reported in 16% of subjects overall, when including the respiratory and infection SOCs. All the respiratory AEs were in the TI treated subject and included throat irritation, upper respiratory tract infection, and nasopharyngitis. There were a total of 15 events in 12 subjects (See Table 64).

<b>Table 64: Summary of Most Frequently Reported Respiratory Adverse Events by PT (Study MKC-TI-026)</b>		
Preferred Term	TI (n = 75)	control (n = 15)
Total Subjects with Respiratory AE	12 (16)	0
Total Respiratory AEs	15	0
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>	<b>5 (6.7) [7]</b>	<b>0</b>
Throat irritation	5 (6.7) [7]	0
<b>Infections and Infestations</b>	<b>7 (9.3) [8]</b>	<b>0</b>
Upper Respiratory Tract Infection	2 (2.7) [3]	0
Nasopharyngitis	5 (6.7) [5]	0
Source table: Table 16, Page 54, MKC-TI-026 CSR, Module 5.		
Number in ( ) = percentage of subjects in treatment group		
Number in [ ] = number of events		

**a) Cough** (Section 8.3.2, p. 63)

A total of 15 of 75 (20%) TI subjects and 0 control subjects experienced cough. Of the 15 subjects who experienced cough, the majority experienced intermittent coughing (53%), followed by a single defined cough (33%), and lastly continuous coughing (13%).

Approximately half of the subjects experienced cough within 10 minutes of inhalation of TI. No subjects discontinued the trial secondary to cough.

**7. Pulmonary Function Tests** (Section 8.4, p. 79)

PFTs included spirometry at Weeks 0 and 14. Baseline and mean changes for both treatment groups are summarized in Table 65 below.

<b>Table 65: Pulmonary Function Tests – Summary of Mean Change - LOCF (Study MKC-TI-026)</b>						
<b>PFT</b>	<b>TI</b>			<b>Control</b>		
	<b>Baseline</b>	<b>Week 14</b>	<b>Change from BL</b>	<b>Baseline</b>	<b>Week 14</b>	<b>Change from BL</b>
FEV1	n=75	n=72	n=75	n = 15	n = 15	n = 15
Mean (L)	2.72	2.66	-0.06	2.58	2.51	-0.07
SD	0.59	0.60	0.27	0.69	0.67	0.27
FVC	n=75	n=72	n=72	n = 15	n = 15	n = 15
Mean (L)	3.45	3.39	-0.05	3.20	3.15	-0.05
SD	0.73	0.71	0.34	0.86	0.80	0.33

Source tables: Tables 22 and 23, p 65-66, MKC-TI-026, CSR, Module 5.

**a) FEV1** (Section 8.4.1.2, p. 65)

For FEV1, the mean change from baseline for the TI group was -0.06 L and -0.07 L for the control group. There was no statistical difference within or between the two groups.

**b) FVC** (Section 8.4.1.1, p. 64)

For FVC, the mean change from baseline at 14 weeks was -0.05 L in both the TI group and the control group. These changes were not statistically significant within or between groups.

**8. Insulin Antibodies** (Section 8.6.4.2, p. 74)

At the end of the trial, in the TI group, insulin antibody concentrations of 20 U/mL or greater were reported for 5 subjects (6.7%), of whom 2 subjects had concentrations greater than 60 U/mL. In comparison, no subjects in the control group had a post-baseline insulin antibody concentration of greater than 20 U/mL.

**D. Conclusions**

Study MKC-TI-026 was a Phase 2b, randomized, controlled, open-label, multicenter, 12 week efficacy and safety trial to evaluate the effect of prandial administration of inhaled TI on HbA1C levels in subjects with type 2 DM. Subjects were to be insulin-treatment naïve, and to be currently receiving treatment with diet and exercise and/or single or combination oral anti-

hyperglycemic agents with suboptimal glycemic control. Subjects were randomized in a 5:1 ratio to treatment with TI, administered in an unblinded fashion, or no TI treatment (control arm). The study included a 2 week screening period and an 12-week treatment period. Relevant pulmonary safety monitoring included spirometry at Weeks 0 and Week 14 and AEs collected at each scheduled visit. A special cough CRF was used to assess this AE.

A total of 90 subjects were included in the Safety Population: 75 subjects in the TI group and 15 subjects in the control group. One TI subject discontinued after developing pharyngitis 1 month into TI treatment, and the other due to the development of an upper respiratory infection. Respiratory AEs were reported in 16% of subjects overall, when including the respiratory and infection SOCs. All the respiratory AEs were in the TI treated subjects and included throat irritation, upper respiratory tract infection, and nasopharyngitis. There were a total of 15 events in 12 subjects. A total of 15 of 75 (20%) TI subjects and 0 control subjects experienced cough. Of the 15 subjects who experienced cough, the majority experienced intermittent coughing (53%), followed by a single defined cough (33%), and lastly continuous coughing (13%). Approximately half of the subjects experienced cough within 10 minutes of inhalation of TI. No subjects discontinued the trial secondary to cough.

Pulmonary function monitoring included measurement of FEV1 and FVC at Weeks 0 and 14. For FEV1, the mean change from baseline for the TI group was -0.06 L and -0.07 L for the control group. For FVC, the mean change from baseline at 14 weeks was -0.05 L in both the TI group and the control group. There was no statistical difference within or between the two groups for either parameter. DLCO was not measured in this study. Overall, the pulmonary function findings were not of clinical significance in this trial.

## 6.6 Study MKC-TI-014

### A. Title

A Phase 3 Randomized, Open Label, Multi-Center, Comparative Study of Technosphere Insulin Inhalation Powder Versus Rapid Acting Insulin in Subjects with Type 2 Diabetes Mellitus Receiving Lantus as Basal Insulin with a 22-Week Post-Treatment Follow-Up Period on Conventional Therapy.

**Dates:** December 24, 2004 to July 11, 2006

**Centers:** 27 sites in Russia

### B. Protocol

Study MKC-TI-014 was a randomized, open label, multicenter clinical trial comparing glycemic control in subjects with type 2 diabetes receiving insulin glargine as basal insulin and prandial TI with subjects receiving basal insulin and subcutaneous rapid-acting insulin as a comparator group. The following subjects were excluded:

- COPD, emphysema, or asthma
- Current smokers or smoking history within the past 6 months

- Upper respiratory infection in the last 15 days or a lower respiratory tract infection in the last 30 days.
- History of malignancy in the last 5 years, except basal cell carcinoma.
- FEV1  $\leq$  70% predicted

The study consisted of a 24-week treatment phase (17 visits), at the end of which, subjects had the option of continuing in the trial for an additional 22 weeks of conventional therapy at the investigator’s discretion. The purpose of the follow-up period was additional pulmonary safety assessment. The study began with a 3 week run-in period to stabilize all subjects on insulin glargine. Randomization to TI versus subcutaneous prandial insulin occurred at Visit 5 (Week 0). Relevant pulmonary safety monitoring included: 1) Spirometry (Week -4, Weeks 0, 4, 24, 28, 36, and 48), 2) Chest X-rays during run-in, Week 24 (end of treatment), and Week 48 (follow-up). AEs were also collected at each scheduled visit. A special cough CRF was used to assess this AE.

### C. Results

The safety analysis was based on the Safety Population, defined as all randomized subjects who took at least 1 dose of study medication. A total of 309 subjects were included in the Safety Population: 151 subjects in the TI group and 158 subjects in the control group.

*Reviewer’s comment: All subsequent references refer to sections within the clinical study report for MKC-TI-014 located in Module 5.3.5.1 of the eCTD.*

#### 1. Patient Disposition (Section 6.2, p. 56)

Patient disposition is summarized in Table 66. Of the 309 randomized patients, 35 subjects discontinued prematurely from the trial, 30 (20%) in the TI group, and 5 (3%) in the control group. The greatest percentage of discontinuations were due to adverse events, exclusively in the TI treatment group (n=15, 10%). Respiratory AEs comprised the majority of AEs leading to discontinuation. This is discussed further under Adverse Events below.

	<b>TI</b>	<b>SC Insulin</b>	<b>Total</b>
Disposition	<b>n (%)</b>	<b>n (%)</b>	<b>N (%)</b>
Randomized	151	158	309
Completed (thru Visit 13)	123 (82)	153 (97)	276 (89)
Premature Discontinuation	30 (20)	5 (3)	35 (11)
Withdrawal of Consent	10 (7)	0	10 (3)
Adverse Event	15 (10)	0	15 (5)
Respiratory AE	11 (7)	0	
Investigator Decision	3 (2)	0	3 (1)
Lost-to-follow-up	1 (0.7)	0	1 (0.3)
Protocol Violation	1 (0.7)	4 (3)	5 (2)
Other			

Source table: Table 7, Page 57, MKC-TI-014 CSR, Module 5.

*Reviewer’s comment: When comparing the number of patients who completed and were prematurely discontinued, there is an apparent discrepancy of 2 patients. An IR was sent to the*

*Applicant, and the discrepancy was clarified. Two patients finished the study through Visit 13 (Week 24), but discontinued prior to the follow-up visit (Visit 14, Week 48), and therefore are counted as both completed and prematurely discontinued.*

**2. Baseline Characteristics** (Section 6.3.1, p. 59, Table 10)

Each group contained more females than males (approximately 75% vs. 25%). Only Caucasian patients were studied. Other baseline and demographic characteristics were similar in the two treatment groups.

**3. Extent of Exposure** (Section 6.5, p. 63, Table 13)

The mean exposure to TI was approximately 148 days.

**4. Deaths and SAEs** (Section 8.2, p. 91, Tables 35 and 36)

Two deaths occurred during the trial, both in subjects in the subcutaneous insulin control group. One subject died during the randomized treatment period and one during the follow-up period. Both subjects died of acute coronary syndromes.

A total of 13 subjects experienced SAEs during the randomized treatment period, 4 (2.6%) in the TI group, and 9 (5.7%) in the control group. Of the 4 subjects with SAEs in the TI treatment group, one subject experienced an asthma exacerbation which led to discontinuation. Subject 514/984 experienced angioneurotic edema, and was also discontinued from the trial. There were no pulmonary SAEs reported during the follow-up period. These 2 pulmonary/allergy SAEs are described in further detail:

- Subject 508/186 was a 67-year old Caucasian female who began to experience coughing with TI inhalation 5 months after starting treatment. Her symptoms progressed to dyspnea and a self-described “suffocation episode” which led to hospitalization. Initial spirometry did not reveal airway obstruction and chest x-ray was similarly unrevealing. Prior to bronchoscopy, 6 days after presentation, spirometry was repeated, and there was no evidence of obstruction. Bronchoscopy revealed “catarrhal endobronchitis”. Re-challenge with inhaled insulin was attempted after symptoms had been quieted down, and resulted in similar pulmonary symptoms, and the patient was permanently discontinued from the trial.
- Subject 514/984 was a 69 year old Caucasian female who experienced facial edema and respiratory difficulty while receiving the second inhalation of TI. Symptoms included skin hyperemia, pruritis, angioedema of mouth and face, and hoarse voice. The patient was treated appropriately and was permanently discontinued from the trial.

**5. Discontinuation due to AEs** (Section 8.2.3, p. 93, Table 37)

A total of 15 subjects (10%) who were randomized to TI discontinued from the study due to AEs. No subjects randomized to sc insulin discontinued prematurely due to AEs. Eight (8) of the 15 subjects discontinued secondary to cough that was mild to moderate in severity, which

resolved upon discontinuation of TI. Three subjects discontinued secondary to SAEs. Of these SAEs, only 2 were of pulmonary/allergy etiology as described above. One patient discontinued secondary to reported dyspnea, but cough was a major component per the narrative. One patient discontinued secondary to pharyngitis.

To summarize, of the 15 subjects who discontinued secondary to AEs in the TI group, 11 were due to pulmonary/allergy etiologies.

**6. Respiratory Adverse Events** (Section 8.1.1.1 and 8.1.1.2, p. 85, Tables 29-32)

Respiratory adverse events were reported with relatively equal frequency in both treatment groups. For example, during the randomized treatment periods, nearly equal percentages of patients experienced nasopharyngitis and respiratory tract infections. Similar events were reported during the follow-up period, with the addition of acute bronchitis and influenza.

**a) Cough** (Section 8.4, p. 101)

Of the 151 subjects in the TI group, 20% (n=29) reported 45 coughing episodes. There were no more than 5 episodes reported per subject and most cough events were non-sputum producing intermittent or single defined coughs. Approximately half of the cough events in the TI-treated subjects were experienced within 10 minutes of TI inhalation. A total of 6 (4%) of TI-treated subjects reported continuous coughing. As in previously discussed trials, the incidence of cough decreased over time (Figure 5, p. 103, MKC-TI-014 CSR).

**7. Pulmonary Function Tests** (Section 8.5, p. 103)

PFTs included spirometry (no DLCO) at Weeks -4, Weeks 0, 4, 24, 28, 36, and 48. Baseline and mean changes for both treatment groups are summarized in Table 67 below.

The mean change from baseline in the TI group was -0.07L and -0.05L for the control group. When pulmonary function was reassessed at Week 48, the change from baseline in FEV1 was relatively unchanged (Table 45, p. 106). Similarly there was no meaningful change in FEV1 (mean change was 0.003 L) from the end of the treatment period to the end of the follow-up period (Visit 13 to Visit 17). As shown in Figure 30, both treatment groups showed similar trend for changes in FEV1 over the course of the trial, from baseline to follow-up. During the follow-up period, the final FEV1 measurement showed a slight increase, most likely due to the inherent variability of the test.

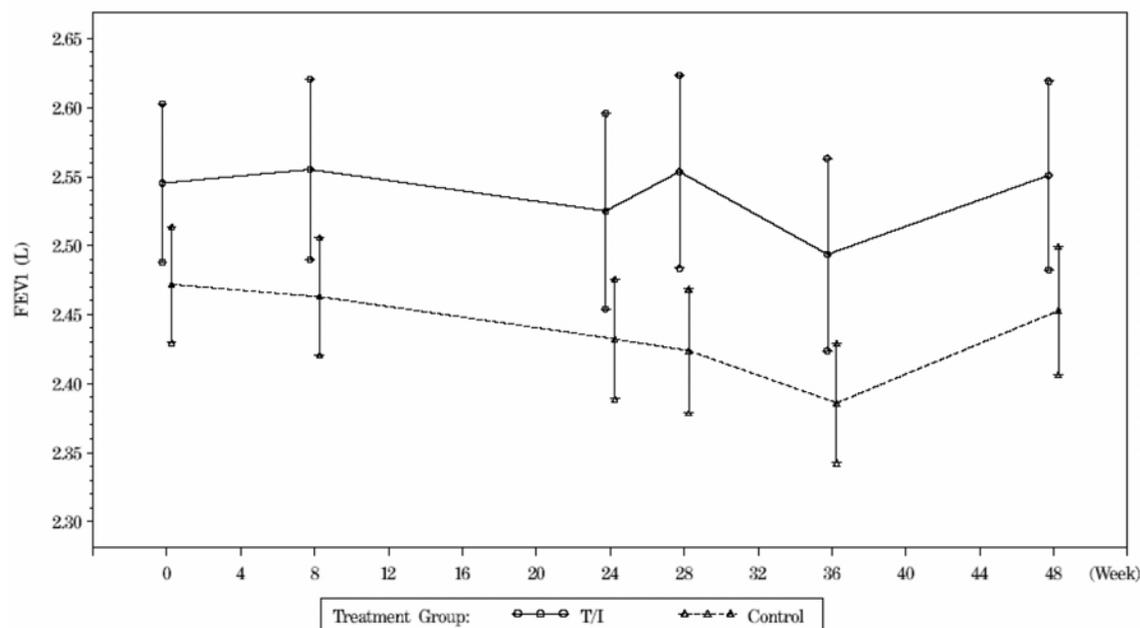
**Table 67: Pulmonary Function Tests – Summary of Mean Change –Study MKC-TI-014**

PFT	TI			SC Insulin		
	Baseline	Week 24	Change from BL	Baseline	Week 24	Change from BL
FEV1						
Mean (L)	2.55	2.53	-0.07	2.47	2.43	-0.05
SD	0.70	0.76	0.29	0.53	0.53	0.17

Source tables: Module 5, MKC-TI-014 CSR, Table 44, p. 104

**Figure 30 Observed Values for FEV1 (L), from Randomization to End of Follow-Up, by Week**

**(Follow up population N =258)) – Study MKC-TI-014 (Source: Figure 8, pg. 108)**



A PFT finding was defined as a decrease of  $\geq 15\%$  in FEV1. A total of 11 subjects (7 subjects (4.6%) in the TI group and 4 subjects [2.5%] in the control group had decreases of  $\geq 15\%$  from baseline in FEV1. None of the decreases from baseline of  $\geq 15\%$  in PFT parameters resulted in discontinuation from the trial. All of these subjects were without any respiratory symptoms, had unremarkable medical histories, and had normal chest x-rays at baseline and treatment endpoint.

### **8. Chest X-Rays** (Section 8.7.4, p. 123)

Chest X-rays were performed at Baseline, Treatment Endpoint (24 weeks), and End of the Follow-up Period (48 weeks). Overall, changes in chest x-ray findings from baseline to endpoint and follow-up do not reveal any clinically significant changes.

### **9. Insulin Antibodies** (Section 8.7.6, p. 125)

The mean concentration of insulin antibodies increases approximately 3.5 fold in the TI treated group from baseline to treatment endpoint. There was no increase in insulin antibodies in the SC insulin control group.

### **D. Conclusions**

Study MKC-TI-014 was a randomized, open label, multicenter clinical trial comparing glycemic control in subjects with type 2 diabetes receiving insulin glargine as basal insulin and prandial TI

with subjects receiving basal insulin and subcutaneous rapid-acting insulin as a comparator group.

The study included a 24-week treatment phase and a 24-week follow-up phase, to assess additional pulmonary safety parameters. In the TI group, 15 subjects discontinued secondary to AEs, while there were no discontinuations secondary to AEs in the control arm. Of these 15 premature discontinuations, 11 were due to respiratory/allergy etiologies. 13 were due to respiratory etiologies. The most common respiratory event leading to discontinuation in the TI group was cough (n=8). Other respiratory AEs leading to discontinuation were : dyspnea (n=1), asthma (n=1), and angioneurotic edema (n=1), the latter two of which were considered SAEs.

Respiratory adverse events were reported with relatively equal frequency in both treatment groups. For example, during the randomized treatment periods, nearly equal percentages of patients experienced nasopharyngitis and respiratory tract infections. Similar events were reported during the follow-up period, with the addition of acute bronchitis and influenza.

Cough was analyzed separately. Of the 151 subjects in the TI group, 20% (n=29) reported 45 coughing episodes. There were no more than 5 episodes reported per subject and most cough events were non-sputum producing intermittent or single defined coughs. Approximately half of the cough events in the TI-treated subjects were experienced within 10 minutes of TI inhalation. A total of 6 (4%) of TI-treated subjects reported continuous coughing. As in previously discussed trials, the incidence of cough decreased over time.

For FEV1, the mean change from baseline in the TI group was -0.07L and -0.05L for the control group. When pulmonary function was reassessed at Week 48, the change from baseline in FEV1 was relatively unchanged. Similarly there was no meaningful change in FEV1 (mean change was 0.003 L) from the end of the treatment period to the end of the follow-up period (Visit 13 to Visit 17).

Chest X-rays were performed at Baseline, Treatment Endpoint (24 weeks), and End of the Follow-up Period (48 weeks). Overall, changes in chest x-ray findings from baseline to endpoint and follow-up do not reveal any clinically significant changes. The mean concentration of insulin antibodies increases approximately 3.5 fold in the TI treated group from baseline to treatment endpoint. There was no increase in insulin antibodies in the SC insulin control group.

## 6.7 Study MKC-TI-102

### A. Title

A Prospective, Multi-Center, Open-Label, Randomized Controlled Clinical Trial Comparing the Efficacy and Safety in Subjects with Type 2 Diabetes Receiving Subcutaneous Basal Insulin and Prandial Inhalation of Technosphere Insulin Versus Subcutaneous Premixed Insulin Therapy Over a 52-Week Treatment period and a 4-Week Follow-Up

**Dates:** February 23, 2006 to September 8, 2008

**Centers:** Multiple sites in the United States, Europe, Russia, Latin America, Canada, and Mexico

### B. Protocol

Study MKC-TI-102 was a prospective, randomized, open label, multicenter, controlled clinical trial comparing treatment with SC basal insulin in combination with inhaled prandial TI Inhalation Powder with treatment with a SC premix of intermediate-acting and rapid-acting insulin. The following subjects were excluded:

- COPD, emphysema, or asthma
- Current smokers or smoking history within the past 6 months
- Upper respiratory infection in the last 15 days or a lower respiratory tract infection in the last 30 days.
- History of malignancy in the last 5 years, except basal cell carcinoma.
- FEV1  $\leq$  70% predicted, TLC  $\leq$  80% predicted, and DLCO  $\leq$  70% predicted

The study included a 52-week treatment phase and a 4-week follow-up phase.

The study began with screening at Week -3, randomization at Week -1, and Baseline at Week 0. where baseline safety measurements were performed. Randomization occurred at Week -1. Subjects participated in 5 clinical assessment visits during the 52-week treatment period (Weeks 0, 14, 26, 38, and 52) and one follow-up visit at 56 weeks. Relevant pulmonary safety monitoring included: 1) PFTs: Weeks 0, 14, 26, 38, 52, and 56 2) Chest X-rays: Weeks -3 and 52. All PFTs were performed at a pulmonary function laboratory certified by the Applicant and were performed according to current American Thoracic Society guidelines. . A special cough CRF was used to assess this AE.

### C. Results

The safety analysis was based on the Safety Population, defined as all randomized subjects who took at least 1 dose of study medication. A total of 654 subjects were included in the Safety Population: 323 subjects in the TI group and 331 subjects in the control group.

*Reviewer's comment: All subsequent references refer to sections within the clinical study report for MKC-TI-102 located in Module 5.3.5.1 of the eCTD.*

#### **1. Patient Disposition** (Section 10.1, p. 86)

Patient disposition is summarized in Table 53. Of the 677 randomized patients, 23 subjects withdrew prior to receiving study medication, and thus the Safety Population was composed of 323 subjects in the TI group, and 331 subjects in the control group. Of these 654 patients in the safety population, 462 completed the study (52 weeks): 216 (64.7%) in the TI group and 246 (71.7%) in the control group. A total of 191 patients were discontinued from the study. A greater percentage withdrew from the TI arm vs. the SC insulin arm (32% vs. 24%). The greatest number of discontinuations were due to withdrawal of consent. A greater number discontinued in the TI arm vs. the SC insulin arm. More subjects discontinued due to AEs in the TI arm than in the SC insulin arm. Discontinuations secondary to AEs in the TI arm were largely driven by respiratory AEs. Cough accounted for the largest percentage (2%) of respiratory AEs leading to

discontinuation in TI-treated subjects. Respiratory AEs leading to discontinuation are discussed further below.

<b>Table 68: Subject Disposition (Study MKC-TI-102)</b>			
	<b>TI</b>	<b>SC Insulin</b>	<b>Total</b>
Disposition	<b>n (%)</b>	<b>n (%)</b>	<b>N (%)</b>
Randomized	334	343	677
Safety Population	323 (97)	331 (97)	654
Completed	216 (65)	246 (72)	462 (68)
Premature Discontinuation	107 (32)	84 (24.5)	191 (28)
Withdrawal of Consent	50 (15)	32 (9)	82 (12)
Adverse Event	29 (9)	12 (4)	41 (6)
Respiratory AE	19 (6)	1 (0.3)	20 (3)
Investigator Decision	5 (2)	8 (2)	13 (2)
Lost-to-follow-up	6 (2)	22 (6)	28 (4)
Protocol Violation	6 (2)	3 (1)	9 (1)
Subject Died	4 (1)	1 (0.3)	5 (0.7)
Other	7 (2)	7 (2)	14 (2)

Source table: Table 7, Page 87, MKC-TI-102 CSR, Module 5.

*Reviewer’s comment: In this study, withdrawal of consent was further investigated and subjects who withdrew consent were further reviewed by the Applicant and misclassification were identified and reclassified as appropriate (eg. to discontinuation due to an AE) before programmatic generation of tables and files.*

**2. Baseline Characteristics** (Section 11.2.1, p. 90-91, Table 8)

The percentage of females and males was roughly 50% in both treatment arms. Caucasians comprised the majority of both treatment arms (~67%), but African American (8%), Hispanic (20%), Asian (2%), and Other (2%) ethnic groups were included. Other baseline and demographic characteristics were similar in the two treatment groups.

**3. Extent of Exposure** (Section 11.2.4, p. 96, Table 12)

The mean exposure to TI was approximately 9.4 months, with the maximum exposure being 13.4 months. Approximately 70% of the patients were exposed for > 9 months during the 52-week treatment period.

**4. Deaths and SAEs** (Section 12.3.1.1 and Section 12.3.1.2, p. 149, Table 37-39)

A total of 5 subjects died during the course of the study, 4 (1.2%) in the TI group and 1 (0.3%) in the control group. The majority of the deaths were due to cardiovascular causes, with one case of staphylococcal sepsis. SAEs were reported with similar frequency in the 2 treatment groups, 11.5% and 9.4% for TI and control groups, respectively. Of the reported SAEs, the incidence of respiratory SAEs was low, reported in 2 subjects in the TI group and 1 in the control arm. The 2 respiratory SAEs in the TI group were dyspnea and pulmonary edema. There were 5 malignancies during the course of this trial, which were balanced between groups. There were 2 pulmonary neoplasms which are outlined below:

#### SAEs of interest

- Subject 067/2909 – 62 year-old Caucasian male receiving TI for 137 days. While in routine follow-up of a previously resected colon cancer (1999). At this routine visit, a CEA level was elevated, and physical exam revealed an enlarged neck lymph node. CT of the thorax without contrast revealed nodules in the mediastinum and right lung hilum with lymph node enlargement in the right mediastinum. There was a 3 x 2 cm nodule with irregular borders in the peribronchial parenchyma in the right superior lobe. These findings were not seen in a CT scan done 7 months prior. The patient was withdrawn from the study. After failure to make diagnosis by needle aspiration, the patient went on to open cervical ganglion biopsy in the supraclavicular area, which led to the diagnosis of neuroendocrine carcinoma. This was identified as a lesion separate from this subject's previous colon cancer, and was identified as a small cell carcinoma, neuroendocrine type. The patient went on to palliative treatment.
- Subject 311/1906 was a 55-year-old woman with a history of hypertension and smoking (19 pack-years) in the TI group who had an abnormal not clinically significant chest x-ray at Baseline (06 Jun 2007) and nodule of unknown etiology in the right lung on an x-ray done on 19 Feb 2008 considered an abnormal clinically significant. No action was taken with the study drug.

#### **5. Discontinuation due to AEs (Section 12.3.1.2, p. 159, Table 20)**

Discontinuation from the trial secondary to AEs was more frequent in the TI group, and this was driven largely by respiratory AEs, including respiratory tract infections, which accounted for 60% of the discontinuations. Respiratory events leading to discontinuation included cough (1.9%), dyspnea (0.9%), bronchial hyper-reactivity (0.6%), , throat irritation (0.6%), asthma (0.3%), bronchospasm (0.3%), rhonchi (0.3%), throat tightness (0.3%), bronchitis (0.6%), pneumonia (0.3%) and wheezing (0.3%). Of note, one subject accounted for multiple respiratory AEs, including dyspnea, rhonchi, throat tightness, and wheezing. The narratives were reviewed and no additional information was extracted. The subjects with cough mainly reported cough of moderate intensity 10 minutes or less following inhalation of TI.

*Reviewer's comment: When clinically similar preferred terms are considered together, the subjects treated with TI are more likely to experience some sort of bronchial hyper-reactivity (including the terms asthma, bronchial hyper-reactivity , bronchospasm, dyspnea, and wheezing). If these are taken together as a single clinical syndrome, 8 subjects (2.5%) in the TI group discontinued secondary to this constellation of symptoms.*

#### **6. Respiratory Adverse Events (Section 12.2.3.1, p. 133, Table 33)**

Respiratory adverse events were reported more frequently in the TI group as compared to the control group. The incidence of respiratory AEs was higher in the TI group than in the control group (41% vs. 12%, respectively). The most frequently reported respiratory AE was cough, in 33% of TI-treated subjects, followed by throat irritation (3%), and pharyngolaryngeal pain (3%). The incidence of upper respiratory tract infections was 12% in the TI group vs. 7% in the control group. The incidence of lower respiratory tract infections was as follows: bronchitis – 5% of

subjects in the TI group and 2% in the control group; pneumonia 0.6% in the TI group, and 0.3% of subjects in the control group. (See Table 69).

<b>Table 69: Summary of Most Frequently Reported (<math>\geq 1\%</math>) Respiratory Adverse Events by PT occurring more frequently in TI vs. Control (Study MKC-TI-102)</b>		
Preferred Term	TI (n = 323)	SC Insulin (n = 331)
Total Subjects with AE	272 (84.2)	296 (89.4)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Cough	106 (32.8)	20 (6.0)
Throat irritation	11 (3.4)	0
Pharyngolaryngeal pain	10 (3.1)	8 (2.4)
Dyspnea	6 (1.9)	1 (0.3)
Epistaxis	4 (1.2)	2 (0.6)
Rhinorrhea	4 (1.2)	0
<b>Infections and Infestations</b>		
Upper respiratory tract infection	39 (12.1)	24 (7.3)
Nasopharyngitis	30 (9.3)	28 (8.5)
Influenza	18 (5.6)	18 (5.4)
Bronchitis	16 (5.0)	7 (2.1)
Pharyngitis	10 (3.1)	8 (2.4)
<b>Investigations</b>		
Pulmonary function test decreased	4 (1.2)	2 (0.6)
Source table: Table 33, Page 133, MKC-TI-102 CSR, Module 5.		

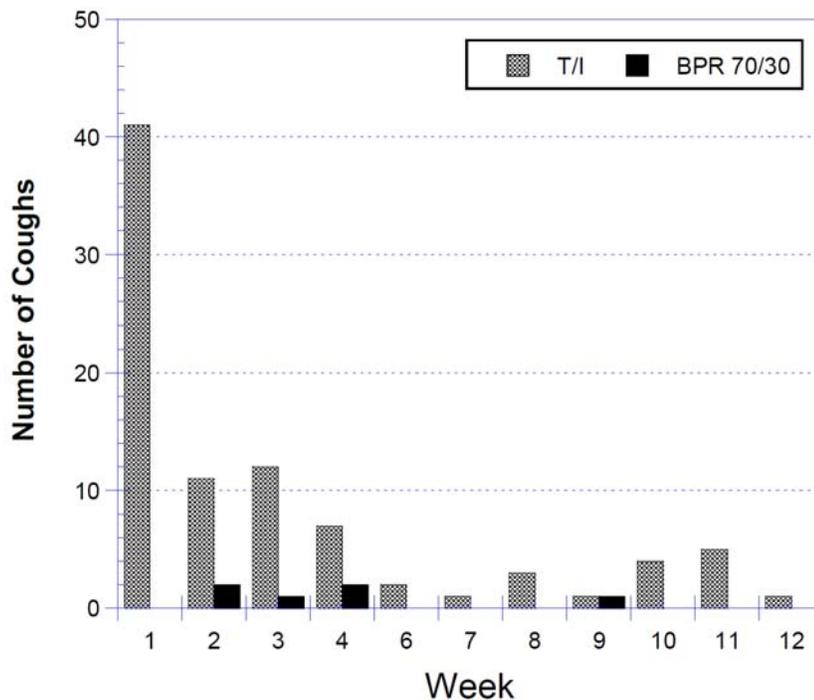
**a) Cough** (Section 12.5, p. 190)

Of the 323 subjects in the TI group, 33% reported at least 1 coughing episode, and 2% discontinued from the trial due to cough. When cough was reported as an AE, it was generally mild to moderate. There was one subject who considered his cough to be severe in nature, and discontinued as a result. Most cough in the TI group was characterized as intermittent (64%) or a single, defined episode (34%). The large majority (77%) of cough events occurred within 10 minutes of TI inhalation.

As shown in Figure 31, the mean frequency of cough decreased over time, with the greatest frequency occurring during the first week of treatment, which then subsequently decreased to very low levels by week 12.

*Reviewer’s comment: This might suggest some acclimatization to the inhaled drug. Similar findings were seen in study 101 which was of shorter duration.*

**Figure 31 Mean Frequency of Cough By Treatment Interval – Study MKC-TI-102**



Source Figure: Figure 12, Page 192, MKC-TI-102 CSR, Module 5.

### 7. Pulmonary Function Tests (Section 12.6, p. 194)

PFTs included spirometry and DLCO performed at Baseline, Weeks 14, 26, 38, 52, and at follow-up approximately 4 weeks after stopping treatment at the end of the trial. Baseline and mean changes for both treatment groups are summarized in Table 70 below.

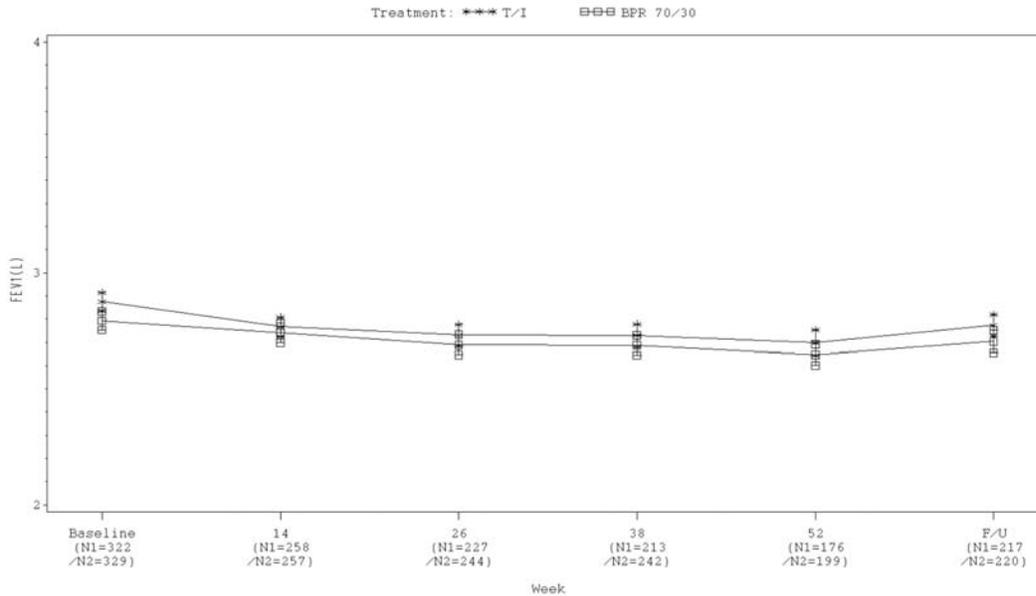
<b>Table 70: Pulmonary Function Tests – Summary of Mean Change – Study MKC-TI-102</b>						
	<b>TI</b>			<b>SC Insulin</b>		
<b>PFT</b>	<b>Baseline n = 322</b>	<b>Week 52 n = 176</b>	<b>Change from BL</b>	<b>Baseline n = 329</b>	<b>Week 52 n = 199</b>	<b>Change from BL</b>
FEV1						
Mean (L)	2.88	2.70	-0.13	2.79	2.65	-0.09
SD	0.70	0.72	0.22	0.72	0.65	0.20
	<b>Baseline n = 322</b>	<b>Week 52 n = 170</b>	<b>Change from BL</b>	<b>Baseline n = 330</b>	<b>Week 52 n = 196</b>	<b>Change from BL</b>
DLCO						
Mean (mL/min/mm Hg)	24.13	22.67	-0.80	23.74	22.06	-1.11
SD	5.63	5.15	2.45	5.99	5.07	2.51

Source tables: Module 5, MKC-TI-102 CSR, Table 60, p. 196

**a) FEV1**

For FEV1, the mean change from baseline was -0.13 L for the TI treated group and -0.09 L for the control group. There was no statistically significant difference between groups. This is graphically represented in Figure 32. At Week 56, the values began to return towards baseline.

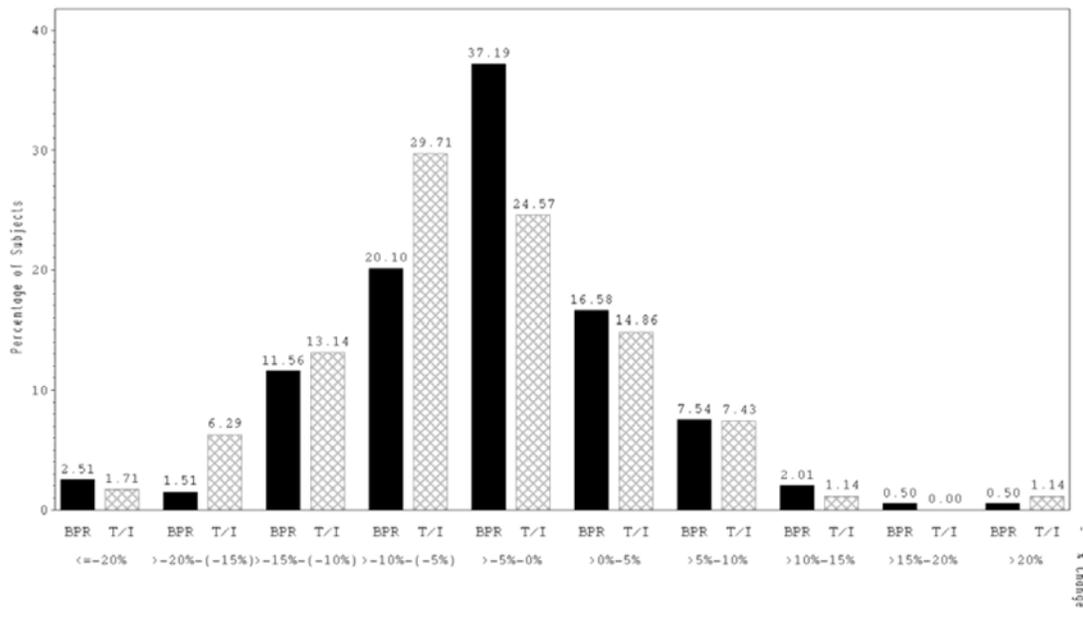
**Figure 32 Mean (SE) FEV1 Over Time (Safety Population) – Study MKC-TI-102 (Source: Figure 13, pg. 197)**



N1 = TI Inhalation Powder, N2 = BPR 70/30  
 Error bars denote  $\pm 1$  standard error of the mean.

The distribution of subjects by percentage change in FEV1 is summarized by treatment group in Figure 33. Approximately 6.3% of subjects in the TI group experienced a 15%-20% decline in FEV1, with only 1.5% in the control group.

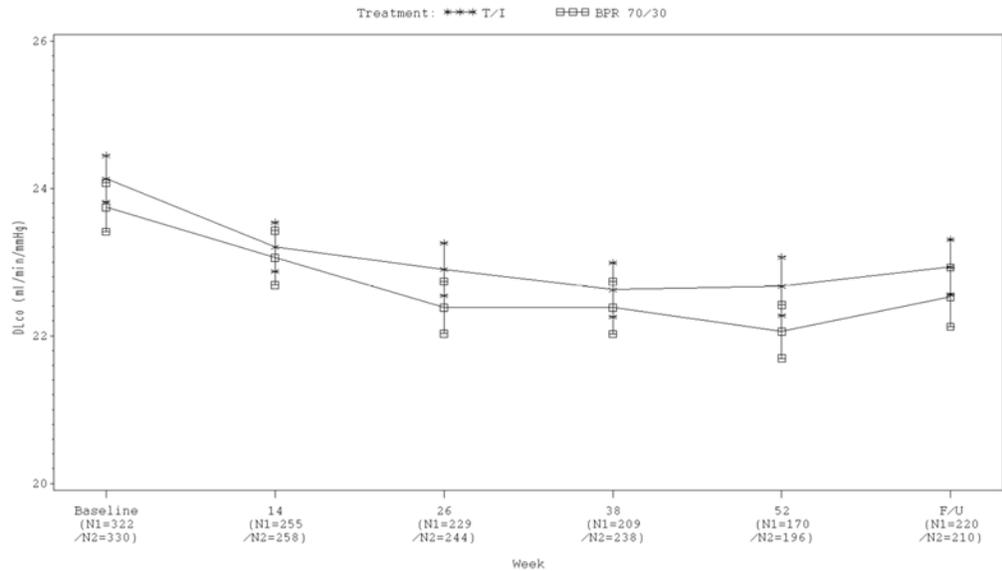
**Figure 33 Distribution of Percent Change from Baseline to Week 52 in FEV1 (L) – Safety Population, Study MCK-TI-102 (Source, Figure 17, pg. 200)**



**b) DLCO (Section 8.4.2, p. 185)**

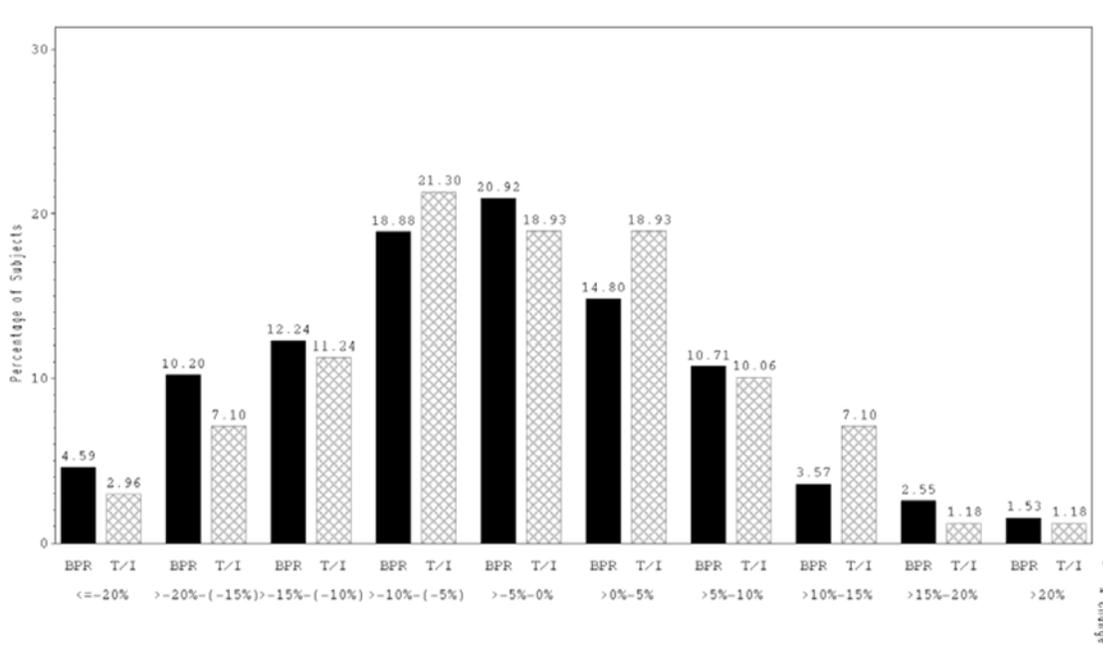
For DLCO, the mean change from baseline at 52 weeks was -0.80 mL/min/mm Hg in the TI group and -1.11 mL/min/mm Hg in the control group. There were no statistical differences between groups. See Figure 34.

**Figure 34 Mean (SE) DLCO (ml/min/mm Hg) Over Time (Safety Population) – Study MKC-TI-102 (Source: Figure 16, p. 199)**



As shown in Figure 35, more higher percentages of subjects in the control group experienced DLCO declines than in the TI-treated group.

**Figure 35 Distribution of Percent Changes in DLCO from Baseline to Week 52 (Source Figure 20, p. 202)**



8.

**Chest X-Rays (Section 12.9, p. 215)**

Chest X-rays were performed at Screening and Week 52, or at termination of the study. Overall, changes in chest x-ray findings from baseline to week 52 indicate that the shifts from baseline were similar in the 2 treatment groups. However, there were 2 notable cases:

- Subject 067/2909 was a 62-year-old Caucasian male ex-smoker with previous history of colon carcinoma in 1999. He had an abnormal not clinically significant chest x-ray at Baseline (06 Jul 2007) and an abnormal clinically significant chest x-ray at the last measurement. On 04 Mar 2008, a chest x-ray revealed a lesion in mediastinum in the pulmonary hila and at the right paratracheal area, along with an area of hypoventilation in the surrounding pulmonary parenchyma at the level of the superior lobe. There were also very small nodules with loss of the right paratracheal line that could be related with an associated component of lymphatic node enlargement; and an image of nodular aspect in the supraclavicular region in the left side, which could represent distant adenopathy. A biopsy of the lymph nodes revealed a diagnosis of neuroendocrine tumor.
- Subject 311/1906 was a 55-year-old woman with a history of hypertension and smoking (19 pack-years) in the TI group who had an abnormal not clinically significant chest x-ray at Baseline (06 Jun 2007) and nodule of unknown etiology in the right lung on an x-ray done on

19 Feb 2008 considered an abnormal clinically significant. No action was taken with the study drug.

*Reviewer's Comment: Given the concern for pulmonary malignancy, I have included these two cases in this review. The final diagnosis of Subject 311/1906 is not known.*

### **9. Insulin Antibodies** (Section 12.11.2, p. 218)

Subjects treated with TI experienced an increase in mean and median insulin antibody levels that was apparent by Week 14 of treatment; the median change from baseline in the TI group was 3.70 U/ml at Week 14 vs 1.70 U/mL in the control group. The mean and median levels continued to rise in the TI group and appeared to reach a peak at Weeks 26-38, followed by a decline thereafter. At Week 52, the median change from baseline in insulin antibody level was 6.60 Kronus U/mL in the TI group vs 3.00 Kronus U/mL in the control group. In the TI group, the highest individual mean reported value at Week 52 was 183.8 Kronus U/mL; in the control group, the highest individual reported mean value was 197.3 Kronus U/mL.

### **D. Conclusions**

Study MKC-TI-102 was a prospective, randomized, open label, multicenter, controlled clinical trial comparing treatment with SC basal insulin in combination with inhaled prandial TI Inhalation Powder with treatment with a SC premix of intermediate-acting and rapid-acting insulin.

The study included a 52-week treatment phase and a 4-week follow-up phase. Discontinuation from the trial secondary to AEs was more frequent in the TI group, and this was driven largely by respiratory AEs, including respiratory tract infections, which accounted for 60% of the discontinuations. Respiratory events leading to discontinuation included cough (1.9%), dyspnea (0.9%), bronchial hyper-reactivity (0.6%), , throat irritation (0.6%), asthma (0.3%), bronchospasm (0.3%), rhonchi (0.3%), throat tightness (0.3%), bronchitis (0.6%), pneumonia (0.3%) and wheezing (0.3%).

Respiratory adverse events were reported more frequently in the TI group as compared to the control group. Under the Respiratory SOC, cough, pharyngolaryngeal pain, nasal congestion, asthma, dyspnea, wheezing, throat irritation, bronchospasm, increased upper airway secretion, allergic rhinitis, and rhinorrhea were reported more frequently in the TI group as compared to the control group. Under the Infections and Infestations SOC, influenza, tonsillitis, bronchitis, and rhinitis were reported more frequently in the TI group. Cough was analyzed separately. Of the 293 subjects in the TI group, 32% reported at least 1 coughing episode, for a total of 169 reported episodes. Most (143 of 169) coughing episodes occurred within 10 minutes of study drug inhalation, and most (105 of 169) were classified as a intermittent. The mean frequency of cough decreased over time. For FEV1, the mean change from baseline for both groups was -0.06 L (-1.7%) . The decline in FEV1 was most prominent during the first 3 weeks in both groups. As shown in Figure 25, the mean FEV1 values in the TI group showed a decline of about 60 cc by Week 14, although there was no statistical difference within or between the two groups. For DLCO, the mean change from baseline at 52 weeks was -1.97 mL/min/mm Hg in the

TI group and -1.24 mL/min/mm Hg in the control group. The DLCO decreased significantly more in the TI group than in the control group ( $p = 0.0202$ ). The greatest decline was noted by Week 14 (-1.61 mL/min/mm Hg in the TI group and -0.72 mL/min/mm Hg in the control group). Thereafter, DLCO declined steadily in both groups over the remainder of trial (See Figure 9). At the follow-up visit 4 weeks after the cessation of the trial therapy, mean DLCO values had returned towards baseline, but did not fully recover. Chest X-rays were performed at Screening and Week 52. Overall, changes in chest x-ray findings from baseline to week 52 indicate that the shifts from baseline were similar in the 2 treatment groups. Insulin antibodies increased significantly in the TI group, but correlation to clinical worsening is unclear.

## 6.8 Study MKC-TI-030

### A. Title

Pulmonary Outcomes within a 2-year Period in Subjects with Diabetes Mellitus Treated with Technosphere Insulin or usual Anti-diabetic Treatment and in Subjects without Abnormalities in Glucose Control.

**Dates:** July 2005 to August 2008

**Centers:** 220 sites in North America, Russia, and Europe

### B. Protocol

Study MKC-TI-030 was a prospective, 2-year, multicenter clinical trial that incorporated 2 design strategies: (a) a randomized, open-label clinical trial comparing treatment with TI Inhalation Powder to usual anti-diabetes treatment in subjects with diabetes (type 1 or type 2), and (b) an epidemiological or observational investigation comparing subjects with diabetes who received usual anti-diabetes treatments with subjects without abnormalities in glycemic control. Subjects with diabetes were randomized to a treatment group at the second visit. Subjects without abnormalities in glycemic control were not randomized to, nor did they receive, any clinical trial treatments.

The pertinent pulmonary exclusion criteria were as follows:

- Current smokers or smoking history within the past 6 months
- History of COPD, asthma, other significant pulmonary disease, or sleep apnea
- Active respiratory infection
- History of malignancy in the last 5 years, except basal cell carcinoma.
- Subjects with current or previous chemotherapy or radiation therapy that may result in pulmonary toxicity
- History of lung neoplasm, any type
- FEV1 and DLCO  $\leq 70\%$  predicted, TLC  $\leq 70\%$  predicted
- Radiological examination of lungs with evidence of any clinical relevant abnormalities at Screening

The clinical trial consisted of 7 clinical trial site assessment visits for all subjects during a 2 year period. Screening and eligibility assessments began at Visit 1, and were completed by Visit 2, when clinical trial eligibility was confirmed. Thereafter, assessment visits took place at the clinical trial site for all subjects at months 3, 6, 12, 18, and 24. In addition to these visits, subjects in the TI group had supplementary clinical trial site visits for titration/dose evaluation and valuation of selected clinical trial assessments, at Days 7 and 21 from Visit 2, and at months 9, 15, and 21. There was a 1 month follow-up telephone visit for all clinical trial subjects at Month 25 or following the subject's last visit.

Pulmonary function testing, including spirometry, lung volumes, and DLco were performed according to current American Thoracic Society guidelines before the first administration of trial medications. PFTs were performed at Screening, and Months 3, 6, 12, 18, and 24.

Approximately 240 subjects (120 in each treatment group) with diabetes at sites in the US were randomized at Visit 1 to receive either HRCT or a CXR. Subjects received chest radiologic examination at Screening, and Months 12 and 24.

AEs were also collected at each scheduled visit. A special cough CRF was used to assess this AE, but it was also recorded on the regular CRF.

### C. Results

The safety analysis was based on the Safety Population, defined as all randomized subjects who took at least 1 dose of study medication. For the diabetes subjects, a total of 923 subjects were included in the TI group, and 949 subjects in the Usual Care (UC) group. For the non-diabetes subjects, the safety population included 163 subjects. *Reviewer's comment: All subsequent references refer to sections within the clinical study report for MKC-TI-030 located in Module 5.3.5.1 of the eCTD.*

#### 1. Patient Disposition (Section 10.1, p. 71)

A total of 789 (38.4) subjects were discontinued from the trial, 463 (50%) subjects in the TI group, 289 (30.4%) in the UC group, and 37 (23%) in the non-diabetic group. See Table 71. The relative percentage of subjects that discontinued in the TI group and the UC group in the subset of subjects with type 1 diabetes was 53.2% and 26.6%, respectively, and with type 2 diabetes was 47.8% and 31.9%, respectively. The most common reason for discontinuation in both groups was because subjects withdrew consent. Twice as many subjects with type 1 diabetes withdrew consent in the T group (79/269, 30%) compared to the UC group (39/271, 14%).

<b>Table 71: Subject Disposition (Study MKC-TI-030)</b>			
	<b>TI</b>	<b>Usual Care</b>	<b>Non-diabetes</b>
Disposition	<b>n (%)</b>	<b>n (%)</b>	<b>N (%)</b>
Randomized	938	951	164
Safety Population	923	949	163
Completed	475 (51%)	662 (70%)	127 (77%)
Premature Discontinuation	463 (50%)	289 (30%)	37 (23%)
Withdrawal of Consent	218 (23)	166 (18)	18 (11)
Adverse Event	104 (11)	9 (1)	0
Respiratory AE			
Investigator Decision	15 (2)	2 (0.2)	1 (0.6)
Lost-to-follow-up	56 (6)	80 (8.4)	5 (3.0)
Protocol Violation	34 (4)	9 (1)	5 (3)
Subject died	4 (0.4)	3 (0.3)	0
Other	29 (3)	18 (2)	8 (5)

Source table: Table 5, Page 72, MKC-TI-030 CSR, Module 5.

**2. Baseline Characteristics** (Section 10.4.1, p. 75, Table 7)

At Baseline, the TI and UC treatment groups were similar with respect to age, gender, race, weight, BMI, HbA1c (%), duration of diabetes and history of smoking. In the Safety Population, both the TI and UC treatment groups consisted of approximately 60% males and 40% females, with a mean age of 50 years, and with 70% of subjects having type 2 diabetes. In both the TI and UC groups, mean baseline HbA1c was 8.7%, duration of diabetes was 12 years and 30% of subjects were past smokers. As expected, there were differences between diabetic and non-diabetic subjects. The group of non-diabetic subjects had fewer males than females, were younger, weighed less and had a smaller BMI than diabetic subjects. The pre-bronchodilator FEV<sub>1</sub> was 50 mL less in the TI group compared to the UC group (3.24L vs. 3.29 L). As expected, FEV<sub>1</sub> at Screening was larger in the non-diabetic group than either the TI or UC group.

**3. Extent of Exposure** (Section 10.6, p. 82, Tables 14 and 15)

The mean exposure time to TI was 14.3 months. Only 52% of subjects in the TI group were exposed to TI for > 21 months (trial duration was 2 years). Overall, the exposure duration was comparable between Type 1 and Type 2 diabetes. Type 2 diabetics had a slightly higher mean daily dose (141 U vs. 138 U) when compared with Type 1 diabetics. The mean daily dose of TI increased over time, with the largest increase occurring in the first 3-6 months, and was comparable in subjects with type 1 or type 2 diabetes.

**4. Deaths and SAEs** (Section 12.5.1 and Section 12.5.2, p. 139, Table 37-39)

A total of 7 subjects died during the course of the study, 4 in the TI group and 3 in the usual care group. None of these deaths were due to pulmonary causes. SAEs were reported with similar frequency in the two treatment groups (TI: 10%, UC: 9.6%). Of the SAEs reported, pneumonia (n = 6) and pulmonary tuberculosis (n = 2) were the only SAEs referable to the respiratory tract,

and these occurred either equally or more frequently in the usual care group. There were no pulmonary malignancies.

**5. Discontinuation due to AEs** (Section 12.5.3, p. 145, Table 40)

A larger percentage of subjects discontinued because of AEs in the TI group (104, 11%) than the UC group (9, 1%). The most common reason for discontinuation in the TI group was cough in 43 subjects (5%), which accounted for 41% (43/104) of the discontinuation due to AEs in the TI group. Discontinuation from the trial secondary to AEs was driven largely by respiratory AEs, which accounted for 60% of the discontinuations. The pulmonary events leading to discontinuation were located in the infections and infestations, investigations, and respiratory SOCs as outlined in Table 72 below.

<b>Table 72: AEs Leading to Discontinuation by SOC and PT For Safety Population – Study MKC-030</b>		
	<b>TI n (%)</b>	<b>UC n (%)</b>
Any AE leading to DC	104	9
<b>Infections and Infestations</b>		
Bronchitis	2 (2)	0
Pulmonary tuberculosis	1 (1)	1 (1)
Upper respiratory infection	3 (3)	0
<b>Investigations</b>		
Pulmonary function test ↓	2 (2)	0
<b>Respiratory/Thoracic</b>		
Cough	43 (41)	0
Dyspnea	6 (6)	0
Congestion	3 (3)	0
Throat irritation	2 (2)	0
Source: Table 40, p.147, MKC-TI-030 CSR, Module 5.3.5.		
Note: % denoted is a percent of AEs, not of the total population in that treatment group.		

**6. Respiratory Adverse Events** (Section 12.4.2.1, p. 132, Table 34)

Respiratory adverse events were reported slightly more frequently in the TI group as compared to the control group (79% vs. 71%). The incidence of respiratory AEs was higher in the TI group than in the control group (37% vs. 9%, respectively). The most frequently reported respiratory AE was cough, in 28% of TI-treated subjects, followed by pharyngolaryngeal pain (3%), and throat irritation (2.5%). The pulmonary infections were relatively balanced between treatment and usual care groups as were the decrease in pulmonary function tests.

<b>Table 73: Summary of Most Frequently Reported (<math>\geq 1\%</math>) Respiratory Adverse Events by PT and SOC: Study MKC-TI-030</b>		
Preferred Term	TI (n = 923)	Usual Care (n = 949)
Total Subjects with AE	729 (79.0)	674 (71.0)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Cough	257 (27.8)	42 (4.4)
Pharyngolaryngeal pain	25 (2.7)	5 (0.5)
Throat irritation	23 (2.5)	1 (0.1)
Productive cough	19 (2.1)	14 (1.5)
Dyspnea	18 (2.0)	3 (0.3)
Nasal congestion	9 (1.0)	5 (0.5)
<b>Infections and Infestations</b>		
Upper respiratory tract infection	119 (12.9)	143 (15.1)
Nasopharyngitis	67 (7.3)	69 (7.3)
Influenza	38 (4.1)	41 (4.3)
Bronchitis acute	22 (2.4)	19 (2.0)
Sinusitis	21 (2.3)	23 (2.4)
Bronchitis	21 (2.3)	23 (2.4)
Viral Upper Respiratory Tract Infection	14 (1.5)	14 (1.5)
<b>Investigations</b>		
Pulmonary function test decreased	20 (2.2)	15 (1.6)
Source table: Table 34, Page 133, MKC-TI-030 CSR, Module 5.		

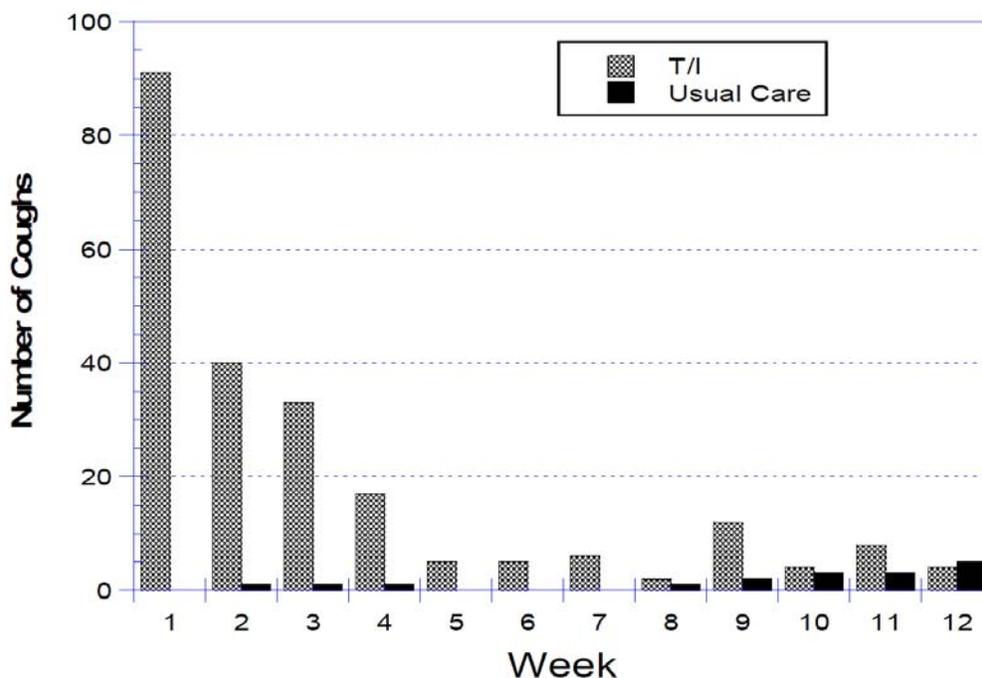
**a) Cough** (Section 12.7, p. 168 and Table 64)

Of the 923 subjects in the TI group, 28% reported at least 1 coughing episode, whereas only 5% of usual care patients reported cough. The majority of the coughing episodes were described as intermittent (53%) followed by single-defined (39%). Eight percent of subjects experienced continuous coughing. Most coughing (80%) occurred within 10 minutes of drug inhalation, and was not sputum producing. The majority of subjects reported only one episode of cough.

Overall, the percentage of subjects with new onset of cough was highest (20%) during the first 3 months, predominantly during the first 4 weeks after initiation of TI therapy. After the first 3 months, the onset of new cough declined rapidly over time. The percentage of subjects with new onset and existing coughs in the TI group was 20% during months 0-3 and declined over time to 10.1% in Months 21 to 24. Similar to cough incidence, both the number of coughs and cough decreased over time, with the greatest frequency occurring during the first three weeks of treatment, which then subsequently decreased to very low levels by week 12.

*Reviewer's comment: Similar findings were seen in the other pivotal studies.*

**Figure 36 Mean Frequency of Cough By Week – Study MKC-TI-030**



Source Figure: Figure 35, Page 169, MKC-TI-030 CSR, Module 5.

**7. Pulmonary Function Tests (Section 12.2.1, p. 89)**

PFTs were performed according to current American Thoracic Society guidelines before the first administration of trial medications. PFTs were performed at Screening, and Months 3, 6, 12, 18, and 24.

**A) Forced Expiratory Volume in 1 second (FEV1)**

FEV1 Change from Baseline to Month 24

The pre-specified analysis was a mixed model repeated measure analysis (MMRM) to examine the change in FEV1 from Baseline to Month 24 (in terms of the least square mean treatment difference). The Applicant used an MMRM model for a non-inferiority analysis; in this analysis, if the upper limit of the model adjusted 95% CI for the treatment difference (UC-TI) in annualized change was less than 50 mL per year (100 ml for 2 years), this would demonstrate that the TI group was non-inferior to the UC group. Per the sponsor’s analysis, the observed LS mean treatment difference (UC-TI) in change in FEV1 from Baseline to Month 24 was 0.037L, thereby demonstrating that the TI group was non-inferior to the UC group (See Table 74). The Sponsor also performed an ANCOVA with the data, and achieved similar results.

**Table 74: MMRM Model for FEV1 (L): Non-Inferiority Analysis, Change from Baseline to Month 24 for All Subjects and by Type and type 2 Diabetes (ITT Population) – Study MKC-TI-030**

	Difference in LSM (SE) Usual Care – TI	95% CI
All subjects with diabetes	0.037 (0.012)	(0.014, 0.060)
Type 1 DM	0.045 (0.022)	(0.002, 0.088)
Type 2 DM	0.037 (0.0142)	(0.009, 0.064)

Source: Table 19, P. 89, MKC-TI-030 CSR, Module 5.

Annual Rate of Change in FEV1 Between 3 and 24 Months

The Applicant also analyzed the annual rate of change (slope) in FEV1 in the TI and UC groups between 3 months (first post-baseline measurement) and 24 months (final study assessment). The slope was estimated using a random effect model. Based on these estimates, treatment group difference along with 95% CI for the difference was calculated.

After the initial slightly greater decline in the first 3 months, the annualized change in FEV1 was not statistically different in subjects treated with TI and UC between 3 and 24 months (See Table 75).

*Reviewer’s comment: In other studies that were greater than 12 weeks in duration, the same effect was noted on FEV1. There was an initial decline and then a leveling out. The mechanism of this is unclear, but the change does appear to be non-progressive.*

*Reviewer’s comment: The Applicant does not present any analysis or comparison of treatment groups during the first 3 months. The Agency’s biometrics reviewer, Joy Mele, will be looking at this issue.*

**Table 75: Mean Annual Rate of Change in FEV1 (L/year) Over 24 months and Between Month 3 and Month 24 (ITT Population) – Study MKC-TI-030**

	Mean Annual Rate of Change Over 24 Months		Mean Annual Rate of Change Between Months 3 and Month 24	
	Mean ± SEM	95% CI	Mean ± SEM	95% CI
TI	-0.073 ± 0.005		-0.047 ± 0.005	
UC	-0.054 ± 0.004		-0.036 ± 0.004	
Non-diabetics	-0.037 ± 0.009		-0.024 ± 0.010	
UC-TI	0.021 ± 0.006	0.010, 0.033	0.010 ± 0.006	-0.003, 0.022

Source: Table 21, p. 91, MKC-TI-030 CSR, Module 5.

Decrease in FEV1 ≥ 15% from Baseline to End of Trial

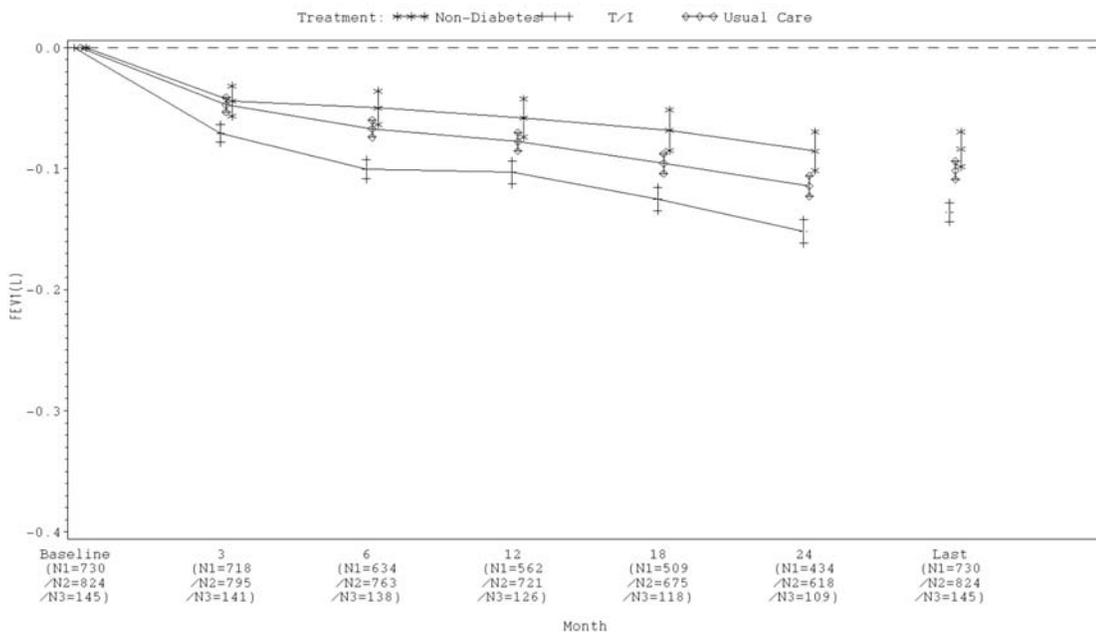
The Applicant performed a non-inferiority analysis comparing TI to UC in terms of the proportion of subjects with a decrease of ≥15% in FEV1 from Baseline to end of trial. When

looking at all subjects in the ITT population, 5.8% in the TI group had a  $\geq 15\%$  decline in FEV1 over the course of the trial compared to 3.3% in the UC group. This met the Sponsor’s pre-specified definition for non-inferiority. However, when the groups were broken down into Type 1 and Type 2 DM, Type 1 DM had a statistically greater number of subjects with  $\geq 15\%$  decline in FEV1 (5.5% TI vs. 0.8% UC). The analysis results for Type 2 diabetics was similar to that for all subjects.

Absolute Change in FEV1 Over Time

The mean change in FEV1 over time in the TI, UC, and non-diabetes groups is displayed for the ITT Population in Figure 37. Changes from Baseline in FEV1 for the subset of subjects with type 1 and type 2 diabetes are presented Figure 38 and Figure 39, respectively.

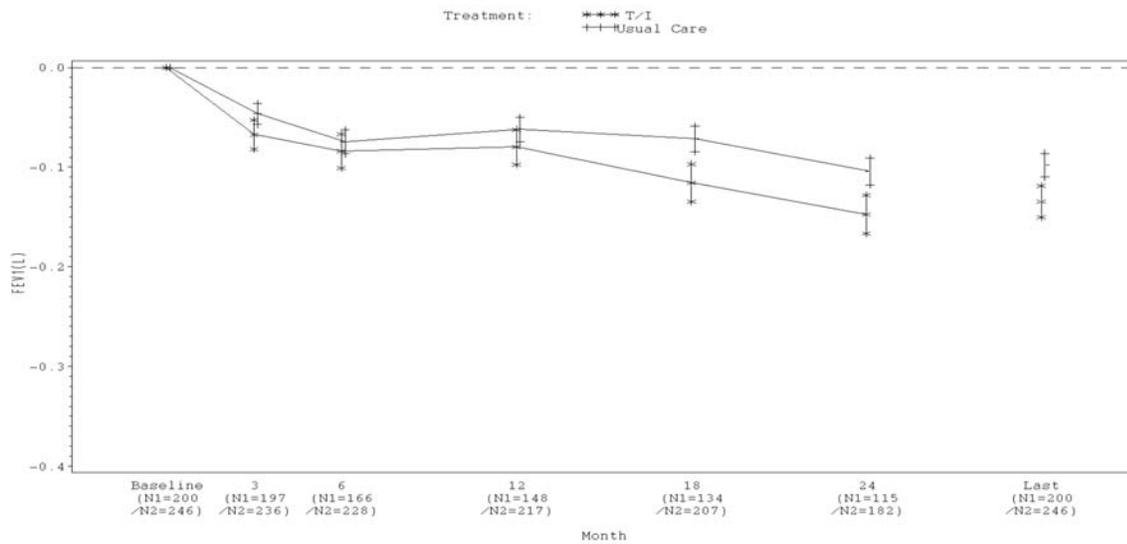
**Figure 37 Mean (SE) Change from Baseline in FEV1 (L) by Time Point in the TI, UC, and Non-Diabetes Groups (ITT Population) – Study MKC-TI-030**



N1 = TI group; N2 = UC group; and N3 = Non-diabetes group; Last = Last FEV<sub>1</sub> measurement.

Source: Figure 3, p. 95, MKC-TI-030 CSR, Module 5.

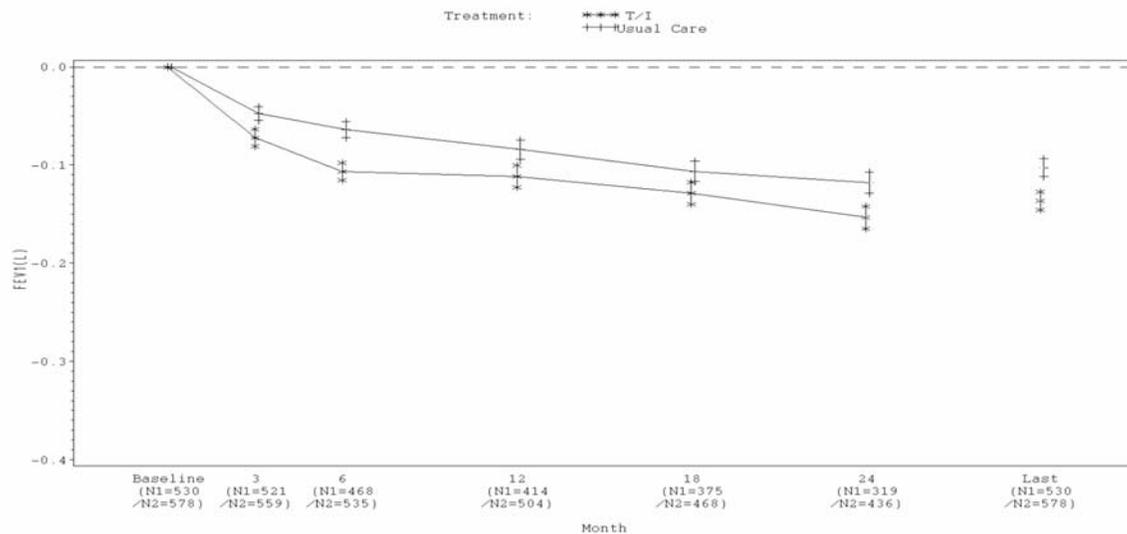
**Figure 38 Mean (SE) Change from Baseline in FEV1 (L) by Time Point in the TI and UC groups in Subjects with Type 1 DM (ITT Population) – Study MKC-TI-030**



N1 = TI group; N2 = UC group; Last = Last FEV<sub>1</sub> measurement.

Source: Figure 4, p. 95, MKC-TI-030 CSR, Module 5.

**Figure 39 Mean (SE) Change from Baseline in FEV1 (L) by Time Point in the TI and UC groups in Subjects with Type 2 DM (ITT Population) – Study MKC-TI-030**



N1 = TI group; N2 = UC group; Last = Last FEV<sub>1</sub> measurement.

Source: Figure 5, p. 96, MKC-TI-030 CSR, Module 5.

FEV1 declined in all subjects over time, more in the diabetic patients than in those without diabetes. There was a decline in FEV1 over time in both the TI and the UC groups, although the decline in the TI group is graphically larger than that in the UC group. However, numerically, the difference between groups is quite small. The overall trend is similar in subjects with type 1 and type 2 diabetes.

**B) DLCO** (p.103, MKC-TI-030 CSR)

DLco Change from Baseline to Month 24

Similar to FEV1, a MMRM model with a non-inferiority analysis was used. At the end of 2 years of treatment, the adjusted difference using this MMRM model, per the Applicant’s analysis, was 0.27 mL/min/mm Hg for DLco. The difference was small and not statistically significant.

Annual Rate of Change in DLco Between 3 and 24 Months

The Applicant also analyzed the annual rate of change (slope) in DLco in the TI and UC groups between 3 months (first post-baseline measurement) and 24 months (final study assessment). The slope was estimated using a random effect model. Based on these estimates, treatment group difference along with 95% CI for the difference was calculated.

After the initial slightly greater decline in the first 3 months, the annualized change in DLCO was not statistically different in subjects treated with TI and UC between 3 and 24 months (See Table 76).

*Reviewer’s comment: In other studies that were greater than 12 weeks in duration, the same effect was noted on DLco. There was an initial decline and then a leveling out. The mechanism of this is unclear, but the change does appear to be non-progressive.*

*Reviewer’s comment: The Applicant does not present any analysis or comparison of treatment groups during the first 3 months. The Agency’s biometrics reviewer, Joy Mele, will be looking at this issue.*

<b>Table 76: Mean Annual Rate of Change in DLco (mL/min/mmHg) Over 24 months and Between Month 3 and Month 24 (ITT Population) – Study MKC-TI-030</b>				
	<b>Mean Annual Rate of Change Over 24 Months</b>		<b>Mean Annual Rate of Change Between Months 3 and Month 24</b>	
	Mean ± SEM	95% CI	Mean ± SEM	95% CI
<b>TI</b>	-0.787 ± 0.062		-0.507 ± 0.067	
<b>UC</b>	-0.672 ± 0.050		-0.455 ± 0.055	
<b>Non-diabetics</b>	-0.608 ± 0.127		-0.466 ± 0.139	
<b>UC-TI</b>	0.167 ± 0.082	0.007, 0.327	0.117 ± 0.089	-0.058, 0.292

Source: Table 24, p. 106, MKC-TI-030 CSR, Module 5.

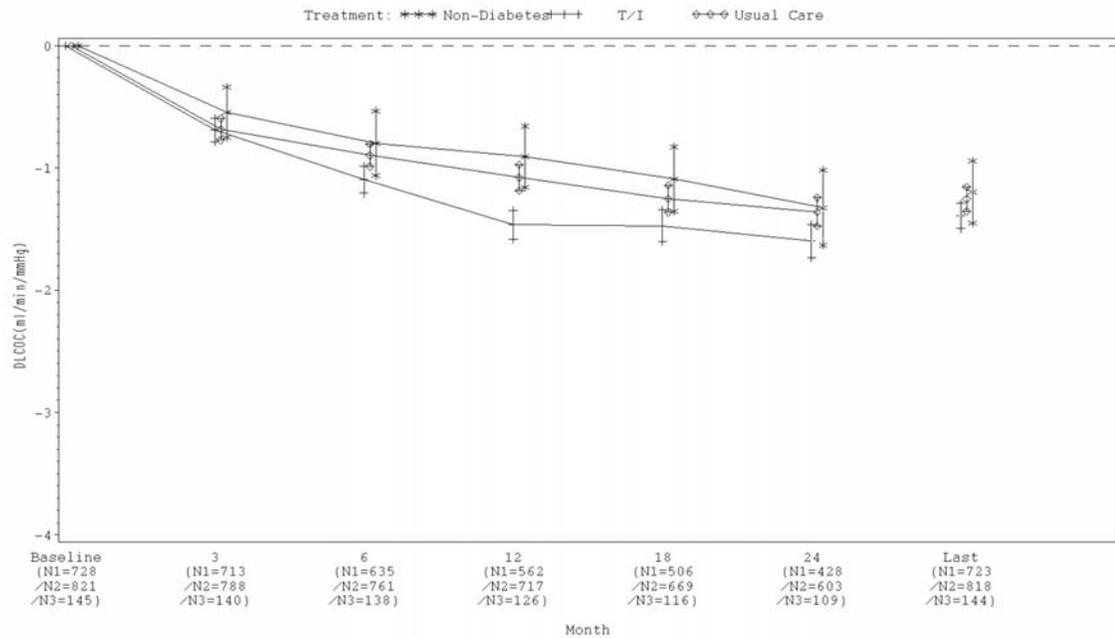
Decrease in DLco  $\geq$  15% from Baseline to End of Trial

The proportion of subjects with a decrease in DLco of  $\geq$  15% from Baseline to Last Measurement was slightly larger in the TI than in the UC group, and was similar in diabetics and non-diabetics.

Absolute Change in DLCO Over Time

The mean change in DLco over time in the TI, UC, and non-diabetes groups is displayed for the ITT Population in Figure 40. Changes from Baseline in DLco for the subset of subjects with type 1 and type 2 diabetes are presented in Figure 41 and Figure 42.

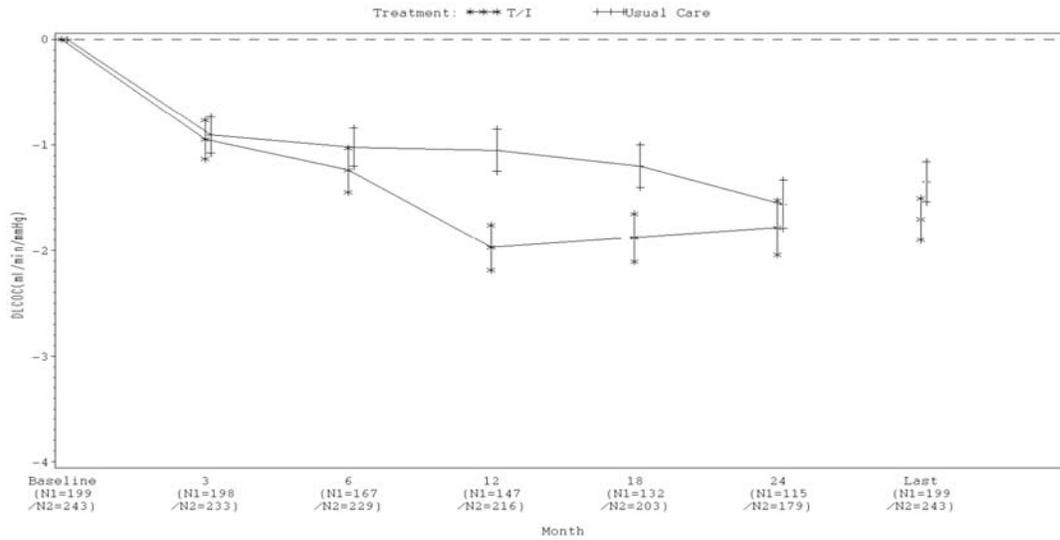
**Figure 40 Mean (SE) Change from Baseline in DLCO by Time Point in the TI, UC, and Non-Diabetes Groups (ITT Population) – Study MKC-TI-030**



N1 = TI group; N2 = UC group; and N3 = Non-diabetes group; Last = Last DLco measurement

Source: Figure 15, p. 104, MKC-TI-030 CSR, Module 5.

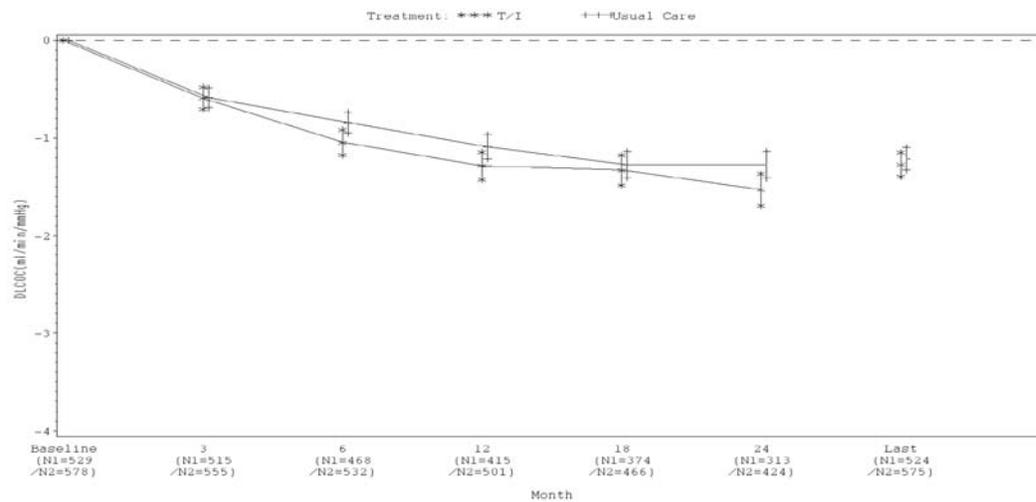
**Figure 41 Mean (SE) Change from Baseline in DLco by Time Point in the TI and UC groups in Subjects with Type 1 DM (ITT Population) – Study MKC-TI-030**



N1 = TI group; N2 = UC group.

Source: Figure 16, p. 105, MKC-TI-030 CSR, Module 5.

**Figure 42 Mean (SE) Change from Baseline in FEV1 (L) by Time Point in the TI and UC groups in Subjects with Type 1 DM (ITT Population) – Study MKC-TI-030**



N1 = TI group; N2 = UC group; Last = Last DLco measurement.

Source: Figure 17, 105, MKC-TI-030 CSR, Module 5.

DLco declined in all subjects over time, more in the diabetic patients than in those without diabetes. The differences between groups were small.

**8. Chest X-Rays and HRCT** (Section 12.9.5, p. 181)

Chest X-rays were performed at Screening, Month 12, Month 24, and Early Termination. Shifts from baseline to last measurement were similar in the 2 treatment groups. At least measurement, 7 subjects (1.2%) in the TI group and 6 subjects (0.9%) in the usual care group had abnormal clinically significant chest x-rays. In review of the line listings, the majority of these clinically significant abnormalities were bony abnormalities of the spine.

A total of 127 subjects were also evaluated with HRCT, 55 subjects in the TI group and 72 subjects in the usual care group. Of the total number of patients who had an HRCT, 10 subjects demonstrated clinically significant abnormalities, 7 in the TI group and 3 in the usual care group. This is summarized in Table 77.

<b>Table 77: HRCTs in Trial MKC-TI-030</b>		
	<b>TI</b>	<b>Usual Care</b>
<b>HRCT (#)</b>	55	72
Normal thru 24 months	10 (18.2)	14 (19.4)
Abnormal, not clinically significant	38 (69.1)	55 (76.4)
Abnormal, clinically significant	7 (12.7)	3 (4.2)

Review of the 7 abnormal CT reports in the TI group revealed that the 3 of the abnormal imaging studies were due to mosaic attenuation in patients who were former smokers, and this mosaic attenuation is consistent with air trapping. However, there were 4 patients with new, sub-centimeter nodules or ground glass opacities, that were not further characterized.

*Reviewer’s comment: These patients will need to be followed up and thus the need for longer term follow up to determine malignancy risk*

**9. Insulin Antibodies** (Section 12.10, p. 185)

Mean and median changes from Baseline to last measurement in insulin antibody levels were higher in the TI than in the UC group (Table 60). At last measurement, the median change from Baseline in insulin antibody level was 4.50 Kronus U/mL in the TI group and 1.80 Kronus U/mL in the UC group.

#### D. Conclusions

Study MKC-TI-030 was a prospective, 2-year, multicenter clinical trial that incorporated 2 design strategies: (a) a randomized, open-label clinical trial comparing treatment with TI Inhalation Powder to usual anti-diabetes treatment in subjects with diabetes (type 1 or type 2), and (b) an epidemiological or observational investigation comparing subjects with diabetes who received usual anti-diabetes treatments with subjects without abnormalities in glycemic control.

The clinical trial consisted of 7 clinical trial site assessment visits for all subjects during a 2 year period. A larger percentage of subjects discontinued because of AEs in the TI group (104, 11%) than the UC group (9, 1%). The most common reason for discontinuation in the TI group was cough in 43 subjects (5%), which accounted for 41% (43/104) of the discontinuation due to AEs in the TI group. Discontinuation from the trial secondary to AEs was driven largely by respiratory AEs, which accounted for 60% of the discontinuations.

compared to the control group (79% vs. 71%). The incidence of respiratory AEs was higher in the TI group than in the control group (37% vs. 9%, respectively). The most frequently reported respiratory AE was cough, in 28% of TI-treated subjects, followed by pharyngolaryngeal pain (3%), and throat irritation (2.5%). The pulmonary infections were relatively balanced between treatment and usual care groups as were the decrease in pulmonary function tests.

Of the 923 subjects in the TI group, 28% reported at least 1 coughing episode, whereas only 5% of usual care patients reported cough. The majority of the coughing episodes were described as intermittent (53%) followed by single-defined (39%). Eight percent of subjects experienced continuous coughing. Most coughing (80%) occurred within 10 minutes of drug inhalation, and was not sputum producing. The majority of subjects reported only one episode of cough.

Overall, the percentage of subjects with new onset of cough was highest (20%) during the first 3 months, predominantly during the first 4 weeks after initiation of TI therapy. After the first 3 months, the onset of new cough declined rapidly over time. The percentage of subjects with new onset and existing coughs in the TI group was 20% during months 0-3 and declined over time to 10.1% in Months 21 to 24. Similar to cough incidence, both the number of coughs and cough decreased over time, with the greatest frequency occurring during the first three weeks of treatment, which then subsequently decreased to very low levels by week 12.

For FEV1, the pre-specified analysis was a mixed model repeated measure analysis (MMRM) to examine the change in FEV1 from Baseline to Month 24 (in terms of the least square mean treatment difference). The Applicant used an MMRM model for a non-inferiority analysis; in this analysis, if the upper limit of the model adjusted 95% CI for the treatment difference (UC-TI) in annualized change was less than 50 mL per year (100 ml for 2 years), this would demonstrate that the TI group was non-inferior to the UC group. Per the sponsor's analysis, the observed LS mean treatment difference (UC-TI) in change in FEV1 from Baseline to Month 24 was 0.037L, thereby demonstrating that the TI group was non-inferior to the UC group.

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For DLCO, similar to FEV<sub>1</sub>, a MMRM model with a non-inferiority analysis was used. At the end of 2 years of treatment, the adjusted difference using this MMRM model, per the Applicant's analysis, was 0.27 mL/min/mm Hg for DLco. The difference was small and not statistically significant per the sponsor's analysis.

Chest X-rays were performed at Screening, Month 12, Month 24, and Early Termination. Shifts from baseline to last measurement were similar in the 2 treatment groups. At least measurement, 7 subjects (1.2%) in the TI group and 6 subjects (0.9%) in the usual care group had abnormal clinically significant chest x-rays. In review of the line listings, the majority of these clinically significant abnormalities were bony abnormalities of the spine. A total of 127 subjects were also evaluated with HRCT, 55 subjects in the TI group and 72 subjects in the usual care group. Of the total number of patients who had an HRCT, 10 subjects demonstrated clinically significant abnormalities, 7 in the TI group and 3 in the usual care group. Review of the 7 abnormal CT reports in the TI group revealed that the 3 of the abnormal imaging studies were due to mosaic attenuation in patients who were former smokers, and this mosaic attenuation is consistent with air trapping. However, there were 4 patients with new, sub-centimeter nodules or ground glass opacities, that were not further characterized.

## 7 References

1. Anthonisen NR, Connett JE, et al. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med* 2002; Vol 166: 675-679.
2. Lange P, Parner J et al. A 15 year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339: 1194-1200.
3. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343:1902-9.
4. Lange P, Parner J, Schnohr P, Jensen G. Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and non-diabetic adults. *Eur Respir J* 2002; 20: 1406-12.
5. Litonjua AA, Lazarus R, Sparrow D, Demolles D, Weiss ST: Lung function in type 2 diabetes: The Normative Aging Study. *Resp Med* 2005; 99: 1583-90.
6. Davis WA, Knuiman M, Kendall P, Grange V, Davis TME. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: The Fremantle Study. *Diabetes Care* 2004; 27: 752-37.
7. Yeh HC, Punjabi NM, Wang NY, Pankow JA, et al. Cross Sectional and prospective study of lung function in adults with type 2 diabetes: Atherosclerosis Risk in Communities Study. *Diabetes Care* 2008; 31: 741-6.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	INSULIN HUMAN (RDNA ORIG)INH POWDER

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BANU A KARIMI SHAH  
12/28/2009

SALLY M SEYMOUR  
12/28/2009

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 22,472  
Priority or Standard S

Submit Date(s) 16 March 2009  
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Reviewer Name(s) Lisa B. Yanoff, M.D.  
Review Completion Date 24 December 2009

Established Name Technosphere insulin  
(Proposed) Trade Name Afrezza  
Therapeutic Class Inhaled insulin  
Applicant MannKind

Formulation(s) Inhalation powder (pre-metered)  
Dosing Regimen Dose-titrated premeal inhalation  
Indication(s) The treatment of adults with type  
1 or type 2 diabetes mellitus for  
the control of hyperglycemia.  
Intended Population(s) Adult Type 1 and Type 1  
Diabetics

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## **1 Recommendations/Risk Benefit Assessment**

This document contains the clinical efficacy and general clinical safety review for Technosphere Insulin Inhalation Powder (Afrezza). The pulmonary clinical safety review for Afrezza is contained in a separate document prepared by Dr. Banu Karimi-Shah which is not yet finalized at the time of this review. Therefore, recommendations on regulatory action and risk benefit assessment are based on the clinical efficacy and general clinical safety review alone, and contain only a high-level consideration of pulmonary findings which have been discussed during internal meetings within the Division. For a comprehensive risk/benefit analysis that incorporates all known efficacy and safety information the reader is referred to the cross discipline team leader memo prepared by Dr. Hylton Joffe.

### **1.1 Recommendation on Regulatory Action**

Based on my review of clinical efficacy and non-pulmonary safety, I recommend approval of Afrezza for the treatment of Type 1 and Type 2 diabetes in adults.

The dosing regimen proposed by the Sponsor is also adequate based on my review of clinical efficacy and non-pulmonary safety. As discussed in this review, while titration of Afrezza was generally inadequate across clinical trials, in my opinion this was due to failure of investigators to titrate to glycemic goals rather than due to a systematic problem with dosing guidelines.

### **1.2 Risk Benefit Assessment**

For Type 2 diabetic patients there is clear evidence of efficacy of Afrezza compared with placebo which, along with clinical pharmacology trials, provides evidence that Afrezza is functioning as exogenous insulin. Afrezza plus a long-acting injected insulin is also non-inferior to twice-daily injected premixed insulin analogue therapy (Novolog 70/30) and, in combination with the oral antidiabetic drug metformin is non-inferior to the combination of metformin and an oral secretagogue. Afrezza plus a long-acting injected insulin is inferior to the combination of a short-acting injected insulin plus a long-acting injected insulin (called basal/bolus injected therapy). However, the finding of inferiority of Afrezza versus basal/bolus injected therapy in Type 2 diabetes patients should not preclude approval of Afrezza because, with its novel route of delivery, Afrezza should not be required to be as good as the most effective injected insulin therapy available, but instead should be required to show at least substantial benefit without

excess risk. For Type 2 diabetics, Afrezza appears to meet this requirement based on the findings of this clinical review. For Type 2 diabetic subjects the potential benefits of Afrezza outweigh the risks, which from a non-pulmonary standpoint appear to be minimal. Based on data from the clinical development program there does not appear to be an excess risk of lung malignancy (this finding applies to both Type 2 patients and Type 1 patients who are discussed in the following paragraphs) associated with Afrezza use although due to limitations to the program, this will need to be evaluated further in post marketing studies. In addition, Afrezza has the added benefit of a reduced risk of severe hypoglycemia versus premixed twice-daily injected insulin. Among Type 2 patients a common scenario is one in which a patient has failed oral therapy and has been recommended to initiate insulin therapy, but has been reluctant to do so, in part, because of the injections required. Afrezza could provide an alternative more personally acceptable therapy for this type of patient.

For Type 1 diabetic patients, the risk benefit assessment is more challenging. For Type 1 patients, there was only one confirmatory efficacy trial. In this trial, Afrezza was inferior to a standard-of-care intensive insulin regimen which consisted of basal/bolus subcutaneous insulin therapy. Drawing conclusions about efficacy of Afrezza for Type 1 diabetic patients should not be based strictly on statistical criteria, but instead should take clinical context into account. The clinical trial results should be interpreted in light of the natural history of Type 1 diabetes in which patients do not produce their own insulin and without exogenous insulin could quickly deteriorate and develop diabetic ketoacidosis. Because of the well-characterized natural history of Type 1 diabetes, single-arm clinical trials have sometimes historically been utilized to establish efficacy of insulin therapies in this population. The finding that in the pivotal one-year efficacy trial for Type 1 diabetes, a large proportion of patients treated with Afrezza were able to avoid deterioration in glycemic control over one year (based on HbA1c) is evidence alone of the efficacy of Afrezza in the Type 1 population. In the review of general safety, the major non-pulmonary risk associated with Afrezza use among Type 1 patients was the “risk” of inferior efficacy compared with an intensive injected insulin regimen. Type 1 diabetic patients in the Afrezza clinical development program demonstrated a higher discontinuation rate in the individual clinical trials due to reasons related to lack of efficacy and an overall higher rate of diabetic ketoacidosis in safety analyses. These risks are important, and in the case of diabetic ketoacidosis, serious, because diabetic ketoacidosis requires hospitalization and can result in death if not appropriately treated. However, the risk of diabetic ketoacidosis in Type 1 diabetic patients observed in the Afrezza clinical development program appeared to be consistent with historical controls and all subjects recovered from the diabetic ketoacidosis without sequelae, and in most cases continued Afrezza therapy without further incident. The risk of severe hypoglycemia with Afrezza appears to be no higher than the risk of severe hypoglycemia with intensive basal/bolus insulin regimens.

The findings with Afrezza in patients with type 1 diabetes are consistent with the findings in patients with type 2 diabetes – in both populations, Afrezza is not as good as basal-bolus therapy. However, as explained above, there is evidence of some efficacy for Afrezza even in patients with type 1 diabetes, such that it should be available as an appropriate treatment option in selected patients with type 1 diabetes. There is no known physiological reason why Afrezza would have efficacy in patients with type 2 diabetes but not in patients with type 1 diabetes,

particularly because patients with type 1 diabetes tend to be less insulin-resistant and therefore, require less insulin than patients with type 2 diabetes.

Therefore, my recommendation for approval in Type 1 patients, is based on the provision that labeling will be sufficient to inform patients that Afrezza is not effective for all Type 1 diabetic patients, is less effective than injected basal/bolus therapy, that patients should be carefully selected for Afrezza therapy, and that patients should be carefully monitored early and often when initiating Afrezza therapy and should switch back to injected insulin therapy if the desired glycemic control is not achieved or in settings when Afrezza would not be appropriate (e.g., infections). I agree with the Sponsor's proposed labeling that Afrezza should not be used for the treatment of diabetic ketoacidosis. I also further recommend that Afrezza should not be used as first line therapy in Type 1 diabetic patients as there are no clinical data supporting the use of Afrezza in this clinical scenario (Type 1 patients in the clinical development program were studied in a "switch" scenario in which Afrezza was substituted for patients' injected insulin therapy), and because the degree of efficacy demonstrated among Type 1 patients is not strong enough to extrapolate efficacy for Type 1 patients who are new to insulin. All newly diagnosed Type 1 diabetic patients should first be treated with injected insulin therapy to attain adequate glycemic control and only then, when they have a "grasp" on their disease, should selected patients be given the choice to try inhaled insulin therapy.

My recommendation is based on the position that, given an alternative therapy with a different risk benefit profile (even if "benefit" may be other than glycemic control, i.e. the alternative route of administration may be the "benefit") than that of available therapies, patients should be given a choice as long as there are no major safety concerns that may preclude that choice. Afrezza has the unique benefit of being the only alternative route of insulin therapy that, if approved, would be marketed. Alternative routes of insulin therapy have often been dubbed the "holy grail" of diabetes therapy. Although the efficacy of Afrezza is clearly not as strong as that of "intensive" subcutaneous insulin, for some patients, Afrezza appears to offer the benefit of glycemic control without undesirable injection therapy.

Interpretation of the phase 3 studies was complicated by relatively poor titration of insulins (both Afrezza and comparators) across trials with low percentages of patients reaching glycemic goals, leading to difficulty in determining how efficacious Afrezza would be if optimally titrated. In addition, the maximum recommended dose of Afrezza by the Sponsor is 90 units with each administration based on clinical pharmacology findings. However, in the clinical development program, titration to goal was poor and few patients were exposed to more than 240 units per day for at least 1 year. Because this product is an insulin, and the primary concern of higher doses of insulin are related to hypoglycemia for which the risk is individually managed by patients and clinicians, the major remaining safety concern would be related to the pulmonary route of administration. Based on preliminary comments from the pulmonary reviewer there was not an increased risk of pulmonary adverse events with higher exposures to Afrezza. However, the pulmonary safety review findings will need to be taken into consideration when determining the maximum recommended dose.

### 1.3 Recommendations for Postmarket Risk Management Activities

The clinical reviewer recommends comprehensive postmarketing risk management activities focusing on ensuring the proper patient population receives Afrezza (i.e. non-smoking adults without lung disease). The clinical reviewer agrees with the general approach of the Sponsor's postmarketing risk management plan, and reviews from DRISK and DMEPA are ongoing at the time of this review to further hone the Sponsor's plan.

The Sponsor submitted a voluntary REMS to include a Medication Guide and communication plan, "Dear healthcare professional" letter, including Product Information and Dosing Guide, Patient Instruction Sheet, and Usage Guide. The Sponsor also proposed (b) (4)

[Redacted]

The Sponsor also proposed (b) (4):

[Redacted]

(b) (4)

The clinical reviewer recommends that this (b) (4) be evaluated by the Agency's OSE Epidemiology review team because the clinical reviewer recommends that evaluation of lung malignancy risk be a postmarketing requirement (PMR) and this proposal may not be adequate to study lung malignancy for the following reason: (b) (4)

(b) (4)

However, the clinical reviewer does not recommend a required cardiovascular safety PMR because, as stated, Afrezza is insulin, and also because there have been no concerning cardiovascular safety signals in the premarketing clinical development program.

#### **1.4 Recommendations for Postmarket Studies/Clinical Trials**

The Sponsor has the following ongoing trial to evaluate Afrezza in patients with chronic lung disease:

Protocol MKC-TI-134 entitled "A Phase 3, Multicenter, Open-label, Randomized Clinical Trial to Evaluate the Safety of Technosphere® Insulin Inhalation Powder in Type 1 or Type 2 Diabetic Subjects With Mild Obstructive Pulmonary Disease Over a 12-month Treatment Period with a 3-Month Follow-up".

Completion of this trial is recommended as a post marketing requirement. At the time of the 120-day safety update (31 May 2009), no subjects had been enrolled in this trial. The Sponsor suspended screening and enrollment in MKC-TI-134 on 29 May 2009 at the recommendation of the Data Safety Monitoring Board based on concerns from clinical pharmacology studies. The Sponsor plans to change the inclusion criteria for the protocol to enhance subject safety.

#### Pediatric Studies

Pediatric studies to comply with PREA requirements are to be performed.

The following communication was sent to the Sponsor following the PeRC meeting:

Pediatric Waiver Request for ages 0 (b) (4)

Please decrease the upper age limit of the waiver request to 3 years 11 months. We will require pediatric studies in age 4 – 16 years 11 months. Your product should be aligned with subcutaneous insulins for which the Agency grants waivers for less than 4 years of age. You should assess feasibility of use of your product in this younger age group of children. If accrued data with your product show that children as low as 4 years of age cannot reliably use your product, this important information will be included in labeling and you will be released of the postmarketing requirement to study children in those younger age groups.

Pediatric Deferral Request for ages (b) (4) 17

Accordingly, please update the request to ages 4 – 16 years 11 months.

Pediatric Plan

Trial 143: Update protocol 143 to include children as young as 4 years of age. Please add another arm to your study for ages 4 – 5 such that the total number of subjects studied is increased by 12 to 15 subjects. The age group studied in your PK and efficacy/safety trials will still depend on the results of the feasibility study. However, we would like you to determine feasibility in a younger age group.



A written response was received from the Sponsor on 23 Dec 2009. The Sponsor has agreed to all requests made by the Agency and is in the process of updating protocols accordingly.

Other recommendations

- Study of the pulmonary safety of Afrezza in African American diabetics. African Americans have been described to have lower normative values for baseline lung function than those seen in Caucasian Americans and Mexican-Americans. Input from DPAP should be sought to determine whether pulmonary safety in African Americans was sufficiently studied in the premarketing clinical development program, and if not, to help propose an appropriate trial design for a PMR.
- Due to the high rate of insulin antibody formation seen in inhaled insulin group patients, the clinical reviewer recommends that the Sponsor also use the proposed epidemiologic

lung cancer study to gather data on allergic and immune disorders in inhaled insulin users.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

#### Product description

MannKind Corporation has developed a dry powder formulation of recombinant human insulin (called Technosphere insulin) designed to be delivered systemically via pulmonary inhalation with the MedTone Inhaler. The drug product is manufactured from recombinant human insulin and the proprietary excipient fumaryl diketopiperazine (FDKP). The Technosphere Insulin Inhalation Powder / MedTone Inhaler system includes single-use, pre-metered cartridges that are manually inserted into a re-useable, breath-powered, high resistance dry powder inhaler. The pre-metered powder is provided in two different fill weights: 5 mg and 10 mg, containing 15 U and 30 U, of insulin, respectively.

Note that the clinical trials reviewed in this document were conducted with the Model C MedTone inhaler, while the to-be-marketed version of the inhaler is the Model D. The difference between these two models is very slight and does not appear to be of concern; this issue is addressed by the chemistry, manufacturing and controls reviewer and the Center for Devices and Radiologic Health reviewer. The Sponsor is also developing a new, smaller and simpler inhaler device called the Gen2 inhaler that is intended to deliver Technosphere insulin (the same drug formulation that is intended for use with the MedTone inhaler) in a more patient friendly manner. There are no data with the Gen2 inhaler reviewed in this document.

#### Established name and proposed trade name

The established name of this product is Technosphere Insulin. The proposed trade name is Afrezza. This trade name has been approved by the Division of Medication Error Prevention and Analysis (DMEPA). The original proposed trade name, Afresa, was denied by DMEPA.

For the purposes of this review, Technosphere Insulin administered with the MedTone Inhaler is abbreviated "TI." In some placebo controlled studies in the clinical development program, Technosphere Inhalation Powder (without insulin) was administered as the placebo and for the purposes of this review is abbreviated "TP."

#### Chemical class

Recombinant human insulin

Pharmacologic class

Inhaled insulin. Afrezza is the second NDA for an inhaled insulin to be reviewed by the Agency. The first, Exubera (NDA 21,868) was approved by the Division of Metabolism and Endocrinology Products in January 2006. Exubera was subsequently withdrawn from the market for reported business reasons (see section 2.4).

Sponsor's proposed indication, dosing regimen, age group

The Sponsor proposes the following language for the "Indications and Usage" section of the product label:

[REDACTED] (b) (4)

The applicant's proposed dosing regimen is as follows:

AFREZZA is administered via oral inhalation using the AFREZZA Inhaler. AFREZZA should be administered at the beginning of a meal. In some patients, the total dose per meal may be split before and after the meal when using more than one cartridge. [REDACTED] (b) (4)

Insulin naïve patients should start on a 4 unit dose of AFREZZA at each meal [REDACTED] (b) (4)

**Reviewer's comment: the Sponsor has been instructed to update the numbering of Afrezza units to reflect the actual units of insulin in the cartridge not the units of equivalent subcutaneous insulin. Therefore, the label should actually state "[REDACTED] (b) (4) [REDACTED] In addition, the label should state that [REDACTED] (b) (4) are needed for each cartridge.**

For patients transitioning from insulin regimens that include short acting and / or longer or intermediate acting insulin, the starting dose of AFREZZA should be based on their total daily subcutaneous insulin dose. Patients should replace 50% of the total daily insulin dose with a corresponding dose of AFREZZA divided between main meals. Additional doses may be taken to accommodate additional meals. The remaining 50% of the total dose of subcutaneous insulin should be given as longer acting insulin.

(b) (4)

After initiating AFREZZA therapy, as with other glucose-lowering agents, dose adjustment may be required based on the patient's needs. Each patient should be titrated to their optimal dose, which is typically between 4 and 24 units at mealtimes.

The proposed age group, as stated in "indications and usage" is adults.

## **2.2 Tables of Currently Available Treatments for Proposed Indications**

Patients with type 2 diabetes (T2DM) often undergo an initial trial of diet and exercise. If control is inadequate, a variety of oral agents is available (Table 2.1). If adequate blood glucose control is not achieved with oral agents, subcutaneous insulin is often used.

**Table 2.1. Currently approved pharmacologic therapies for type 2 diabetes mellitus**

Drug Class	Examples	Mechanism of action	Expected decrease in HbA1c (%)*	Pros	Cons
Biguanides	Metformin	Decreases hepatic glucose production Increases insulin sensitivity	1.5	Weight neutral Inexpensive Low risk of hypoglycemia	GI side effects Rare lactic acidosis Contraindicated in renal failure
Sulfonylureas	Glimepiride Glyburide Glipizide	Insulin secretagogue	1.5	Inexpensive	Hypoglycemia Weight gain
Thiazolidinediones	Rosiglitazone Pioglitazone	Increases insulin sensitivity	0.5-1.4	Lower risk of hypoglycemia	Fluid retention Weight gain Contraindicated in heart failure Expensive
Insulin	Lispro NPH insulin Glargine	Stimulates glucose uptake in muscle and adipose tissues	1.5-2.5	No dose limit Improved lipid profile	Injections Frequent monitoring Hypoglycemia Weight gain
Alpha-glucosidase inhibitors	Acarbose Miglitol	Slows GI absorption of carbohydrates	0.5-0.8	Weight neutral	Frequent GI side effects Three times/day dosing Expensive
Meglitinides	Repaglinide Nateglinide	Insulin secretagogue	1-1.5	Short duration	Three times/day dosing Expensive
Amylin analogues	Pramlintide	Slows gastric emptying Suppresses glucagon secretion Promotes satiety Decreases appetite	0.5-1.0	Weight loss	Three times/day dosing Frequent GI side effects Expensive Limited clinical experience
GLP-1 analogues	Exenatide	Stimulates glucose-dependent insulin release Slows gastric emptying Inhibits glucagon secretion Reduces food intake	0.5-1.0	Weight loss Theoretically lower risk of hypoglycemia	Frequent GI side effects Expensive Limited clinical experience Pancreatitis
DPP-IV inhibitors	Sitagliptin Saxagliptin	Inhibits the enzyme DPP-IV prolonging the action of endogenous GLP-1 and GIP	0.5-0.8	Weight neutral Lower risk of hypoglycemia	Limited clinical experience Expensive Hypersensitivity reactions
Bile acid sequestrant	Colesevelam	Unknown	0.4-0.8	Favorable lipid effects	Frequent GI side effects
Dopamine agonist	Bromocriptine	Unknown	0.4-0.6	Weight neutral Minimal hypoglycemia	Gastrointestinal side effects

\* Expected decrease in HbA1c is not placebo-corrected. Note: Part of the extent of reduction depends on the patient characteristics – e.g., baseline HbA1c etc.

GI = gastrointestinal; GLP-1 = glucagon-like peptide-1, DPP-IV = Dipeptidyl peptidase 4, GIP = glucose-dependent insulinotropic polypeptide

Source: Adapted from Stumvoll et al. (2005), Nathan et al. (2008), Cycloset prescribing information, and WelChol prescribing information

Type 1 diabetes (T1DM) is currently treated almost exclusively with subcutaneously administered insulin, which is available in a variety of formulations and analogs, with a spectrum of time-action profiles. Because Type 1 diabetics have virtually no residual pancreatic islet beta cell function, these patients have an absolute requirement for administered insulin for survival, and cannot be managed with diet and exercise alone. Patients generally receive one or two subcutaneous injections per day of a relatively long-acting insulin as "basal" insulin, and take a short-acting subcutaneous insulin before each meal (prandial insulin). Continuous subcutaneous infusion via insulin pump of short-acting insulin, with mealtime boluses, is also used. Pramlintide, an amylin analog, was recently approved as the first agent other than insulin for treatment of Type 1 diabetes, but pramlintide is an adjunct to mealtime insulin, rather than a substitute for subcutaneous insulin.

The applicant considers Afrezza faster in time-action profile to subcutaneously administered rapid-acting insulin analogs, which have a rapid onset of action (about 15 minutes), a short time to peak action (0.5- 1.5 hours), and a short duration of action (2-5 hours). Currently marketed rapid-acting analogs available in the United States include insulin aspart and insulin lispro. Regular soluble crystalline zinc insulin is also sometimes used as a prandial insulin; it has an onset of action at 30-45 minutes, peak action between 1.5 and 4 hours, and a duration of action of 5-8 hours.

There are no currently available inhaled insulin therapies for diabetes. As is discussed in section 2.1 and 2.4, Exubera is an inhaled insulin therapy that was approved for the treatment of type 1 and type 2 diabetes in adults in January 2006. Pfizer withdrew Exubera from the market in early 2009 for business reasons (presumably poor sales). (b) (4)

(b) (4) If approved, Afrezza would be the only marketed non-subcutaneously delivered insulin therapy.

### **2.3 Availability of Proposed Active Ingredient in the United States**

The active ingredient used in the production of the inhalation powder is a recombinant human insulin which is not approved for marketing in the United States. (b) (4), the manufacturer of the active ingredient insulin, has authorized MannKind to cross reference the Drug Master File (DMF) for this insulin, and that DMF (number (b) (4)) is under review by the FDA Office of New Drug Quality Assessment.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Only one inhaled insulin product, Exubera (NDA 21,868, recombinant human insulin powder for oropulmonary inhalation) has been approved in any country. It was approved in January 2006.

The following information was obtained from a review dated 20 May 2008 by Dr. Cynthia Kornegay from the Division of Epidemiology, Office of Surveillance and Epidemiology.

“At the time of approval of Exubera there were three cases of malignant neoplasm of the lung in individuals exposed to Exubera versus one in a non-exposed patient. In December 2007, the sponsor submitted an information update for clinical trials that described nine cases of lung cancer, eight of which were in patients exposed to inhaled insulin. Of these eight cases, six are thought to be potentially directly associated with Exubera exposure.

The data, while somewhat compelling, are quite preliminary. Details on the individual studies where the cases arose are not provided, so the study data could not be pooled and analyzed in a more rigorous manner. While cases originated in the US, Canada, and Europe, the only lung cancer background rates available were those for the US. Since the number of US study participants was not provided, it is not clear if the lung cancer rate seen in US Exubera study participants would be in excess of the US lung cancer background rate.”

Based on Dr. Kornegay’s review and reviews from the Division of Metabolism and Endocrinology Products, the following language was added to the WARNINGS section of the U.S. Prescribing Information:

*"In clinical trials of Exubera, there have been 6 newly diagnosed cases of primary lung malignancies among Exubera-treated patients, and 1 newly diagnosed case among comparator-treated patients. There has also been 1 postmarketing report of a primary lung malignancy in an Exubera-treated patient. In controlled clinical trials of Exubera, the incidence of new primary lung cancer per 100 patient-years of study drug exposure was 0.13 (5 cases over 3800 patient-years) for Exubera-treated patients and 0.03 (1 case over 3900 patient-years) for comparator-treated patients. There were too few cases to determine whether the emergence of these events is related to Exubera. All patients who were diagnosed with lung cancer had a prior history of cigarette smoking."*

The following information was obtained from a memorandum to file dated 7 Apr 2009 from Dr. Karen Mahoney, the Division of Metabolism and Endocrinology Products medical reviewer for Exubera.

“Pfizer Pharmaceuticals, the manufacturer of Exubera decided to withdraw this NDA. Their decision to withdraw was based on business reasons, and was not due to reasons of safety or efficacy of the drug, or the drug-device combination with its dedicated inhaler. The Agency did not request removal of the drug from the market.

A recent review had resulted in the addition of information regarding cases of lung cancer to the Full Prescribing Information (FPI), and to the Medication Guide. However, this safety information did not prompt withdrawal of the drug. Pfizer had notified the Agency of its intention to stop distribution of the drug prior to the Agency’s request to Pfizer for the addition of this safety information to the FPI and Medication Guide. Although Pfizer had stopped

distributing Exubera at the time the Agency requested addition of the lung cancer data to the FPI and Medication Guide.”

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

During the development of Afrezza, there were several meetings and written communications between the Agency and the Sponsor. The following are clinical highlights of some of those interactions:

3 Jan 2001 – IND 61,729 for Technosphere Insulin Inhalation Powder submitted

12 Oct 2004 – End of Phase II (EOP2) Meeting

The Division was asked for comments on the outlined initial Phase IIIA study. The Division stated that the Phase III treatment population as a whole needed to be increased to study at least 300 patients with Type 1 diabetes and at least 300 patients with Type 2 diabetes for 6 months. The following table was provided to the Sponsor in the meeting minutes which shows the minimum required population numbers for the clinical development program:

	3 months	6 months	12 months	24 months
Type 1		300	100	100
Type 2		300	200	100
Total		600	300	200

Staff from the pulmonary division were present at the meeting and provided general comments on pulmonary safety trials. The pulmonary division requested long-term controlled pulmonary safety data in both type 1 and type 2 diabetic patients studied for at least 2 years. Assessments were to include pulmonary function tests, high resolution CT of the chest, and insulin antibodies. The Agency also requested adequate long-term controlled pulmonary safety data, including safety and efficacy assessment of the following groups of patients, studied for at least 1 year, in a controlled fashion: patients with COPD (at least 100 patients) and patients with asthma (at least 100 patients).

14 Jul 2008 – Pre-NDA Meeting

The Sponsor was informed that the Phase III trials 009, 102, 103, and 030 must be complete at the time of NDA submission.

The Sponsor was requested to provide analyses of non-serious safety based on all subjects who enrolled in clinical trials, not just subjects who had been exposed for more than 14 days of treatment.

Discussion occurred regarding the pulmonary safety evaluation and analysis of insulin antibodies.

A discussion of the definition of hypoglycemia occurred. Agreement was made to analyze the components of the definition of hypoglycemia separately (i.e. needing assistance, neurologic symptoms, and blood glucose criteria).

Discussion also occurred regarding the fact that the pivotal phase 3 studies used the Model C MedTone inhaler but the to-be-marketed device is the Model D inhaler. Comments from Clinical, Clinical Pharmacology, CMC, and the Center for Devices and Radiologic Health were provided to the Sponsor on how to resolve this potentially problematic issue. The Sponsor committed to submitting a human factors study for Model C and Model D.

## **2.6 Other Relevant Background Information**

Foreign Commercial Marketing History: Afresa is not approved in any other country, nor is it submitted to any foreign health authority.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

During review, the clinical reviewer noted errors in certain of the applicant's tables and figures that limited the interpretability of these data sources. In general, the applicant has been responsive in submitting missing and corrected data. Applications are expected to be complete and correct at the time of initial NDA submission; waiting for corrected data complicated the review of this application.

### **3.2 Compliance with Good Clinical Practices**

Each protocol report included a statement that the protocols complied with good clinical practices. All subjects in all trials were required to provide informed consent. Review of the consent forms for the Phase 3 studies revealed adequate descriptions of the potential risks of participation. The Sponsor documented protocol violations when they occurred. In the major trials before database lock, a medical adjudication review was conducted to identify protocol violations that affected subject eligibility to be included in the "Per Protocol" population (a

prespecified analysis population that included only subjects who completed trials without significant protocol violations). Primary efficacy endpoints were analyzed with the Per Protocol populations to support robustness of efficacy results.

The Division of Scientific Investigations (DSI) conducted audits for site-specific issues regarding good clinical practices. Site selection was performed by the clinical reviewer along with Dr. Susan Leibenhaut from DSI based on relatively larger numbers of subjects enrolled at the selected sites. There was no potential financial conflict of interest influencing the site selection. DSI reviews are still pending at the time of this review and will be addressed in the Cross Discipline Team Leader memo. According to Dr. Leibenhaut there do not appear to be any significant issues with the inspections so far.

In general, the Sponsor involved in the development of this product appears to have complied with the principles of good clinical practice.

### **3.3 Financial Disclosures**

The Sponsor submitted a completed Financial Certification Form FDA 3454 and Financial Disclosure Form FDA 3455. All investigators who participated in the MannKind Corporation clinical program for NDA 22-472 were reviewed.

One investigator (b)(6) MD) responded positively to receiving significant payments from MannKind Corporation. Dr. (b)(6) was Investigator # (b)(6) and participated in two trials: 0008 and 010. In trial 0008, Dr. (b)(6) enrolled (b)(6) subjects and all (b)(6) subjects completed this trial. This multi-center, double-blind, placebo-controlled randomized trial included a total of 123 randomized subjects: 61 in the TI group and 62 in the placebo group. A review of the primary analysis with and without the subjects enrolled by Dr. (b)(6) was completed by the Sponsor. The Sponsor stated that the low number of subjects enrolled by Dr. (b)(6) did not introduce undue bias affecting trial outcomes.

Trial 010 was a multi-center, open-label, four-year, safety and tolerability, “follow-on” trial of both trial 0008 and trial 005. Trial 010 included 229 subjects. All subjects received TI. Dr. (b)(6) enrolled (b)(6) subjects and (b)(6) subjects completed this trial. The low number of subjects enrolled by Dr. (b)(6) did not introduce undue bias affecting trial outcomes.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

## 4.1 Chemistry Manufacturing and Controls

The chemistry manufacturing and controls (CMC) review was performed in two parts. Dr. Alan Schroeder reviewed limited parts of the NDA (i.e., the inhaler device and the drug product performance). Dr. Theodore Carver performed a separate review for the rest of the CMC material in the NDA. Note that the device is currently being separately evaluated by the CDRH reviewer, Dr. Melanie Choe.

### Significant issues in Dr. Schroeder's review

Dr. Schroeder concluded that the application is approvable pending satisfactory responses to several outstanding comments.

His summary basis for approvability is as follows:

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] This information has been shared with the clinical reviewers for their consideration.

Over 10,000 model C inhalers were given to patients in phase 2 and phase 3 studies. The applicant has stated that no serious adverse events associated with device failure and/or malfunction were reported. The applicant also claims to be unaware of any adverse events resulting from device failure. The main complaints about the product in the clinical studies were for [REDACTED] (b) (4), and these defects are said to have been rectified through design modifications.

The Model C inhaler (with the Model C cartridge) was used in phase III studies, and the Model D inhaler (with the Model D cartridge) is proposed for marketing. It is claimed that the improvements in Model D did not alter the air flow path through the device relative to Model C, and the functionality of the device was not changed. Model D has a somewhat higher mean emitted dose in this study than does Model C, and this applies to both the 30 U and 15 U cartridges. This mean difference in emitted dose (i.e., greater emitted dose for Model D than for Model C) is (b) (4)% for the 15U cartridges, and (b) (4)% for the 30U cartridges. The aerodynamic particle size distributions (APSD) are similar (especially for fine particles) between Model C and Model D in the data which were provided for a small sampling of C and D inhalers, although not identical. Some of the APSD differences may only be due to variability of the test. The data

provided in the original NDA do support the similarity of the performance of the Model C and Model D inhalers.

Overall, the stability data (for drug product stored at (b) (4) C) show that the aerodynamic particle size distribution and the delivered dose uniformity are not trending parameters.

The CMC review also recommended a number of post marketing requirements as follows:

1)

2)

3)

4)

5)

6)

7) The standard stability commitment is provided, plus the following stability commitments:

- “Continuation of on-going stability protocols, which includes the first 3 production batches from the validated process.
- Minimum of 5% of the batches manufactured per year for the first three years (not to exceed 10 additional batches of each marketed strength product) will be placed in the post approval stability program.
- For year four and beyond, representative samples from one batch of each marketed strength product will be included in the program for each year.

- Results from on-going and future studies will be periodically submitted to the application in the NDA annual report.
- If any significant manufacturing changes occur that require re-validation of the process then the stability program will revert back to the protocol provided for the first three production batches incorporating the manufacturing changes.”

## 4.2 Clinical Microbiology

A microbiology review was completed by Dr. Denise A. Miller on 22 Sep 2009. There were no significant microbiology issues identified and approval was recommended.

## 4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology reviewer, Dr. Tsai-Turton, recommended approval of the NDA with no further nonclinical studies.

An overview of nonclinical findings (excerpted from Dr. Tsai-Turton’s review) is as follows:

In nonclinical studies, both Technosphere® Insulin (TI), insulin absorbed to Technosphere® particles) and Technosphere® particles (T) alone were tested. Technosphere® particles are comprised of a novel excipient, fumaryl diketopiperazine (FDKP). TI doses were limited by the pharmacology of insulin, which resulted in hypoglycemia, so higher doses of Technosphere® particles were administered alone to maximize FDKP exposure.

The **toxicology** of TI and T was characterized in **repeated-dose inhalation** studies in rats and dogs. TI and T were well-tolerated in general. The primary toxicity was related to expected exaggerated insulin pharmacology (hypoglycemia) at high doses. In 26 week rat study, 11.7 mg/kg/day for T and 1.05/0.404 (male/female, low-dose TI) and 1.91/1.28 (male/female, high-dose TI) mg/kg/day TI were tested by nose only inhalation. There were some findings: **1)** increased lung weights in rats with no histological correlation, **2)** eosinophilic globules and epithelial degeneration observed in nasal cavities of T group, which regressed in females but remained in males after a 4-week recovery, **3)** slightly increased bronchial proliferating cell nuclear antigen activity in the upper respiratory tract, probably related to exposure duration and upper airway particulate impaction in T alone (in males) and low/high-dose TI (in males and females) groups, and **4)** degeneration and necrosis of the myocardium and infiltration of mononuclear cells in approx. 50% males treated with T, which remained in males after 4 week recovery. Such cardiac finding, associated with T, was not observed in dog histopathological finding. The airway findings were consistent with minimal to mild respiratory irritation at 2x human systemic exposure and did not correlate to any preneoplastic or neoplastic findings. This suggests the possibility of some mild airway irritation with clinical use. The NOAEL (T) was <

11.7 mg/kg/day and the NOAEL (TI) was 1.91/1.28 (male/female) mg/kg/day. The safety margin based on FDKP exposure was approx 1.5-fold greater than maximum anticipated daily exposure. In 39 week dog study, 2.4 (low-dose T) and 10.9 (high-dose T) mg/kg/day T and 0.39 (low-dose TI) and 1.92 (high-dose TI) mg/kg/day TI were tested. There were some findings: **1)** increased minimal to mild neutrophil infiltrate of lungs in high-dose TI group, which regressed after an 8-week recovery and **2)** thymic atrophy, hypocellularity of the seminiferous epithelium, and germ cell degeneration seen in both T and/or TI groups. The NOAEL (T) was 10.9 mg/kg/day and the NOAEL (TI) was 1.92 mg/kg/day. The safety margin based on FDKP exposure was approx 2-fold greater than maximum anticipated daily exposure.

Dr. Tsai-Turton concluded that there might be lung irritation with clinical use of this product, based on 39 week inhalation dog study, where minimal to mild alveolar/bronchial interstitial neutrophil infiltration was seen in lungs of all TI-treated groups. These findings regressed following 8 weeks recovery.

**Genotoxicity** studies were conducted in vitro with Technosphere (T) and Technosphere + insulin (TI) and in a mouse micronucleus assay (T only). T and TI showed no apparent genotoxic potential.

**Carcinogenicity** studies in rats (inhalation) and transgenic mice (subcutaneous) were conducted. There was no evidence of increased oncogenicity, as well as microscopic pathological findings, related to TI or T. NOAELs for T in the mouse (75 mg/kg/day) and rat (46 mg/kg/day) carcinogenicity studies were at the maximum doses tested, and represented approx. 1.2- and 0.2-fold of the projected maximum human exposure (or max blood levels) respectively.

In the rat study, both T and TI were well-tolerated by inhalation. Exposure to FDKP increased with increasing dose in all treated groups. TK analysis was not definitive due to the variability in circulating insulin concentrations measured in TI treatment groups. There were no indications of carcinogenic potential of either T alone or TI in both males and females. In addition, lung PCNA analysis showed that alveolar and bronchiolar cells were not different across all groups.

Technosphere® particles were evaluated in **reproductive and developmental toxicity** studies in rats and/or rabbits (subcutaneous). In rats, there was no T-induced impairment of fertility and no teratogenic findings at 100 mg/kg/day, and some effects (learning impairment and decreased male reproductive organ weights) on offspring at 30 and 100 mg/kg/day. Exposure was confirmed in pregnant animals, and a separate rat fetal TK study confirmed in-utero. FDKP was also present in the mother's milk in rats at about 10% of the maximum concentration detected in the systemic circulation. FDKP was also detected in rat fetal circulation at concentrations comparable to the maternal plasma concentrations of GD (gestation day) 18. In rabbits, there was maternal weight loss and malformations observed at 2 mg/kg/day T. In addition, T had safety margins for tolerability and embryo/fetal development, ranging from approx. 3 to 8-fold human exposure multiples in rats and rabbits) during pregnancy.

Additional studies to evaluate **toxicity of process impurities** were also performed. Seven impurities were identified and qualified in toxicology studies. Major impurities were further

studied in 28-day SC rat study and there was no additional systemic toxicity seen in these animals, compared to the parent drug.

An overview of pharmacologic activity (excerpted from Dr. Tsai-Turton's review) is as follows:

***In vitro*** study results, from an evaluation of FDKP binding to 63 diverse receptors or enzyme of neurotransmitter-related receptors, steroids, ion channels, secondary messenger, prostaglandins, growth factors or hormones, and brain or gut peptides showed that only 1 of 63 receptors  $\gamma$ -Bungarotoxin insensitive nicotinic receptor was inhibited at > 50%. In follow-up experiments, the  $K_i$  values ranged from 95.9 to 333  $\mu\text{M}$ , suggesting weak inhibition. The anticipated maximum concentration of FDKP in humans is approx. 1.04  $\mu\text{M}$ , so the safety margin is 96-fold the maximum anticipated clinical dose for this receptor.

***In vitro*** study results, from inhalation studies in rats and dogs, showed that blood glucose reductions were observed in rats and dogs, in a dose-dependent manner,. In dogs, following TI inhalation, the nadir in glucose levels happened approx. 20 to 60 min postdose. This was correlated to mean peak serum insulin levels that occurred approximately 10 minutes postdose. On the other hand, following T inhalation, no reduction in blood glucose was observed, suggesting that FDKP had no effect on blood glucose levels.

#### 4.4 Clinical Pharmacology

See section 5.1 for tables of clinical studies.

The clinical pharmacology program comprised 31 trials, 27 using inhaled TI and 4 using TP (Technosphere Inhalation Powder [without insulin]). One of these trials is ongoing at the time of NDA submission (Trial 118). Approximately 661 subjects have been evaluated during the clinical pharmacology program. The trials were conducted in healthy normal volunteers; in subjects with type 1 and type 2 diabetes mellitus, renal dysfunction, liver dysfunction, chronic obstructive pulmonary disease (COPD), asthma, and upper respiratory infections; and in smokers. The objectives of the studies included pharmacokinetics (PK), pharmacodynamics (PD), bioavailability, dose linearity, drug-disease interactions, and drug-drug interactions. The metabolism and elimination of radiolabeled FDKP, the disposition of TI Inhalation Powder in bronchial fluid, and the effect of Technosphere particles on QT/QTc prolongation were also evaluated.

Thirteen studies were primarily or partly biopharmaceutic in nature, although most also included other clinical pharmacology endpoints (for that reason, the number of studies in this paragraph do not sum to 13). One study evaluated the absolute bioavailability of insulin after TI Inhalation Powder administration; 10 studies included evaluation the relative exposure of TI Inhalation Powder compared to subcutaneous (sc) insulin; 1 study evaluated the dose-exposure relationship of insulin; 1 study evaluated the bioequivalence of 2 formulations, 1 of which is the formulation

intended for marketing; 1 study evaluated mass balance of FDKP; and 1 study evaluated the effect on bioavailability of increasing the insulin content on Technosphere particles.

Dr. Chung, the clinical pharmacology reviewer, recommended approval of the NDA with no postmarketing requirements. However, he did note some methodological problems with the clinical pharmacology development program as follows:

In assessing insulin pharmacokinetics (PK) and pharmacodynamics (PD), this reviewer noted that the critical study design elements were significantly different among the trials with different endpoints (e.g.,  $AUC_{0-235\text{min}}$  to  $AUC_{0-540\text{min}}$ ), different insulin baseline adjustments (e.g., average of predose, time zero, average of later phase, C-peptide, or no adjustment), different inhalers, different clamp procedure status, and different subject types. Furthermore, glucose parameters were often confounded by additional injection of regular human insulin or insulin analogue to rescue hyperglycemia, or additional glucose load to rescue hypoglycemia. These differences make the cross-study comparison of insulin PK and PD information difficult. Therefore, insulin data should be interpreted within specific trial elements and the cross-study comparison for insulin pharmacokinetics and pharmacodynamics should be cautiously exercised.

#### 4.4.1 Mechanism of Action

The mechanism of action of Afrezza is to replace inadequate endogenous insulin (quantitatively or functionally inadequate due to insulin resistance) thereby lowering blood glucose.

#### 4.4.2 Pharmacodynamics

The insulin pharmacodynamic (PD) effect on blood glucose was estimated using the area under glucose infusion rate ( $GIR_{0-360\text{min}}$ ). The PD effect following 100 U TI was about 14% by the GIR referencing that of 5-U IV insulin and the PD effect was about 9% compared with that of 10-U SC regular insulin. Differences related to age, gender, or race were not evaluated in pharmacological studies. Dosing was individualized to achieve a blood glucose target in the pivotal clinical trials, and the mean dosing was about 36-66 U per dosing in the pivotal clinical pharmacology trials. The AUC ranged from 3502 to 12322  $\mu\text{U}\cdot\text{min}/\text{mL}$  following from 25 to 100-U TI dosing, and AUCs increased proportionally with dose. Variability in insulin pharmacokinetic following AFREZZA® was lower than that of EXUBERA® based on cross study comparison; 34% and 53% CV in C-peptide baseline adjusted AUCs for AFREZZA® and EXUBERA®, respectively. The TI dosing resulted in a rapid onset of action on blood glucose with earlier time to peak effect on glucose infusion rate ( $GIR\ t_{\text{max}}$ ; median of 35 minutes) than that of SC rapid-acting insulin analog (median  $GIR\ t_{\text{max}}$  of 110 minutes for RAA). The above baseline corrected insulin PD data were obtained from T1D under clamp procedures using the pivotal clinical trial inhaler (Model C).

#### 4.4.3 Pharmacokinetics

##### TI

The pharmacokinetic profile of TI makes it suitable as a prandial insulin. The absolute bioavailability of insulin following 100-U TI was about 15% by the area under concentration-time curve ( $AUC_{0-360min}$ ) referencing that of 5-U intravenous (IV) insulin.

The relative bioavailability was about 28% by the AUC as compared with that of 10-U subcutaneous (SC) insulin. The time to reach serum insulin maximum concentrations ( $t_{max}$ ) following TI (median of 10 minutes) was shorter than that of SC administration (median of 60 min) in T1D. The observed serum insulin  $C_{max}$  ranged from 55 to 219  $\mu U/mL$  following TI dosing ranging from 25 to 100-U and those included the physiologic  $C_{max}$  (about 76  $\mu U/mL$ ) in healthy subjects after a standardized meal.

The clinical pharmacology reviewer concluded that the  $T_{max}$  of TI was shorter than that of subcutaneous insulin, but was not as short as the endogenous first-phase insulin response in healthy individuals (about 5 minutes) as the Sponsor asserts in the NDA.

##### T alone (FDKP)

The major elimination route of FDKP was renal (97% following IV), and absorption from the gastrointestinal tract was negligible (<4% absolute bioavailability). Approximately, 20% of the FDKP dose was excreted in the urine following TI inhalation powder. The FDKP was not metabolized in the body. The  $t_{max}$  of FDKP following TI inhalation powder ranged from 9 to 25 minutes. The terminal half-life ( $t_{1/2}$ ) ranged from 114 to 198 minutes, and it increased to 270 minutes in subjects with moderate renal impairment.

#### 4.4.4 Drug-drug and drug-disease interactions

Insulin exposure was lower with COPD (91%) and asthma (71%), and according to the clinical pharmacology reviewer may not significant concern under the proposed titration dosing. Smoking increased insulin AUC by 25% and GIR by 35%. Therefore, the clinical pharmacology reviewer recommended that dose titration should be cautious in subjects with smoking for an unexpected hypoglycemia potential. The clinical pharmacology reviewer also stated that FDKP exposure change in the renal and hepatic impairment studies may not warrant dose adjustment because of no particular safety concern.

Drugs that can be potentially co-administered such as albuterol and fluticasone did not significantly affect insulin pharmacokinetics following TI.

## **5 Sources of Clinical Data**

The primary sources of clinical data for this review were the clinical trial data submitted by the applicant. Most sources of data were submitted with the original NDA submission with several Agency solicited requests for information during the review cycle. The clinical reviewer also reviewed relevant information including postmarketing safety information related to the inhaled insulin product Exubera which was approved by the Division of Endocrinology and Metabolism Products in January 2006. The Division of Pulmonary and Allergy Drug Products is conducting a separate review of the pulmonary safety of Technosphere Insulin.

## 5.1 Tables of Studies/Clinical Trials

### Tables of Biopharmaceutics and Clinical Pharmacology Studies

Key: BA=bioavailability, BAL=bronchoalveolar lavage, BE=bioequivalence, BG=blood glucose, CLD=chronic liver disease, COPD=chronic obstructive pulmonary disease, DNP=diabetic nephropathy, FDKP=fumaryl diketopiperazine, FEV1=Forced expired volume in one second, HV=healthy volunteers, IMP=investigational medicinal product, IU=international units, MCT=methacholine challenge test, OAD=oral antidiabetic drug, OL=open-label, PD=pharmacodynamic, PK=pharmacokinetic, RAA=rapid acting insulin, RHI=regular human insulin, T1DM=Type 1 diabetes/diabetics, T2DM= type 2 diabetes/diabetics, TI=Technosphere insulin inhalation powder, TP=Technosphere inhalation powder (without insulin), U=units, URI=upper respiratory infection

Note: route of administration for TI and TP is inhaled unless otherwise specified (trial 123)

<b>Table 5.1 – Biopharmaceutics and Clinical Pharmacology Studies</b>						
<b>Type of Study</b>	<b>Study Identifier/ Study Status</b>	<b>Study Objective</b>	<b>Study Design</b>	<b>Test Product(s): Dosage Regimen and Route of Administration</b>	<b>Subjects (number and diagnosis)</b>	<b>Duration of Treatment</b>
BA	PDC-INS-0001A Completed Full	evaluate relative bioeffect and bioavailability of 25 U of inhaled TI vs. 10 IU of sc RHI	OL, randomized 2-way crossover - euglycemic clamp	Test Product: TI Dosage: TI 25 U, 2 single doses on 2 separate treatment visits	9 HV	Short. 1 day each, TI and reference therapy
BA	PDC-INS-0001B Completed Abbreviated	characterize the PK and PD profiles of 25 U of insulin from 3 different TI formulations	OL, randomized, 4-way crossover study	Test Product: TI Dosage: TI 25 U with 3 formulations, single dose	11 T1DM	Short. 4 single doses administered over 2 to 14 days
BA	PDC-INS-0002 Completed Full	compare the bioeffect of inhalation of 3 doses of TI to 10 IU sc insulin in HV	Prospective, OL, randomized, 4-way crossover study	Test Product: TI Dosage: TI 25 U, 50 U, or 100 U per meal, 4 single doses on 4 separate treatment visits at least 3 days apart.	12 HV	Short (4 single doses on 4 treatment visits $\geq$ 3 days apart; 3 single doses of TI and 1 dose of RHI
<b>Table continued until page 33</b>						

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BA, BE	MKC-TI-110 Completed Full	compare the bio-equivalence of TI formulations and the bioavailability of each TI formulation with that of sc insulin in T1DM	Prospective, single site, OL, 3-way crossover study	Test Product: TI Dosage: 30 U or 60 U	47 T1DM	Medium. 3 treatment visits scheduled 7-14 d apart
BA, BE	MKC-TI-116 Completed Full	determine the bioequivalence and safety parameters of two 15 U cartridges vs. one 30 U cartridge and the relative bio-availability of a 30 U cartridge compared to a single sc injection of 10 IU of RAA	Phase 2, OL, randomized, 2-way crossover hyper-insulinemic -euglycemic clamp clinical study	Test Product: TI Dosage: 30 units Cartridges contained either 15 U or 30 U	30 T1DM	Short. 1 dose at each of 2 visits
BA, BE	MKC-TI-138 Completed Full	evaluate the bioequivalence of TI when administered using MedTone Inhalers, Model C and Model D	Phase 1, OL, single dose, randomized, 2-way crossover study	Test Product: TI Dosage: 30 U via MedTone Inhaler	75 T1DM	Short (2 single doses over 2 treatment days)
PD & PK/PD	PDC-INS-0007 Completed Full	evaluate distribution of TI labeled with 99m technetium in the lung directly after inhalation of TI using $\gamma$ scintigraphy, to assess the PK profile and safety of a single administration of TI	Prospective, OL, Non-comparative study	Test Product: 5 U 99m technetium-labeled TI Dosage: Variable, prandial dosing to a maximum of 10 U TI	5 HV	Short (single dose)
PK	MKC-TI-122 Completed Full	determine pulmonary concentrations of insulin and FDKP in the lungs utilizing BAL after administration of TI	Phase 1, OL, randomized, controlled clinical study	Test Product: TI Dosage: single 60 U dose before each bronchoscopy	13 HV	Short. Single dose at 1 treatment visit
PK,	MKC-TI-123 Completed Full	study controlled elimination and metabolism of [14C]-FDKP administered as an intravenous (iv) infusion and as an oral solution (Hepatic Metabolism study)	Single-dose, OL, 2-period crossover, nonrandomized, repeat administration controlled elimination and metabolism study	Test Product: [14C] FDKP solution Dosage: 1 iv infusion of 10 mg [14C] FDKP solution; 1 oral dose of 20 mg [14C] FDKP solution Route: iv; oral	7 male HV	Medium. Approx. 7 wk: 4 visits (2 treatment visits separated by 2 weeks) over 42 days
BA	PDC-INS-0001C Completed Abbreviated	compare the effect on postprandial bioavailability of 3 formulations of TI with sc insulin measured during study 0001B and to evaluate the time-action profiles of the TI formulations	OL, randomized, 3-way crossover study	Test Product: TI Dosage: Prandial TI 36 U of 3 formulations, single dose	7 T1DM	Short (3 single doses administered over 2- 14 days)

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PD & PK/PD	MKC-TI-003B Completed Full	compare prandial inhalation of TI to sc regular insulin in T2DM on intensified insulin therapy	Prospective, OL, randomized, controlled, crossover study	Test Product: TI Dosage: TI 12 U, 24 U, 36 U, 48 U per meal, single dose	16 T2DM	Short (3 doses/day administered over two 1-week periods)
PD & PK/PD	MKC-TI-003B2 Completed Full	evaluate the safety and efficacy of prandial TI vs. sc RHI on BG after 1 wk of daily multiple doses; to compare serum insulin concentrations after a single dose of TI or sc RHI	Controlled, OL, randomized, replicated, crossover isoglycemic glucose clamp study	Test Product: TI Dosage: Prandial TI 48 U, single dose	13 T2DM	Medium (3 single doses of TI on 3 separate occasions over 6 - 13 wk)
PD & PK/PD	PDC-INS-0003 Completed Full	Evaluate intra-patient variability of the biologic action of inhaled TI vs. sc RHI during euglycemic clamp experiments	OL, randomized, 4-way crossover study	Test Product: TI Dosage: Prandial TI 100 U, single dose on 3 separate occasions	13 T2DM	Short (single dose administered on 4 separate occasions)
PD & PK/PD	PDC-INS-0003A Completed Full	evaluate the variability of the insulin absorption after pulmonary application of TI in comparison to sc RHI in T2DM and to collect safety information about repeated applications of TI	6-way crossover, randomized study	Test Product: TI & TIP Dosage: TI 48 U, 6 single doses; TIP, practice inhalations	15 T2DM	Short (6 single doses on 6 treatment visits separated by 2 - 14 days)
PD & PK/PD	MKC-TI-025 Completed Full	compare 2 prototype TI cartridges for inhalation with sc RHI	Prospective, controlled, OL, randomized, replicated, crossover PK study	Test Product: TI Dosage: Prandial TI 30 U (using cartridge Prototype A and B) at each of 6 visits	20 T1DM	Short (3 phases separated by $\geq 14$ days, each with 3 treatment visits separated by 7 - 10 days)
PK	MKC-TI-113 Completed Full	compare PK parameters of TI alone and with albuterol and/or after MCT in subjects with asthma vs. matched healthy, subjects without asthma demonstrating normal lung function	Phase 1, OL, controlled clinical study	Test Product: TI Dosage: <i>All Subjects:</i> • 45 U TI • albuterol 200 $\mu$ g <i>Subjects with FEV1 &gt; 65% of predicted:</i> • Methacholine in increasing doses until FEV1 > by 20%	Asthma: 17  Normal lung function: 13	Medium. 4 treatment visits, 1 dose/visit

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Intrinsic factor PK	MKC-TI-027 Completed Abbreviated	evaluate and compare, in a 2-part study, the PK and PD effects of TI over a 7-day treatment period in asthmatic and non-asthmatic subjects	Parallel OL, single dose of TI PFT; parallel prospective, controlled, 2-center, euglycemic clamp procedure	Test Product: TI Dosage: Three 30 U single doses, and individualized doses 3 or 4 times a day	21 asthmatic and non-asthmatic subjects with T2DM	Short (7 days)
PK	MKC-TI_105 Abbreviated (discontinued due to low enrollment)	compare prandial sc insulin with prandial TI in subjects with T2DM and asthma	12-month randomized, OL, parallel-group clinical study	Test Product: TI Dosage: Subject A: TI 15 U Subject B: TI 30 U	3 T2DM requiring insulin; concurrent asthma	Short. Subject A: 3 doses/day x 30 days; Subject B: 3 doses/day x 7days
PK in renal impairment	MKC-TI-017 Completed	compare FDKP administered as TP in subjects with mild or moderate DNP vs. matched subjects with normal renal function	Phase 1, single dose, OL, parallel design, controlled PK comparison study	Test Product: TP Dosage: Single dose, 20 mg TP	36 T1DM or T2DM with DNP or without DNP	Short: 1 dose administered at 1 treatment visit
PK in hepatic impairment	MKC-TI-111 Completed	compare FDKP administered as TP in subjects with mild or moderate CLD vs. matched subjects without CLD	Single-dose, OL, parallel design, controlled PK comparison study	Test Product: TP Dosage: Single dose, 20 mg TP	33 T2DM with CLD or without CLD	Short. 3 visits (1 treatment visit)
Other	PDC-INS-0011 Completed Full	evaluate effects of the timing of an individualized dose of TI on BG control in patients with T1DM before or after eating an isocaloric or hypercaloric meal	Prospective, randomized, 8-way crossover, open label study	Test Product: TI Dosage: Prandial TI 6 U, 12 U, 24 U; individualized dose of TI calculated at each visit according to a predetermined formula	13 T1DM	Short (4 - 10 wk consisting of 8 treatment visits, each separated by 1 - 14 days)
PK	MKC-TI-114 Completed Full	investigate the effect of albuterol and fluticasone on the PK of TI	Phase 1 OL study	Test Product: TI Dosage: 45 U	13 HV	Medium. single dose at 3 treatment visits
PK in smokers	MKC-TI-016 Completed Full	compare prandial inhalation of TI in smokers and nonsmokers	Parallel, controlled, multicenter, single-dose, 1-period euglycemic clamp study	Test Product: TI Dosage: Prandial 30 U TI, single dose	24 T2DM	Short (single dose at Visit 2)

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PK	MKC-TI-112 Completed Full	evaluate PK and safety parameters of TI in subjects with T1DM or T2DM who develop a URI, comparing the subjects' status after resolution of the URI, and to assess the PK profile of FDKP after dosing with TI	Phase 2 multicenter, sequential enrollment, open-label study of TI after meal challenges in consenting subjects randomized in MKC-TI-030	Test Product: TI Dosage: TI 15 or 30 U administered before meal challenge	20 T1DM or T2DM with a URI also enrolled in MKC-TI-030	Short. 2 treatment visits (2nd visit scheduled 15-45 d after resolution of URI)
PD & PK/PD	PDC-INS-0001 Completed Full	compare inhalation of 100 U TI via dry powder inhaler to 10 IU of sc insulin or 5 IU of iv insulin	Unblinded, OL, randomized, 3-way crossover study	Test Product: TI Dosage: Prandial TI 100 U, 3 single doses on 3 separate treatment days $\geq$ 3 days apart.	5 HV	Short. 3 single doses of TI on 3 treatment visits at least 3 days apart
PD & PK/PD	PDC-INS-0002A Completed Full	compare inhalation of 4 different doses of TI to 2 different doses of sc insulin	Prospective, OL, randomized, 6-way crossover study	Test Product: TI & TIP Dosage: Variable, 6 U, 12 U, 24 U, or 48 U, and 1 to 3 TP practice doses	13 HV	Short. 6 single-dose visits separated by 1 - 14 days
PD & PK/PD	PDC-INS-0004 Completed Abbreviated	evaluate the effects of TI on postprandial BG excursions, compared with iv administration of RHI or sc insulin lispro	OL, randomized, 4-way, single dose crossover study	Test Product: TI Dosage: TI 12 U or 24 U, single dose	12 T2DM	Short (4 single crossover doses separated by 3- 28 days each)
PD & PK/PD	PDC-INS-0004A Completed Full	compare the effect of different doses of TI on daily BG control under isocaloric and hypocaloric dietary regimens	Prospective, OL study	Test Product: TI Dosage: 12 U, 24 U, or 48 U TI	26 T2DM	Short (4 treatment visits of 2 days duration separated by 2- 14 days)
PD & PK/PD	PDC-INS-0006 Completed Abbreviated	compare the effects of postprandial pulmonary delivery of a body-weight related dose of TI with preprandial sc injection of RHI on BG profiles	2-way crossover, randomized, double-blind study; pre-prandial sc insulin + postprandial placebo; preprandial placebo + postprandial TP as control	Test Product: TI & TP Dosage: TI 6 U, 12 U, 24 U per meal, based on body weight; TIP: 1 to 3 $\times$ 5 mg Technosphere particles practice inhale	30 T2DM	(Short. Single dose each on 2 treatment days, 1 - 6 days apart)
Other	MKC-TI-104 Completed Full	compare the effects of prandial TI in multiple regimen formats vs. a prandial bolus fast-acting insulin analogue on postprandial BG in subjects using continuous sc insulin infusion	OL, single center	Test Product: TI Dosage: Variable; 15 to 90 U TI per meal	7 T1DM	4 seven day trial cycles

PK	MKC-TI-015 Completed Full	compare PK and safety of a single dose of TI in a cohort of nondiabetic subjects with COPD with a matched cohort of nondiabetic subjects without COPD	Phase 1b, single dose, OL, parallel-group, controlled hyperinsulinemic euglycemic clamp study	Test Product: TI Dosage: 1 dose of 30 U TI during a hyperinsulinemic euglycemic clamp procedure	38 nondiabetic subjects with and without COPD	Short: single dose of TI at 1 visit
Thorough QT study	MKC-TI-131 Completed Full	compare QTc-interval differences between healthy subjects exposed to therapeutic and suprathreshold doses of TP, placebo control, and active control	Phase 1, randomized, double-blind, crossover, placebo- and active-controlled cardiac safety study	Test Product: TP Dosage: • Suprathreshold: 40 mg • Therapeutic: 20 mg	48 HV	Short. 4 treatment visits separated by $\geq 72$ h
Other	MKC-129 Completed Full	determine inspiratory flow rates using the Medtone Inhaler and an empty cartridge to evaluate pulmonary function and to study pressure profiles achieved by subjects	Single-visit pilot study of use of inhalation device with subjects from other MannKind TI studies	Test Product: Medtone Inhaler Dosage: N/A	56 T1DM or T2DM randomized to a TI group for $\geq 3$ mos. in Trials 009, 030, 102 or 103	Short. 1 visit with 2 inhalations
Other	MKC-TI-118 Ongoing at NDA submission	compare the effect of TI, insulin lispro, and Exubera on endogenous glucose production after a meal challenge and during a euglycemic glucose clamp procedure in T2DM	Randomized, OL, 2-way crossover arm with 7 visits for each completed subject.	Test Product: TI Dosage: 60 U to 90 U of TI depending on effect at initial visit	30 T2DM	Medium (2 treatment visits for the meal challenge, followed by 2-to 6-week blood-loss Recovery period, and 2 visits for glucose clamp procedure

**Table 5.2 – Clinical Efficacy and Safety Studies**

Study Identifier/ Study Phase	Study Objective	Study Design	Test Product(s): Dosage Regimen and Route of Administration	Subjects (number and diagnosis)	Duration of Treatment
<b>Type 2 Diabetes Trials</b>					
MKC-TI-005 Phase 2	To evaluate safety and glycemic response of TI dosed prandially, in addition to basal administration of Lantus	Multicenter, randomized, prospective, double-blind, placebo controlled, stepwise forced titration study	<ul style="list-style-type: none"> <li>• TI Inhalation Powder (placebo) + glargine</li> <li>• TI 14 U + glargine</li> <li>• TI 28 U + glargine</li> <li>• TI 42 U + glargine</li> <li>• TI 56 U + glargine</li> </ul>	227 suboptimally treated T2DM	Short (11 weeks)

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PDC-INS-0008 Phase 2	To evaluate the efficacy and safety of inhaled TI compared to TP following diabetes education	Prospective, double-blind, randomized, placebo-controlled, parallel-group study, as an add-on to oral therapy, dose finding	•TI + OAD •T Inhalation Powder (placebo) + OAD	126 suboptimally treated T2DM	Short (12 weeks)
MKC-TI-010 Phase 3	To evaluate, using serial pulmonary function testing and imaging, the safety and tolerability of inhaled TI in subjects with type 2 diabetes	OL uncontrolled extension for pts who completed the two above trials	TI variable dosage 15 U to 90 U	229 T2DM	4 years
MKC-TI-026 Phase 2	To evaluate the safety and tolerability of 12 wks of treatment with TI	Prospective, controlled, OL, randomized, 12-week safety and efficacy study	•TI + OAD •No TI (control) + OAD	90 suboptimally treated T2DM	Short (12 weeks)
MKC-TI-014 Phase 3	To compare the efficacy of prandial TI + basal insulin vs. prandial rapid acting sc insulin + basal insulin	Randomized, OL, non-inferiority comparative study	•TI + insulin glargine •Insulin aspart + insulin glargine	309 T2DM receiving Lantus as basal insulin	Medium. 24 wk
MKC-TI-103 Phase 3	To evaluate the efficacy and safety of prandial inhalation of TI in combination with metformin or TI alone vs. 2 OADs (metformin and a secretagogue)	24-wk OL, randomized, controlled superiority study	•TI •Metformin + secretagogue •TI + metformin	528 suboptimally controlled T2DM	Medium. 6 months with primary endpoint at 3 months
MKC-TI-102 Phase 3	To evaluate the efficacy and safety of prandial inhalation of TI in combination with basal insulin vs. a prandial premix of intermediate- and rapid-acting insulin in subjects treated with sc insulin ± OADs	Prospective, OL, randomized, non-inferiority controlled study	•TI + insulin glargine •Premix 70/30 Novolog insulin	677 T2DM	Long (52 wk of treatment + 4 weeks of follow-up)

<b>Type 1 Diabetes Trials</b>					
<b>Study Identifier/ Study Phase</b>	<b>Study Objective</b>	<b>Study Design</b>	<b>Test Product(s): Dosage Regimen and Route of Administration</b>	<b>Subjects (number and diagnosis)</b>	<b>Duration of Treatment</b>
MKC-TI-101 Phase 2	To evaluate use of prandial inhaled TI in combination with basal sc Lantus® as basal insulin versus prandial sc NovoRapid® insulin in combination with basal sc Lantus® insulin	Randomized, open-label, multisite substitution study	•TI + insulin glargine •Insulin aspart + insulin glargine	120 subjects receiving basal prandial insulin therapy for T1DM	Medium. 12 wk
MKC-TI-009 Phase 3	To evaluate the efficacy and safety of TI in subjects with type 1 diabetes receiving sc basal insulin + prandial TI vs. prandial sc insulin + basal insulin	Prospective, OL, randomized, controlled, non-inferiority study	•TI + insulin glargine •Insulin aspart + insulin glargine	589 T1DM	Long (52 wk of treatment + 4 weeks of follow-up)
<b>Combined Type 2 and Type 1 Diabetes Trials</b>					
MKC-TI-030 Phase 3	Pulmonary safety trial - To study changes in pulmonary function outcomes over a 2-year period in subjects with type 1 or type 2 diabetes and diabetes-related abnormalities treated with TI vs. usual antidiabetic treatment and in subjects without abnormalities in glucose control	Prospective, multisite, multi-country, study incorporating 2 design strategies: 1) a randomized, OL clinical study comparing 2 groups of subjects with diabetes, and 2) an epidemiologic or observational clinical study comparing alternate study groups	•TI + usual antidiabetes treatment •Usual antidiabetes treatment	2053 T1DM or T2DM and nondiabetic control subjects at a ratio of approximately 10:1 (10 diabetics for every one nondiabetic)	Long (2 years)
MKC-TI-126	To evaluate pulmonary function in subjects who have completed trials 009, 102, 103, or 030 for an additional 2-month safety follow-up period	2-month safety follow-up study	Usual care without TI	Subjects with T1DM or T2DM who have completed previous efficacy and safety trials	2 months

## 5.2 Review Strategy

For the efficacy review, the clinical reviewer primarily emphasized evaluation of the long-term (one-year) active controlled Phase 3 Trials [009 (T1DM patients), 102 (T2DM patients)] but also included a discussion of two phase 2 trials (0008 and 005), because these were trials in which a placebo group was included as the control and blinded efficacy data were available (the phase 3 trials were open label design). Per the Sponsor, pivotal efficacy trials for the TI program are 0008, 009, and 102. All other trials in the program provided supportive efficacy data.

For the safety review, the clinical reviewer emphasized review of the controlled Phase 2 and Phase 3 studies for comparison of rates of events. Safety review was augmented by review of all serious adverse event data from all human trials. Trial 030 is a pivotal pulmonary safety trial.

Separate reviews are being conducted by Biostatistics (separate reviewers for selected safety parameters, such as hypoglycemia and for efficacy), Animal Pharmacology and Toxicology, Biopharmacology, Chemistry (multiple reviewers), and Microbiology. A pulmonary safety review is being performed by Dr. Karimi-Shah from the Division of Pulmonary and Allergy Products.

Although the proposed indication lists both T1 and T2DM together, the data were presented by the Sponsor for T1 and T2DM separately, as the underlying pathogenesis of each disease is quite distinct. This reviewer agrees with that approach because of the differences between the two diseases and because a similar approach has been applied previously by the Division for review of insulin products including the review of Exubera, the only approved inhaled insulin to date (now withdrawn). Therefore, the current review discusses efficacy and safety separately for T1 and T2DM.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Overview of Clinical Trials

See tables 5.1 and 5.2 for a tabular listing of all clinical trials

#### 5.3.1.1 Overview of Efficacy Trials:

All primary efficacy trials were conducted in either T2DM or T1DM subjects. Therefore, in this review the efficacy trials are presented first for T2DM and then T1DM.

Two of the trials used a placebo control that consisted of a MedTone inhaler with Technosphere powder only (i.e. no insulin); Technosphere powder only (placebo) is abbreviated as TP. The actual Technosphere Inhalation Powder with insulin is abbreviated TI (stands for Technosphere insulin).

### **5.3.1.1.1 Type 2 Diabetes Efficacy Trials**

#### **5.3.1.1.1.1 Placebo-controlled efficacy trials**

- Trial 0008 was designed to assess a significant difference in change in HbA1c between TI (Technosphere Insulin) and TP (Technosphere Powder / placebo) after 12 weeks of treatment.
- Trial 005 was designed to compare TI to TP (placebo) based on a difference in HbA1c between treatment group and placebo (end of study values normalized to baseline). This study was designed as a forced dose randomization trial.

#### **5.3.1.1.1.2 Long-term active-control efficacy trial**

- Trial 102 was an open-label trial designed to assess the noninferiority of TI + insulin glargine in comparison with Premix Analog (Novolog 70/30) with a pre-specified noninferiority margin of 0.4%.

#### **5.3.1.1.1.3 Short/Intermediate-term active-controlled efficacy trials**

- Trial 014 was an open-label trial designed to assess equivalence of TI + insulin glargine with insulin aspart + insulin glargine with a pre-specified equivalence margin of 0.4%.
- Trial 026 was an open-label trial designed to detect a difference between Baseline and end of study between TI + usual anti-diabetic care when compared to usual anti-diabetic care alone.
- Trial 103 was an open-label trial designed to assess the superiority of TI + metformin in comparison with metformin + secretagogue.

### **5.3.1.1.2 Type 1 Diabetes Efficacy Trials**

#### **5.3.1.1.2.1 Long-term active-control efficacy trial**

- Trial 009 was an open-label, one-year trial designed to assess noninferiority of TI + insulin glargine compared to insulin aspart + insulin glargine. The pre-specified noninferiority margin was 0.4%.

#### **5.3.1.1.2.2 Short/Intermediate-term active-control efficacy trial**

- Trial 101 was an open-label, 12-week phase 2 study with a 4 week run-in designed to evaluate the effect of substitution of prandial sc insulin with prandial TI in comparison to subjects who maintained sc insulin on PPG excursions after a meal challenge.

### **5.3.1.2 Overview of Safety Trials**

Safety information is gleaned from the above efficacy trials. There were, however, dedicated safety studies in the TI development program as described in the following sections.

### **5.3.1.2.1 Type 2 and Type 1 Diabetes Safety Trials**

#### **5.3.1.2.1.1 Long-term Active-Controlled Safety Study**

- MKC-TI-030, a randomized, open-label 2-year safety study compared pulmonary function and the incidence of reduced pulmonary function in subjects with T1 and T2DM treated with TI or usual antidiabetic treatment. The trial included an observational cohort of non-diabetic subjects who were followed for pulmonary function testing only and were not treated with any IMP.

#### **5.3.1.2.1.2 Long-term Uncontrolled Safety Study**

- MKC-TI-010 - a long-term (up to 4-year) open-label safety follow-up trial with no parallel control in T2DM who had completed trials 0008 and 005

#### **5.3.1.2.1.3 Follow-up Uncontrolled Safety Study**

- MKC-TI-126 - a 2 month follow-up observational trial evaluating pulmonary function in T1 or T2DM subjects who were previously exposed to TI or Comparator in any of these four trials: 009, 102, 103 and 030

### **5.3.2 General Considerations Related to Individual Clinical Trials**

The clinical trials in the TI development program were quite varied. Therefore, an in depth discussion of each trial is included following this section. However, the T1DM and T2DM programs supporting the efficacy of TI had a number of design features in common as follows:

#### Randomization:

Subjects were randomized centrally in all trials. The randomization schedule linked the treatment codes allocated at randomization to the subject numbers.

#### Blinding and Control:

Two T2DM Phase 2 trials were randomized, double-blind, controlled studies comparing TI (active) to TP (placebo) (PDC-INS-0008 and MKC-TI-005). All remaining efficacy studies were open-label, active-controlled clinical trials.

**Reviewer's comment: The open-label design of the majority of the trials is acceptable for an insulin development program because it is not practical to blind insulin therapies. In addition, it is considered unethical to incorporate placebo arms without other insulin therapy in prolonged trials in type 1 diabetes.**

#### General Trial Entry Criteria:

All study entry criteria included current nonsmoking males and females (history of smoking was allowed) between the ages of 18 and 80 years. Since TI is delivered by inhalation, subjects with asthma or chronic obstructive pulmonary disease were excluded from the major trials. Please see Dr. Karimi-Shah's pulmonary review for a discussion of pulmonary function entry criteria in the trials. All subjects were required to have alanine aminotransferase [ALT] and aspartate aminotransferase [AST] < 3 times the upper limit of normal and generally good renal function. Subjects with mild creatinine elevations were permitted in the studies as representative of the general population of subjects with diabetes.

There were differences across trials in the entry criteria for several disease characteristics including baseline HbA1c among others. These key enrollment criteria are demonstrated in the tables below (Table 5.3 for T2D and Table 5.4 for T1D). Other important differences among the trials were the treatments before each trial, as each trial attempted to investigate distinct groups of diabetic patients (i.e. in the T2DM trials, previous subcutaneous insulin use vs. no previous insulin use). These differences are shown in Table 5.5 for T2D and T1D (along with the treatments administered in each trial to provide context). As expected in the T1DM trials, all subjects were previously using subcutaneous insulin therapies.

Subjects included in the studies were on established therapy for at least 6 months before enrollment and were randomized without a washout period. This procedure would be expected to result in minimization of within-group HbA1c changes from baseline to study endpoint, but the primary comparison between groups would be expected to be largely unaffected despite the lack of washout.

<b>Table 5.3 – T2DM Program Key Entry Criteria</b>				
Study	Duration of T2DM (years)	HbA1c (%)	Fasting Glucose	BMI (kg/m <sup>2</sup> )
0008	> 2 and < 12	> 6.6 and < 10.5	≤ 270 mg/dL	< 38
005	> 3 and < 20	> 7.0 and < 12.0	≥ 108 mg/dL	< 38
102	Not specified	> 7.0 and ≤ 11.0	< 2 severe hypoglycemic episodes within the preceding 6 months	≤ 40
014	≥ 2	≥ 7.0 and ≤ 11.5	Not specified	< 44
026	> 2 and < 20	> 7.5 and < 12.0	≥ 108 mg/dL	< 38
103	≥ 6 months	≥ 7.5 and ≤ 11.0	< 2 severe hypoglycemic episodes within 6 months of screening and baseline	≤ 40
030 <sup>a</sup>	≥ 2	≥ 6.6 and ≤ 12.0	< 2 severe hypoglycemic episodes within 6 months of screening and baseline	< 42
<sup>a</sup> Trial 030 included subjects with T1DM and T2DM and subjects with no abnormalities in glucose control. Entry criteria are summarized for subjects with diabetes.				
Source: Study reports for each of the trials: 0008, 005, 102, 014, 026, 103, 030				

<b>Table 5.4 – T1DM Program Key Entry Criteria</b>				
Study	Duration of T1DM (years)	HbA1c (%)	Fasting Glucose	BMI (kg/m <sup>2</sup> )
101	≥ 2	≥ 7.0 and ≤ 11.5	Not specified	< 40
009	≥ 1	≥ 7.0 and ≤ 11.0	Not specified	< 35
030 <sup>a</sup>	≥ 2	≥ 6.6 and ≤ 12.0	Not specified	< 42
<sup>a</sup> Trial 030 included subjects with T1DM and T2DM and subjects with no abnormalities in glucose control. Entry criteria are summarized for subjects with diabetes.				
Source: Study reports for each of the trials: 101, 009, 030				

<b>Table 5.5 – Treatments Before and During Each Trial</b>			
<b>T2DM Program</b>			
Study	Treatment Before Study	Treatment During Study	
0008	≥3 months on a stable regimen, insulin naïve and/or treated with single or combination OAD such as metformin, sulfonylurea, and/or thiazolidinedione	Prandial	TI
		Comparator	Technosphere Inhalation Powder (placebo)

005	≥2 months on a stable dose of ≥ 1 of the following: sulfonylurea, alpha glucosidase inhibitor, metformin, meglitinide, thiazolidinedione, and/or insulin glargine	Prandial	TI
		Comparator	Technosphere Inhalation Powder (placebo)
		Basal	Insulin glargine
102	Stable doses of sc insulin 2 to 3 times per day. Subjects receiving certain OADs were allowed. See trial 102 inclusion criteria for details of acceptable insulin regimens and OADs	Prandial	TI
		Basal	Insulin glargine
		Comparator	Premix analog (Novolog 70/30)
014	≥3 months on sc insulin. Could be on sc glargine, sc NPH, sc 70/30 premix. Could also be on oral agents.	Prandial	TI
		Comparator	Insulin aspart
		Basal (both groups)	Insulin glargine
026	Insulin naïve on diet and exercise or a stable regimen ≥ 2 months on ≥ 1 of the following: sulfonylurea, alpha glucosidase inhibitor, metformin, meglitinide, or thiazolidinedione	Prandial	TI
		Comparator	No TI
		Basal (both groups)	Same OADs as before study enrollment
103	Stable regimen of metformin ≥ 1 g/day or maximum tolerated dose and a secretagogue (sulfonylurea or meglitinide) at ≥ half the maximum recommended dose No dose adjustments in the preceding 6 weeks	Prandial	TI
		Background	None
		Prandial	TI
		Background	Metformin
		Prandial	Secretagogue (SU or meglitinide)
Background	Metformin		
<b>T1DM Program</b>			
<b>Study</b>	<b>Treatment Before Study</b>	<b>Treatment During Study</b>	
009	Any insulin type but total daily dose had to be ≤ 1.4 U/kg/day	Prandial	TI
		Comparator	Insulin aspart
		Basal	Insulin glargine
101	Insulin glargine or other basal insulin with regular/aspart/or lispro insulin	Prandial	TI
		Comparator	Insulin aspart
		Basal	Insulin glargine
Key: OAD=oral antidiabetic drug, sc=subcutaneous, NPH=neutral protamine Hagedorn Source: Study reports for trials 0008, 005, 102, 014, 026, 103, 009, and 101			

General Trial Exclusion Criteria:

Across trials subjects were generally excluded for the following reasons although slight differences existed among trials:

1. Severe complications of diabetes including: history of: blindness from grade III or IV diabetic retinopathy, renal failure requiring dialysis or transplantation, amputation of limbs or digits related to diabetic vasculopathy or foot ulcers;
2. Treatment with another investigational drug within 3 months prior to trial entry and for the duration of the trial;
3. History of drug or alcohol dependency;
4. Significant hepatic disease (as evidenced by ALT or AST  $\geq 3$  times the normal upper reference range or bilirubin  $> 1.5$  times the normal upper reference range);
5. Significant renal disease (as evidenced by creatinine  $> 1.5$  mg/dL for males or 1.3 mg/dL for females) or proteinuria  $> 1,000$  mg/24 hours;
6. History of chronic obstructive pulmonary disease, or history of other known chronic pulmonary diseases, such as reactive airway disease, chronic bronchitis, emphysema, or asthma;
7. Heart failure graded as class III or class IV according to New York Heart Association criteria;
8. Prior treatment with, or participation in a clinical trial involving an inhaled insulin product;
9. Current smokers;
10. Previous participation in a TI or TP clinical trial;
11. Allergy to insulin or to any drugs to be used as part of the clinical trial;
12. History of malignancy within 5 years of trial entry (other than basal cell carcinoma);
13. Anemia (hemoglobin level less than 11 g/dL for females or 12 g/dL for males at trial entry);
14. Diagnosis of Acquired Immunodeficiency Syndrome (AIDS) and AIDS Related Complex
15. A major psychiatric disorder that would have precluded satisfactory participation in this trial;
16. Subjects who have had a myocardial infarction or stroke within the preceding 6 months;
17. Prior diagnosis of systemic autoimmune or collagen vascular disease requiring previous or current treatment with systemic corticosteroids, cytotoxic drugs, or penicillamine;
18. History of severe or multiple allergies;
19. Progressive fatal disease;
20. Recent loss (within the past 2 months) of  $> 5\%$  of body weight;
21. Evidence of “moderate” or greater ketones in urine or history of ketoacidosis;
22. Use of medications known to modify glucose metabolism (e.g. oral, parenteral and inhaled steroids, or greater than 25 mg hydrochlorothiazide daily) or the ability to recover from hypoglycemia;
23. Women who were pregnant or lactating; and
24. Women of childbearing potential practicing inadequate birth control (adequate birth control is defined as using oral contraceptives, condoms or diaphragms with spermicide, intrauterine devices, or surgical sterilization).

#### General Trial Withdrawal Criteria:

In general, a patient was to be withdrawn from a trial for any of the following reasons:

1. The patient withdrew consent.
2. The patient started smoking.
3. The patient began using another investigational drug or excluded medication.
4. The patient became pregnant.
5. The patient failed to maintain  $\geq 75\%$  compliance with study drug administration.
6. The patient experienced one episode of severe hypoglycemia. Definition of severe hypoglycemia differed slightly among trials. The definitions of hypoglycemia are discussed in section 7.
7. The patient experienced a serious adverse event (SAE) that was possibly, probably, or definitely related to the study drug or device.
8. The Investigator believed withdrawal to be medically necessary.

Note that in the clinical development program certain but not all trials included severe hyperglycemia as a reason for trial withdrawal. Discontinuations due to hyperglycemia were coded as adverse events. The criteria for what blood glucose level constituted “hyperglycemia” were trial specific.

In trial 0008, severe hyperglycemia was a withdrawal criterion and was defined as any glucose reading  $> 495$  mg/dL. In trials 005, 026, and 101 hyperglycemia was defined as a fasting glucose value of  $> 270$  mg/dL or a non-fasting glucose value of  $396$  mg/dL. For trials 005, 026, and 101, discontinuation of a subject’s participation in the trial due to hyperglycemia was at the discretion of the Investigator. However, any glucose reading  $> 495$  mg/dL was to result in automatic withdrawal from the trial. In trial 014, if despite increases in TI dosage to  $60$  U per meal, the measured fasting glucose levels were repeatedly  $\geq 270$  mg/dL, subjects were to be permanently discontinued from the trial. Additionally, any glucose reading  $> 495$  mg/dL was to result in automatic withdrawal from the trial. For trials 103, 102, and 009 the protocols did not specify any blood glucose levels that would result in trial withdrawal.

There were few other withdrawal criteria that were specific to each trial.

#### Investigational Medicinal Product (IMP) Training:

Every subject randomized to TI received standardized MedTone Inhaler training including verbal instruction (per standardized manual), viewing a video, practice inhalations using an empty cartridge, and using Technosphere Inhalation Powder (placebo). Training on the administration of insulin glargine and insulin aspart was also provided as appropriate. The MedTone Inhaler Model C version was used in all phase 2/3 trials reviewed in sections 6 and 7.

#### Investigational Medicinal Product (IMP) Initial Dosing and Titration:

TI was packaged as single dose cartridges with  $15$  or  $30$  U insulin adsorbed onto Technosphere® particles ( $5$  or  $10$  mg of dry powder, respectively). TI doses are based on the number of insulin units in the cartridge (nominal dose). The bioavailability of insulin administered as TI is approximately  $18-24\%$  relative to subcutaneous rapid acting analog or regular human insulin.

Therefore, in the trials, when subcutaneous insulin was converted to TI, the subcutaneous dose was generally multiplied by 3 to obtain the TI dose. This slightly low conversion factor was used to ensure subject safety and prevent hypoglycemia. TI dosage strengths are linear and interchangeable (i.e., two 15 U cartridges equals one 30 U cartridge) (data supporting this claim are from trial 116).

**Reviewer’s comment: The choice of a conversion factor of 3 may have underestimated the dose of TI required to substitute for subcutaneous insulin in the “therapy switch” studies, i.e. the studies in which subjects already using subcutaneous insulin were converted to TI + basal insulin. If uptitration occurred slowly for any reason such as lack of familiarity with the product, patients may not have reached titration goals by trial endpoints.**

In every trial, TI was administered immediately before the start of each meal (i.e., prandially, 3 to 4 times per day). Occasionally, and as allowed by protocol, additional TI doses were administered in the postprandial period to provide sufficient extension of insulin action, as appropriate.

Insulin glargine was used in all treatment groups requiring basal insulin and insulin aspart was used as the prandial insulin in all studies requiring a prandial insulin comparator.

**Reviewer’s comment: the choice of glargine and aspart insulin is acceptable because these insulin products are commonly used and are considered to be standard of care.**

In an attempt to ensure that equal attempts were made to achieve glycemic control as proposed in the protocol, blinded feedback was given to investigators about overall glycemic control and centrally-measured individual patient HbA1c levels.

A standardized Dosing Guideline was included in the protocols for the following four Phase 3 trials: 102, 103, 030, 009. Other trials were not treat-to-target.

The Dosing Guideline included recommendations from the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE). The target values listed below were provided to investigators for all treatment groups:

- Pre-meal and fasting glucose < 110 mg/dL
- 2-Hour postprandial glucose (PPG) of < 140 mg/dL
- HbA1c of < 7% (ADA) and < 6.5% (AACE) in all but trial 103

In every efficacy trial, investigators used the subject’s hand-held glucose meter results to titrate insulin doses and maintain glycemic control. Subjects used hand-held glucose meters provided by the Sponsor for home glucose monitoring, and subjects recorded fasting glucose and PPG concentrations in diaries. Investigators evaluated 7-point glucose profiles at scheduled clinic and/or telephone visits specific to each trial to titrate insulin doses. Additionally, subjects were encouraged to call investigators if home blood glucose monitoring changed or did not meet glycemic goals.

### Study Endpoints:

The change from baseline in HbA1c (%) was analyzed as a primary or secondary endpoint in every study. HbA1c measurements within each study were performed by a central lab. Except for one study (0008) where measurement was performed by (b) (4), all HbA1c measurements in all studies were performed by one central lab ( (b) (4) ).

Standardized meal challenges were primary or secondary endpoints in many of the studies. These tests included characterization of changes in postprandial glucose (PPG) over time. Meals were standardized within each trial but meal content and measurement parameters differed from trial to trial.

### Statistical Methods:

The Sponsor defined the following analysis populations:

- Safety Population

The Safety Population included all randomized subjects who received at least one dose of study medication.

- Intention-to-treat (ITT) Population

The ITT Population included all randomized subjects who received at least 1 dose of TI or comparator, had a baseline value and at least 1 post-baseline value for the study-specific primary efficacy endpoint. The ITT Population was defined the same way in all trials.

- Per Protocol (PP) Population

The PP Population included all subjects in the ITT Population who completed the trial according to the requirements of the protocol, including the following:

- They met the eligibility criteria, i.e., there were no inclusion/exclusion violations.
- They received treatments according to the randomization schedule.
- In addition, subjects had to provide complete measurements for the study specific primary efficacy variable at baseline and study end.
- Note: In trial 0008 this type of population was called the “Primary Efficacy Population.” The definition of the Primary Efficacy Population in trial 0008 was essentially the same as the PP Population.

Last observation carried forward (LOCF) was the pre-specified method of imputation applied to data from trials 102, 009, 026 and 103. No method of imputation was employed in the primary analysis for the other trials.

A Mixed Model Repeated Measures (MMRM) analysis was used as a secondary analysis of the primary endpoint in trials 102 and 009. This model evaluates the variability associated with the same subject being measured over time and accounts for missing data in the analysis.

PPG was measured at the clinical sites during standardized meal tests. Three different meals with varying caloric and fat content were used during the development of TI. Subjects' usual breakfast dose of TI was given before the standard meal. The Sponsor believed that this made the subjects' meal test data less representative of their individual daily diet. As a result, mean PPG curves were evaluated using a permutation test rather than applying a statistical method based on individual patient data.

### 5.3.3 Individual Clinical Trials

In this section, the following items will be discussed for each trial supporting efficacy.

- Study title, phase, and purpose
- Study design including dates conducted
- Study sites
- Subjects (inclusion, exclusion, withdrawal criteria)
- Study procedures
- Treatments
- Efficacy endpoints
- Statistical analysis plan

The following information for each trial will be discussed in sections 6 and 7.

- Patient disposition
- Demographics, underlying disease and drug treatments
- Outcome of efficacy (exposure/response)
- Outcome of safety assessments
- Discussion of findings/conclusions

#### 5.3.3.1 Type 2 Diabetes Program:

##### 5.3.3.1.1 Placebo-controlled efficacy trials T2DM

**Trial 0008** (TI + OADs vs. TP placebo + OADs)

Study Title: Efficacy and Safety of Inhaled Technosphere Insulin Compared to Technosphere Placebo in Patients with Type 2 Diabetes Mellitus Following Diabetes Education

Study Phase: 2b

Study Purpose: The primary objective of this study was to evaluate the effect of a 12-week treatment period with prandial administration of TI compared to TP placebo on glucose control in subjects with type 2 diabetes mellitus and suboptimal control.

Study Design: A prospective, multicenter, double-blind, randomized (1:1), placebo-controlled, parallel-group study. The study was conducted from 03 Dec 2003 to 04 Nov 2004.

Study Sites: Multicenter in the United States (24 centers)

Subjects: 200 (enrolled with 160 completing). Slow recruitment and time restraints prompted a reassessment of the minimum number of subjects required to assess the endpoint. The recalculated total number of subjects to be enrolled was 130.

Inclusion Criteria: Males or females aged 18 to 80 years, with type 2 diabetes mellitus who were insulin treatment naïve. Although subjects who were not taking antidiabetic medications could have been enrolled, in actuality all were taking single or combination OADs such as metformin, sulfonylurea, or thiazolidinediones. Subjects had to have suboptimal glucose control and have been on a stable oral anti-diabetic medication regimen for at least 3 months. The inclusion criteria were body mass index < 38 kg/m<sup>2</sup> and HbA1c 6.6 to 10.5%.

Also see section 5.3.2 general inclusion criteria and tables 5.3 and 5.4.

Exclusion Criteria: See section 5.3.2 for general exclusion criteria.

Withdrawal Criteria: See section 5.3.2 for general withdrawal criteria. In addition, hyperglycemia was defined as a fasting glucose value of > 270 mg/dL or a non-fasting glucose value of 396 mg/dL. Withdrawal of a subject from the trial due to hyperglycemia was at the discretion of the Investigator. However, any glucose reading > 495 mg/dL was to result in automatic withdrawal from the trial.

Study Procedures:

The study comprised 10 visits (Figure 5.1). The primary purpose of each visit was:

Visit 1: Screening

Visit 2: Diabetes education instruction; and, at selected sites, starting baseline continuous glucose monitoring (CGM)

Visit 3: Randomization and meal challenge test

Visit 4: Evaluation of treatment

Visit 5: Telephone visit - adjust dosing

Visit 6: Meal challenge test

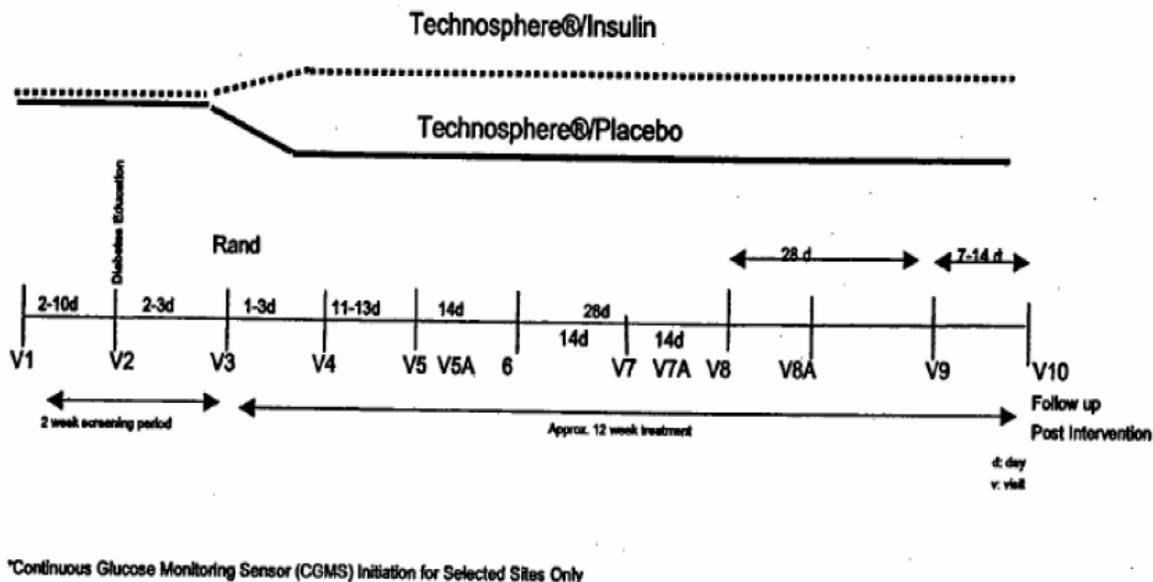
Visit 7: Telephone visit (same as Visit 5)

Visit 8: Meal challenge test; start insulin glargine, if indicated

Visit 9: Meal challenge test; end of study procedures

Visit 10: Telephone follow-up

**Figure 5.1 – Study 0008 Schematic**



Note: Standardized meal challenge tests were performed at Visits 3, 6, 8, and 9.

Source: Figure 1, Trial 0008 CSR

Treatments and Titration of Insulins:

Subjects underwent diabetes education intervention training before randomization. All subjects were receiving stable oral antidiabetic medications at enrollment and continued their usual oral regimen throughout the trial without any changes or additions unless there was a clinical indication for change due to medical necessity. Starting at Visit 3 all subjects received either TI or TP placebo in a randomized, double-blind, parallel-group design. In the early development of TI one of the formulations that was evaluated was a 0.9 U/mg formulation which, when filled at 6.7 mg, provided a 6 U cartridge dose. This formulation was not pursued further following the 0008 study.

Subjects randomized to TI started at 6 U prandially (3 – 4 times per day) at the start of each meal. Subjects were asked to determine blood glucose levels immediately before and 2 hours after the principal meals of each day. The investigator adjusted the dose of study drug during the trial based on blood glucose values (either home or in clinic measurements) in increments of 6 U up to 48 U three to four times daily prandially to maintain fasting blood glucose < 200 mg/dL. However, no specific titration guidelines were included in this protocol. If at Visit 8, the blood glucose was greater than 280 mg/dL, the investigator was to start subcutaneous insulin glargine up to 30 IU once daily in the evening as a rescue medication. (Note: only two subjects ultimately required glargine therapy in this trial).

Efficacy Endpoints: The primary efficacy variable as defined by the protocol was the change from Baseline in HbA1c after 12 weeks of treatment. HbA1c was also measured at 4 weeks and

8 weeks of treatment. The secondary endpoint was postprandial BG area under the concentration-time curve (AUC).

**Statistical Analysis Plan:** The prespecified statistical analysis was a one-sided 2-sample  $t$  test to detect any significant trend between Baseline and final treatment, and to detect any significant difference between treatment groups. The within-group change was tested with a one-sided paired  $t$  test. The primary analysis of HbA1c (%) change from Baseline used the ITT Population and incorporated LOCF imputation. A repeated-measures ANCOVA was performed for analyses of the secondary endpoint of postprandial BG AUC<sub>0-120</sub> minutes. The model included effects for subjects, period, and treatment.

**Reviewer's comment:** The Agency statistical reviewer recommended a two-sided  $t$  test or ANCOVA ideally, because ANCOVA would take into account the baseline HbA1c value, instead of the analysis performed by the Sponsor. The Agency statistician performed these analyses and found them to be similar to the Sponsor's analysis.

**The length of time studied for the glucose AUC analyses is different among trials. For example, in trial 0008 the Sponsor used 2 hours – in 005 they use 5 hours. The implications of this difference is discussed in the clinical pharmacology review but in sum, has made cross-comparison of results across trials difficult.**

Subgroups of the ITT Population were also to be analyzed:

- Group A - Baseline HbA1c 6.6 to 7.9%
- Group B - Baseline HbA1c 8.0 to 10.5%

**Reviewer's comment:** Analyses of these subpopulations were not protected from type 1 error.

**Trial 005** (dose response of TI in combination with insulin glargine)

**Study Title:** A Randomized, Double-blind, Controlled, Stepwise Titration Study to Evaluate Dose Response to Prandial Administration of Inhaled Technosphere Insulin or Technosphere in Patients with Type 2 Diabetes Mellitus Who Are Sub-optimally Treated.

**Study phase:** 2b

**Purpose:** Trial 005 was a placebo-controlled (Technosphere Inhalation Powder [TP] served as the placebo) forced dose-titration study in suboptimally controlled subjects with T2DM. This trial was designed to demonstrate a dose-response relationship to support efficacy.

**Study design:** Prospective, multicenter, randomized (1:1:1:1:1) double-blind, placebo-controlled, parallel group titration study. The study was conducted from 17 Jun 2004 to 30 Aug 2005. TI doses were assigned by randomization group and not by blood glucose concentrations.

Study sites: 31 sites in Western and Eastern Europe (mostly Bulgaria and Czech Republic)

Subjects: 260 to be enrolled and approximately 210 to finish.

**Inclusion criteria:** Male and female subjects from 18 to 80 years with T2DM of a duration of > 3 to < 20 years, glycemic control at upper end of acceptable level or sub-optimal (HbA1c between 7.0 % and 12 %); minimum of 2 months treatment with a stable dose of one or more of the following anti-hyperglycemic agents: sulfonylureas, alpha glucosidase inhibitors, metformin, meglitinides, thiazolidinediones, and/or Lantus basal therapy; fasting blood glucose (FBG):  $\geq 108$  mg/dL; C-peptide:  $\geq 0.5$  nmol/L; BMI < 38 kg/m<sup>2</sup>. Also see section 5.3.2 for general inclusion criteria and tables 5.3 and 5.4.

**Exclusion criteria:** See section 5.3.2 for general exclusion criteria.

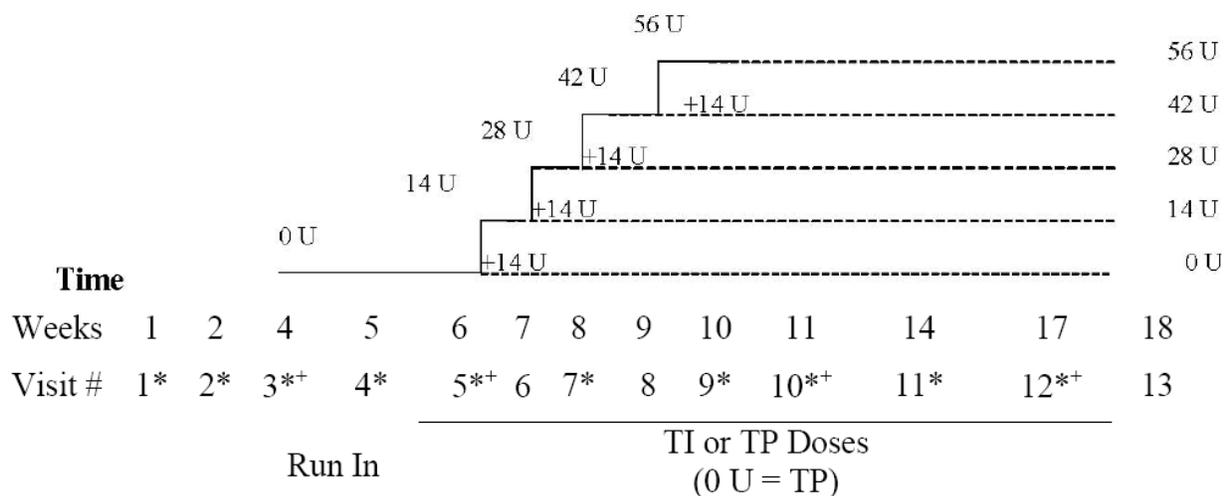
**Withdrawal Criteria:** See the section 5.3.2 for general withdrawal criteria. Additionally, two withdrawal criteria that were specific to trial 005 were the following:

- The subject did not achieve target blood glucose levels at Visits 5, 5a, 5b, 5c, or 10; as described below, an additional 1-3 weeks (Visits 5a, 5b, or 5c) were used to make clinically appropriate adjustments in Lantus dosing to achieve adequate fasting blood glucose (FBG) control.
- The subject experienced hyperglycemia that was excessive from the point of view of the investigator or a blood glucose reading that was greater than 495 mg/dL.

Study Procedures:

(Figure 5.2) At Visit 1 (Week 1) was the screening visit. After screening, qualified subjects were instructed to continue on their OADs and/or Lantus basal insulin therapy. The study run-in period began at visit 2 (Week 2) where subjects were instructed to continue on their OADs and/or Lantus basal insulin therapy and to keep home BG records. At Visit 3 (Week 4) subjects were randomized to one of the following 5 trial groups: TP (Technosphere Powder placebo), 14 U TI, 28 U TI, 42 U TI or 56 U TI but received TP in a single-blind manner for 2 weeks until Visit 5 (Week 6).

**Figure 5.2 - Study 005 schematic**



\*Indicates in-clinic visit

+ Indicates a meal challenge

Source: Figure 3 Trial 005 CSR

At Visit 4 (Week 5), subjects who had not been taking Lantus prior to this visit initiated Lantus at a dose of 10 IU as basal insulin and discontinued OADs while continuing inhalation of single-blind TP for another week. Those already taking Lantus plus OADs discontinued the oral anti-hyperglycemic medication and increased the Lantus dose by 5 IU daily. Subjects taking Lantus but no oral antihyperglycemic medication continued on the same Lantus regimen.

Adjustment of the once daily sc Lantus dose upward by 5-10 IU was undertaken (as clinically appropriate) if any 2 consecutive days of FBG, during Week 5, exceeded the mean FBG plus one standard deviation of the mean established during the 2 weeks of home glucose measurements during the period between Visits 2 and 4 (when the subject was continuing previously prescribed oral agent therapy and/or Lantus). An additional 1-3 weeks (Visits 5a, 5b, or 5c) were used to make clinically appropriate adjustments in Lantus dosing to achieve adequate FBG control. In other words, Visit 5 could be repeated up to two more times if adequate Lantus titration was not achieved by Visit 5. If the subject required additional Lantus titration at Visit 5c, the subject was to be withdrawn from the trial.

At Visit 5 (Week 6), double-blind treatment was initiated in which all subjects randomized to TI began titration at TI 14 U; subjects randomized to TP continued to receive it for the remainder of the trial. Following Visit 5 (Week 6), subjects in the TI 28 U, 42 U, and 56 U groups were force-titrated upward by increases of 14 U to their assigned randomization dose. The TP/TI titration schedule for all subjects was completed at Visit 8 (Week 9). Following Visit 8, subjects remained at their final assigned dose of TP/TI through Visit 12 (Week 17) unless they were prematurely withdrawn from the trial. If, 1 week after completing the last titration step (after Visit 8 [Week 9]), a patient had FBG levels recurrently > 160 mg/dL, the dose of Lantus could

be increased in 5-10 IU increments weekly, to provide sufficient basal insulin to control FBG levels at < 160 mg/dL.

**Reviewer's comment: The study has a less than optimal design. Titration of TI occurred for the highest dose (56U) as few as 8 weeks before the final visit. The effect of the uptitration would not be fully expressed in the final HbA1c measurement because HbA1c is a better reflection of the previous 12 weeks of glycemic control. Also, Lantus could be uptitrated until the end of the study.**

Treatments and Titration of Insulins: Treatments in this trial were Lantus and TI at varying doses as described above. No OADs were permitted after TI was started.

Subjects were to have their TI titrated up as long as there was no hypoglycemia. Lantus was to be titrated downward in the event of hypoglycemia. Lantus could be discontinued if dose becomes less than 10 IU per day and the subject would stay on TI (or placebo) as long as there was no hypoglycemia.

Investigators/subjects were instructed to:

1. Continue titration of TI or TP if:
  - a. No symptomatic hypoglycemia and
  - b. FBG > 72 mg/dL.
2. Reduce Lantus by 10 IU daily and continue titration of TI dose if (any one of the following):
  - a. Symptomatic hypoglycemia confirmed by blood glucose (BG) measurement < 63 mg/dL measured at any time at a frequency of at least once weekly;
  - b. FBG < 72 mg/dL.
3. If the Lantus dose cannot be reduced by 10 IU (Lantus has already been discontinued) and the subject experiences the criteria in #2 (above), stop titration and keep TI dose the same through the end of the trial.
4. If any of the following apply, reduce Lantus by 10 IU daily, stop the TI titration, and keep the TI dose the same through the end of the trial:
  - a. Symptomatic hypoglycemia confirmed by BG measurement < 63 mg/dL measured at any time at a frequency of twice weekly; or
  - b. 2-hour post prandial glucose < 90 mg/dL at a frequency of 4 or more measurements over a 1 week period after any main meal; or
  - c. FBG < 72 mg/dL  $\geq$  3 times per week.
  - d. If the Lantus dose cannot be reduced by 10 IU (Lantus has already been discontinued) and the subject experiences the above, stop the titration and withdraw the subject from the trial.

Efficacy Endpoints:

The primary efficacy variables or endpoints were:

- Change from baseline in HbA<sub>1c</sub> (%) after 11 weeks of treatment [i.e. between Visit 5 (Week 6 /Baseline) and Visit 12 (Week 17)]
- Postprandial BG area under the concentration-time curve (AUC) parameters

The secondary efficacy variables were:

- Fasting blood glucose
- Glycemic control responder rates
  - HbA1c change of  $\leq -0.6\%$  from Baseline
  - HbA1c value  $< 7.0\%$

**Statistical Analysis Plan:**

For the HbA1c endpoint, the primary efficacy analysis was performed on the ITT Population with no imputation for missing data. The primary efficacy analysis was a one-sided *t* test with significance level set at 0.05. A step-down procedure (to reduce type 1 error) using a series of 2-sample *t* tests was applied to perform multiple comparisons between means of TI doses and TP (placebo control) for the primary endpoint. If significance was achieved at the 56 U TI dose level, then the 42 U dose level was tested, and so on, until significance was no longer found.

**Reviewer’s comment: The Agency statistician confirmed that results were comparable when using one-sided t-test and 2-sided t test in these analyses.**

An ANCOVA was also used to analyze the change from Baseline in HbA1c. Three ANCOVA models were used as follows (TALE=time adjusted Lantus exposure):

	Common Main Effects	Common Covariate	Interactions	Other Covariate
Model 1	Treatment, site			Baseline HbA1c
Model 2	Treatment, site	TALE		Baseline HbA1c
Model 3	Treatment, site	TALE	Treatment x TALE	Baseline HbA1c

Time adjusted Lantus exposure =  $[\sum (\text{Lantus dose level} \times \text{dose time})] / (\text{total exposure time})$   
 where: dose level = Lantus dose level at a particular time period, dose time = number of days taking dose level and total exposure time =  $[\sum (\text{dose time})]$ .

For the endpoint of mean PPG excursions ( $AUC_{\text{glucose}}$ ) from 0-300 minutes during a standardized meal challenge, analyses of baseline-corrected PPG  $AUC_{0-300}$  were initially in the SAP. Due to high baseline blood glucose concentrations at the meal challenges, a proportion of the subjects had negative PPG AUCs after baseline-correction. Therefore, nonbaseline-corrected AUCs were calculated for all subjects instead. The summary of change in baseline-corrected  $AUC_{0-300}$  from Visit 5 was presented by treatment group and compared between each TI group and placebo group using the step-down procedure described above.

**5.3.3.1.2 Long-term active-controlled efficacy trials T2DM**

5.3.3.1.2.1 Trial 102 (TI + insulin glargine vs. 70/30 insulin mix)

Study Title: A Prospective, Multi-Center, Open-Label, Randomized, Controlled Clinical Trial Comparing the Efficacy and Safety in Subjects With Type 2 Diabetes Receiving Subcutaneous Basal Insulin and Prandial Inhalation of Technosphere® Insulin Versus Subcutaneous Premixed Insulin Therapy Over a 52-Week Treatment Period and a 4- Week Follow-up

### Study Phase: 3

Study Purpose: The primary objective of this trial was to compare the efficacy of prandial administration of TI in combination with subcutaneous (sc) basal insulin therapy (TI group) vs. a premix of intermediate-acting and rapid-acting insulin (70/30 Novolog mix comparator group) in subjects with suboptimally-controlled T2DM, previously treated with regimens of sc insulins ± OADs.

Study Design: A 52-week treatment period with 4-week follow-up period, prospective, multicenter, open-label, randomized (1:1), controlled trial. The study was conducted from 23 Feb 2006 to 08 Sep 2008.

Study sites: Multiple sites in the United States, Canada, Chile, Argentina, the Russian Federation, Brazil, Mexico, Spain, Poland, and the United Kingdom

Subjects: A sample size of 250 subjects per arm with 52-week data was planned. A total of 677 subjects were randomized to treatment, 334 into the TI arm and 343 into the 70/30 mix arm.

Inclusion Criteria: Eligible subjects were males and females  $\geq 18$  and  $\leq 80$  years of age with a clinical diagnosis of T2DM, an HbA1c  $>7.0\%$  and  $\leq 11.0\%$ , a BMI of  $\leq 40$  kg/m<sup>2</sup>, and had to be non-smokers. Subjects were receiving sc insulin 2-3 times daily administered as any of the following 3 regimens: self-mix regimen, pre-mix regimen, or long-acting analogue and regular or rapid-acting insulin analogue not to exceed 3 daily injections and the total daily dose not to exceed 1.4 IU/kg body weight. Subjects may also have received (in addition to these insulin regimens), OADs including metformin, or thiazolidinediones. Treatment with oral secretagogues (i.e., sulfonylureas, meglitinides), pramlintide, incretin therapy such as exenatide, and alpha glucosidase inhibitors was exclusionary. Eligible subjects had an absence of any dose adjustments for insulin and oral anti-diabetic agents within the preceding 6 weeks.  
Also see section 5.3.2 general inclusion criteria.

Exclusion Criteria:

Also see section 5.3.2 general inclusion criteria.

Exclusion criteria specific to this protocol include

1. Unstable diabetes mellitus control, defined as 2 or more episodes of severe hypoglycemia (requiring third party intervention) and/or any hospitalization or emergency room visit due to poor diabetic control or hyperglycemia requiring hospitalization within the preceding 6 months

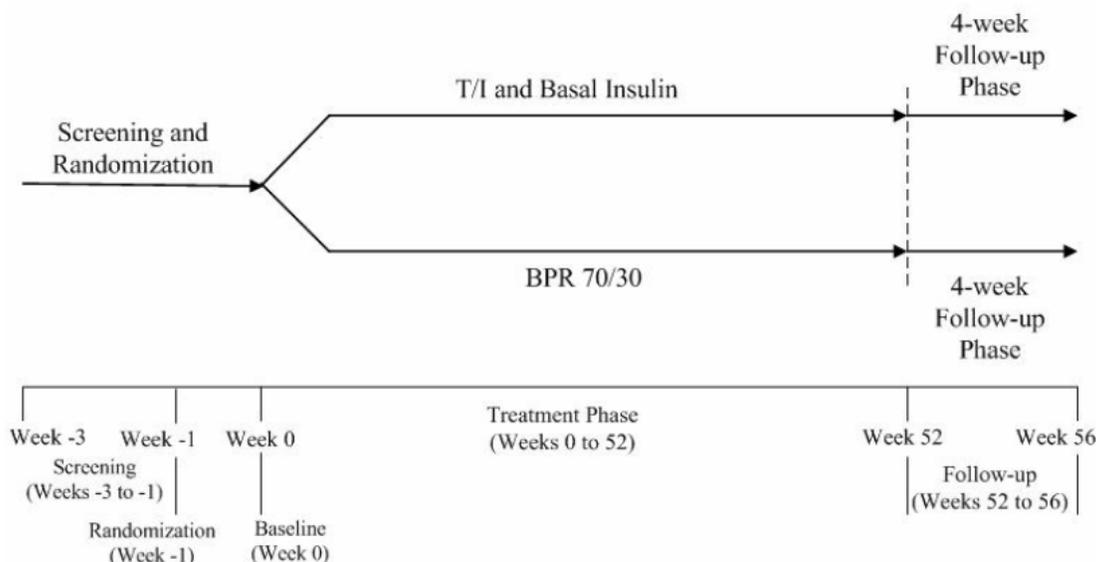
Withdrawal Criteria: see section 5.3.2 general withdrawal criteria.

Study Procedures: (Figure 5.3) Screening occurred at Week-3 (Visit 1). Randomization occurred at Week -1 (Visit 2); subjects were randomized in a 1:1 ratio to one of the following 2 groups:

- TI Inhalation Powder + basal insulin
- 70/30 Novolog insulin mix

Baseline measurements were taken at Week 0 (Visit 3) before the first dose of study treatment. Dose was titrated during Weeks 1 through 10 (the first 10 weeks of the treatment period). Study treatment continued through Week 52.

**Figure 5.3 – Study 102 Schematic**



Source: Figure 2, Trial 102 CSR

**Treatments and Titration:**

Subjects were allowed to continue specified oral anti-diabetic agents that they were using at trial entry.

Subjects in the TI group received sc basal Lantus 1 time per day at bedtime and received inhaled TI 2 to 4 times a day, based on clinical need, prandially. Adjustment of the TI dose and frequency of use to greater than 3 times a day was at the discretion of the investigator. To determine the initial TI dose, the pre-randomization total daily sc insulin dose was calculated. Subjects replaced 50% of the total daily sc insulin dose with a corresponding dose of TI divided between main meals, while the remaining 50% of the total dose of sc insulin was given as basal insulin glargine. At the time of design of the trial, bioavailability of TI was estimated at approximately 24% to 28%. For safety reasons, i.e., to prevent overdosing at the initiation of TI, a conversion factor of 30% was applied. Thus, a 15-U cartridge of TI would correspond to a sc dose of approximately 5 IU of regular insulin or rapid-acting insulin analogs. A subject would require 1 to 3 successive cartridges depending on the total dose of TI required for a meal.

Subjects in the comparator group received sc injection of Novolog Mix 70/30 twice per day (once pre-breakfast and once before main evening meal). Novolog Mix 70/30 was supplied in Novolog Mix 70/30 Penfill cartridges designed for use with the Novopen. Novolog Mix 70/30

Penfill was a mixture of 70% insulin aspart protamine suspension and 30% insulin aspart. The concentration was 100 IU of insulin/mL. Initial 70/30 mix insulin dose was calculated based on the subjects' pre-trial insulin doses. Subjects who entered the clinical trial already on premixed insulins, including BPR (BiPhasic Rapid Acting Insulin) 70/30 and 75/25 and BHI (BiPhasic Human Insulin) 50/50, and who were randomized to comparator (BPR 70/30), were instructed to continue with the same starting daily doses (AM and PM) using Novolog® Mix 70/30. The Investigators educated subjects about the timing of the rapid-acting component in the BPR 70/30 mixture, which should be administered no later than 15 minutes prior to meal initiation.

Subjects who were randomized to BPR 70/30 and who entered the trial on self-mixed insulin regimens (e.g., regular or rapid acting + NPH or Lente or Ultralente) or on long-acting analogue + regular or rapid-acting regimens were initiated as follows:

- If the regular or rapid acting component was  $\geq 20\%$  of the total daily dose (TDD), then the subject was instructed to start BPR 70/30 at the equivalent TDD.
- The distribution of BPR 70/30 dose between meals was to remain unchanged (e.g., if 60% of TDD was administered pre-breakfast, subjects continued with 60% of TDD BPR 70/30 administered pre-breakfast, and the remaining 40% TDD BPR 70/30 administered pre-supper).
- If the subject was receiving a pre-lunch injection, this dose was factored into the prebreakfast dose, and if the subject was receiving a bedtime injection, this dose was factored into the pre-supper dose.
- If the regular or rapid acting component was  $\leq 20\%$  of the TDD, an initial reduction in dose may have been required due to the higher ratio of fast-acting component in the 70/30 Novolog formulation.

Home blood glucose monitoring was used to adjust the dosing of TI/Lantus or Novolog 70/30. At scheduled clinic visits, review of 7-point blood glucose profiles was used for dose titration decision making. In between clinic visits, dose titration decisions were made at the discretion of the Investigator. Subjects were instructed to measure blood glucose at home and communicate this information to the site.

Target blood glucose goals included:

- Pre-meal blood glucose of  $< 110$  mg/dL
- 2-hour postprandial blood glucose of  $< 140$  mg/dL

Target HbA1c goals were  $< 7.0\%$  (ADA recommendation) or  $< 6.5\%$  (AACE recommendation) at the investigators' discretion.

Basal insulin dose was titrated based on the subject's HBGM measurement of fasting plasma glucose. If the FPG 3-day trend was  $> 110$  mg/dL, basal insulin was to be increased by 2-4 IU; if the FPG 3-day trend was  $< 70$  mg/dL, basal insulin was to be decreased by 2-4 IU.

Doses of TI were adjusted in increments of 15 U, as needed, up to a maximum of 90 U per meal. Subjects were allowed small additional doses of TI in the postprandial period (e.g., 15 U at 60 to 90 minutes) in order to provide sufficient extension of insulin action (e.g., subjects with delayed

gastric emptying or when subjects ate very large or fat-rich meals). TI dose titration for a particular meal was based on *trends* of at least 3 recent HBGM values (for that meal) occurring over a period of 3 days (e.g., the 3 days of 7-point blood glucose profiles as follows:

- The pre-breakfast TI dose was titrated based on the subject's pre-lunch blood glucose trend,
- The pre-lunch TI dose was titrated based on the subject's pre-supper blood glucose trend,
- The pre-supper TI dose was titrated based on the subject's bedtime blood glucose trend:
  - If the preprandial glucose trend of the next meal or bedtime glucose was  $> 110$  mg/dL, TI was to be *increased* by 15 U, unless hypoglycemia had occurred in the postprandial period.
  - If the preprandial glucose trend of the next meal or bedtime glucose was  $\leq 110$  mg/dL (6.1 mmol/L), and  $> 80$  mg/dL (4.5 mmol/L), no TI adjustment was necessary.
  - If the preprandial glucose trend of the next meal or bedtime glucose was  $< 80$  mg/dL, TI was to be *reduced* by 15 U.
- The maximum TI dose was 90 U per meal. For most subjects, the requirement was likely to be the same for each meal; in some subjects, different doses were required for breakfast, lunch, or supper.
- Adjustment of mealtime TI dose may have required an adjustment of the basal insulin dose. FPG was closely monitored when dosing of TI was adjusted.

Pre-breakfast and pre-evening meal Novolog 70/30 mix doses were adjusted *independently* of each other as follows:

- Any dose titration or adjustment was to be based on trends of at least 3 recent HBGM fasting and/or pre-supper values;
- Novolog 70/30 was to be titrated and adjusted to achieve target FPG and pre-supper plasma glucose values of between 80-110 mg/dL; and
- Novolog 70/30 pre-supper dose was to be titrated or adjusted based on FPG values while Novolog 70/30 pre-breakfast dose was to be titrated or adjusted based on pre-supper plasma glucose.

#### Efficacy Endpoints:

The primary efficacy endpoint was the change from Baseline (Week 0) to Week 52 in HbA1c. Secondary efficacy endpoints included percentages of subjects reaching HbA1c targets of  $\leq 6.5\%$ ,  $\leq 7.0\%$ , and  $\leq 8.0\%$ , postprandial BG area under the concentration-time curve (AUC) parameters, and fasting plasma glucose. This reviewer also examined body weight.

Statistical Analysis Plan: Non-inferiority was assessed using pre-specified Analysis of Covariance (ANCOVA) and Mixed Model Repeated Measures (MMRM) analyses using the ITT Population. The pre-determined non-inferiority margin was 0.4%. A confidence interval (CI) approach was utilized to assess the hypothesis as follows: if the upper limit of the 95% CI of the mean difference in HbA1c between TI and Comparator was  $< 0.4\%$ , TI treatment was noninferior to the Comparator treatment.

#### **5.3.3.1.3 Short/intermediate term active-controlled efficacy trials T2DM**

Trial 014 (TI + insulin glargine vs. insulin aspart + insulin glargine)

**Study Title:** A Phase 3 Randomized, Open Label, Multi-Center, Comparative Study of Technosphere® Insulin Inhalation Powder Versus Rapid Acting Insulin in Subjects with Type 2 Diabetes Mellitus Receiving Lantus® as Basal Insulin with a 22-Week Post Treatment Follow-up Period on Conventional Therapy

**Study Phase:** 3

**Study Purpose:** The primary efficacy objective was to compare the efficacy of prandial TI plus basal insulin versus prandial rapid-acting sc insulin plus basal insulin after 24 weeks in subjects with T2DM.

**Study Design:** A randomized (2:2), open label, multi-center study. The study was conducted from 24 Dec 2004 to 11 Jul 2006.

**Study Sites:** Multiple sites all in Russia

**Subjects:** The goal was to have 240 evaluable subjects (120 in each arm). With a projected 20% dropout rate, each treatment arm would need to enroll approximately 150 subjects with a total enrollment of approximately 300 subjects.

**Inclusion Criteria:** Eligible subjects were males or females  $\geq 18$  and  $\leq 80$  years of age with a diagnosis of T2DM for at least 2 years, body mass index (BMI)  $< 44$  kg/m<sup>2</sup>, HbA1c  $\geq 7.0\%$  and  $\leq 11.5\%$ , serum creatinine  $< 2.0$  mg/dL for males and  $< 1.8$  mg/dL for females and had been receiving sc insulin for at least 3 months prior to entry in the trial. See also section 5.3.2 for tables of specific inclusion criteria across trials.

**Exclusion Criteria:** See section 5.3.2 for general exclusion criteria.

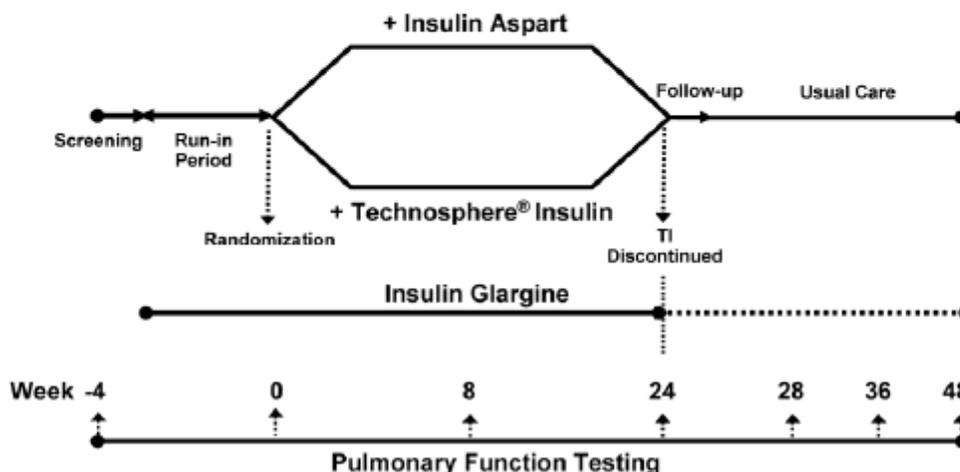
**Withdrawal Criteria:** See section 5.3.2 for general withdrawal criteria. In addition, the following criterion was specific to this trial.

1. If, despite increases in TI Inhalation Powder doses to 60 U per meal, the measured fasting blood glucose (BG) levels were repeatedly  $\geq 270$  mg/dL then the subject should be withdrawn from the trial. Note: at the time this trial was designed type 2 subjects had been studied for up to three months with doses of TI ranging from 6 to 48 U TID (see trial 0008) which is why a maximum of 60 U was selected for trial 014. Subsequent studies used higher doses.

**Study Procedures:** (Figure 5.4) The trial consisted of 17 visits; a Screening Visit (Visit 1), a run-in period to stabilize subjects on insulin glargine (Visits 2 through 5), followed by randomization, MedTone inhaler training (for those subjects randomized to TI Inhalation Powder), administration of first dose of trial medication at Visit 5, and subsequent titration of prandial insulin therapy. Subjects were randomized to TI Inhalation Powder plus insulin glargine or insulin aspart plus insulin glargine and remained on their assigned treatment regimen for a period of 24 weeks.

**Figure 5.4 – Trial 014 Study Schematic**

Visit	V <sub>1</sub>	V <sub>2</sub>	V <sub>3</sub>	V <sub>4</sub>	V <sub>5</sub>	V <sub>6</sub>	V <sub>7</sub>	V <sub>8</sub>	V <sub>9</sub>	V <sub>10</sub>	V <sub>11</sub>	V <sub>12</sub>	V <sub>13</sub>	V <sub>14</sub>
Days	-28 to -22	-21	-14	-7	1	7	14	28	56	84	112	140	168	182
Week	-4	-3	-2	-1	0	+1	+2	+4	+8	+12	+16	+20	+24	+26
Phase	Screening	Run-in		Treatment (Technosphere® Insulin Inhalation Powder or Insulin Aspart [NovoRapid®])										Follow-up



Source: Figure 3, Trial 014 CSR

**Treatments and Titration:** At Visit 2 (Week -3), subjects were discontinued from their prescribed anti-diabetic medications (oral agents, previous insulins). Only TI, insulin aspart, and insulin glargine were allowed antihyperglycemic drugs from Visit 2 onward. At Visit 2, glargine was started at 10 or 20 IU to be given at bedtime. Dosing guidelines included a limit on insulin glargine dosing during the run-in period to ensure that subjects were not over-insulinized with basal insulin prior to the titration period with TI or insulin aspart. During the treatment phase of the trial (after the initiation of prandial insulin therapy), insulin glargine titration at the discretion of the investigator was allowed weekly as necessary to maintain fasting blood glucose  $\geq 81$  mg/dL and  $\leq 162$  mg/dL.

Starting at Visit 5, both TI and insulin aspart were taken immediately before each of three main meals of the day, with a fourth dose taken if the subject consumed an additional mixed meal or snack. Subjects randomized to the TI group started at TI 15 U and were titrated as needed, to a maximum of 60 U per meal. Subjects randomized to the insulin aspart group started at an insulin aspart dose between 4 and 8 IU and were titrated up in increments of 2-4 IU per meal. Titration occurred at the investigator’s discretion on the basis of in clinic or home blood glucose monitoring reports. Investigators were not given a specific HbA1c or FPG goal to treat to. Investigators were allowed to titrate the prandial insulins at their clinical discretion.

**Efficacy Endpoints:** The primary efficacy variable was the mean change in HbA1c (%) from Baseline to the end of the 24-week treatment period.

**Statistical Analysis Plan:**

The Sponsor pre-defined the Per Protocol Population (PP) as the primary efficacy analysis population. All efficacy analyses performed on the PP Population were also performed on the ITT Population. A Last Observation Carried Forward (LOCF) method was used for imputation of missing data. ANCOVA models including site and treatment group as fixed effects and baseline value as covariate were used to establish equivalence between the 2 treatment groups based on mean change in HbA1c (%) from baseline to 24 weeks. An approach using CIs was conducted, where 90% and 95% CIs of the difference between the least squares means of the 2 treatment groups was measured. Equivalence of 2 treatment groups would be established if the lower bound of the CI was greater than -0.4% and the upper bound of the CI was less than 0.4%.

**Trial 026** (TI + usual care [diet/exercise ± OADs] vs. usual care)

**Study Title:** A Prospective, Controlled, Multi-Center, Open-label, Randomized, 12-Week Safety and Efficacy Trial of Inhaled Technosphere® Insulin in Patients with Type 2 Diabetes Mellitus Who Are Suboptimally Treated

**Study Phase:** 2b

**Study Purpose:** To evaluate HbA1c (%) following 12 weeks of TI dosing.

**Study Design:** A Phase 2b, randomized, (5:1), controlled, open-label, multicenter, 12-week efficacy trial. The Study was conducted from 12 Aug 2004 to 28 Jan 2005. *The Sponsor notes that because this trial was one of the first long-term trials with TI, an unbalanced design (75 subjects in the TI group and 15 subjects in the control group) was chosen in order to obtain maximal experience with TI treatment. The primary objective in this early trial was to evaluate the effect of TI, rather than make a formal comparison to conventional treatment.*

**Study Sites:** Multiple sites in the Russian Federation.

**Subjects:** Ninety subjects were planned (TI, N=75; control, N=15).

**Inclusion Criteria:** The trial population included male and female subjects who had been diagnosed with T2DM >2 to <20 years prior to screening and who were sub-optimally controlled (HbA1c of 7.5-12%) on a regimen of diet and exercise and/or one or more OADs, and who were insulin naive. Subjects were to have a fasting blood glucose (FBG) concentration  $\geq 108$  mg/dL and a historical record of blood glucose >200 mg/dL 2 hours postprandially or 2 hours following a glucose tolerance test. Subjects also were to have a body mass index (BMI) <38 kg/m<sup>2</sup>.

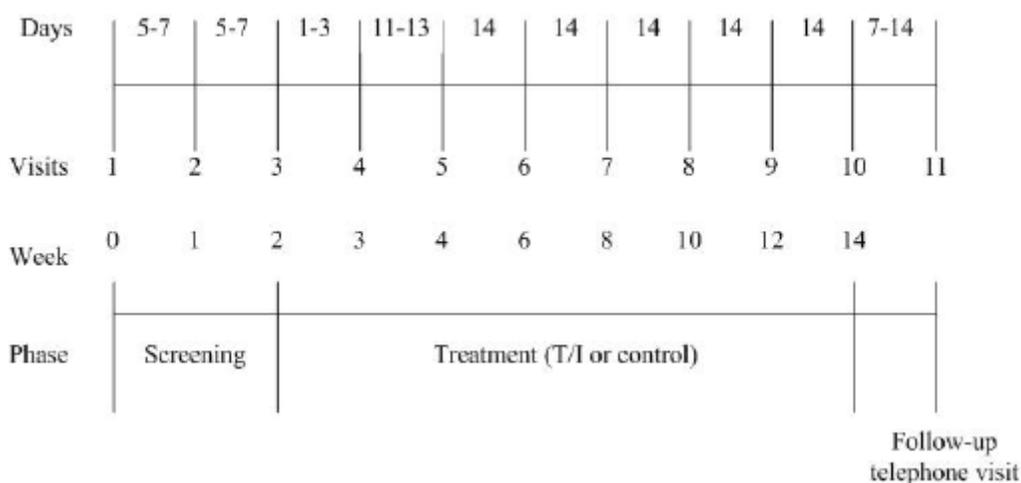
See also tables in section 5.3.2

Exclusion Criteria: See general exclusion criteria in section 5.3.2,

Withdrawal Criteria: Similar to those described in section 5.3.2. In addition, hyperglycemia was defined as a fasting glucose value of > 270 mg/dL or a non-fasting glucose value of 396 mg/dL. Withdrawal of a subject from the trial due to hyperglycemia was at the discretion of the Investigator. However, any glucose reading > 495 mg/dL was to result in automatic withdrawal from the trial.

Study Procedures: (Figure 5.5) Trial 026 included 11 visits during a 15- to 16-week period. Key visits included: Visit 1 (Week 0, screening); Visit 2 (Week 1, randomization and training in glucose monitoring and use of the MedTone Inhaler for those randomized to TI), Visit 3 (Week 2, initiation of active treatment); Visit 10 (Week 14) (final visit of the treatment period); and Visit 11 (follow-up telephone contact visit).

**Figure 5.5 –Trial 026 Study Schematic**



Source: Figure 3, Trial 026 CSR

Treatments: Subjects in both groups were to continue to take their previously prescribed oral antihyperglycemic therapy (if any) at unaltered doses. Subjects were to receive either TI (15-60 U) 3 or more times daily, depending on eating routine, or no TI for 12 consecutive weeks depending on randomization group. Subjects in the TI treatment group initially received 15 U TI immediately prior to meals starting at Visit 3 (Week 2). At Visit 4 (Week 3), the dose could be increased to 30 U if necessary. At subsequent visits, the dose could be adjusted in 15 U increments or decrements or could remain at the current level, as needed based on fasting and 2-hour postprandial blood glucose levels or the occurrence of symptomatic hypoglycemia.

Efficacy Endpoints: HbA1c (%) following 12 weeks of TI dosing.

Statistical Analysis Plan: The ITT Population was defined as the primary efficacy population for this trial. Supportive analyses were done with the PP Population. For the analysis of change

from baseline in HbA1c, a one-sample (paired) t-test with significance level of 0.05 was to be used to test the difference in HbA1c between baseline (Week 2) and study end (Week 14) within the TI and control groups. LOCF approach was used for imputation of missing data for subjects with at least one post-baseline HbA1c value.

**Trial 103 (TI + Metformin vs. TI alone vs. Metformin + Secretagogue)**

Study Title: A Phase 3, 24-Week, Multi-Center, Open Label, Randomized, Controlled Trial Comparing the Efficacy and Safety of Prandial Inhalation of Technosphere® Insulin in Combination with Metformin or Technosphere® Insulin Alone Versus 2 Oral Anti-Diabetic Agents (Metformin and a Secretagogue) in Subjects With Type 2 Diabetes Mellitus Sub-Optimally Controlled on Combination Metformin and a Secretagogue

Study Phase: 3

Study Purpose: The primary objective of this study was to demonstrate the efficacy of prandial TI in combination with metformin versus combination metformin and a secretagogue (sulfonylurea or meglitinide) in subjects with suboptimally controlled type 2 diabetes mellitus.

Study Design: 24-week, multi-center, open label, randomized (1:1:1), controlled study conducted from 31 May 2006 to 03 Mar 2008.

Study Sites: Multiple sites worldwide

Subjects: A sample size of 140 subjects per treatment group for a total of 560 subjects was planned.

Inclusion Criteria: Eligible subjects were males and females  $\geq 18$  and  $\leq 80$  years of age with a clinical diagnosis of T2DM for  $\geq 6$  months, an HbA1c  $\geq 7.5\%$  and  $\leq 11.0\%$ , a BMI of  $\leq 40$  kg/m<sup>2</sup>, and a non-smoker. Subjects were on a stable regimen of metformin  $\geq 1000$  mg/day (or maximum tolerated dose) and a secretagogue (sulfonylurea or meglitinide)  $\geq \frac{1}{2}$  the manufacturer-recommended daily dose (or maximum tolerated dose) without any dose, brand and/or formulation (i.e., immediate or extended release) adjustments within the preceding 6 weeks. Fixed dose combination products of metformin and sulfonylurea were acceptable as long as each dose met the inclusion criteria. Treatment with any other diabetic therapy including insulin was not allowed (see exclusion criteria below).

See also section 5.3.2 tables 5.3 and 5.4

**Reviewer's comment: The metformin dose ideally should have been near maximal or maximal (i.e.  $\geq 1500$  mg/day).**

Exclusion Criteria: See section 5.3.2 tables 5.3 and 5.4. Additional exclusion criteria were:

- Treatment with any type of anti-diabetic therapy, other than metformin and secretagogues (sulfonylureas or meglitinides), within the preceding 12 weeks;
- Currently on insulin or has been discontinued from insulin within the preceding 12 weeks;
- Two or more severe hypoglycemic episodes within 6 months of screening or episode of severe hypoglycemia between Visit 1 (Screening) and Visit 2 (Baseline);
- Any hospitalization or emergency room visit due to poor diabetic control within 6 months of screening or hospitalization or emergency room visit due to poor diabetic control between Visit 1 (Screening) and Visit 2 (Baseline);
- Active respiratory infection;
- Uncontrolled hypertension with a systolic blood pressure of > 180 mm Hg and/or diastolic blood pressure > 110 mm Hg at Screening, despite pharmacologic treatment;

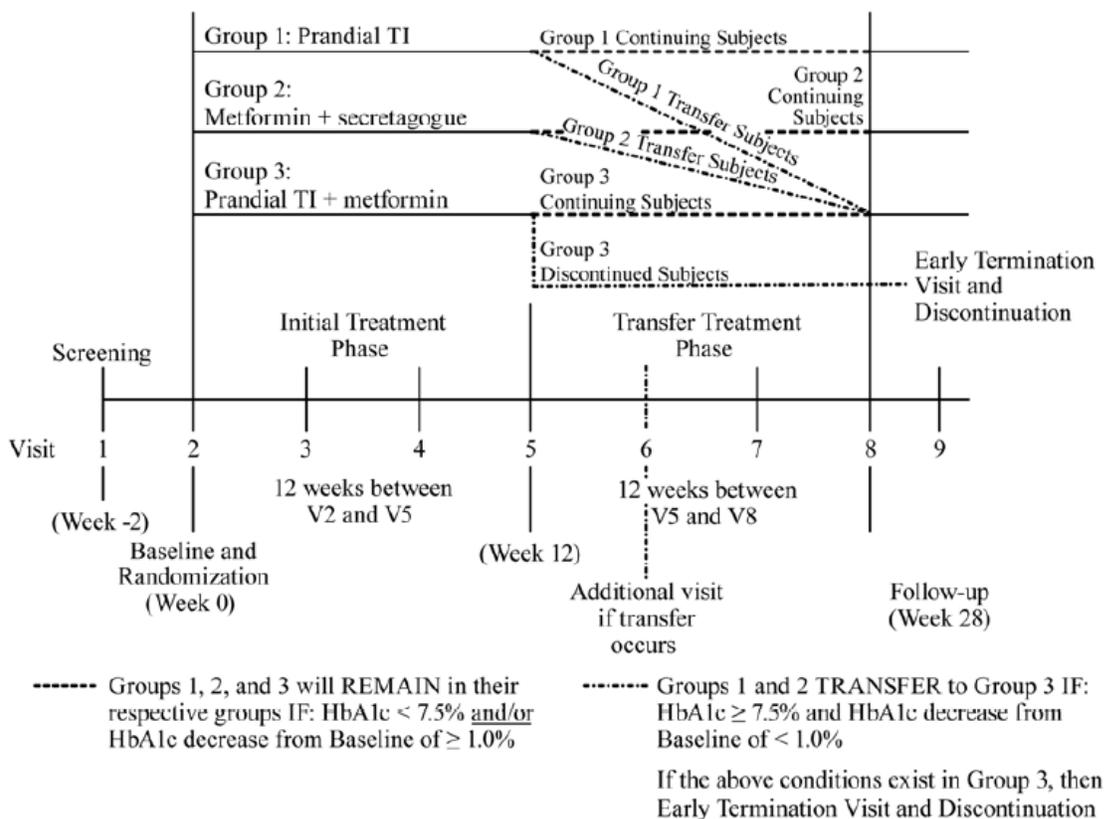
Withdrawal Criteria: See section 5.3.2.

Study Procedures: (Figure 5.6) This study had 2 treatment periods. The initial 12-week period was a randomized 3-arm study where subjects experiencing suboptimal glycemic control on metformin plus a secretagogue were randomized in a 1:1:1 ratio to either TI alone, TI + metformin, or metformin + secretagogue. Randomized subjects received anti-diabetic treatment based on their randomization group for the first 12 weeks; the subsequent 12-week period was considered observational in nature.

Subjects in Groups 1 and 2 with continued suboptimal control (HbA1c of  $\geq 7.5\%$  and reduction from Baseline  $< 1\%$ ) after 12 weeks of therapy, in any of the 3 treatment groups, were required to transfer to TI Inhalation Powder + metformin. Subjects in Group 3 discontinued participation in the study. The total duration of the treatment period was 24 weeks.

The clinical study consisted of 9 clinic visits for subjects; a screening visit, Baseline visit, 6 treatment phase visits and 1 follow-up visit. Additionally, there were 5 telephone contacts during the treatment phase (Figure 5.6).

**Figure 5.6 – Study Schematic for Trial 103**



Source: Figure 4, Trial 103 CSR

**Treatments and Titration:** Treatments were TI and metformin and secretagogues (sulfonylureas or meglitinides). TI Inhalation Powder was administered immediately prior to each meal (i.e., 2 to 4 times per day). Subjects started at TI 15 U per meal and were titrated as needed, to a maximum of 90 U per meal, at the Investigator’s discretion on the basis of in clinic or home BG monitoring reports. There was no maximal daily dose specified by the protocol. (If subjects gave themselves a fourth dose for a fourth meal or for a postprandial dose the total dose could be higher than 270.) For the oral agents, any brand or formulation could be used but the brand/formulation had to stay constant throughout the treatment period. Treatment with anti-diabetic therapies other than TI Inhalation Powder, metformin, and secretagogues was not allowed. The Investigators were not given a specific HbA1c goal and were allowed to titrate TI Inhalation Powder at their clinical discretion with upper limits specified for preprandial (<110 mg/dL), postprandial (<140 mg/dL), and bedtime (< 110 mg/dL) blood glucose (BG) levels. Subsequent dose adjustments (when appropriate) were made at scheduled clinic visits and/or telephone contacts. At each scheduled study visit or telephone contact, it was suggested that dose titration decision-making be based principally on the 7-point capillary blood profiles (i.e., preprandially, 2-hour postprandially and at bedtime) conducted on any 3 days during the week immediately preceding each visit or telephone contact. Subjects could perform additional BG

monitoring according to the recommendations of the Investigator and subjects were instructed to contact the clinical site should they note changes in their SBGM. Initially, subjects were advised to monitor BG preprandially and at bedtime. To further improve glycemic control, subjects were advised that assessments of 2-hour postprandial BG levels by SBGM would be helpful for secondary “fine-tuning”. For subjects in the TI + metformin arm, adjustments of the metformin dose were allowed and were made on the basis of SBGM profiles, laboratory results and/or clinical findings at the discretion of the Investigator and according to standard practice of diabetes management. Adjustments of the metformin and/or secretagogue doses, up to manufacturer-recommended maximal daily doses and in consideration of clinical parameters such as renal function, were allowed as well, and were made on the basis of SBGM profiles, laboratory results and/or clinical findings at the discretion of the Investigator and according to the same glucose goals as for the TI titration.

**Reviewer’s comment: It is not ideal to change OAD therapy during the treatment portion of the clinical trial.**

Efficacy Endpoints: The primary efficacy endpoint was a comparison of the mean change from Baseline (Week 0) to Visit 5 (Week 12) in HbA1c (%) between subjects treated with TI in combination with metformin and the combination metformin and secretagogue treatment group. The TI alone group was not included in the primary efficacy analysis. Secondary/other endpoints included fasting plasma glucose and body weight.

Statistical Analysis Plan: The primary objective was to demonstrate the superiority of TI in combination with metformin over the combination metformin and a secretagogue in an ANCOVA model using the ITT Population with Last Observation Carried Forward (LOCF). The analysis model included treatment group and investigator site as the class variables and Baseline HbA1c (%) values as a covariate. Adjusted (Least-Square) estimate of the mean difference along with its 2-sided 95% CIs were calculated and used for the superiority assessments. Superiority was concluded if the upper limit of the 95% confidence interval (CI) of the mean difference between 2 treatment groups in change from Baseline at Week 12 was less than zero.

### **5.3.3.2 Type 1 Diabetes Program:**

#### **Long-term active-controlled efficacy trial T1DM**

**Trial 009** (TI + insulin glargine vs. insulin aspart + insulin glargine)

Study Title: A Prospective, Multi-Center, Open-Label, Randomized, Controlled Clinical Trial Comparing the Efficacy and Safety in Subjects with Type 1 Diabetes Receiving Subcutaneous Basal Insulin and Prandial Inhalation of Technosphere®/Insulin Versus Subcutaneous Basal and Prandial Insulin Over a 52-Week Treatment Period and a 4-Week Follow-up

Study Phase: 3a

Study Purpose: The primary objective was to evaluate the efficacy (change in HbA1c) over a 52-week period of prandial administration of TI in combination with basal insulin therapy versus rapid-acting prandial sc insulin aspart in combination with basal insulin (a standard of care regimen) in subjects with T1DM previously treated with regimens of basal plus prandial insulin therapy.

Study Design: A prospective, multi-country, multicenter, open label, randomized (1:1), controlled clinical trial. The study was conducted from 23 Feb 2006 to 26 May 2008.

Study Sites: Multiple sites in Argentina, Brazil, Canada, Chile, Mexico, Poland, the Russian Federation, Spain, the United Kingdom, and the United States.

Subjects: A total of 590 subjects were planned to be randomized to complete 500.

Inclusion Criteria: Eligible subjects were males and females  $\geq 18$  and  $\leq 80$  years of age with a clinical diagnosis of type 1 diabetes for at least 1 year, maintenance of a treatment regimen of insulin  $\leq 1.4$  IU/kg/day, body mass index  $\leq 35$  kg/m<sup>2</sup>, HbA1c  $> 7.0\%$  and  $\leq 11.0\%$ , and serum creatinine  $\leq 1.8$  mg/dL in female subjects and  $\leq 2.0$  mg/dL in male subjects

See also general inclusion criteria.

Exclusion Criteria: See section 5.3.2 general exclusion criteria. Additional exclusion criteria specific to this protocol are:

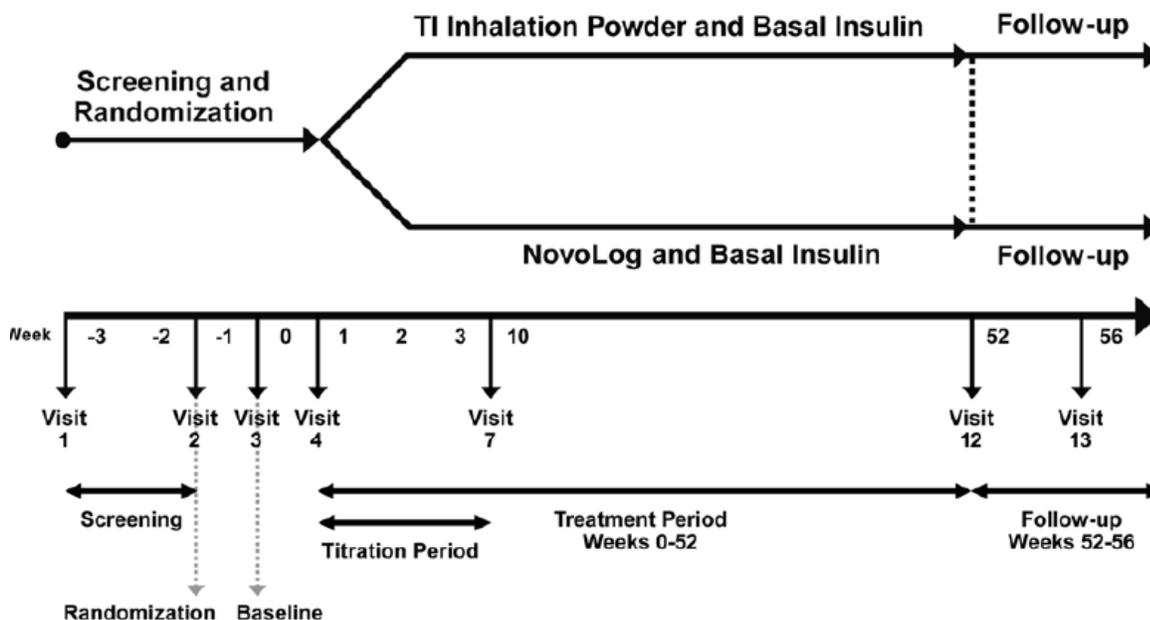
1. Insulin delivery pump within the preceding 8 weeks AND change from insulin delivery pump to multiple daily insulin injections based on medical indications (e.g., a multiple daily- injection regimen is deemed superior to insulin delivery pump for subject)
2. C-peptide  $> 0.20$  pmol/mL
3. Unstable diabetes control, defined as  $\geq 2$  episodes of severe hypoglycemia requiring third-party intervention or a hospitalization or emergency room visit due to poor diabetic control within the preceding 6 months
4. Poorly controlled arterial hypertension despite pharmacologic treatment, defined as systolic blood pressure  $> 180$  mm Hg or diastolic blood pressure  $> 110$  mm Hg at screening
5. Active respiratory infection

Withdrawal Criteria: See section 5.3.2 general withdrawal criteria.

Study Procedures:

This study included a 52-week treatment phase and a 4-week follow-up phase (Figure 5.7). The study began with enrollment and screening procedures starting at Week -3.

**Figure 5.7 – Trial 009 Study Schematic**



Source: Figure 1, Trial 009 CSR

At Week -1, subjects were randomized in a 1:1 ratio to receive one of the following treatments:

- Basal insulin + prandial TI
- Basal insulin + prandial sc insulin aspart

The beginning of treatment and the baseline measurement of efficacy variables occurred at Visit 3 (Week 0). At the beginning of the treatment phase, subjects had several titration/dose evaluation visits to adjust insulin therapy. Titration visits occurred once a week for the first 4 weeks. At Week 6, Week 8, and Week 10, there were 3 telephone “visits” to titrate dose if necessary. However, dose titration was allowed throughout the trial.

A meal challenge test was performed at Week 4 (during dose titration), Week 26, and Week 52.

Subjects participated in 5 clinical assessment visits during the 52-week treatment phase (Week 0 and Weeks 14, 26, 38, and 52).

During the 4-week follow-up phase, pulmonary function and selected clinical laboratory assessments were scheduled. One follow-up visit occurred at Week 56 for safety evaluations.

Treatments and Titration:

Subjects assigned to the TI group (TI + basal insulin therapy) received sc basal insulin glargine (Lantus) once daily at bedtime and inhaled TI 3 to 4 times daily, immediately before main meals or a snack as based on clinical need. Doses of TI Inhalation Powder were adjusted in increments of 15 U, as needed, up to a maximum of 90 U per meal.

Subjects were transferred from prior insulin regimens to starting doses of TI based on the following guidelines. The previous total daily insulin dose of each subject was calculated. 50% of the previous daily dosage was given as insulin glargine with the rest of their daily requirements being provided by TI. After calculating the daily sc prandial insulin dose to be replaced by TI, these sc doses were multiplied by 3 and then rounded down to the nearest 15 U when calculating the corresponding TI dosage.

Subjects in the comparator group received sc basal insulin glargine once daily (at bedtime) and sc injection of rapid-acting insulin (NovoLog/NovoRapid) 3 to 4 times daily, immediately before main meals (no later than 10 minutes before meals).

Subjects who entered the trial while taking a rapid-acting insulin or regular insulin and were randomized to comparator continued on rapid-acting insulin. Prior regular insulin or rapid acting insulin treatment was replaced by a 1:1 unit transfer to insulin aspart. Rapid-acting insulin comprised 50% to 70% of the total daily dose of insulin, divided according to the number of daily meals.

Basal insulin was provided as glargine. Subjects using other basal insulins were transferred to comparable doses of glargine. The basal insulin dose was titrated based on the subject's HBGGM of FPG. The decision to increase, decrease, or remain at the current dose of basal insulin was based on the trends of at least 3 recent FPG values from 3 days (e.g., the 3 days of 7-point glucose profiles):

- If FPG trend was  $> 110$  mg/dL, basal insulin was increased by 2 - 4 IU
- If FPG trend was  $< 70$  mg/dL, basal insulin was decreased by 2 - 4 IU

Investigators were instructed to titrate basal and prandial insulins to acceptable glycemic control based on ADA recommendations but without a forced titration algorithm.

Glycemic control targets for adjustment of dosage of TI Inhalation Powder or insulin aspart included:

- Pre-meal BG  $< 110$  mg/dL
- 2-hour postprandial BG  $< 140$  mg/dL
- HbA1c  $< 7.0\%$  (ADA guidelines) or  $< 6.5\%$  (AACE guidelines)

At scheduled clinic visits, the 7-point BG profiles were reviewed to guide dose titration. Between clinic visits, dose titration decision-making was made at the direction of the investigator. Subjects were instructed to measure BG at home and communicate this information to the site. It was suggested that subjects initially monitor their BG preprandially and at bedtime. Later, 2-hour postprandial BG assessments could be used to further titrate doses. If a subject did not provide 3 HBGGM values for a particular meal's dose titration or FPG either at clinic visits or between clinic visits, a dose titration for that particular meal or FPG could not be made.

#### Efficacy Endpoints:

The primary efficacy endpoint was the change from Baseline to Week 52 in HbA1c (%).

Secondary efficacy endpoints included percentages of subjects reaching HbA1c targets of  $\leq 6.5\%$ ,  $\leq 7.0\%$ , and  $\leq 8.0\%$ , postprandial BG area under the concentration-time curve (AUC) parameters, fasting plasma glucose, and body weight.

Statistical Analysis Plan:

An ANCOVA model was used to attempt to demonstrate noninferiority of TI Inhalation Powder + basal insulin over the comparator drug + basal insulin with a predetermined margin of 0.4%. The analysis model included pooled investigator sites and treatment group as the class variables and baseline HbA1c (%) values as a covariate. The ITT Population with LOCF was used as the primary analysis population. An MMRM analysis was also performed. For analysis of secondary endpoints, in order to maintain an overall type I error rate of 0.05, selected secondary efficacy endpoints were evaluated sequentially, with each endpoint tested at an alpha of 0.05 and with pair-wise comparisons performed at the 2-sided alpha level of 0.05.

**Short/intermediate term active control trial T1DM**

**Trial 101** (TI + Lantus vs. Insulin aspart + Lantus)

Study Title: Phase 2 Randomized, Open Label, Multicenter Substitution Study of the Use of Prandial Inhaled Technosphere® Insulin in Combination with Basal Subcutaneous Lantus® Insulin versus Prandial Subcutaneous NovoRapid® Insulin in Combination with Basal Subcutaneous Lantus® Insulin in Subjects with Type 1 Diabetes

Study Phase: 2

Study Purpose: The primary objective of this study was to evaluate the effect of the substitution of prandial subcutaneous (sc) insulin with TI, in comparison to subjects who maintain sc therapy, as expressed by postprandial glucose excursions in subjects with T1DM.

Study Design: Randomized, open-label substitution study conducted from 03 Mar 2005 to 27 Dec 2005.

Study Sites: Multicenter in Russia

Subjects: Planned population size of 90

Inclusion Criteria: Nonsmoking males and females  $\geq 18$  and  $\leq 80$  years of age with a diagnosis of T1DM for at least 2 years and receiving sc insulin at meal times and Lantus or other basal insulin in stable doses with no record of lasting changes in total insulin dose of  $> 20\%$  during the past 3 months; body mass index (BMI)  $> 40$  kg/m<sup>2</sup>; HbA1c (%)  $\geq 7.0\%$  and  $\leq 11.5\%$ ; serum creatinine  $< 2.0$  mg/dL for males and  $< 1.8$  mg/dL for females

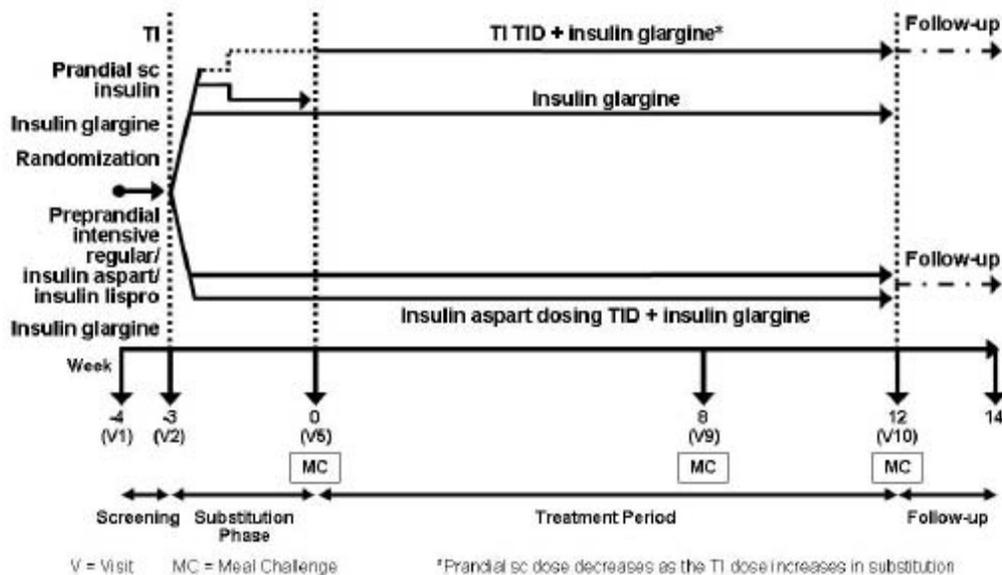
See also section 5.3.2 for general inclusion criteria

Exclusion Criteria: see general exclusion criteria. Additionally subjects were excluded for having an upper respiratory infection within the 15 days prior to study enrollment.

Withdrawal Criteria: See section 5.3.2 for general withdrawal criteria. In addition, hyperglycemia was defined as a fasting glucose value of > 270 mg/dL or a non-fasting glucose value of 396 mg/dL. Withdrawal of a subject from the trial due to hyperglycemia was at the discretion of the Investigator. However, any glucose reading > 495 mg/dL was to result in automatic withdrawal from the trial.

Study Procedures: (Figure 5.8) The study comprised 4 periods: a screening period of up to 7 days, a 3-week substitution period during which sc insulin was replaced with TI in a stepwise fashion in the TI group), a 12-week treatment period, and a 2-week follow-up period (total duration of study, approximately 18 weeks) (Figure 5.8).

**Figure 5.8 – Trial 101 Study Schematic**



Source: Figure 1, Trial 101 CSR

After the 1-week screening period (Visits 1-2), subjects were randomized and entered the 3-week substitution period (Visits 2-5). On the first visit of the substitution period (Visit 2/Week -3) subjects were randomized to either TI prandially plus Lantus, or sc NovoRapid prandially plus Lantus. As part of the entry criteria, subjects were to have been receiving sc insulin at mealtimes and Lantus as basal insulin for at least 3 months in stable doses (with no dose change of  $\geq 20\%$ ). Subjects in either treatment group not previously receiving sc NovoRapid were to be switched at

Visit 2 to NovoRapid. Subjects not using Lantus as their basal insulin were to be transferred to Lantus over the 3-week substitution period.

During the substitution period, subjects in the TI group received increasing doses of TI, replacing sc insulin in a stepwise fashion described later and subjects in the NovoRapid group continued on their established dose of NovoRapid. A goal of the substitution period was 100% replacement of TI for prandial sc insulin in the TI group.

During the 12-week treatment period (Visits 5-10), subjects received treatment according to the established dosing regimens. Subjects returned for a follow-up visit (Visit 11) no later than 14 ( $\pm 7$ ) days after completing the treatment period.

Treatments and Titration: TI was administered with major meals. Specific doses were not assigned for this study. Rather, each subject's established dose of prandial sc insulin was replaced with a corresponding dose of TI, assuming a relative bioavailability of TI of approximately 30%. Doses could be adjusted based on the results of blood glucose monitoring during the study. A maximum mealtime dose of 90 U TI was allowed.

The control drug was NovoRapid (insulin aspart), a rapid-acting analog of human insulin. It was provided in PenFill cartridges for injection 3 times daily before meals. Doses were generally those used prior to the study, with the possibility of titration based on the results of glucose monitoring during the study.

Lantus (insulin glargine) was administered once daily at bedtime as basal insulin therapy concomitant with both the TI and the control treatment.

Efficacy Endpoints: The primary efficacy endpoint was the change in blood glucose following a standard meal, expressed as the area under the plasma concentration-time curve of the change in glucose concentration from 0 to 300 minutes ( $AUC_{0-300}$  min) and 0 to 420 minutes ( $AUC_{0-420}$  min) (Visit 10 only).

Statistical Analysis Plan: The planned analysis of AUC was a parametric analysis based on a standard analysis of the mean of AUCs of individual subjects. This analysis required log-transformation of the baseline (Time 0)-corrected AUCs ( $AUC_{0-300}$  for Visits 5 and 9 and  $AUC_{0-420}$  for Visit 10) prior to testing, and comparison between treatment groups using a 2-sample *t* test or an ANCOVA analysis, to examine the effect of covariates. Associated *p* values together with confidence intervals of the differences were presented.

### **5.3.3.3 Safety Trial in Combined T2DM and T1DM Subjects:**

**Trial 030** (TI + usual care vs. usual care vs. non-diabetic controls)

**Study Title:** Pulmonary Outcomes within a 2-Year Period in Subjects with Diabetes Mellitus Treated with Technosphere® Insulin or Usual Antidiabetic Treatment and in Subjects without Abnormalities in Glucose Control

**Study Phase:** 3

**Study Purpose:** The primary objective of this trial was to assess long term pulmonary safety in patients using TI compared with patients not using TI and compared with non-diabetics.

**Study Design:** The study incorporated 2 design strategies: (a) a randomized, open-label clinical trial comparing treatment with TI to usual antidiabetes treatment in subjects with diabetes, and (b) an epidemiological or observational investigation comparing subjects with diabetes who received usual antidiabetes treatments with subjects without abnormalities in glycemic control. The study was conducted from 25 Jul 2005 to 29 Aug 2008.

**Study Sites:** Multiple sites in North America, Russia, and Europe

**Subjects:** 1720 subjects with diabetes and 170 subjects without abnormalities in glycemic control were planned (approximate 10:1 ratio). Based on recruitment strategies, one third of the sample of subjects with diabetes had type 1 diabetes. Although the clinical trial was not powered to examine subgroup differences by diabetes type, a sample of at least 150 completers with type 1 diabetes facilitated a preliminary consideration of differences.

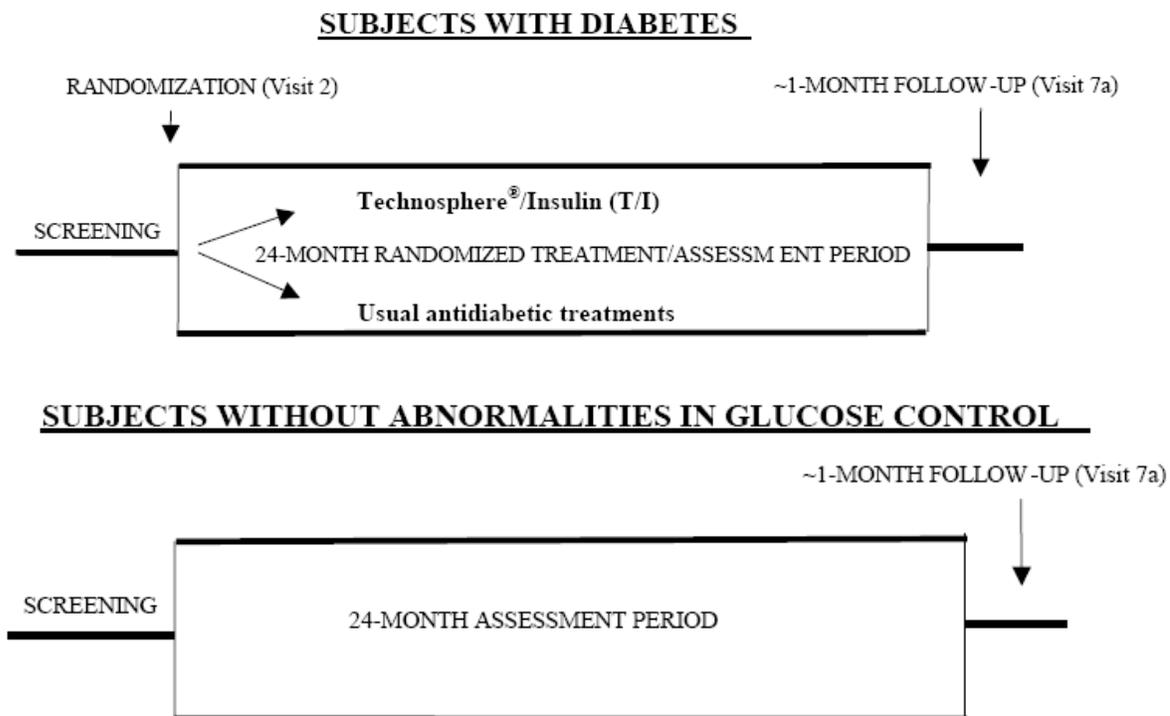
**Inclusion Criteria:** Men or women between 18 and 80 years of age, with a BMI < 42 kg/m<sup>2</sup>, and essentially normal lung function (see Dr. Karimi-Shah's pulmonary safety review for specific pulmonary related inclusion criteria) Subjects with diabetes had a diagnosis of type 1 or type 2 diabetes for at least 2 years, and a HbA1c ≥ 6.6% and ≤ 12.0%. Subjects without abnormalities in glycemic control had no history of diabetes and normal results from a formal GTT.

**Exclusion Criteria:** See general exclusion criteria section 5.3.2. Also, subjects were excluded for insulin delivery pump use within the preceding 8 weeks, two or more severe hypoglycemic episodes within 6 months of Screening or an episode of severe hypoglycemia between Visit 1 and Visit 2, and any hospitalization or emergency room visit due to poor diabetic control within 6 months of Screening or between Visit 1 and Visit 2.

**Withdrawal Criteria:** See general withdrawal criteria in section 5.3.2.

**Study Procedures:** (Figure 5.9) Subjects with diabetes were randomized to treatment group at Visit 2. Subjects without abnormalities in glycemic control were not randomized to, nor did they receive, any clinical trial treatments. During the 2-year clinical trial period, all subjects were requested to participate in 7 evaluation visits, which included clinical, radiological, laboratory, and self-reported assessments. The study schematic is shown in Figure 5.9.

**Figure 5.9 – Trial 030 Study Schematic**



Source: Figure 1 Trial 030 CSR

**Treatments and Titration:**

TI randomized group: Insulin-naïve subjects were started on a 15 U dose of TI at each meal. Subjects treated with sc prandial insulin and long acting basal insulin replaced the prandial insulin with a corresponding dose of TI (3 times the current sc insulin daily dose of regular insulin or rapid acting analog, then divided equally among the meals). Subjects treated with other insulin regimens replaced 50% of the total daily sc insulin dose with a corresponding dose of TI, divided between meals, while the remaining 50% of the total dose of sc insulin was given as basal insulin. After 1 week, the adjustments in the prandial dose of TI or in the basal insulin were made on the basis of laboratory, clinical or home blood glucose findings at the discretion of the Principal Investigator. Doses of TI were adjusted in increments of 15 U, as needed, up to a maximum of 90 U per meal. Oral antihyperglycemic agents were continued as required.

Usual Care randomized group: At the discretion of their physicians, subjects received antidiabetes treatment consisting of diet and exercise, oral antihyperglycemic agents, and/or insulin. All subjects were treated according to established guidelines of the American Diabetes Association and the American Association of Clinical Endocrinologists.

Investigators could select concomitant antidiabetic medication freely, both in the TI and the usual care groups, with few limitations placed on use.

Study Endpoints: The primary endpoints in this trial were pulmonary safety endpoints. (These are discussed in Dr. Karimi-Shah's pulmonary safety review and Ms. Mele's statistical safety review). However, a secondary objective of this trial was to evaluate and compare glycemic control based on HbA1c. This endpoint is reviewed in section 6 of this document.

Statistical Analysis Plan: See Ms. Mele's statistical safety review.

## **6 Review of Efficacy**

### **Efficacy Summary**

The summary of efficacy is based on an integrated discussion of Dr. Liu's statistical efficacy review as well as a discussion of the implications of the efficacy results. Table 6.1 summarizes the efficacy trials in the TI clinical development program.

#### Summary of efficacy results of the primary endpoint HbA1c

##### Type 2 DM

##### Placebo-controlled trials in T2DM

In the TI development program, TI, when combined with either insulin glargine (Lantus) or OAD(s), was effective in lowering HbA1c when compared with placebo for type 2 diabetic patients (trials 005 and 0008). Dose dependence of efficacy results was not definitively demonstrated likely due to trial design limitations.

##### Active-control trials in T2DM

In the T2DM active-controlled trials, the mean reductions in HbA1c from baseline to endpoint were all numerically less in the TI arm than in the comparator arm. Assessment of non-inferiority with respect to active controls produced varying results. In the one year pivotal trial in T2DM, trial 102, Treatment with TI + Lantus was found to be non-inferior to Premixed 70/30 Novolog insulin in reducing HbA1c. However, in trial 014, TI was not non-inferior to treatment with insulin aspart + Lantus. TI was also compared with OADs in trial 103: treatment with TI + metformin was found to be non-inferior to metformin + secretagogue in lowering HbA1c.

##### Active-control trials in T1DM

There was essentially only one confirmatory trial in T1DM (trial 009) because trial 101 was underpowered to detect a difference in HbA1c. In trial 009, the combination of TI + Lantus was both not non-inferior and statistically worse than insulin aspart + Lantus.

<b>Table 6.1 – Summary of Efficacy Trials</b>									
Study (Phase)	Treatment Duration  Design: OL vs. DB	Clinical Scenario	Base-line HbA1c (%)	Treatment Group (ITT no.)	Primary Hypothesis Test	Treatment Difference (TI – control)			Statistical Conclusion
						LS Mean (SE)	95% CI	p-value	
<b>Type 2 Diabetes Program</b>									
<b>005</b> (2)	11-week DB	Substitution from OADs	8.72	•TI 14, 28, 42, 56 U + Lantus (43, 43, 41, and 42, respectively) •T (placebo) + Lantus (41)	S	14: -0.52 (0.21)	(-1.03, -0.01)	0.0439	•All doses (especially 28, 42, and 56 U) significantly better than placebo
						28: -0.82 (0.21)	(-1.33, -0.31)	0.0004	
						42: -0.72 (0.21)	(-1.24, -0.21)	0.0026	
						56: -0.82 (0.21)	(-1.33, -0.31)	0.0004	
<b>0008</b> (2b)	12-week DB	Add-on to OADs	7.82	•TI •T (placebo)	S	-0.39 (0.13)	(-0.64, -0.13)	0.003	•Significantly better than placebo
<b>026</b> (2b)	12-week OL	Add-on to OADs	9.54	•TI (75) •No Treatment (control) (15)	Within Group	-0.03 (0.25)	(-0.52, 0.46)	0.90	•Significant change from baseline •No difference from no-treatment group
<b>014</b> (3)	24-week OL	Substitution from OADs or sc insulin	8.92	•TI + Lantus (150) •Insulin aspart + Lantus (155)	E	+0.36 (0.11)	(0.14, <b>0.58</b> )	0.002	•Not NI (reviewer's analysis) •Statistically worse
<b>102</b> (3)	52-week OL	Substitution from sc insulin	8.68	•TI + Lantus (302) •Premix 70/30 analog (316)	NI	+0.12 (0.09)	(-0.05, <b>0.29</b> )	0.16	•NI
<b>103</b> (3)	12-week OL	Substitute TI for secretagogue	8.91	•TI (176) •Met. + Secretagogue (162) •TI + Metformin (169)	S (of TI+M vs. M+S)	TI+M vs. M+S: +0.10 (0.10)	(-0.13, <b>0.33</b> )	0.51	•Not S (TI + M vs. M + S) •NI (stat reviewer's analysis)
<b>Type 1 Diabetes Program</b>									
<b>009</b> (3a)	52-week OL	Substitution from sc insulin	8.44	•TI + Lantus (277) •Insulin aspart + Lantus (262)	NI	+0.24 (0.08)	(0.08, <b>0.40</b> )	0.003	•Not NI •Statistically worse
<b>101</b> (2)	12-week OL	Substitution from sc insulin	8.94	•TI + Lantus (51) •Insulin aspart + Lantus (56)	Non-HbA1c primary endpt.	+0.18 (0.21)	(-0.24, <b>0.60</b> )	0.39	•Not NI (stat reviewer's analysis)
S=Superiority, NI=Non-inferiority, E=equivalence, OL=open-label, DB=double-blind NI margin is 0.4% Source: Adapted from Dr. Liu's statistical table									

The figure and table below from Dr. Liu’s statistical review concisely show the mean difference in HbA1c between TI and placebo or comparators across trials and the summary statistics for HbA1c across trials. Please see her review for the original figures and related details.

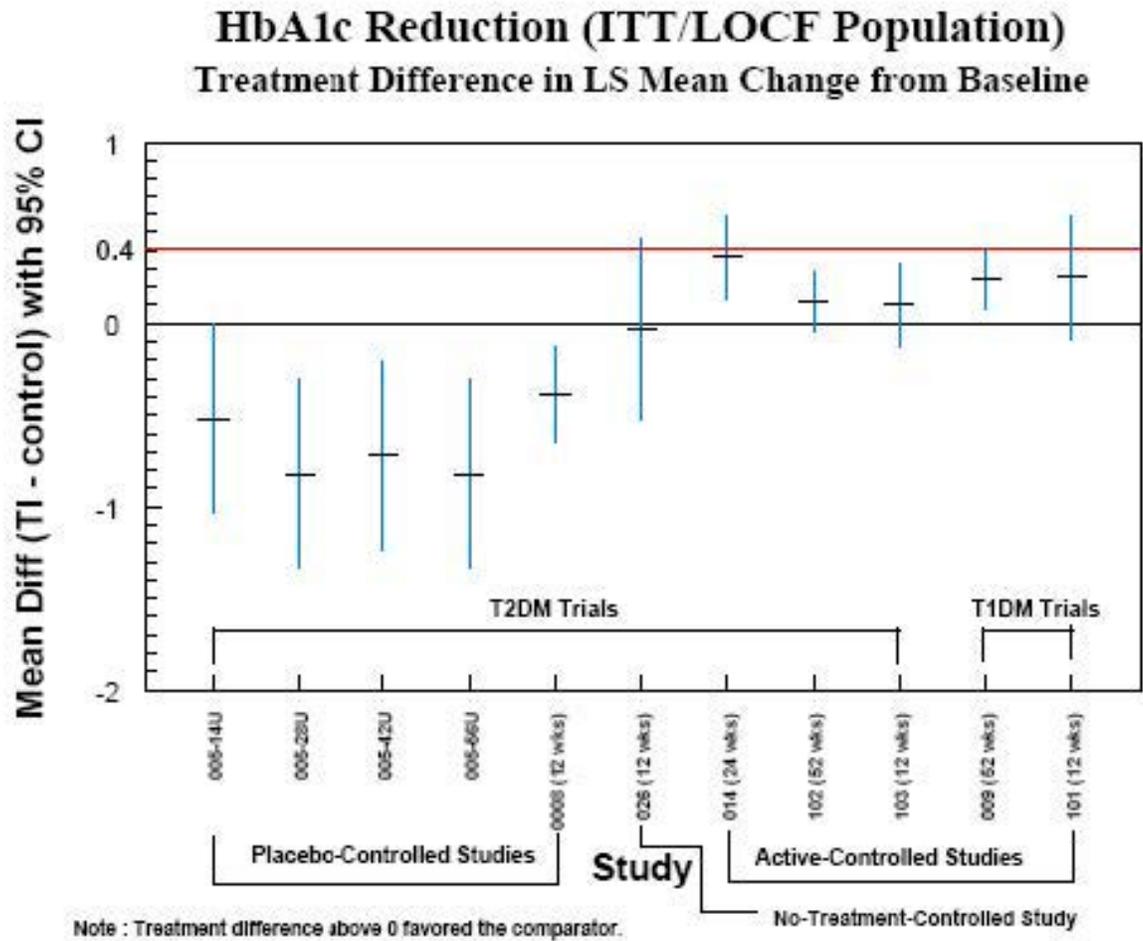


Table 24 – Summary Statistics for HbA1c across Trials

Study (Duration)	Treatment Group (ITT with LOCF)	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change From Baseline	
					Raw Mean (SD)	LS Mean (SE)
<b>Type 2 Diabetes Mellitus</b>						
005 (11-week)	T (placebo)	41	8.70 (1.30)	8.94 (1.30)	0.24 (0.91)	0.23 (0.15)
	TI 14 U	43	8.91 (1.38)	8.55 (1.30)	-0.35 (1.15)	-0.29 (0.14)
	TI 28 U	43	8.59 (1.36)	8.05 (1.16)	-0.54 (1.15)	-0.59 (0.14)
	TI 42 U	41	8.68 (1.16)	8.21 (1.20)	-0.47 (0.91)	-0.49 (0.15)
	TI 56 U	42	8.82 (1.16)	8.20 (1.25)	-0.62 (1.11)	-0.59 (0.15)
0008 (12-week)	TI	58	7.87 (1.15)	7.16 (1.09)	-0.71 (0.77)	-0.70 (0.09)
	T (placebo)	61	7.78 (1.11)	7.48 (1.12)	-0.30 (0.72)	-0.31 (0.09)
026 (12-week)	TI	75	9.58 (1.39)	8.18 (1.12)	-1.40 (1.15)	-1.38 (0.10)
	No Treatment Control	15	9.33 (1.50)	8.09 (1.06)	-1.24 (0.93)	-1.35 (0.23)
014 (24-week)	TI + Lantus	150	8.85 (1.10)	7.96 (1.34)	-0.89 (1.14)	-0.92 (0.08)
	Insulin aspart + Lantus	155	9.00 (1.31)	7.69 (1.09)	-1.31 (1.08)	-1.28 (0.08)
102 (52-week)	TI + Lantus	302	8.69 (1.12)	8.11 (1.26)	-0.58 (1.22)	-0.59 (0.06)
	Premixed 70/30 analog	316	8.68 (1.08)	7.98 (1.16)	-0.70 (1.16)	-0.71 (0.06)
103 (12-week)	TI alone	176	8.92 (0.95)	9.15 (1.27)	0.23 (1.19)	0.21 (0.07)
	Metformin + Secretagogue	162	8.90 (0.94)	8.15 (1.04)	-0.75 (0.90)	-0.78 (0.08)
	TI + Metformin	169	8.95 (0.97)	8.25 (1.09)	-0.70 (1.01)	-0.67 (0.07)
<b>Type 1 Diabetes Mellitus</b>						
009 (52-week)	TI + Lantus	277	8.41 (0.92)	8.28 (1.19)	-0.14 (1.03)	-0.13 (0.06)
	Insulin aspart + Lantus	262	8.48 (0.97)	8.09 (1.13)	-0.39 (0.93)	-0.37 (0.06)
101 (12-week)	TI + Lantus	51	9.01 (1.22)	8.19 (1.10)	-0.81 (1.10)	-0.78 (0.12)
	Insulin aspart + Lantus	56	8.88 (1.18)	7.89 (0.95)	-0.99 (1.07)	-1.02 (0.12)

It is clear from the efficacy trials that TI functions as exogenous insulin as evidenced by the difference from placebo in trials 005 and 0008. However, TI appears to be not as effective as a subcutaneous basal bolus regimen in both T1 and T2 patients. This “intensive” regimen is considered standard of care for T1DM and is often used in T2DM as well when insulin therapy is needed. On the other hand, in T2DM, TI was non-inferior to the less “intensive” subcutaneous insulin regimen: twice daily 70/30 Novolog insulin as well as non-inferior to the combination of the oral medications metformin and a secretagogue.

Summarizing an absolute numerical reduction in HbA1c for TI is difficult because TI is individually titrated and because clinical trial scenarios differed so greatly. Therefore, the clinical relevance of the reduction in HbA1c should best be assessed within trials. Within trials, few numbers of subjects reached glycemic goals; however, this was true of both TI and comparator groups.

Concluding substantial efficacy among T1DM subjects based on statistical criteria alone is problematic because TI was found to be inferior to comparator in the one confirmatory trial. These trial results should be interpreted in light of the natural history of T1DM in which patients do not produce their own insulin and without exogenous insulin would quickly deteriorate and develop DKA. Because of the well characterized natural history of T1DM, single-arm clinical trials have historically been utilized to test efficacy of insulin therapies in this population. The finding that in trial 009, the TI arm was able to maintain glycemic control for one year without an increase in HbA1c is evidence of the efficacy of TI in the T1DM population, albeit less so than the intensive basal /bolus subcutaneous regimen.

Interpretation of the phase 3 studies was complicated by relatively poor titration of insulins (both TI and comparators) across trials with low percentages of subjects reaching glycemic goals, leading to difficulty in determining how efficacious TI would be if optimally titrated.

## 6.1 Indication

The Sponsor’s proposed indication is as follows:

(b) (4)

### 6.1.1 Methods

Details of the methods of individual trial designs are discussed in section 5.3. For the T2DM program, first, placebo controlled trials in T2DM are discussed, followed by the long term pivotal phase 3 trial in T2DM and then shorter supportive efficacy trials in T2DM. For the

T1DM program, first the long-term pivotal phase 3 trial is discussed followed by the shorter-term phase 2 trial for supportive efficacy data.

## 6.1.2 Demographics and Disease History

### 6.1.2.1 Demographics and Disease History - Placebo-Controlled Trials in T2DM

Demographic information and baseline characteristics for the two placebo controlled trials in type 2 DM are presented in Table 6.2. In trial 0008, 67% were male, 65% were Caucasian, and the mean age was 55 years. The mean BMI was around 30 kg/m<sup>2</sup>. In trial 005, 54% were male, almost 100% were Caucasian, the mean age was 57 years, mean BMI was 30 kg/m<sup>2</sup>.

<b>Table 6.2 – Demographics of the T2DM Placebo-Controlled Trial Population - ITT</b>								
Study	Treatment Group, TI Dose	N	Sex (%)	Age (years) mean (range)	Race (%)	BMI (kg/m <sup>2</sup> ) Mean (range)	Duration of Diabetes (years) Mean Median (Range)	Study Location and Sites
0008	TP placebo + OAD	61	M=70.5% F=29.5%	54 (26 to 74)	Caucasian (62%) Hispanic (23%) Black (5%) Asian (8%) Other (2%)	30 kg/m <sup>2</sup> (21 – 39)	7.5 7.3 (1.6 – 18.2)	USA: 24 sites in 13 states
	TI +OAD	58	M=64% F=36%	56 (34 to 75)	Caucasian (67%) Hispanic (19%) Black (10%) Asian (2%) Other (2%)	30 kg/m <sup>2</sup> (22 – 38)	6.7 6.2 (2.1 – 13.3)	
005	TP placebo + glargine	41	M=46% F=54%	58 (36 to 76)	Caucasian (100%)	30 kg/m <sup>2</sup> (22 – 39)	8.9 8.6 (3.6 – 14.9)	Germany: 4 sites Netherlands: 3 sites Bulgaria: 10 sites Czech Republic: 14 sites
	TI 14 U + glargine	44	M=50% F=50%	58 (42 to 76)	Caucasian (100%)	30 kg/m <sup>2</sup> (19 – 43)	11.5 10.7	
	TI 28 U + glargine	44	M=61% F=39%	58 (39 to 79)	Caucasian (100%)	31 kg/m <sup>2</sup> (23 – 42)	(3.1 – 21.0)	
	TI 42 U + glargine	41	M=58.5% F=41.5%	59 (36 to 82)	Caucasian (100%)	29 kg/m <sup>2</sup> (22 – 36)		
	TI 56 U + glargine	42	M=59.5% F=40.5%	56 (39 to 71)	Caucasian (97.6%) Other (2.4%)	30 kg/m <sup>2</sup> (19 – 37)		

Source: Table 3 ISE, Table 12 Trial 0008 CSR, Table 2.1B Trial 005 CSR

### Prior Antidiabetic Medications - Placebo-Controlled Trials in T2DM

Please see section 5.3.2 for descriptions of the allowed antidiabetic medications prior to trial enrollment. In trial 0008 all subjects were on one or more previous OADs and these were to be continued through the trial. In trial 0008, 68% of patients were using a sulfonylurea, 57% were using metformin, and 32% were using a thiazolidinedione. The treatment groups were relatively balanced with respect to prior antidiabetic medications. In trial 005 prior therapy was discontinued and trial medications (TI and Lantus) were substituted. The most commonly used antidiabetic medications, prior to their discontinuation, in this trial were sulfonylurea (185 subjects, 81.5%), metformin (177 subjects, 78.0%), rosiglitazone (44 subjects, 19.4%), insulin glargine (43 subjects, 18.9%), and repaglinide (23 subjects, 10.1%). In trial 0008 doses of prior therapy were stable for at least 3 months prior to study enrollment, and in trial 005 doses of prior therapy were stable for at least 2 months prior to study enrollment.

### 6.1.2.2 Demographics and Disease History - Long Term Active-Control Efficacy Trial in T2DM

#### Demographics - Trial 102

Table 6.3 summarizes subject demographics and baseline characteristics by randomized treatment group for the ITT Population. At baseline, both randomization groups were similar with respect to age, race, and BMI. There were slightly more men in the TI arm. This trial population had a clinical diagnosis of T2DM with a median duration of disease of 11.5 and 12.3 years for the TI and 70/30 mix arms, respectively.

<b>Table 6.3 – Trial 102 - Demographics of the ITT population</b>								
Study	Treatment Group	N	Sex (%)	Age (years) mean (range)	Race (%)	BMI (kg/m <sup>2</sup> ) Mean (range)	Duration of Diabetes (years) Mean Median (range)	Study Location and Sites
102	TI + Insulin glargine	302	M=51% F=49%	56 (19 to 79)	Caucasian (67%) Hispanic (20%) Black (8%) Asian (3%) Other (2%)	32 kg/m <sup>2</sup> (20 –44 )	13.0 11.5 (0-34)	Argentina: 6 sites Brazil: 12 sites Canada: 8 sites Chile: 5 sites Mexico: 6 sites
	Premix 70/30 insulin analog	316	M=44% F=56%	56 (24 to 78)	Caucasian (68%) Hispanic (20%) Black (9%) Asian (1%) Other (2%)	31 kg/m <sup>2</sup> (19–41 )	13.7 12.3 (0-52)	Poland: 7 sites Russia: 17 sites Spain: 9 sites UK: 4 sites USA: 78 sites in 24 states

Source: Table 3, ISS; Table 8, Trial 102 CSR

### Prior Antidiabetic Medications – Trial 102

As specified by the inclusion criteria, all subjects who entered the trial were using insulin. Metformin and thiazolidinediones were also allowed by the inclusion criteria and could be continued after randomization and initiation of study medication. The percentage of subjects using metformin and thiazolidinediones at trial entry was evenly distributed between treatment groups; 35% in each arm were using metformin and 7% in each arm were using thiazolidinediones. Note: other than metformin and thiazolidinediones, no other anti-diabetic medications were allowed in the trial.

### 6.1.2.3 Demographics and Disease History - Short/Intermediate Term Active Control Trials in T2DM

The demographics for each of the three trials presented in this section are different in a few respects so are presented separately. The sex distribution was different among the trials with smaller percentages of males in trials 014 and 026. Trial 014 and 026 participants were almost entirely Caucasian.

### Demographics - Trial 014

The demographics of the PP population are shown in Table 6.4. (Note the PP population is presented here rather than the ITT population because the PP Population was the Sponsor’s predefined primary analysis population. However, the characteristics of the ITT population and the PP population were almost identical to each other.

<b>Table 6.4 – Trial 014 - Demographics of the PP population</b>								
Study	Treatment Group	N	Sex (%)	Age (years) mean (range)	Race (%)	BMI (kg/m <sup>2</sup> ) Mean (range)	Duration of Diabetes (years) Mean Median (range)	Study Location and Sites
014	TI + Insulin glargine	112	M=30% F=70%	59 (33 to 78)	Caucasian (99%) Other (1%)	31 kg/m <sup>2</sup> (19 –44)	11.8 11.0 (0-35)	Russia: 26 sites in 8 cities
	Insulin aspart + Insulin glargine	146	M=20% F=80%	58 (33 to 78)	Caucasian (100%)	30 kg/m <sup>2</sup> (20–42)	12.3 11.0 (2-32)	

Source: Table 2.2, Trial 014 CSR Additional Tables and Figures

Prior Antidiabetic Medication - Trial 014

Subjects in trial 014 were using subcutaneous insulin at the time of screening (as per protocol requirement of prior insulin use), while only a minority were simultaneously using an OAD. All previously prescribed anti-diabetic medications were discontinued during the run-in period of this trial.

Demographics - Trial 026

The demographics of the ITT population for trial 026 are shown in Table 6.5.

<b>Table 6.5 – Trial 026 - Demographics of the ITT population</b>								
Study	Treatment Group	N	Sex (%)	Age (years) mean (range)	Race (%)	BMI (kg/m <sup>2</sup> ) Mean (range)	Duration of Diabetes (years) Mean Median (range)	Study Location and Sites
026	TI + OADs or diet/exercise	75	M=25% F=75%	54 (35 to 60)	Caucasian (100%)	31 kg/m <sup>2</sup> (21 – 38)	7.7 6.8 (2.2 – 19.8)	Russia: 10 sites in 4 cities
	OADs or diet/exercise	15	M=20% F=80%	53 (46 to 58)	Caucasian (100%)	33 kg/m <sup>2</sup> (27 – 39)	6.8 5.4 (2.7 – 19.6)	

Source: Table 8, Trial 026 CSR

### Prior antidiabetic medications - Trial 026

In trial 026 use of insulin was an exclusion criterion. At trial entry metformin was being used by 73% of TI subjects and 80% of control subjects. During the trial, metformin was used by 60% of TI subjects and 73% of control subjects. At trial entry, sulfonylureas were used by 96% of TI subjects and 87% of control subjects. During the trial, sulfonylureas were used by 85% of TI subjects and 87% of control subjects. A total of 41 subjects (54.7%) in the TI group were taking a combination of oral antihyperglycemic medications and a total of 9 subjects (60.0%) in the control group were taking a combination of oral antihyperglycemic medications. No other single medication for diabetes was taken by more than 5% of subjects overall.

### Demographics - Trial 103

The demographics of the ITT population for trial 103 are shown in Table 6.6.

<b>Table 6.6 – Trial 103 - Demographics of the ITT population</b>								
Study	Treatment Group	N	Sex (%)	Age (years) mean (range)	Race (%)	BMI (kg/m <sup>2</sup> ) Mean (range)	Duration of Diabetes (years) Mean Median (range)	Study Location and Sites
009	TI	177	M=47.5% F=52.5%	57 (26 – 75)	Caucasian (75%) Hispanic (15%) Black (5%) Asian (2%) Other (3%)	31 kg/m <sup>2</sup> (22 –43)	10.5 9.0 (1 – 33)	Argentina: 5 sites Brazil: 7 sites Canada: 5 sites Chile: 4 sites Czech Republic: 8 sites Mexico: 3 sites Poland: 8 sites Russia: 12 sites Spain: 4 sites Ukraine 12 sites USA: 41 sites
	Metformin + secretagogue	162	M=46% F=54%	58 (18 – 75)	Caucasian (70%) Hispanic (16%) Black (5%) Asian (3%) Other (6%)	31 kg/m <sup>2</sup> (18 –42)	10.7 10.0 (2 – 41)	
	TI + metformin	169	M=40% F=60%	57 (37 – 77)	Caucasian (76%) Hispanic (14%) Black (7%) Asian (1%) Other (2%)	31 kg/m <sup>2</sup> (22 –40)	11.2 10.5 (1 – 34)	
Source: Table 3 ISE, Table 12 Trial 103 CSR, Table 6.3.2.2.1 Trial 103 Tables and Figures								

Prior antidiabetic medications - Trial 103

As required by the protocol, all subjects entered into the study were using both metformin and a secretagogue. The secretagogue could be a sulfonylurea or a meglitinide.

6.1.2.4 Demographics and Disease History - Active-Control Trials in T1DM

Demographics - Trial 009

Table 6.7 summarizes subject demographics and baseline characteristics by randomized treatment group for the ITT Population.

<b>Table 6.7 – Trial 009 - Demographics of the T1DM – ITT population</b>								
Study	Treatment Group	N	Sex (%)	Age (years) mean (range)	Race (%)	BMI (kg/m <sup>2</sup> ) Mean (range)	Duration of Diabetes (years) Mean median (range)	Study Location and Sites
009	TI + insulin glargine	277	M=53% F=47%	38 (18 to 69)	Caucasian (86%) Hispanic (5%) Black (6%) Asian (2%) Other (1%)	26 kg/m <sup>2</sup> (17 –38)	18.1 16.2 (1-61)	Argentina: 8 centers Brazil: 6 centers Canada: 3 centers Chile: 5 centers; Mexico: 3 centers
	Insulin aspart + insulin glargine	262	M=52% F=48%	38 (18 to 76)	Caucasian (87%) Hispanic (6%) Black (5%) Asian (1%) Other (1%)	26 kg/m <sup>2</sup> (18–36)	18.7 15.5 (1-64)	Poland: 7 centers Russia: 17 centers; Spain: 4 centers United Kingdom: 5 centers United States: 61 centers

Source: Table 37, ISS; Table 7, Trial 009 CSR

### Demographics - Trial 101

The demographics of the ITT population for trial 101 are shown in Table 6.8.

<b>Table 6.8 – Trial 101 - Demographics of the T1DM – ITT population</b>								
Study	Treatment Group	N	Sex (%)	Age (years) mean (range)	Race (%)	BMI (kg/m <sup>2</sup> ) Mean (range)	Duration of Diabetes (years) Mean median (range)	Study Location and Sites
101	TI + insulin glargine	51	M=25.5% F=74.5%	33 (18 to 56)	Caucasian (100%)	25 kg/m <sup>2</sup> (18 –36)	10.9 8.5 2.2 – 31.0	Russia: 16 centers in 5 cities
	Insulin aspart + insulin glargine	56	M=50% F=50%	36 (18 to 59)	Caucasian (100%)	24 kg/m <sup>2</sup> (18–34)	14.1 12.0 2.3 – 39.5	

Source: Table 37, ISS; Table 6, Trial 101 CSR

### Prior Antidiabetic Medications - Trial 009 and Trial 101

As specified by the protocols, and as expected because of their T1DM status, all subjects who entered trials 009 and 101 were using insulin. A majority of subjects in each treatment arm were using a combination of fast-acting plus intermediate- or long-acting insulin at trial entry. The proportion of subjects using each type of diabetes treatment at Screening was balanced across the two trial treatment groups.

#### 6.1.2.5 Demographics and Disease History – Pulmonary Safety Trial 030

Trial 030 was not a primary efficacy trial; therefore, the demographics of the trial population are not described in detail in this section, but are incorporated into the pooled safety population discussed in section 7. However, the clinical reviewer did note that there were no statistically significant differences in baseline characteristics including sex, race, and age between the two randomization groups in trial 030.

#### 6.1.2.6 Demographics and Disease History Summary and Conclusions

Balance of demographic variables across randomization groups: Across the trials, randomization groups were generally well balanced with some small differences that should not affect efficacy analyses. This conclusion was confirmed with Dr. Liu the statistical efficacy reviewer. Dr. Liu is performing subgroup analyses of the primary efficacy analyses to confirm that the small differences in baseline demographics, especially sex, are not affecting the primary efficacy analyses.

Overall demographic characteristics of trial populations: In order for trial results to be generalizable to the U.S. diabetic population as a whole, the trial populations should be demographically representative of the U.S. diabetic population. For the pivotal phase 3 studies, trial 102 for T2DM and trial 009 for T1DM, at least a third of subjects were from the U.S. and these trials should be considered generalizable based on demographic characteristics except that they had a relatively low percentage of African American subjects. Some other supportive trials were conducted entirely in foreign populations and were not as representative of the U.S. population such as trials 014, and 026 which were conducted in Russia and studied essentially an entirely Caucasian population.

Overall disease history characteristics of trial populations: In the opinion of the clinical reviewer, the clinical development program was sufficient in studying T2DM subjects in a variety of clinical scenarios. Trial 0008 studied subjects with a mean duration of diabetes of roughly 7 years and who were on oral antidiabetic medication at trial entry. Trial 005 studied subjects with a mean duration of T2DM of roughly 9 years and were on a wide variety of antidiabetic therapies. The pivotal trial 102 studied T2DM subjects with a mean duration of

diabetes of 13 years and were using insulin at baseline. Trial 103 studied T2DM subjects using both metformin and a secretagogue.

As expected due to the nature of T1DM, all T1DM subjects were using insulin at trial entry. The duration of diabetes at trial entry (roughly 17 years) was sufficient to ensure that subjects were not being studied during the “honeymoon” phase of T1DM when insulin requirements are often reduced.

For the most part, exclusion criteria used in Phase 2 and Phase 3 trials were unlikely to limit the general applicability of trial results. However, the following exclusion criteria could have excluded significant numbers of diabetics who might be encountered in clinical practice: smoking up to 6 months prior to study entry; underlying chronic lung disease such as asthma or COPD; history of severe hypoglycemia; and severe diabetic complications.

### 6.1.3 Subject Disposition

Subject disposition in this section is discussed in the context of efficacy. Therefore, each trial is discussed individually. See also section 7 for a discussion of discontinuations due to adverse events in the pooled safety population.

Note that in the clinical development program there was no prespecified category on case report forms for investigators to report withdrawals due to lack of efficacy. The trials did not have rescue therapy as part of the trial designs. However, certain trials included hyperglycemia as a reason for trial withdrawal. Discontinuations due to hyperglycemia were supposed to be coded as adverse events. The criteria for what blood glucose level constituted “hyperglycemia” were trial specific and are discussed in section 5.3.2.

#### 6.1.3.1 Subject Disposition - Placebo Controlled Trials in Type 2 DM

Subject disposition for trials 0008 and 005 is shown in table 6.9. In trial 0008, 123 subjects were randomized to study treatment. Of the 119 subjects in the ITT Population, 12 (4 of 58 receiving TI and 8 of 61 receiving TP) withdrew from the study prematurely. The completer rate was 88.5% in the TI group and was slightly higher than the 85.5% completer rate in the TP group. There were no discontinuations due to hyperglycemia in either trial arm.

**Reviewer’s comment: The completer rate in trial 0008 is sufficiently high. The completer rate was higher in the TI group than in the TP group. There were no discontinuations due to hyperglycemia in either trial arm.**

In trial 005, at Visit 3, 227 subjects were randomized to TP or TI. Per trial design, however, the double-blind treatment was not initiated until Visit 5 (Week 6). Twelve subjects who received

single-blind TP beginning at Visit 3 (Week 4) did not receive double-blind TP or TI. Twenty-two subjects discontinued prematurely from the trial, 6 (13.0%) in the TP group and 16 (8.8%) in the TI groups; 90.3% of subjects completed the trial.

	<b>Trial 0008 (12 Week Treatment Period)</b>			<b>Trial 005 (11 Week Treatment Period)</b>					
	TI	TP	All	TP	TI 14 U	TI 28 U	TI 42 U	TI 56 U	All
	n (%)	n (%)	N	n (%)	n (%)	n (%)	n (%)	n (%)	N (%)
Recruited			133						357
Enrolled			126						227
Treated			126						227
Randomized	61	62	123	46	45	46	45	45	227
Single-blind TP Treatment only <sup>a</sup>	NA	NA		5 (10.9)	1 (2.2)	1 (2.2)	3 (6.7)	2 (4.4)	12 (5.3)
Single-blind TP Treatment plus Double-blind Treatment <sup>b</sup>	NA	NA		41 (89.1)	44 (97.8)	45 (97.8)	42 (93.3)	43 (95.6)	215 (94.7)
Excluded from ITT population	4	1	5	5	1	2	4	3	14
Completed	54 (88.5)	53 (85.5)	107 (87.0)	40 (87.0)	42 (93.3)	41 (89.1)	41 (91.1)	41 (91.1)	205 (90.3)
Discontinued	7 (11.5)	9 (14.5)	16 (13.0)	6 (13.0)	3 (6.7)	5 (10.9)	4 (8.9)	4 (8.9)	22 (9.7)
Adverse Event	2 (3.3)	1 (1.6)	3 (2.4)	0	0	1 (2.2)	1 (2.2)	0	2 (0.9)
Protocol Violation	0	1 (1.6)	1 (0.8)	1 (2.2)	0	2 (4.3)	0	0	3 (1.3)
Patient Withdrew Consent	0	5 (8.1)	5 (4.1)	5 (10.9)	0	2 (4.3)	1 (2.2)	3 (6.7)	11 (4.8)
Physician decision	1 (1.6)	0	1 (0.8)	0	0	0	1 (2.2)	0	1 (0.4)
Other	4 (6.6)	2 (3.2)	6 (4.9)	0	3 (6.7)	1 (2.2)	1 (2.2)	1 (2.2)	6 (2.6)
<b>Analysis Datasets</b>									
Safety Population	61	62	123	46	45	46	45	45	227
ITT Population	58	61	119	41	44	44	41	42	212
ITT Group A Population	38	36	74						
ITT Group B Population	22	23	45						
PP Population				36	41	37	38	38	190
Primary Efficacy Population <sup>c</sup>	48	43	91						
Primary Efficacy Group A Population <sup>d</sup>	31	24	55						
Primary Efficacy Group B Population <sup>e</sup>	17	19	36						

<sup>a</sup>TP-only treatment: Beginning at Visit 3, treatment was initiated with single-blind TP. The subjects in this row were withdrawn before double-blind treatment.  
<sup>b</sup>TP or TI: At Visit 5, double-blind treatment was initiated with TP or TI.  
<sup>c</sup>Trial 0008 defined a “primary efficacy population” which is similar to other protocols’ PP population  
<sup>d</sup>Group A includes subjects with Baseline HbA1c between 6.6% and 7.9%  
<sup>e</sup>Group B includes subjects with Baseline HbA1c between 8.0% and 10.5%.  
 Source: Table 8, 9; Trial 0008 CSR; Table 7, 8, 9, 10, 11 Trial 005 CSR

Eleven subjects in Study 005 withdrew consent: 5 (10.9%) of subjects in the TP group, and 6 (3.3%) of subjects in the TI treatment group. Reasons for withdrawal of consent are presented in Table 6.10.

Treatment Group/Subject #	Reason
TP/2584	Did not want to inject Lantus
TP/6287	Did not want to inject Lantus
TP/1114	Too many blood samplings
TP/5891	Refused to continue
TP/5420	Does not have enough time
TI 28 U/1195	Dissatisfaction with blood sugar
TI 28 U/7127	The trial is time consuming
TI 42 U/4388	Not satisfied with trial
TI 56 U/5282	Lost to follow-up
TI 56 U/5382 <sup>a</sup>	Dissatisfied with blood sugar and adverse events
TI 56 U/7523	Subject asked for insulin injection

<sup>a</sup> Subject 5382 was randomized but received only single-blind TP before discontinuation  
 Source: Table 10, Trial 005 CSR

Five subjects who discontinued due to physician decision, withdrawal of consent, and ‘other’ were subsequently reclassified as having adverse events leading to discontinuation. The subjects, their original classification for withdrawal, and the corresponding adverse events leading to discontinuation are listed in Table 6.11.

Treatment Group/Subj #	Original Classification	Reclassified Reason for Withdrawal
TI 14 U/2905	Other	Lack of efficacy – Hyperglycemia
TI 14 U/7607	Other	Continuous hyperglycemia; metabolic decompensation
TI 28 U/4680	Other	Hyperglycemia
TI 42 U/5298	Physician Decision	Hyperglycemia
TI 56 U/5382	Withdrew Consent	Dissatisfied with blood sugar and adverse events

Source: Table 11, Trial 005 CSR

**Reviewer’s comment: The completer rate in Study 005 is sufficiently high. The completer rate was slightly higher among the TI groups than in the TP group. Based on the information provided by the Sponsor the clinical reviewer estimates the rate of discontinuation due to hyperglycemia in trial 005 appears to be low, 5 or 6 subjects out of 227 (2.6%).**

### 6.1.3.2 Subject Disposition - Long-Term Active-Control Trial in Type 2 DM

#### Subject Disposition - Trial 102

In trial 102, 677 subjects were randomized: 334 in the TI + glargine group and 343 in the 70/30 mix group. The ITT Population in trial 102 was comprised of 618 subjects with 302 in the TI + glargine group and 316 in the 70/30 mix group.

Subject disposition by randomized treatment group is displayed in Table 6.12. The imbalance in randomization was due to stratification by site. Of the randomized subjects, 23 (3.4%) subjects withdrew before receiving study medication 11/334 (3.3%) in the TI + glargine arm and 12/343 (3.5%) in the 70/30 mix arm. Of the randomized subjects, 216 (64.7%) subjects completed the TI + glargine arm and 246 (71.7%) completed the 70/30 mix arm. Overall, a greater number of subjects discontinued in the TI + glargine (32.0%) vs. the 70/30 mix arm (24.5%).

**Reviewer’s comment: Due to the relatively low completer rate in this trial, the Agency statistician examined efficacy for both the completer and dropout cohorts. The results based on the completers were similar to the ones based on the whole ITT/LOCF population. Therefore, there was no major impact on efficacy by the high dropout rate in this trial.**

<b>Table 6.12 – Trial 102 Subject Disposition (52 Week Treatment Period)</b>			
Population	TI + glargine	70/30 mix	Overall Total
Number of Subjects (%)			
Screened			2064
• Screen failures			1391
• Eligible			673
Randomized	334	343	677
Safety Population	323 (96.7)	331 (96.5)	654 (96.6)
Completed	216 (64.7)	246 (71.7)	462 (68.2)
Prematurely Discontinued	107 (32.0)	84 (24.5)	191 (28.2)
• Adverse Event	29 (8.7)	12 (3.5)	41 (6.1)
• Protocol Violation	6 (1.8)	3 (0.9)	9 (1.3)
• Subject Withdrew Consent	50 (15.0)	32 (9.3)	82 (12.1)
• Subject Died	4 (1.2)	1 (0.3)	5 (0.7)
• Physician Decision	5 (1.5)	8 (2.3)	13 (1.9)
• Lost to Follow-up	6 (1.8)	22 (6.4)	28 (4.1)
• Other	7 (2.1)	7 (2.0)	14 (2.1)
Intention to Treat Population	302 (90.4)	316 (92.1)	618 (91.3)
Per Protocol Population	211 (63.2)	237 (71.7)	448 (66.2)

Source: Table 7, Trial 102 CSR

Discontinuations in the TI arm due to adverse events were largely driven by respiratory AEs. Discontinuations due to hyperglycemia or “diabetes mellitus inadequate control” reported as AEs were 3 (0.9%) in the TI + glargine arm and 0 in the 70/30 mix arm.

The greatest percentage of discontinuations was due to subjects who withdrew consent (50 [15.0%] subjects in the TI arm and 32 (9.3%) subjects in the 70/30 mix arm). Subjects who withdrew consent were reviewed by the Sponsor and misclassifications were identified and re-classified as appropriate (e.g., to discontinuation due to an AE) prior to programmatic generation of tables and files. The Sponsor reported that in the Russian Federation, it was not permissible to ask subjects for a reason for withdrawing consent.

**Reviewer’s comments: The Sponsor states that the higher withdrawal rate in the TI arm may have occurred, in part, because this was an open label trial where subjects in the 70/30 mix arm were aware that they were on current standard of care therapy for type 2 diabetes.**

**After accounting for discontinuations due to respiratory AEs the discontinuation rate due to AEs is similar between treatment groups (13 subjects in the TI + glargine arm and 11 subjects in the 70/30 mix arm). The discontinuation rate due to “withdrew consent” does show an imbalance, however.**

Further information regarding verbatim reasons for discontinuation among patients who withdrew for the reason of “withdrew consent” was requested from the Sponsor. The Sponsor was requested to provide numbers of withdrawals for adverse events of hyperglycemia, blood glucose increased, diabetes mellitus inadequate control, ketoacidosis, diabetic ketoacidosis, or any other preferred term representing inadequate glycemic control and any other withdrawal due to lack of efficacy including investigator’s decisions that upon examination appear to be due to lack of efficacy. The Sponsor was also asked to further specify reasons for subjects withdrawing consent.

The Sponsor submitted an updated table of subject disposition (Table 6.13). In the opinion of the clinical reviewer, dissatisfaction with therapy should be considered potentially due to unsatisfactory glycemic control. Therefore, a reasonable estimate of subjects discontinuing for ineffective therapy is 18 (5.6%) vs. 11 (3.3%) in the TI and comparator arms, respectively. A conservative estimate is 14 (4.2%) to 10 (2.9%) in the TI and comparator arms, respectively. In terms of the other discontinuations due to “withdrew consent” there was no apparent pattern that would indicate a safety or efficacy concern. However, there were more subjects in the TI arm who did not give any reason for withdrawal.

<b>Table 6.13 – Trial 102 Updated Subject Disposition Summary</b>		
Disposition	TI	Comparator
Randomized	334	343
Safety Population	323 (96.7)	331 (96.5)
Completed	216 (64.7)	246 (71.7)
Prematurely Discontinued	107 (32.0)	84 (24.5)
<ul style="list-style-type: none"> <li>Events of hyperglycemia, blood glucose increased, diabetes mellitus inadequate control, ketoacidosis, diabetic ketoacidosis, or any other preferred term representing inadequate glycemic control and any other withdrawal due to lack of efficacy including investigator’s decisions that upon examination appear to be due to lack of efficacy</li> </ul>	14 (4.2)	10 (2.9)
<ul style="list-style-type: none"> <li>Adverse Event other than those related to hyperglycemia</li> </ul>	32 (9.6)	10 (2.9)
<ul style="list-style-type: none"> <li>Protocol Violation</li> </ul>	6 (1.8)	3 (0.9)
<ul style="list-style-type: none"> <li>Subject Withdrew Consent</li> </ul>	37 (11.1)	28 (8.2)
<ul style="list-style-type: none"> <li> <ul style="list-style-type: none"> <li>Dissatisfied with treatment/therapy</li> </ul> </li> </ul>	4 (1.2)	1 (0.3)
<ul style="list-style-type: none"> <li>Subject Died</li> </ul>	4 (1.2)	1 (0.3)
<ul style="list-style-type: none"> <li>Physician Decision</li> </ul>	3 (0.9)	4 (1.2)
<ul style="list-style-type: none"> <li>Lost to Follow-up</li> </ul>	6 (1.8)	21 (6.1)
<ul style="list-style-type: none"> <li>Sponsor/site decision mostly for lack of drug availability at site</li> </ul>	5 (1.5)	6 (1.7)

**Reviewer’s comment: The rate of discontinuation for lack of efficacy is only slightly higher in the TI arm vs. the comparator arm.**

### 6.1.3.3 Subject Disposition - Short / Intermediate Term Trials in T2DM

#### Subject Disposition - Trial 014

A summary of subject disposition for trial 014 is shown in Table 6.14. A total of 309 subjects were randomized. A total of 35 subjects discontinued prematurely from the trial, 30 (19.9%) subjects in the TI group and 5 (3.2%) subjects in the insulin aspart group.

<b>Table 6.14 – Trial 014 Subject Disposition (24 Week Treatment Period)</b>			
Population	TI	Insulin Aspart	Overall Total
Number of Subjects (%)			
Screened			476
• Screen failures			151 (31.7)
• Randomized			309 (64.9)
Randomized	151	158	309
Safety Population	151 (100)	158 (100)	309 (100)
Completed 24 weeks	123 (81.5)	153 (96.8)	276 (89.3)
Prematurely Discontinued	30 (19.9)	5 (3.2)	35 (11.3)
• Adverse Event	15 (9.9)	0 (0)	15 (4.8)
• Protocol Violation	1 (0.7)	4 (2.5)	5 (1.6)
• Subject Withdrew Consent	10 (6.6)	0 (0)	10 (3.2)
• Subject Died	0 (0)	1 (0.6)	1 (0.3)
• Physician Decision	3 (2.0)	0 (0)	3 (1.0)
• Lost to Follow-up	1 (0.7)	0 (0)	1 (0.3)
Intention to Treat Population	150 (99.3)	155 (98.1)	305 (98.7)
Per Protocol Population	112 (74.2)	146 (92.4)	258 (83.5)

Source: Tables 5, 7, Trial 014 CSR

The case report forms of the 10 subjects who withdrew consent in the TI arm were reviewed by the Sponsor for potential misclassification. One subject who withdrew consent appears to have withdrawn due to an AE of cough during the 6 days prior to withdrawal of consent. No other subjects who withdrew consent appeared to be misclassified according to the Sponsor.

As shown in Table 6.14, a total of 30 (9.9%) subjects who were randomized to TI permanently discontinued due to AEs; no subjects randomized to insulin aspart discontinued due to AEs. More than half of the subjects discontinuing due to AEs (8 out of 15 subjects, 53%) experienced cough mild to moderate in severity which resolved upon discontinuation of TI. Two TI-treated subjects discontinued due to hyperglycemia with random glucose values > 495 mg/dL. The subject experiencing diabetic retinopathy and eye hemorrhage was randomized to TI but never began treatment with TI (but was included in the Safety Population because of treatment with insulin glargine). Three TI-treated subjects discontinued due to the SAEs: 1) one event of angioneurotic edema considered life-threatening in a subject with medical history of urticaria after first insulin administration, allergies, and a prior episode of angioedema from eating apples, nuts or pears; 2) one event of asthma in a subject with no prior medical history of asthma or reactive airway disease; and 3) one event of inadequate control of diabetes with hypoglycemia. The subject was admitted with decompensated diabetes and upon review of the patient diary, was found to have had prior episodes of “non-severe” hypoglycemia. All of the hypoglycemia-associated blood glucose readings were >36 mg/dL and there were no concomitant neurological symptoms. Of note, the case of angioneurotic edema is the only one to have been reported in the TI clinical development program.

**Reviewer’s comment: More than half of the discontinuations due to AEs were due to cough which is an expected AE related to TI and is more of a tolerability issue than a safety issue. Discontinuations due to lack of efficacy/ hyperglycemia is estimated by the clinical**

**reviewer to be 2/151 (1.3%) in the TI + glargine group and 0/158 (0%) in the insulin aspart + glargine group.**

Subject Disposition - Trial 026

Ninety subjects were randomized: 75 to TI and 15 to control (table 6.15). Overall, 7 subjects were discontinued prematurely from the trial, including 6 subjects (8.0%) in the TI group and 1 subject (6.7%) in the control group. The two AEs that resulted in discontinuations in the TI group were allergic pharyngitis and upper respiratory infection.

<b>Table 6.15 – Trial 026 Subject Disposition (12 Week Treatment Period)</b>			
Population	TI	Control	Overall Total
Number of Subjects (%)			
Screened			151
• Screen failures			61 (40)
• Randomized			90 (60)
Randomized	75	15	90
Safety Population	75	75	90
Completed	69 (92.0)	14 (93.3)	83 (92.2)
Prematurely Discontinued	6 (8.0)	1 (6.7)	7 (7.8)
• Adverse Event	2 (2.7)	1 (6.7)	3 (3.3)
• Protocol Violation	3 (4.0)	0	3 (3.3)
• Subject Withdrew Consent	1 (1.3)	0	1 (1.1)
• Subject Died	0	0	0
• Physician Decision	0	0	0
• Other	0	0	0
Intention to Treat Population	75	15	90
Per Protocol Population	51	9	60

Source: Tables 5,6,7, Trial 026 CSR

**Reviewer’s comment:** There are no reports of discontinuation due to hyperglycemia/lack of efficacy in trial 026. The completer rate was similar between the two trial arms.

Subject Disposition - Trial 103

In trial 103, 528 subjects were randomized (Table 6.16). Only the disposition of subjects up until the primary efficacy endpoint (12 weeks) is discussed in this section. Discontinuations that occurred after the primary efficacy endpoint are discussed in section 7 in the context of safety. Discontinuation for any reason was more frequent among TI treated subjects (27.3% in the TI alone group and 32.0% in the TI + metformin group compared with 10.6 % in the metformin + secretagogue group). The primary reason for discontinuation in all groups was “subject

withdrew consent.” Similar to other trials, after database lock, a review of each subject’s data was performed by Sponsor personnel using final subject CRFs to clarify reasons for discontinuation. In particular, the categories of investigator decision, other, and withdrew consent were investigated as to whether they were actually due to adverse events or lack of efficacy. No additional adverse events were identified in this process. However, some events of inadequate glycemic control were identified. Table 6.17 shows the Sponsor adjudicated reasons for discontinuation. In this trial, discontinuations due to hyperglycemia or inadequate control were not always coded as adverse events.

**Table 6.16 – Trial 103 Subject Disposition (12 Week Treatment Period)**

	TI Alone	Metformin + Secretagogue	TI + Metformin	All
Screened				1512
• Screen failures				977
• Eligible				535
Randomized	183	170	175	528
Safety Population	181 (98.9)	166 (97.6)	174 (99.4)	521 (98.7)
Completed treatment period 1	133 (72.7)	152 (89.4)	119 (68.0)	404 (76.5)
Discontinued before week 12	50 (27.3)	18 (10.6)	56 (32.0)	124 (23.5)
• Adverse Event	8 (4.4)	2 (1.2)	6 (3.4)	16 (3.0)
• Protocol Violation	3 (1.6)	1 (0.6)	0	4 (0.8)
• Subject Withdrew Consent	21 (11.5)	10 (5.9)	20 (11.4)	51 (9.7)
• Lost to follow up	1 (0.5)	3 (1.8)	0	4 (0.8)
• Physician Decision	13 (7.1)	2 (1.2)	10 (5.7)	25 (4.7)
• Other	4 (2.2)	0	20 (11.4)	24 (4.5)
Intention to Treat Population	177 (96.7)	162 (95.3)	169 (96.6)	508 (96.2)
Per Protocol Population	127 (69.4)	139 (81.8)	115 (65.7)	381 (72.2)

Source: Tables 7,11, Trial 103 CSR

**Table 6.17 – Trial 103 Sponsor Adjudicated Reasons for Discontinuation (12 Week Treatment Period)**

	TI Alone	Metformin + Secretagogue	TI + Metformin	All
Discontinued before week 12	50 (27.3)	18 (10.6)	56 (32.0)	124 (23.5)
• Adverse Event	8 (4.4)	2 (1.2)	6 (3.4)	16 (3.0)
• Protocol Violation	4 (2.2)	1 (0.6)	0	5 (0.9)
• Subject Withdrew Consent	13 (7.1)	10 (5.9)	12 (6.)	35 (6.6)
• Lost to follow up	1 (0.5)	3 (1.8)	0	4 (0.8)
• Physician Decision	2 (1.1)	0	7 (4.0)	9 (1.7)
• Other	1 (0.5)	0	0	24 (4.5)
• Lack of efficacy	21 (11.5)	2 (1.2)	31 (17.7)	54 (10.2)

Source: Table 6.7, Trial 103 Tables and Figures

**Reviewer’s comment: Similar to other trials, the discontinuation rate is higher for the TI group. Based on the Sponsor’s adjudication/re-classification of reasons for discontinuation, there is clearly an imbalance in the rate of discontinuation due to lack of efficacy in this trial not favoring the TI groups. The Sponsor attributes this finding, in part, to the slow titration of TI in the trial which resulted in subjects not reaching maximum dosages until month 5, after the primary efficacy endpoint. The Sponsor speculates that investigators may have been reluctant to increase the dose of a new drug with a requirement for numerically larger insulin units relative to usual sc insulins. It is also interesting that TI+metformin had the highest rate – even greater than TI alone.**

The protocol for this study required investigators to titrate treatments such that BG values remained below specified upper limits for preprandial, postprandial, and bedtime blood glucose, or until maximal doses of study treatments were achieved. After initiation of the study, a review of the data from completed Phase 2 studies in the TI clinical development program suggested that subjects were not being titrated actively. For this reason, a program to support treatment optimization in all randomization groups was initiated, based on the scheduled glycemic monitoring for the study. The goal of the Glycemic Monitoring Program was to provide the investigators with systematic and nonbiased reminders to guide the glycemic management of all study subjects according to the dosing and titration guidelines provided in the protocol. On a monthly basis the clinical sites were provided summary metrics, in a blinded fashion, on how they were doing with respect to achievement of glycemic goals. A summary contained the most recent mean HbA1c for all study subjects, regardless of treatment group. A second summary contained the mean change in HbA1c from Baseline for all study subjects, regardless of treatment group. However, 171 subjects had already completed and or terminated from the study prior to initiation of the glycemic monitoring program.

#### 6.1.3.4 Subject Disposition - Active-Control Trials in T1DM

##### Subject Disposition - Trial 009

In trial 009, 589 subjects were randomized, 301 to treatment with TI + glargine and 288 to treatment with insulin aspart + glargine (Table 6.18). The slight imbalance in randomization was due to stratification by site. Of the randomized subjects, 24 (4.1%) subjects withdrew before receiving study medication, 8/301 (2.7%) in the TI arm and 16/288 (5.6%) in the insulin aspart arm. Of the remaining randomized subjects, 198 (65.8%) subjects completed in the TI arm and 220 (76.4%) completed in the insulin aspart arm. The ITT Population in this trial was composed of 539 subjects with 277 in the TI randomization arm and 262 in the insulin aspart arm.

**Reviewer’s comment: Due to the relatively low completer rate in this trial, the Agency statistician examined efficacy for both the completer and dropout cohorts. The results based on the completers were similar to the ones based on the whole ITT/LOCF**

**population. Therefore, there was no major impact on efficacy by the high dropout rate in this trial.**

<b>Table 6.18 – Trial 009 Subject Disposition (52 Week Treatment Period)</b>			
Population	TI + Glargine	Insulin aspart + Glargine	Overall Total
Number of Subjects (%)			
Screened			1420
• Screen failures			822
• Eligible			598
Randomized	301	288	589
Safety Population	293 (97.3)	272 (94.4)	565 (95.9)
Completed	198 (65.8)	220 (76.4)	418 (71.0)
Prematurely Discontinued	94 (31.2)	52 (18.1)	146 (24.8)
• Adverse Event	17 (5.6)	2 (0.7)	19 (3.2)
• Protocol Violation	3 (1.0)	14 (4.9)	17 (2.9)
• Subject Withdrew Consent	47 (15.6)	19 (6.6)	66 (11.2)
• Subject Died	0	0	0
• Physician Decision	15 (5.0)	7 (2.4)	22 (3.7)
• Lost to follow-up	5 (1.7)	5 (1.7)	10 (1.7)
• Other	7 (2.3)	5 (1.7)	12 (2.0)
Intention to Treat Population	277 (92.0)	262 (91.0)	539 (91.5)
Per Protocol Population	188 (62.5)	210 (72.9)	398 (67.6)

Source: Table 6, Trial 009 CSR

Twenty-four (4.1%) randomized subjects discontinued before first dosing with study drug: 8/301 (2.7%) in the TI arm and 16/288 (5.6%) in the insulin aspart arm. A total of 24/589 (4.1%) randomized subjects were discontinued because of site inactivations, 12/301 (4.0%) and 12/288 (4.2%) in the TI and insulin aspart arms, respectively. In summary, 20/301 (6.6%) randomized subjects in the TI arm and 28/288 (9.7%) in the insulin aspart arm discontinued early either before dosing or as a consequence of site-inactivations due to investigator disqualifications. (Note: data from these sites were included in ITT analyses).

The greatest number of discontinuations was due to withdrawal of consent (15.6% and 6.6% in the TI and insulin aspart arms). Subjects who withdrew consent were further reviewed by the Sponsor and misclassifications were identified and reclassified as appropriate (e.g., to discontinuation due to an AE) before programmatic generation of tables and files. Reasons for subjects' withdrawal of consent included randomization choice, new occupation, relocation, and other/unknown. In Russia, it was not permissible to ask subjects for a reason for withdrawing consent.

The higher percentage of discontinuations in the TI arm was primarily due to AEs affecting the respiratory tract (including respiratory tract infections) in 13 subjects. In the SOC of Respiratory Tract, the incidence of discontinuations was 10 subjects (3.4%) for TI versus none in the insulin

aspart group (mostly driven by cough); in the SOC of Infections the incidence of discontinuations was 3 subjects with respiratory tract infections (1.0%) for TI versus none in the insulin aspart group. The other adverse events leading to discontinuation in the TI arm were musculoskeletal chest pain in one subject, breast cancer in one subject, and “weight decreased” in one subject. The two discontinuations due to AEs in the insulin aspart + glargine arm were one case of pregnancy and one case of “metabolic syndrome” that upon review of the subject narrative appears to be miscoded and the reason for discontinuation is hospitalization due to fever.

Similar to trial 102, further information regarding verbatim reasons for discontinuation among patients who withdrew for the reason of “withdrew consent” was requested from the Sponsor. The Sponsor was requested to provide numbers of withdrawals for adverse events of hyperglycemia, blood glucose increased, diabetes mellitus inadequate control, ketoacidosis, diabetic ketoacidosis, or any other preferred term representing inadequate glycemic control and any other withdrawal due to lack of efficacy including investigator’s decisions that upon examination appear to be due to lack of efficacy. The Sponsor was also asked to further specify reasons for subjects withdrawing consent.

The Sponsor submitted an updated table of subject disposition (Table 6.19). In the opinion of the clinical reviewer, dissatisfaction with therapy should be considered potentially due to unsatisfactory glycemic control. Therefore, a reasonable estimate of subjects discontinuing for ineffective therapy is 29 (9.6%) vs. 3 (0.9%) in the TI and comparator arms, respectively. A conservative estimate is 23 (7.6%) to 2 (0.7%) in the TI and comparator arms, respectively. In terms of the other discontinuations due to “withdrew consent” there was no apparent pattern that would indicate a safety or efficacy concern. However, there were more subjects in the TI arm who did not give any reason for withdrawal.

<b>Table 6.19 – Trial 009 Updated Subject Disposition Summary</b>		
Disposition	TI	Comparator
Randomized	301	288
Safety Population	293 (97.3)	272 (94.4)
Completed	198 (65.8)	220 (76.4)
Prematurely Discontinued	94 (31.2)	52 (18.1)
<ul style="list-style-type: none"> <li>• Events of hyperglycemia, blood glucose increased, diabetes mellitus inadequate control, ketoacidosis, diabetic ketoacidosis, or any other preferred term representing inadequate glycemic control and any other withdrawal due to lack of efficacy including investigator’s decisions that upon examination appear to be due to lack of efficacy               <ul style="list-style-type: none"> <li>• Adverse event related to hyperglycemia                   <ul style="list-style-type: none"> <li>• Hyperglycemia</li> <li>• Diabetic ketoacidosis</li> </ul> </li> <li>• Glycemic control issues</li> <li>• Lack of efficacy</li> </ul> </li> </ul>	23 (7.6)	2 (0.7)
<ul style="list-style-type: none"> <li>• Adverse Event other than those related to hyperglycemia</li> </ul>	4 (1.3)	1 (0.3)
<ul style="list-style-type: none"> <li>• Protocol Violation</li> </ul>	3 (1.0)	1 (0.3)
<ul style="list-style-type: none"> <li>• Diabetic ketoacidosis</li> </ul>	1 (0.3)	0
<ul style="list-style-type: none"> <li>• Glycemic control issues</li> </ul>	5 (1.7)	1 (0.3)
<ul style="list-style-type: none"> <li>• Lack of efficacy</li> </ul>	14 (4.7)	0
<ul style="list-style-type: none"> <li>• Adverse Event other than those related to hyperglycemia</li> </ul>	20 (6.6)	4 (1.4)
<ul style="list-style-type: none"> <li>• Protocol Violation</li> </ul>	3 (1.0)	14 (4.9)
<ul style="list-style-type: none"> <li>• Subject Withdrew Consent               <ul style="list-style-type: none"> <li>• Dissatisfied with treatment/therapy</li> </ul> </li> </ul>	29 (9.6)	15 (5.2)
<ul style="list-style-type: none"> <li>• Subject Withdrew Consent               <ul style="list-style-type: none"> <li>• Dissatisfied with treatment/therapy</li> </ul> </li> </ul>	6 (2.0)	1 (0.3)
<ul style="list-style-type: none"> <li>• Subject Died</li> </ul>	0	0
<ul style="list-style-type: none"> <li>• Physician Decision</li> </ul>	7 (2.3)	7 (2.4)
<ul style="list-style-type: none"> <li>• Lost to Follow-up</li> </ul>	5 (1.7)	5 (1.7)
<ul style="list-style-type: none"> <li>• Sponsor/site decision mostly for lack of drug availability at site</li> </ul>	7 (2.3)	5 (1.7)

**Reviewer’s comment: The rate of withdrawal due to lack of efficacy was higher in the TI arm than in the comparator arm.**

Subject Disposition - Trial 101

In trial 101, 111 subjects were randomized and 107 comprised the ITT population. No subject prematurely discontinued in the insulin aspart + Lantus arm (Table 6.20). Five subjects discontinued in the TI + Lantus arm. One subject was recorded as having an AE of an unspecified respiratory disorder. Two subjects who withdrew consent did so because of cough, but these were not coded as AEs. One subject withdrew consent because of difficulty in performing the study procedures. Duration of treatment was 47 days. One subject was permanently discontinued from the study because of a protocol violation, lack of compliance with the treatment regimen (< 75% compliance). Duration of treatment was 215 days. No subject withdrew due to hyperglycemia or lack of efficacy/inadequate diabetes control.

<b>Table 6.20 – Trial 101 Subject Disposition (12 Week Treatment Period)</b>			
Population	TI + Lantus	Aspart + Lantus	Overall Total
Number of Subjects (%)			
Screened			181
• Screen failures			61
• Eligible			120
Randomized	55	56	111
Safety Population	54	56	110
Completed	49 (91)	56 (100)	105 (96)
Prematurely Discontinued	5 (9.3)	0	5 (4.5)
• Adverse Event	1 (2)	0	3 (3)
• Protocol Violation	1 (2)	0	1 (1)
• Subject Withdrew Consent	3 (6)	0	1 (1)
Intention to Treat Population	51	56	107
Per Protocol Population	48	55	103

Source: Table 4, table 5 trial 101 report

**Reviewer’s comment: There were few discontinuations in this small trial. No subjects apparently withdrew due to hyperglycemia.**

#### 6.1.3.5 Subject Disposition Pulmonary Safety Trial

Trial 030 was not a primary efficacy trial; therefore, the disposition of the trial population is not described in detail in this section, but is incorporated into the pooled safety population discussed in section 7. The overall trial population included 938 subjects randomized to TI of which 50.6% completed, 951 subjects randomized to usual care of which 69.6% completed, and 164 non-diabetic subjects (77.4% who completed). Adverse events and “subject withdrew consent” were the primary reasons for discontinuation in the TI arm.

#### 6.1.3.6 Subject Disposition – Summary and Conclusions

In the placebo controlled T2DM trials (005 and 0008), the rate of discontinuations were similar between TI and TP placebo treated subjects and were actually slightly higher among TP treated subjects. This finding in these blinded trials lends credence to the Sponsor’s hypothesis that the open-label design of many of the trials led to a disproportionately higher rate of discontinuation in TI treated patients seen in the open-label trials. The estimated overall rate of discontinuation due to lack of efficacy was low, 2.6%, in trial 005 and was not dose dependent, and was zero in trial 0008.

In the pivotal T2DM trial, after accounting for discontinuations due to respiratory AEs the discontinuation rate due to AEs was similar between treatment groups. These AEs were generally mild and are considered by the clinical reviewer as evidence of intolerability of TI by some patients rather than as a safety concern. Discontinuations due to lack of efficacy are estimated to be low (0.9%) in the TI + glargine arm and 0 in the 70/30 mix arm, although further characterization of discontinuations is pending from the Sponsor.

In the short term T2DM trials 014 and 026, findings were similar to the pivotal trial 102. A large proportion of discontinuations classified as AEs were due to respiratory events, predominantly cough. The percentage of discontinuations due to lack of efficacy was low.

Trial 103 is notable for a clear difference in discontinuations due to lack of efficacy not favoring TI after Sponsor re-classification of reasons for discontinuation. The clinical reviewer considers the Sponsor's explanation possible – that the slow titration of TI led to subjects discontinuing because of dissatisfaction with blood glucose control because the primary efficacy analysis showed the reduction in HbA1c due to TI + metformin to be numerically lower, albeit non-inferior, to the reduction in HbA1c due to metformin + sulfonylurea using the LOCF method, while the reduction in HbA1c due to TI + metformin was numerically higher than the reduction in HbA1c due to metformin + secretagogue among completers (see section 6).

In the T1DM trials, 009 and 101, interestingly there were no reports of discontinuations due to lack of efficacy. Among AEs leading to discontinuation there were no cases of hyperglycemia, “blood glucose increased” or “diabetes mellitus inadequate control” suggesting lack of efficacy. However, there was an imbalance in discontinuations due to “subject withdrew consent” and “investigator decision” that could include discontinuations due to lack of efficacy. Further characterization of these events has been requested from the Sponsor.

#### 6.1.4 Analysis of the Primary Endpoint

The primary efficacy variable for pivotal studies was change from baseline in HbA1c (%) at the end of the treatment period. It is particularly important to have an objective measure of efficacy such as HbA1c in the TI clinical development program because the pivotal trials were open-label. HbA1c is an appropriate endpoint because

1. HbA1c is a widely-accepted, objective, surrogate measure of glycemic control that correlates well with mean blood glucose over the preceding 3 months (Nathan DM 1984).
2. The National Glycohemoglobin Standardization Program (NGSP) has established and promulgated standardized assays for HbA1c based on data from the Diabetes Control and Complications Trial (DCCT). Use of standardized methodology has reduced inter-laboratory coefficients of variation to <5% (College of American Pathologists 1999; Goldstein 1982).
3. HbA1c has excellent reliability, predicts several diabetes-specific complications, and provides the current basis for treatment decisions (American Diabetes Association 2008).

4. Lowering HbA<sub>1c</sub> reduces microvascular complications in patients with type 1 and type 2 diabetes (Diabetes Control and Complications Trial Research Group 1993, UK Prospective Diabetes Study (UKPDS) Group 1998) and possibly macrovascular complications in patients with type 1 diabetes (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group 2005).

For these reasons, the FDA draft guidance entitled Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf>) states, “For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA<sub>1c</sub> (i.e., HbA<sub>1c</sub> is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control.”

The percentage of subjects who reached the pre-defined target for HbA<sub>1c</sub> of <7% and HbA<sub>1c</sub> of ≤ 6.5% was also examined. These are clinically appropriate endpoints because

1. The American Diabetes Association (ADA) currently recommends a target HbA<sub>1c</sub> of <7% for non-pregnant adults in general with diabetes. Lowering HbA<sub>1c</sub> to an average of 7% has been shown to reduce microvascular and, in the case of type 1 diabetes, possibly macrovascular complications of diabetes. Since pregnant subjects are excluded from these clinical trials, <7% is an appropriate endpoint for these trials (ADA 2008).
2. The AACE (American Association of Clinical Endocrinologists) recommended target for HbA<sub>1c</sub> is ≤ 6.5% (<http://www.aace.com/public/awareness/stateofdiabetes/FactsAboutA1C.pdf>)

#### 6.1.4.1 Analysis of the Primary Endpoint- Placebo Controlled Trials in T2DM

##### Analysis of the Primary Endpoint- Trial 005

The primary efficacy endpoint was change from baseline in HbA<sub>1c</sub> (%) from Visit 5 (double-blind baseline) to Visit 12. The Sponsor’s predefined primary efficacy analysis was a one-sided *t* test with significance level set at 0.05. A step-down procedure (to reduce type 1 error) was used as described in section 5.

**Reviewer’s comment:** Although the purpose of this trial was to demonstrate a dose-response relationship, the trial design was flawed as discussed previously because titration of TI occurred weekly starting at Visit 5 (when the baseline HbA<sub>1c</sub> value was measured) up to 8 weeks before the final HbA<sub>1c</sub> was measured. Also, Lantus could be titrated up to the end of the trial, and the background anti-diabetic medications/Lantus could be adjusted in the 1-3 weeks prior to the baseline HbA<sub>1c</sub>. Therefore, it is likely that steady state for the

**primary efficacy variable was not reached by the Visit 12 HbA1c measurement. In addition, the effect of the uptitration would not be fully expressed in the final HbA1c measurement because HbA1c is a reflection of the previous 12 weeks glycemic control. Therefore, the results from this trial might best be interpreted to support an overall effect of TI on HbA1c compared with placebo, rather than to demonstrate a dose-response relationship.**

Baseline HbA1c was similar among treatment groups (Table 6.21). In an ANCOVA model including treatment group as the main effects and baseline HbA1c as a covariate, there was a statistically significant reduction in mean HbA1c between all TI dosage groups compared with TP (placebo) from baseline to 11 weeks of treatment. The placebo-adjusted change in HbA1c (shown in the column labeled “difference from TP”) was clinically relevant for all treatment groups with a range of -0.52% to -0.82%. The placebo-adjusted reduction in HbA1c was not dose-dependent in this trial, most likely due to the limitations in trial design described above.

**Table 6.21 – Trial 005 ANCOVA of Change in HbA1c (%) After 11 Weeks, ITT Population, with LOCF**

Treatment Group	N	Baseline value (raw mean) and (SD)	Final value (raw mean) and (SD)	Change from baseline LS Mean	95% CI for the LS Mean change from baseline	Difference from TP LS Mean (Other - TP)	P value from t test with stepdown procedure
TP	41	8.70 (1.304)	8.94 (1.304)	0.2282	-0.06366, 0.5201		
TI 14 U	43	8.91 (1.381)	8.55 (1.304)	-0.2919	-0.5774, -0.0063	-0.5201	0.0128
TI 28 U	43	8.59 (1.357)	8.05 (1.165)	-0.5930	-0.8785, -0.3076	-0.8213	0.0001
TI 42 U	41	8.68 (1.159)	8.21 (1.201)	-0.4929	-0.7848, -0.2009	-0.7211	0.0007
TI 56 U	42	8.82 (1.162)	8.20 (1.245)	-0.5928	-0.8813, -0.3044	-0.8211	0.0001

The p values for each treatment group vs. TP are based on a one-sided t test ANCOVA model includes treatment group as a fixed effect and baseline HbA1c as covariate  
 Source: Sponsor’ submission 17 Nov 2009

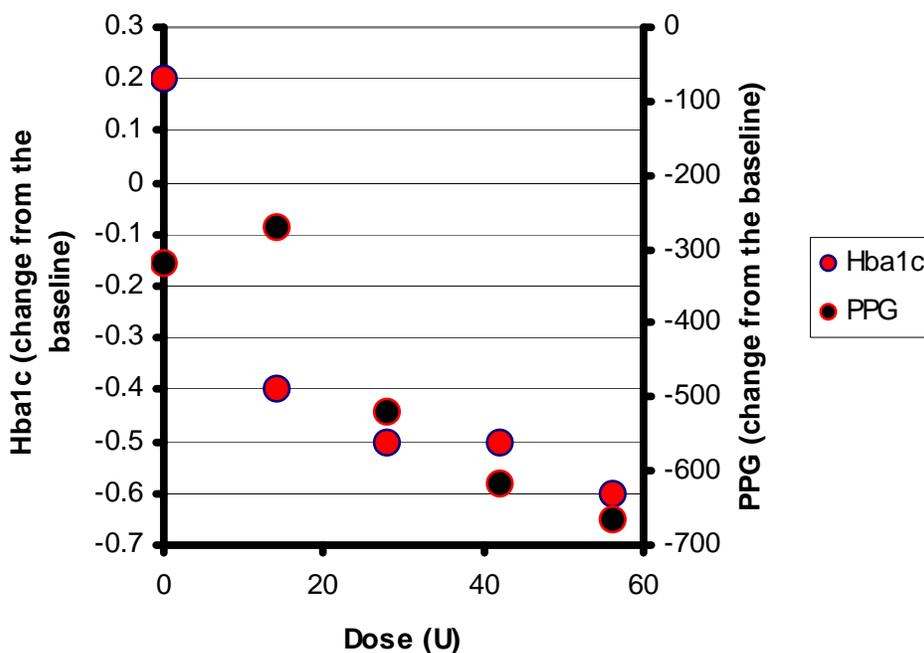
An analysis (Table 6.22) of the ITT Population with an ANCOVA model that included terms for treatment group, baseline HbA1c, time adjusted Lantus exposure (TALE), and the interaction effect of time adjusted Lantus exposure and treatment group showed similar results suggesting that the statistically significant reduction in HbA1c vs. placebo seen in the TI treatment groups was not due to a difference in Lantus exposure.

**Table 6.22 – Trial 005 ANCOVA of Change in HbA1c (%) After 11 Weeks Adjusting for Lantus exposure, ITT Population, with LOCF**

Treatment Group	N	Baseline value (raw mean) and (SD)	Final value (raw mean) and (SD)	Change from baseline  LS Mean	95% CI for the LS Mean change from baseline	Difference from TP LS Mean (Other - TP)	P value from t test with stepdown procedure
TP	41	8.70 (1.304)	8.94 (1.304)	0.2492	-0.03986, 0.5383		
TI 14 U	43	8.91 (1.381)	8.55 (1.304)	-0.3047	-0.5833, -0.0261	-0.5539	0.0071
TI 28 U	43	8.59 (1.357)	8.05 (1.165)	-0.6072	-0.8894, -0.3250	-0.8564	<.0001
TI 42 U	41	8.68 (1.159)	8.21 (1.201)	-0.4910	-0.7757, -0.2063	-0.7402	0.0004
TI 56 U	42	8.82 (1.162)	8.20 (1.245)	-0.6058	-0.8882, -0.3234	-0.8550	<.0001

The p values for each treatment group vs. TP are based on a one-sided t test ANCOVA model includes terms for treatment group, baseline HbA1c, TALE, and the interaction effect of TALE x treatment group.  
 Source: Sponsor' submission 17 Nov 2009

The following figure from Dr. Chung's clinical pharmacology review shows HbA1c data graphically (unadjusted means) and also shows the corresponding mean change from baseline in postprandial glucose AUC seen for each treatment group. (Postprandial glucose AUC is also discussed as a secondary endpoint)



Additional Analyses Related to the Primary Endpoint – Trial 005

Responder Rates Based on HbA1c – Trial 005

The Sponsor defined a “responder rate” as  $\leq -0.6\%$  mean change from Visit 5 to Visit 12. In a logistic regression model including main effects of treatment group, baseline HbA1c, and time adjusted Lantus exposure the difference from TP in responder rates was statistically significant for the TI 28 U, TI 42 U, and TI 56 U groups (Table 6.23).

**Table 6.23 – Trial 005 Analysis of Responder Rate Based on Mean Change of  $\leq -0.6\%$  in HbA1c From Baseline to 11 Weeks, ITT Population**

Treatment Group	N	% Responders	95% CI	P value vs. TP	Odds Ratio vs. TP
TP	41	19.5	6.17 – 37.6	-	-
TI 14 U	43	37.2	19.2 – 65.9	0.1145	2.4
TI 28 U	43	55.8	39.4 – 88.8	0.0003	7.8
TI 42 U	41	41.5	23.4 – 72.0	0.0252	3.5
TI 56 U	42	59.5	44.3 – 92.5	0.0002	8.0

The p values and odds ratios are derived from a logistic regression model which included the main effects of treatment group, baseline HbA1c, and time adjusted Lantus exposure (TALE)  
 Source: Table 23, Trial 005 CSR

**Reviewer’s comment: The three highest dosage groups have a higher proportion of responders as defined by the Sponsor supporting the efficacy of TI vs. placebo. However, there is an inconsistent dose-response effect. These results are consistent with the primary efficacy analysis.**

The Sponsor also defined a responder rate of HbA1c of  $< 7.0\%$  at study endpoint. In a similar logistic regression model as the one used above in Table 6.23, the responder rate was higher than placebo for TI groups 28 U and 56 U but not for TI groups 14 U and 42 U (Table 6.24).

**Table 6.24 – Trial 005 Analysis of Responder Rate Based on HbA1c < 7% After 11 Weeks**

Treatment Group	N	% Responders	95% CI	P value vs. TP	Odds Ratio vs. TP
TP	41	2.4	0.2 – 4.9	-	-
TI 14 U	43	4.7	0.5 – 9.3	0.45	2.6
TI 28 U	43	18.6	5.6 – 35.9	0.04	10.5
TI 42 U	41	4.9	0.6 – 9.8	0.62	1.9
TI 56 U	42	14.3	3.5 – 28.0	0.04	11.0

The p values and odds ratios are derived from a logistic regression model which included the main effects of treatment group, baseline HbA1c, and time adjusted Lantus exposure (TALE)  
 Source: Table 24, Trial 005 CSR

**Reviewer’s comment: A dose-response effect is not seen due to the limitations of trial design described above, but it is unclear why the 42 U group was not better than placebo in this analysis.**

Rates of reported hyperglycemia between treatment groups – Trial 005

The rate of reported hyperglycemia was less than < 4% in all treatment groups of the study.

Lantus Dose Achieved by Subjects – Trial 005

Table 6.25 presents the average Lantus dose by randomization group at Visit 5 (initiation of double-blind IMP dosing) and Visit 12 (trial endpoint). At Visit 5, Lantus dosing was similar across treatment groups, ranging from 19.2 IU in the TP group to 22.4 IU in the TI 56 U group. At Visit 12, there were no differences in Lantus dosing across the treatment groups, ranging from 28.9 IU in the TP group to 29.7 IU in the TI 56 U group.

**Table 6.25 – Trial 005 Summary of Average Lantus Dose (IU) by Treatment Group**

Visit		TP	TI 14 U	TI 28 U	TI 42 U	TI 56 U
5	N	42	44	44	42	43
	Mean	19.2	19.3	18.0	20.6	22.4
	SD	10.23	9.51	11.43	12.61	12.87
12	N	37	38	39	35	34
	Mean	28.9	25.7	25.5	27.0	29.7
	SD	13.11	12.34	12.61	17.25	13.09

Source: Table 14, Trial 005 CSR

**Reviewer’s comment: If there was a dose response effect of TI but similar HbA1c reductions at trial endpoint among active TI treatment groups, one might expect lower required doses of Lantus in the higher TI dose groups. However, this was not the case. In**

**fact, there appears to be a slight trend towards higher mean daily Lantus dose in the higher TI dose groups.**

**Additionally, these results support the finding that Lantus exposure was not driving the significant placebo-adjusted HbA1c reduction achieved by TI because the dose of Lantus used by TP subjects was similar to the dose used by active TI subjects.**

Analysis of the Primary Endpoint - Trial 0008

As described previously, the prespecified statistical analysis was a one-sided 2-sample *t* test to detect any significant trend in HbA1c between baseline and final treatment visit and to detect any significant difference between treatment groups in HbA1c.

Baseline HbA1c was similar between treatment groups. At the end of the 12-week study period, mean HbA1c levels decreased from baseline by -0.71% in the TI group as compared with -0.30% in the TP group (placebo-adjusted reduction in HbA1c of -0.41%) (Table 6.26). Results were similar for the ITT population without LOCF and for the primary efficacy population (-0.76% mean reduction in HbA1c in the TI group compared with -0.39% in the TP [mean treatment difference -0.37%, p=0.0114]).

	TI (n=58)		TP placebo (n=61)	
	Baseline	Mean change at Week 12	Baseline	Week 12
Mean	7.87	-0.71	7.78	-0.30
SD	1.1	0.8	1.1	0.7
Range	6.4 – 12.2	-2.6 – 1.0	6.2 – 10.7	-3.3 – 1.1
95% CI		-0.91 – (-0.51)		-0.49 – (-0.12)
P value: TI vs. TP		0.0026		
P value is based on a two sample t-Test of change between Baseline and week 12 within the treatment group. Source: Section 14.2 Table 10.1, Table 22 Trial 0008 CSR				

**Reviewer’s comment: The placebo-adjusted reduction in HbA1c in trial 0008 is lower than in trial 005. One possible reason is that the baseline HbA1c was lower in trial 0008 than in trial 005 (7.82 % vs. 8.72 %). Because of the design of trial 005 (steady state was not reached at trial endpoint) it is difficult to evaluate differences in TI dosage as a potential contributor to the difference in placebo-adjusted reduction in HbA1c between the two trials.**

Additional Analyses Related to the Primary Endpoint – Trial 0008

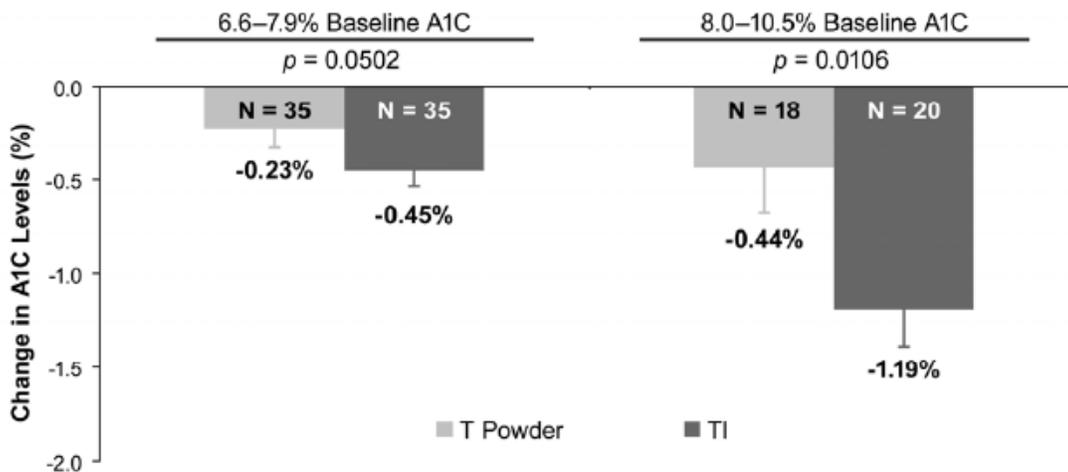
### HbA1c Subgroups

The Sponsor also defined two subgroups of the efficacy population to evaluate separately as follows:

- Group A represents subjects with HbA1c at Baseline between 6.6 and 7.9%.
- Group B represents subjects with HbA1c at Baseline between 8.0 and 10.5%.

In ITT Population with LOCF Group A (Figure 6.1), the change in HbA1c was -0.45% for the TI group as compared with -0.23% for the TP group (placebo-adjusted reduction in HbA1c of 0.22%). In ITT Population with LOCF Group B, the change in HbA1c was -1.19% in the TI group as compared with -0.44% in the TP group (placebo-adjusted reduction in HbA1c of 0.75%). Results for these subgroups of the Primary Efficacy Population were similar to the ITT Population with LOCF results.

**Figure 6.1 – Trial 0008 Groups A and B, Mean Reduction in HbA1c from Baseline to Week 12, ITT Population with LOCF**



Source: Figure 6, Trial 0008 CSR

**Reviewer’s comment:** This pattern of response, i.e. the subgroup with higher HbA1c at baseline appears to respond better to treatment than does the subgroup with the lower HbA1c at baseline is commonly seen with diabetic product trials and is also seen among placebo patients. However, the placebo-adjusted change in HbA1c is also higher in the subgroup with the higher baseline HbA1c.

### Responder Rates Based on Reduction in HbA1c - Trial 0008

In this study, “successful treatment” was defined as a decrease in HbA1c value at 12 weeks by at least 0.6 % compared to HbA1c value measured at baseline. In the ITT population 55.2% (32 of 55 subjects) were “successfully treated” with TI compared to 24.6% (15 of 53 subjects) in the TP group (p=0.0017). Results were similar for the Primary Efficacy Population.

Rates of reported hyperglycemia between treatment groups – Trial 0008

The rate of reported hyperglycemia was 1/61 (16.4%) in the TI group and 10/62 (16.1%) in the TP placebo group.

TI Dose Levels achieved - Trial 0008

The initial dose for all subjects was 6 U of TI with each meal, only 1 subject remained at 6 U of TI throughout the study. Mean dose at 4, 8, and 12 weeks after the start of treatment (measured at the meal-challenge test during each visit) was 20 U, 31 U, and 32 U, respectively, although the ranges of doses were broad (Table 6.27). At both week 8 and week 12 of the trial, 13 subjects in the TI group were receiving 48 U TID.

<b>Table 6.27 – Trial 0008 Mean Prandial Dose of TI (Among TI Randomized Patients) at Baseline and 4, 8, and 12 Weeks of Treatment (Primary Efficacy Population)</b>				
	Baseline	4 Weeks	8 Weeks	12 Weeks
N	48	48	48	48
Mean	6	20	31	32
SD	0	9	12	13
Range	6 - 6	6 - 36	6 - 48	6 - 48

Source: Table 20, Trial 0008 CSR

**Reviewer’s comment: It is important to keep in mind that 48 U was maximum protocol specified dose. Therefore, based on the reported ranges it is possible that by 8 weeks some patients had maxed out their dose but may have required more TI. The Sponsor reported that by week eight slightly more than half of the subjects were receiving between 30 and 48 U of TI.**

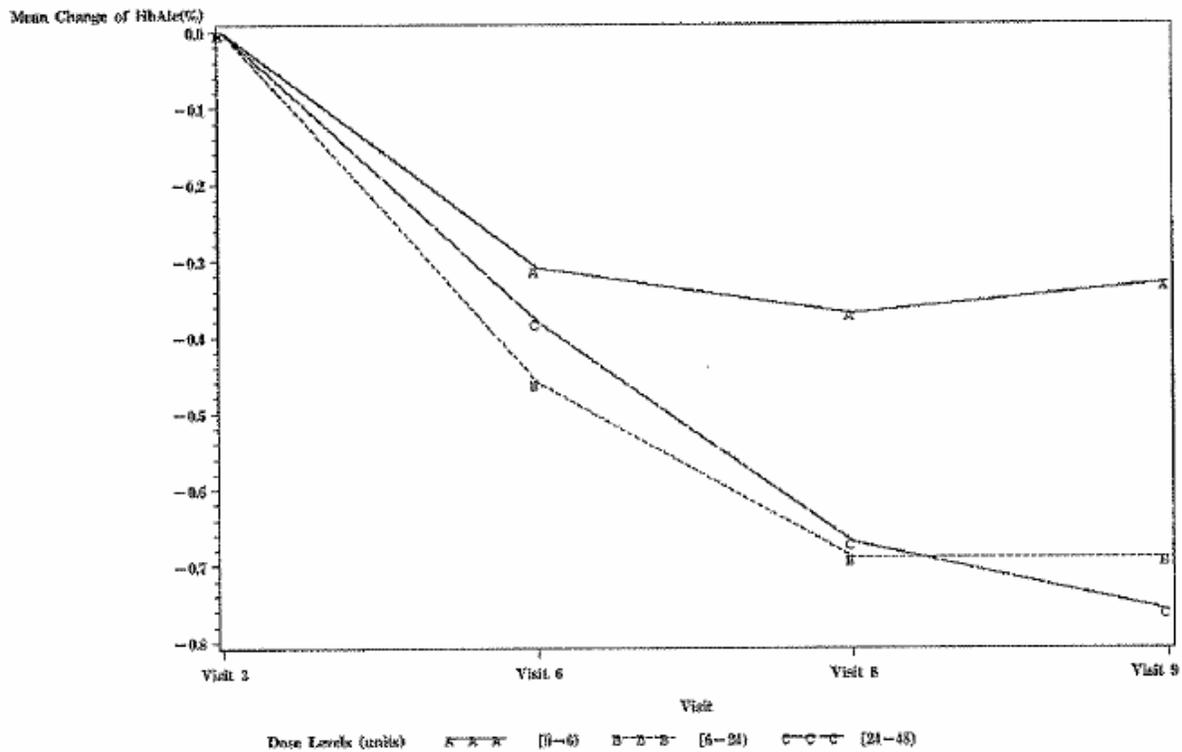
Explorations for Dose Response - Trial 0008

Change in HbA1c as a function of the exposure weighted average dose level of TI is shown for the ITT Population in Figure 6.2. The Sponsor interprets this figure that “at Week 12, a dose-response was observed wherein subjects on the lowest dose or TI Inhalation Powder (6 U) had smaller reductions in HbA1c (~0.3%), subjects on intermediate doses (6 to 24 U) had

intermediate reductions in HbA1c (~0.7%), and subjects on highest doses (24 to 48 U) had the greatest reductions in HbA1c (approaching 0.8% and still declining).”

**Reviewer’s comment: The clinical reviewer disagrees with the Sponsor’s conclusion because the difference between the intermediate and high doses at 12 weeks appears very similar. A claim of a dose response relationship is not supported because the response seen in the low dose group appears similar to the response seen in the placebo group and the two higher dose groups appear almost identical.**

**Figure 6.2 – Mean Change in HbA1c (%) by Weighted Dose Level Over Time (ITT Population)**

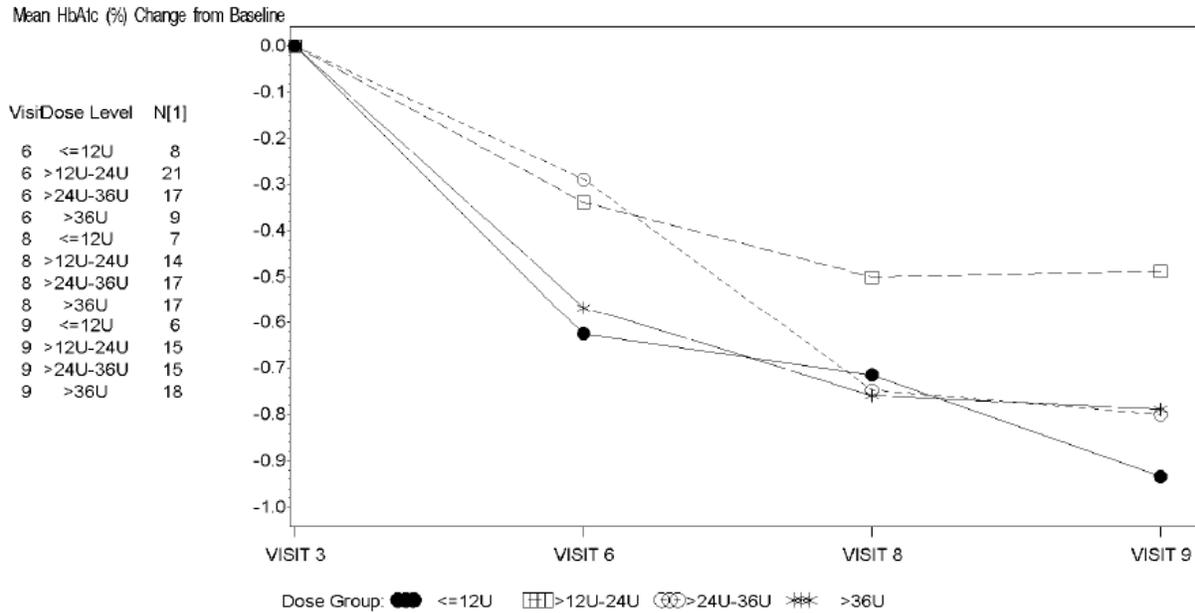


Source: Figure 5, Trial 0008 CSR

Based on the lack of a perceptible difference between the two highest dose groups, an information request was sent to the Sponsor to provide additional analyses with the higher dose groups further subdivided.

Consequently, on 03 Nov 2009, the Sponsor submitted the following figure.

Figure 3  
 Mean Change of HbA1c (%) Versus Exposure Weighted Average Dose by Visits  
 ITT Population without LOCF



The clinical reviewer’s interpretation of the data shown in the figure is that a dose-response effect is still not supported. However, the trial was not designed to examine a dose response effect. Insulin requirements can vary greatly between individual subjects so the response to the same dose of TI might be different between two subjects. Therefore, the lack of evidence of dose-response in this trial does not preclude that there may a dose response within an individual subject.

Doses of Lantus Required by Subjects (If Any) - Trial 0008

The dose of Lantus rescue medication required for each patient, if used, was to be evaluated as a secondary endpoint. If Lantus was used by a significant number of patients then this might preclude a valid analysis of the primary efficacy endpoint because any subject not responding to TI might have Lantus added and it would be unclear if the effect on HbA1c was due to Lantus or to TI. Study results showed that only one patient in each treatment group received Lantus rescue medication.

6.1.4.2 Analysis of the Primary Endpoint - Long-Term Active Control Trial in T2DM

Trial 102 was the pivotal phase 3 efficacy trial for the T2DM program.

Analysis of the Primary Endpoint – Trial 102

Baseline HbA1c was similar between treatment groups. In an ANCOVA model including treatment group and pooled investigator site as fixed effects with baseline HbA1c as a covariate, and using the ITT population with LOCF, the change from baseline in the TI + glargine arm was -0.59% compared with the 70/30 mix arm which showed a change from baseline of -0.71% (Table 6.28). The 95% CI for the difference between TI + basal insulin and 70/30 mix was (-0.05 to 0.29) supporting the non-inferiority of TI + basal insulin compared with 70/30 mix. The PP population showed similar results. The MMRM analysis supported the ANCOVA analysis with similar findings (data not shown).

Time Point	Statistic	TI + Glargine	70/30 Mix	TI vs. 70/30 Mix
Baseline	N	302	316	
	Mean	8.69	8.68	
	SD	1.12	1.08	
	95% CI	8.57 – 8.82	8.56 – 8.80	
Week 52	N	302	316	
	Mean	8.11	7.98	
	SD	1.26	1.16	
	95% CI	7.97 – 8.25	7.85 – 8.11	
Change from Baseline to Week 52	N	302	316	
	LS Mean	-0.59	-0.71	.012
	SE	0.06	0.06	0.085
	95% CI	-0.71 – (-0.47)	-0.83 – (-0.59)	<b>-0.05 – 0.29</b>
Noninferiority margin = 0.4% upper bound of the 95% CI				
Source: Table 16, Trial 102 CSR				

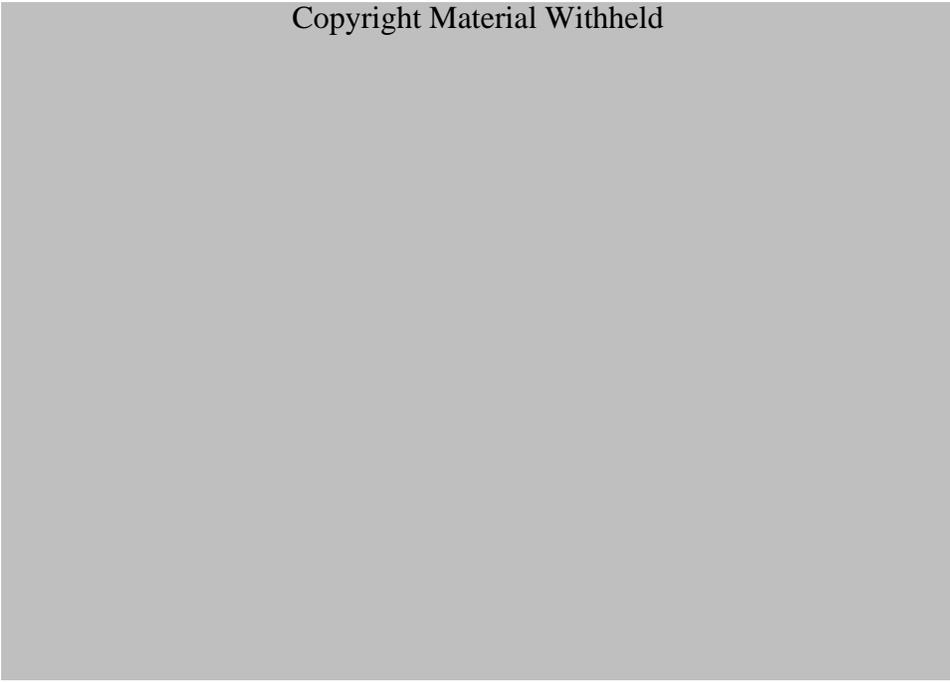
**Reviewer’s comment: Although TI was non-inferior to comparator in this trial, the clinical interpretation is only meaningful if the comparator achieved an acceptable level of glycemic control. Because insulin trials are open-label and are dependent on active titration by investigators to achieve glycemic goals, clinical interpretation can be challenging. The numerical reduction in HbA1c was clinically significant in both treatment groups in this trial. However, the mean HbA1c at study endpoint was above the ADA glycemic goal of < 7% for both treatment groups. This may be partially related to the fact that insulin doses were only to be actively titrated during the first 10 weeks of the 52-week treatment period.**

**To try to interpret these results in the context of other inhaled insulin products, in the Exubera development program, study 108 was a 6 month, open-label, parallel group study done in T2DM subjects who had been on a stable regimen of SQ insulin for at least 2 months prior to study entry. Patients were assigned to receive either TID premeal inhaled insulin plus bedtime Ultralente®, or BID mixed SQ NPH and regular insulin. The Exubera group achieved a HbA1c of 7.4% from a baseline of 8.1% (change -0.7%) while the comparator group achieved a HbA1c of 7.6% from a baseline of 8.2% (change -0.6%).**

**It is not advisable to compare efficacy endpoints across trials. However, in the clinical reviewer's opinion, Exubera appears to have stronger evidence of efficacy because the mean HbA1c achieved at study endpoint by both treatment groups was closer to the ADA goal than the mean HbA1c achieved by trial groups in TI study 102. Part of this difference may be related to the lower baseline A1c in the Exubera trial (~8.1-8.2%) compared to the TI trial (8.7%).**

**In the 4-T trial (Holman, 2009), 708 subjects who had HbA1c levels of 7 to 10% on maximum doses of metformin and sulfonylurea for at least 4 months and were insulin naïve were randomized to receive biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily. The median HbA1c at three years in the biphasic group was 7.1% with an absolute reduction from baseline of 1.3%. The reduction at 1 year was not a predefined statistical endpoint in this study, based on the figure below, it appears that the reduction at 1 year was similar to the reduction at 3 years. This is much better than achieved in the biphasic insulin group in trial 102 suggesting better insulin titration.**

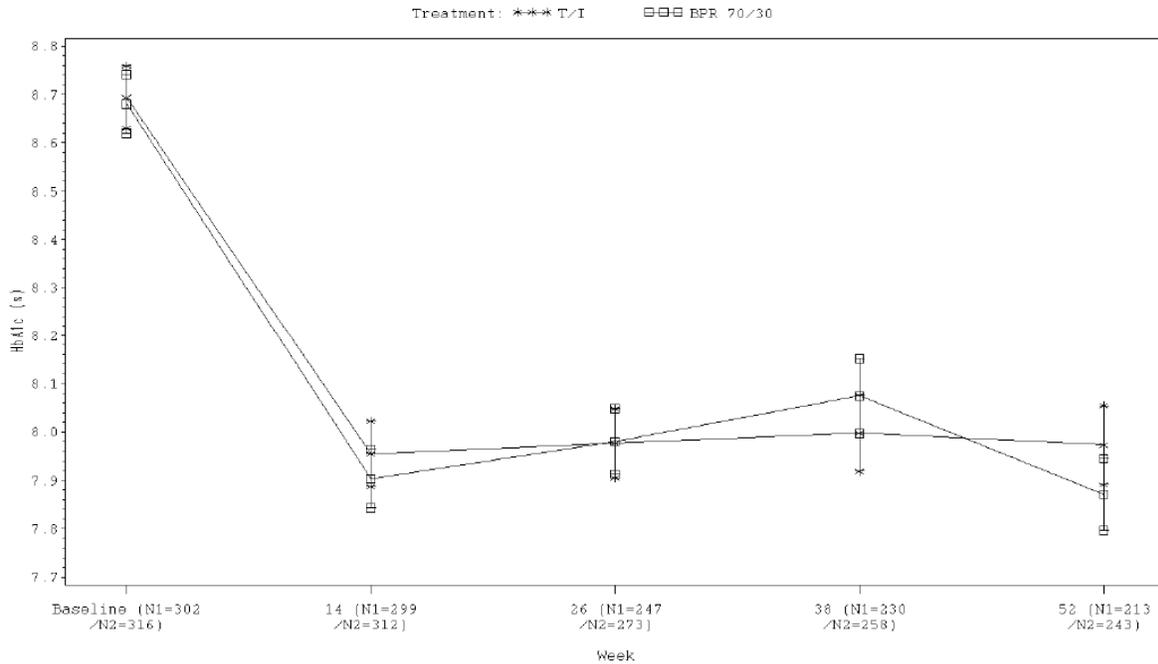
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Source: Holman, 2009 page 1742 (see references)

Figure 6.3 shows the mean HbA1c over time by treatment group for the ITT population. The figure demonstrates that the reduction in HbA1c occurred primarily in the first 14 weeks and was sustained through 52 weeks.

**Figure 6.3 – Trial 102 Mean (SE) HbA1c (%) by Visit and by Treatment Group Over 52 Weeks (ITT Population)**



Source: Figure 5, Trial 102 CSR

Additional Analyses Related to the Primary Endpoint - Trial 102

HbA1c Responder Rates ( $\leq 6.5\%$ ,  $\leq 7.0\%$ , and  $\leq 8.0\%$ ) at Week 52 – Trial 102

The treatment difference in HbA1c responder rates at Week 52 was evaluated using a logistic regression analysis. The percent of responders with an end of study HbA1c  $\leq 6.5\%$ ,  $\leq 7.0\%$ , and  $\leq 8.0\%$  was not statistically different between TI + basal insulin and 70/30 mix (Table 6.29). Similar results were obtained for the PP Population (data not shown). For the ITT population with LOCF the percentages of responders were slightly lower (Table 6.30).

	TI (n=213)	70/30 mix (n=243)	TI vs. 70/30 mix		
Responder Category	n (%)	n (%)	Odds Ratio	95% CI	p Value
HbA1c ≤ 6.5% at Week 52	17 (8.0)	30 (12.4)	0.61	0.3 – 1.2	0.13
HbA1c ≤ 7.0% at Week 52	47 (22.1)	65 (26.7)	0.77	0.5 – 1.2	0.28
HbA1c ≤ 8.0% at Week 52	121 (56.8)	148 (60.9)	0.86	0.5 – 1.3	0.46

Statistics based on logistic regression analysis with terms for site, treatment and baseline HbA1c  
 Source: Table 19 Trial 102 CSR

	TI + glargine	70/30	TI + glargine vs. 70/30		
Responder Category	n (%)	n (%)	Odds Ratio	95% CI	p Value
HbA1c ≤ 6.5% at Week 52	18 (6.0)	32 (10.1)	0.53	0.3 – 1.0	0.05
HbA1c ≤ 7.0% at Week 52	59 (19.5)	71 (22.5)	0.81	0.5 - 1.2	0.33
HbA1c ≤ 8.0% at Week 52	165 (54.6)	177 (56.0)	0.95	0.7 - 1.3	0.78

Source: Sponsor's submission 22 Nov 2009

**Reviewer's comment: Only about a quarter of completers in each treatment group reached the AACE glyceic target of <7% at week 52. This finding suggests poor titration to glyceic goals during the trial in both treatment groups.**

Rates of reported hyperglycemia between treatment groups – Trial 102

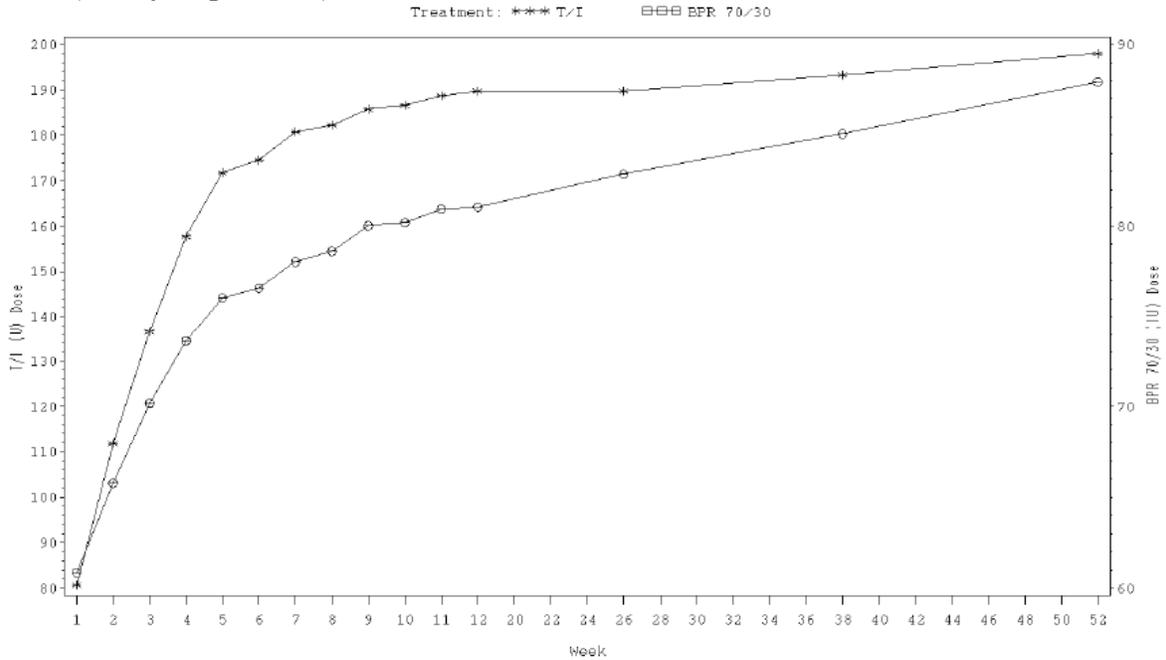
Hyperglycemia as an AE was reported in 7 (2.2 %) subjects in the TI + glargine arm and 3 (0.9%) subjects in the 70/30 mix arm, however, there were not strict criteria as to when to report hyperglycemia as an AE and due to the open-label trial design reporting bias cannot be ruled out.

Investigational Medicinal Product Doses Achieved by Subjects - Trial 102

Figure 6.4 displays the mean total daily dose of TI (top line) and 70/30 insulin mix (lower line) over the 52 week treatment period. The mean total daily dose of TI was titrated rapidly upward over the first 8 weeks and less rapidly after the first 12 weeks. A similar temporal pattern was

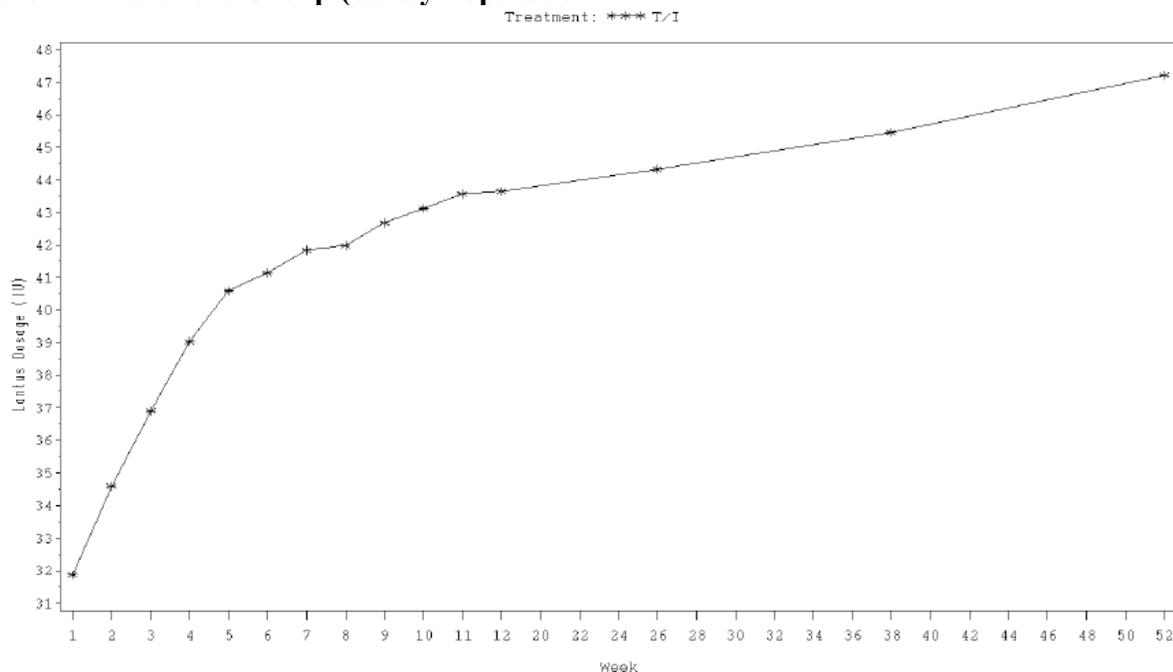
observed in the 70/30 mix arm. A similar pattern was seen for glargine exposure in the TI treatment group (Figure 6.5).

**Figure 6.4 – Trial 102 Mean Total Daily Dose of TI (U) and 70/30 Mix Insulin (IU) Over 52 Weeks (Safety Population)**



Source: Figure 3, Trial 102 CSR

**Figure 6.5 – Trial 102 Mean Total Daily Dose of Insulin Glargine (IU) Over 52 Weeks in the TI Treatment Group (Safety Population**



Source: Figure 4, Trial 102 CSR

**Reviewer’s comment:** It appears from these two figures that the doses of TI, 70/30 mix, and Lantus were all still increasing at the end of the trial indicating titration was not yet complete. The greatest increase in doses occurred during the first 10 weeks of the trial, corresponding to the protocol-specified period of insulin titration. Taken together, these data suggest that patients in both treatment arms were still titrating up their insulin doses at the end of the trial, and that the TI group had not neared the Sponsor’s maximum recommended dose per administration which currently is 90 U. Of note, mean FPG values observed at trial endpoint (Week 52) were higher than optimal in both treatment groups: 140 mg/dL and 156 mg/dL in the TI and 70/30 mix arms, respectively.

A comparison of total insulin usage in the two treatment arms can be roughly estimated as follows: The mean total daily dose of TI being used by subjects at the end of the treatment period was 193 U. A rough estimate of the number of “subcutaneous-equivalent” units per day can be estimated by dividing 193 U by 3 for an upper limit estimate and 5 for a lower limit estimate because the bioavailability is around 20-30% of subcutaneous insulin. The mean total daily dose of insulin glargine among TI treated patients based on the safety population was 47 IU. The mean total daily dose of 70/30 mix used by subjects at the end of the treatment period was 88 IU. The intermediate-acting insulin component of 70/30 mix at > 9-12 months is estimated to be 61.6 IU (calculated by multiplying the total dose by 0.70) and the remainder is the short acting component. A worksheet is shown below.

	Actual units dosed	Subcutaneous equivalent doses
TI	193 U/day	38 - 64 IU
Glargine	43 IU/day	47 IU
Daily Total		81 - 107 IU
Basal/prandial estimate		47/38-64 IU
70/30 mix	88 IU/day	88 IU
Daily Total		88 IU
Basal/prandial estimate		61.6/26.4 IU

**Although the estimated basal/prandial ratio is different between trial groups, the total daily dose is similar.**

Numbers of subjects using metformin or TZDs for more than 50% of the trial were evenly distributed between treatment groups. The mean daily dose of TZDs was not different between groups. The mean daily dose of metformin was similar between treatment groups. Accordingly, concomitant use of metformin or TZDs during the treatment phase of the trial was equivalent between treatment arms and was unlikely to have differentially affected efficacy endpoints.

#### 6.1.4.3 Analysis of the Primary Endpoint - Short/Intermediate-Term Active Control Trials in T2DM

##### Analysis of the Primary Endpoint – Trial 014

Baseline HbA1c was similar between treatment groups. The reduction from baseline was both statistically and clinically significant in both trial arms (both  $p < 0.0001$  for treatment endpoint vs. baseline HbA1c value in both PP and ITT populations, based on paired t test).

As defined by the 95% CIs, TI + Lantus and insulin aspart were not equivalent in the analysis of the ITT Population with LOCF or the completers. In the analysis of the ITT Population TI + Lantus was statistically worse than insulin aspart + Lantus. Table 6.31 shows analyses performed by the Agency statistical reviewer Dr. Liu which were slightly different than the Sponsor's analyses (Dr. Liu's analyses did not include site as a fixed factor) although the conclusions were the same.

**Table 6.31 – Trial 014 Equivalence Analysis of Change in HbA1c (%) after 24 weeks with 95% CI**

Treatment Group (ITT with LOCF)	N	Baseline Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	150	8.85 (1.10)	7.96 (1.34)	-0.89 (1.14)	-0.92 (0.08)
Insulin aspart + Lantus	155	9.00 (1.31)	7.69 (1.09)	-1.31 (1.08)	-1.28 (0.08)
Treatment Comparison	Treatment Difference				
	LS Mean (SE)	95% CI	p-value		
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF)	0.36 (0.11)	(0.14, <b>0.58</b> )	0.002		
TI + Lantus vs. Insulin aspart + Lantus (completers)	0.23 (0.12)	(0.00, <b>0.47</b> )	0.052		
The ANCOVA model included treatment as a fixed factor and baseline HbA1c as the covariate. Similar results were observed when two disqualified sites (Nos. 517 and 518) were excluded from the analysis. Source: Dr. Liu's statistical review					

The Sponsor noted that the originally planned analysis did not consider the effect of concomitant basal insulin treatment. To assess the impact of basal insulin dosing on the primary efficacy variable, the Sponsor reanalyzed the mean change from baseline in HbA1c post hoc with an ANCOVA model adjusted for site, treatment group, baseline HbA1c, and time-adjusted insulin glargine exposure (TALE). The results were not different from the original analysis without adjusting for Lantus exposure. The p value for the interaction term for glargine exposure was 0.19 which suggests that a term for Lantus exposure is not needed in the model. In addition, a summary of mean daily insulin glargine dose by treatment group showed no statistically significant difference in mean daily insulin glargine use at the end of the treatment period (see table 6.31). Therefore, results of these analyses did not change the conclusions of the primary efficacy analysis.

Additional Analyses Related to the Primary Endpoint - Trial 014

Table 6.31 presents the mean daily dose over the course of the trial for each of the Investigational Medicinal Products (IMPs) (TI, insulin aspart, and insulin glargine) by treatment group. The data demonstrate that on average each treatment group was using a similar dose of Lantus. The mean daily TI dose at Visit 12 was 121 U suggesting that subjects were not using the maximum TI dose allowed by the protocol (60 U per meal).

<b>Table 6.31 – Trial 014 IMP Exposure as Mean Daily Dose (U TI, IU Insulin Aspart &amp; Insulin Glargine)</b>				
Statistic	TI (U)	Insulin Aspart (IU)	Lantus	
			TI	Insulin Aspart
<b>PP Population</b>				
N	150	155	150	155
Mean	105	25	32	31
SD	43	9	11	11
Median	94	24	32	32
Range	30 - 233	6 - 58	4 - 61	10 - 71
<b>ITT Population</b>				
N	112	146	112	146
Mean	108	25	32	32
SD	45	9	11	11
Median	98	24	33	33
Range	43 - 233	8 - 58	10 - 61	10 - 71
Source: Table 14, Trial 014 CSR				

**Reviewer’s comment: Because the dose of Lantus was equivalent between the TI and insulin aspart groups, it can be concluded that TI is not as effective as insulin aspart in this trial.**

Rates of reported hyperglycemia between treatment groups – Trial 014

The rate of hyperglycemia in each treatment arm was < 2%.

Analysis of the Primary Endpoint - Trial 026

Table 6.32 shows the results of the Sponsor’s prespecified analysis of the primary endpoint: a one-sample t test of the change between baseline and study end in HbA1c within each treatment group. The Sponsor did not pre-specify a statistical comparison between the two treatment arms.

Baseline HbA1c was similar between the groups. After 12 weeks of treatment, mean HbA1c (%) decreased statistically significantly from baseline by 1.40% (p<0.0001) in the TI group and 1.24% (p=0.0001) in the control group. The mean decrease from baseline in HbA1c (%) was also clinically significant in both treatment groups.

<b>Table 6.32 – Trial 026 Change in HbA1c (%) After 12 Weeks, ITT Population with LOCF</b>			
	Statistic	TI	Control
		N = 75	N = 15
Baseline	Mean	9.58	9.33
	SD	1.39	1.50
	Median	9.50	9.60
	Range	7.2 – 12.5	7.1 – 12.2
	95% CI	9.26 – 9.90	8.5 – 10.16
Endpoint (12 Weeks)	Mean	8.18	8.09
	SD	1.12	1.06
	Median	8.10	7.60
	Range	5.8 – 11.9	7.0 – 11.0
	95% CI	7.93 – 8.44	7.50 – 8.67
Change	Mean	-1.40	-1.24
	SD	1.16	0.93
	Median	-1.20	-1.20
	Range	-4.4 – 0.9	-3.0 – 0.5
	95% CI	-1.66 – (-1.13)	-1.76 – (-0.72)
	P value	<0.0001	0.0001
P value is based on a one-sample t test of change between baseline and treatment endpoint within each treatment group			
Source: Table 12, Trial 026 CSR			

Between group comparison was performed by the Agency statistician using a standard ANCOVA model with treatment as fixed effect and baseline value as covariate and there was no difference between the groups (95% CI contains zero: -0.52 – 0.46). However, the CI is wide due to the small sample size of the control arm.

**Reviewer’s comment: It is interesting that the mean HbA1c decrease in the control group was so large considering these subjects were not on any Investigational Study Medication.**

Additional Analyses Related to the Primary Endpoint - Trial 026

Investigational Medicinal Product Doses Achieved by Subjects – Trial 026

Time-weighted dose is the time-adjusted average prandial dose taken over the course of the trial. The time-weighted (SD) prandial dose of TI was 29.6 U, indicating that most subjects did not use the maximum allowed prandial dose of 60 U.

The Sponsor submitted no analyses of reduction in concomitant OAD use in the TI group which would indirectly support efficacy of TI. However, at trial entry metformin was being used by 73% of TI subjects and 80% of control subjects. During the trial metformin was used by 60% of TI subjects and 73% of control subjects. At trial entry sulfonylureas were used by 96% of TI

subjects and 87% of control subjects. During the trial sulfonylureas were used by 85% of TI subjects and 87% of control subjects.

**Reviewer's comment: These data suggest that subjects in the TI arm may have reduced their used of concomitant OADs which might have led to a less robust decrease in HbA1c in the TI arm than would have been observed if OADs had been kept the same as at baseline.**

#### Analysis of the Primary Endpoint - Trial 103

Baseline HbA1c was similar between treatment groups. In an ANCOVA analysis including treatment group and investigator site as fixed effects and baseline HbA1c as a covariate using the ITT population with LOCF (the pre-specified primary analysis population), the LS mean change in HbA1c from Baseline to Week 12 was -0.78% for metformin + secretagogue, and -0.70% for TI + metformin with a mean treatment difference of 0.08% (Table 6.33). The difference between treatments was not statistically significant ( $p=0.42$ ). However, note that the primary efficacy analysis was intended to show superiority of TI + metformin, and as seen in Table 6.33, TI + metformin was not superior to metformin + secretagogue based on the 95% CI (the upper limit 0.27 is not less than zero).

In the ITT population without LOCF and in the PP population the mean change from baseline in HbA1c was numerically higher in the TI + metformin group than in the metformin + secretagogue group although the difference between treatments was still not statistically significant for either population, and similar to the primary analysis, superiority of TI + metformin using the upper limit of the 95% CI method was not shown with the ITT and PP populations.

Data for the TI alone group are discussed in Dr. Liu's statistical review.

**Table 6.33 – Trial 103 Baseline Statistics and ANCOVA of Mean Change from Baseline to Week 12 in HbA1c (%)**

		Metformin + Secretagogue	TI + Metformin	Comparison Between Groups
<b>ITT Population with LOCF</b>				
Category	Statistic	N=162	N=169	
Baseline (Week 0)	Mean	8.90	8.93	
	95% CI	8.7 – 9.0	8.8 – 9.1	
Week 12	Mean	8.15	8.22	
	95% CI	8.0 – 8.3	8.0 – 8.4	
Change from baseline	LS Mean	-0.78	-0.70	0.08
	LS 95% CI	-0.92 – (-0.64)	-0.84 – (-0.56)	-0.11 – 0.27
	P value			0.4200
<b>ITT Population without LOCF</b>				
		N=162	N=169	
Baseline (Week 0)	Mean	8.90	8.95	
	95% CI	8.7 – 9.0	8.8 – 9.1	
Week 12	Mean	8.13	8.11	
	95% CI	8.0 – 8.3	7.9 – 8.3	
Change from baseline	LS Mean	-0.80	-0.83	-0.03
	LS 95% CI	-0.94 – (-0.66)	-0.98 – (-0.68)	-0.23 – 0.17
	P value			0.7934
<b>PP Population</b>				
		N=139	N=115	
Baseline (Week 0)	Mean	8.93	8.96	
	95% CI	8.8 – 9.1	8.8 – 9.1	
Week 12	Mean	8.12	8.05	
	95% CI	7.9 – 8.3	7.9 – 8.2	
Change from baseline	LS Mean	-0.85	-0.92	-0.07
	LS 95% CI	-1.00 – (-0.70)	-1.08 – (-0.75)	-0.28 – 0.15
	P value			0.5295
P value based on t test				
Source: Table 18, Trial 103 CSR				

**Reviewer’s comment:** These data should be interpreted in the context of subject disposition. The discontinuation rate due to lack of efficacy was higher in the TI + metformin arm of the trial compared with the metformin + secretagogue arm. It is important to keep in mind that subjects in this trial were required to be taking metformin + secretagogue at trial enrollment. Then, based on randomization group subjects were either continued on metformin + secretagogue or had their secretagogue discontinued and started on TI. If titration of TI occurred slowly, more subjects in the TI arm might discontinue early due to lack of efficacy (which occurred) and the ITT with LOCF analysis would show a numerically lower HbA1c reduction in the TI + metformin arm. However, the completer analyses (ITT without LOCF and PP) showed a numerically better HbA1c

**reduction in the TI + metformin suggesting that if subjects continued in the trial until titration of TI was near complete, they would benefit more.**

**In addition, TI titration was occurring during the 12-week treatment period. Therefore, the endpoint HbA1c in the TI treatment groups likely did not adequately reflect glycemic control at the higher TI doses.**

**On the other hand, TI might have shown less efficacy if the trial design were slightly different - if patients on metformin were randomized to add-on sulfonylurea vs. add-on TI. With the current trial design, by switching, some of the patients already on sulfonylurea + metformin may have been sulfonylurea failures.**

**On general, these data support the clinical use of TI as an add-on to metformin.**

#### Additional Analyses Related to the Primary Endpoint – Trial 103

##### Investigational Medicinal Product Doses Achieved by Subjects – Trial 103

In the TI + metformin randomization group, for subjects who discontinued from the study for not meeting protocol-specified glycemic goals at the end of Treatment Period I (Week 12), the mean (SD) daily dose of TI also increased over time, from 91.1 (32.8) U at Month 1, to 166.2 (60.4) U at Month 2, and 191.7 (67.5) U at Month 3. The dose increased slightly more over month 4 and peaked at month 5. The dose levels were not different from those of subjects on TI + metformin who successfully met protocol-specified HbA1c goals at Week 12. Although the protocol allowed titration of up to 90 U TI per meal, the mean per meal dose of TI was in the range of approximately 61-70 U at the end of Treatment Period I (Week 12).

#### 6.1.4.4 Analysis of the Primary Endpoint - Active control trials in T1DM

##### Analysis of the Primary Endpoint - Trial 009

Baseline HbA1c was similar between treatment groups. In an ANCOVA model including treatment group and pooled investigator site as fixed effects and baseline HbA1c as covariate, and using the ITT population with LOCF, the mean change from baseline in the TI + insulin glargine arm was -0.13% compared with the insulin aspart + glargine arm which showed a mean change from baseline of -0.37% (Table 6.34). The between-group difference in change from baseline in HbA1c was 0.24% (not favoring TI) with a corresponding 95% CI of (0.08 to 0.40) not supporting a non-inferiority claim for TI (inferiority margin < 0.4%). The ITT without imputation by LOCF and the PP population showed similar results. The MMRM analysis supported the ANCOVA analysis with similar findings.

When the ANCOVA model included Time Adjusted Lantus Exposure (TALE) as a covariate the 95% CI increased to 0.07 – 0.44 and TI again did not meet the non-inferiority margin.

<b>Table 6.34 – Trial 009 ANCOVA of Mean Change from Baseline in HbA1c (%) at Week 52, ITT Population with LOCF</b>				
Time Point	Statistic	TI + Glargine	Insulin Aspart + Glargine	TI + Glargine vs. Insulin Aspart + Glargine
Baseline	N	277	262	
	Mean	8.41	8.48	
	SD	0.92	0.97	
	95% CI	8.31 – 8.52	8.36 – 8.60	
Week 52	N	277	262	
	Mean	8.28	8.09	
	SD	1.18	1.13	
	95% CI	8.13 – 8.42	7.95 – 8.22	
Change from Baseline to Week 52	N			
	LS Mean	-0.13	-0.37	0.24
	SE	0.058	0.059	0.082
	95% CI	-0.24 – (-0.01)	-0.49 – (-0.25)	<b>0.08 – 0.40</b>
Noninferiority margin = 0.4% upper bound of the 95% CI				
Source: Table 14, Trial 009 CSR				

**Reviewer’s comments:** The Agency statistician Dr. Liu has reanalyzed these data with different populations and different models and in none of these analyses did the trial results meet the non-inferiority margin. In addition, Dr. Liu notes that TI was statistically worse than insulin aspart in this trial (p=0.003).

Looking at these data from a clinical perspective, both arms of the trial showed reductions in HbA1c albeit a lesser reduction in the TI arm. It is important to interpret these data in the context of the pathophysiology of T1DM in which patients do not produce sufficient endogenous insulin; therefore, T1DM patients not given sufficient exogenous insulin would inevitably show increases in HbA1c over time. The finding that subjects on average in the TI group decreased their HbA1c from baseline to 52 weeks suggests that TI is effective in glycemic control. However, similar to trial 014, TI is not as effective as insulin aspart when both are combined with insulin glargine.

Similar to the discussion pertaining to T2DM, in order to obtain a valid comparison of TI to comparator insulin, the comparator insulin must be titrated effectively to achieve reasonable glycemic control. Neither arm of trial 009 achieved glycemic control similar to what has been shown is possible with intensive therapy in the DCCT trial, where mean

**HbA1c in the DCCT at two years was slightly below 7% in the intensive control arm, and slightly below 9% in the conventional control arm, as illustrated in Figure 6.6.**

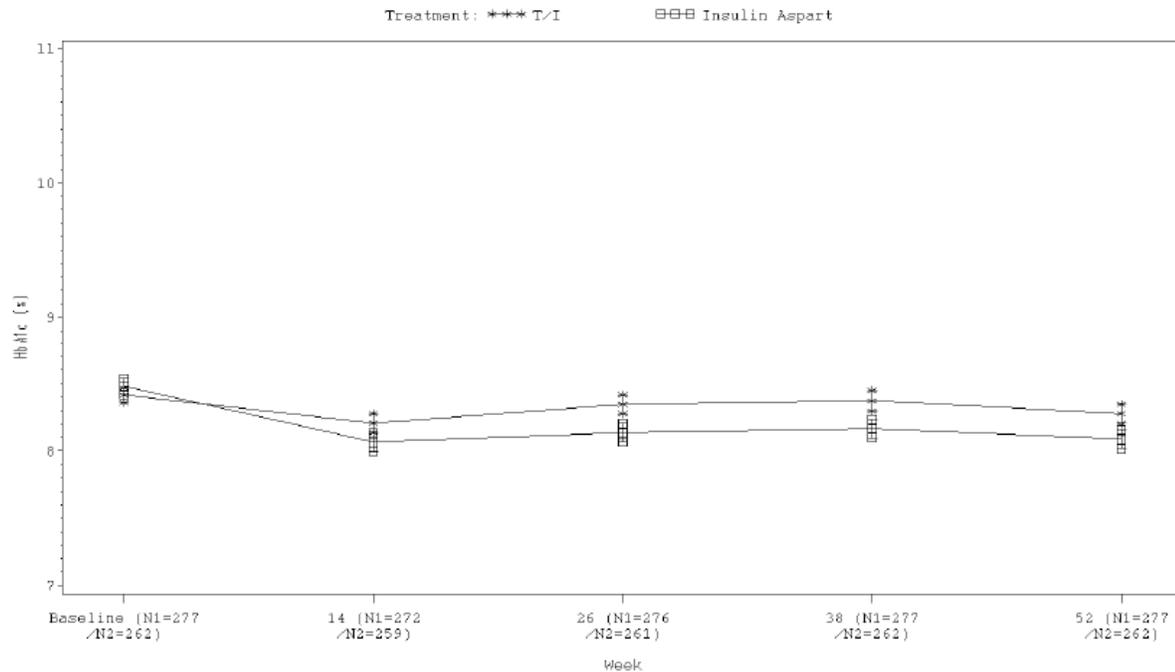
**Figure 6.6 - Mean HbA1c over Time in the Diabetes Control and Complications Trial**  
Copyright Material Withheld



Source: DCCT Research Group, 1993

Figure 6.7 shows the mean change in HbA1c over 52 weeks. The figure suggests an early reduction in HbA1c by week 14 with a sustained minimal reduction out to 52 weeks for both treatment groups.

**Figure 6.7 – Trial 009 Mean (SE) Change in HbA1c (%) Over 52 Weeks (ITT Population with LOCF)**



Source: Figure 3, Trial 009 CSR

**Reviewer’s comment: These data suggest that TI would be expected to result in maximum effect at the same rate as insulin aspart.**

Additional analysis related to the Primary Endpoint - Trial 009

HbA1c Responder Rates ( $\leq 6.5\%$ ,  $\leq 7.0\%$ , and  $\leq 8.0\%$ ) at Week 52 – Trial 009

The treatment difference in HbA1c responder rates at Week 52 was evaluated using a logistic regression analysis. The percent of responders with an end of study HbA1c  $\leq 6.5\%$ ,  $\leq 7.0\%$ , and  $\leq 8.0\%$  was not statistically different between TI and insulin aspart treatment groups (Table 6.35). Similar results were obtained for the PP Population (data not shown). Responder percentages using ITT with LOCF are shown in Table 6.36. The TI arm had fewer subjects with HbA1c  $\leq 8.0\%$  at Week 52 than did the insulin aspart group.

**Table 6.35 – Trial 009 Treatment Difference in HbA1c (%) Responder Rates at Week 52 (ITT Population)**

Responder Category	TI + Glargine (n=202)	Insulin Aspart + Glargine (n=210)	TI + Glargine vs. Insulin Aspart + Glargine		
	n (%)	n (%)	Odds Ratio	95% CI	p Value
HbA1c ≤ 6.5% at Week 52	15 (7.4)	16 (7.3)	0.94	0.4 – 2.0	0.88
HbA1c ≤ 7.0% at Week 52	33 (16.3)	35 (16.0)	0.94	0.5 – 1.7	0.83
HbA1c ≤ 8.0% at Week 52	103 (60.0)	123 (56.2)	0.66	0.4 – 1.0	0.07

Statistics based on logistic regression analysis with terms for site, treatment and baseline HbA1c  
 Source: Table 18 Trial 009 CSR

**Table 6.36 – Trial 009 Treatment Difference in HbA1c (%) Responder Rates at Week 52 (ITT with LOCF Population)**

Responder Category	TI + Glargine	Insulin Aspart + Glargine	TI + Glargine vs. Insulin Aspart + Glargine		
	n (%)	n (%)	Odds Ratio	95% CI	p Value
HbA1c ≤ 6.5% at Week 52	15 (5.4)	16 (6.1)	0.84	0.4 - 1.8	0.65
HbA1c ≤ 7.0% at Week 52	37 (13.4)	37 (14.1)	0.88	0.5 - 1.5	0.65
HbA1c ≤ 8.0% at Week 52	130 (46.9)	141 (53.8)	0.63	0.4 - 0.9	0.02

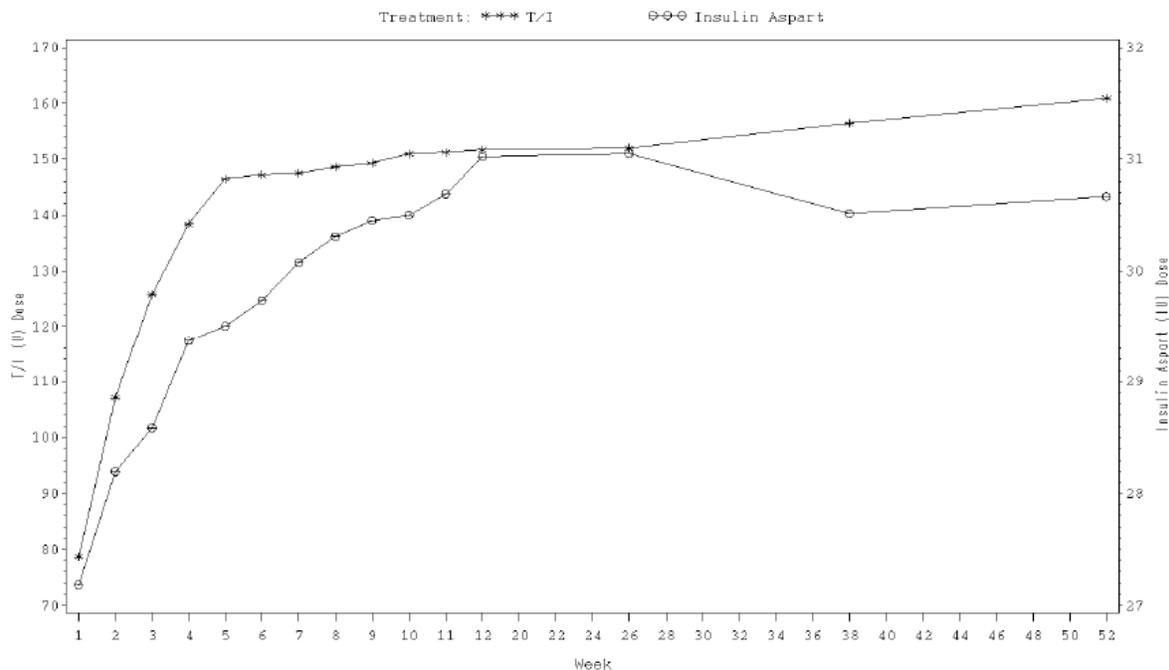
Source: Sponsor's submission 22 Nov 2009

**Reviewer's comment: Few patients in either treatment group reached the AACE glycemic target of <7% at week 52 although the rates were similar between the two treatment groups.**

Investigational medicinal product doses achieved by subjects - Trial 009

The mean daily dose of TI increased over time, rising from 138.4 (SD 62) U at Month 1, to 151.7 (SD 73) U at Month 3, 156.4 (SD 70) U at > 6-9 months, and 160.9 (SD 69) U at > 9-12 months. In the insulin aspart arm, the mean daily dose of insulin was relatively stable over time after an initial 12-week titration period, ranging from 29.4 (SD 28) IU at Month 1 to 30.7 (SD 21) IU at > 9-12 months. Figure 6.8 displays the mean total daily dose of TI and insulin aspart over the 52 week treatment period.

**Figure 6.8 – Trial 009 Dose of TI (U) and Insulin Aspart (IU) Over 52 Weeks (Safety Population)**



Source: Figure 2, Trial 009 CSR

**Reviewer’s comment:** Based on the figure it appears that insulin in the TI treatment arm was still being titrated upwards even at 52 weeks, although minimally so.

A key component of the primary efficacy analysis is a comparison of the use of glargine between the two treatment groups. If TI was effective, one would expect the dose of glargine to be roughly equivalent between the two treatment groups. In fact, a valid comparison of TI and insulin aspart as prandial insulin is only possible if the mean daily dose of insulin glargine is roughly equivalent between the two treatment groups. Table 6.37 shows the overall glargine exposure between the treatment groups. There appears to be at least one outlier in the TI arm (a patient using 304 U per day). Therefore, the median is the best comparison. The median daily glargine dose appears similar between the two groups.

	TI (n = 293)	Insulin aspart (n = 272)
Mean (SD)	32.4 (22.4)	29.8 (12.8)
Median	28.3	27.7
Range	7.1 - 304	8.7 – 75.4

Source: Table 13, Trial 009 CSR

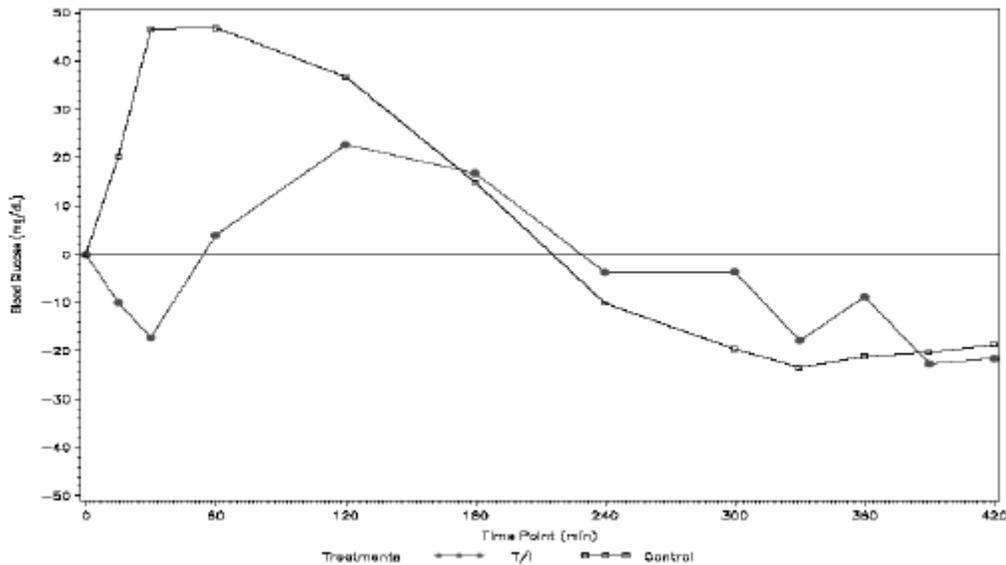
**Reviewer’s comment: The median daily dose of glargine was similar between the TI and aspart groups. Therefore, a meaningful comparison of the effect of TI vs. aspart on HbA1c is possible and it can be concluded that TI is inferior to insulin aspart in this trial when both are combined with insulin glargine.**

Analysis of the primary endpoint - Trial 101

The primary efficacy endpoint was the mean glycemic profile of subjects in response to the meal challenge, expressed as AUC<sub>0-300</sub> for Visit 5 (Week 0) and Visit 9 (Week 8) and AUC<sub>0-420</sub> for Visit 10 (Week 12). Visit 10 was emphasized because of the longer treatment time and the longer observation time during the meal challenge (420 minutes).

The baseline-corrected glycemic profile in response to the meal challenge for the PP population is graphically represented for Visit 10 (Week 12) by the curve drawn through the plot of mean glucose concentrations at individual time points over the course of the postprandial observation period (Figure 6.9). This curve describes the mean impact of the study medication on the postprandial blood glucose excursions at any time point, independent of starting blood glucose values because it is corrected for baseline glucose (i.e. time 0 at week 12).

**Figure 6.9 – Trial 101 Baseline-Corrected Postprandial Blood Glucose Concentrations at Week 12 (PP Population)**



Source: Figure 2, Trial 101 CSR

TI demonstrated an early, transitory drop in blood glucose below baseline, a subsequent rise, and a drop towards baseline at approximately 180 to 240 minutes. In contrast, insulin aspart demonstrated an immediate increase in glucose to levels exceeding those of TI, followed by a decrease, reaching levels considerably below baseline.

**Reviewer’s comment: These data suggest that TI has a slower postprandial glucose excursion and a lower maximum postprandial glucose concentration. However, please see Dr. Sang Chung’s clinical pharmacology review for his interpretation of these data.**

For the purposes of the clinical review, the secondary efficacy variable of mean change from Baseline in HbA1c was treated as a “primary efficacy endpoint” and reviewed by the clinical reviewer. The Visit 1 value was used as baseline for this evaluation, considering that HbA1c at Visit 5 would not be at steady state, because of treatment changes during the run-in period.

Table 6.38 shows the ANCOVA for mean change in HbA1c from Visit 1 (Week -4) to Visit 10 (Week 12). Baseline HbA1c was similar between treatment groups. A clinically and statistically significant ( $p < 0.0001$  for both groups based on a t test) mean decrease in HbA1c (%) from Baseline to Visit 10 was observed in both treatment groups. The differences between treatment groups were not statistically significant. However, TI + Lantus was not non-inferior to aspart + Lantus based on the upper bound of the 95% CI  $> 0.4\%$ . Similar results were obtained for completers.

<b>Table 6.38 – Trial 101 ANCOVA of Mean Change in HbA1c (%) from Baseline to Week 12</b>					
Treatment Group (ITT with LOCF)	N	Baseline Mean (SD)	Week 12 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	51	9.01 (1.22)	8.19 (1.10)	-0.81 (1.10)	-0.81 (0.15)
NovoRapid + Lantus	56	8.88 (1.18)	7.89 (0.95)	-0.99 (1.07)	-0.99 (0.14)
Treatment Comparison			Treatment Difference		
			LS Mean (SE)	95% CI	p-value
TI + Lantus vs. NovoRapid + Lantus (ITT w/ LOCF)			0.18 (0.21)	(-0.24, <b>0.60</b> )	0.39
TI + Lantus vs. NovoRapid + Lantus (completers)			0.15 (0.21)	(-0.27, <b>0.57</b> )	0.48

Source: Dr. Liu’s statistical review

**Reviewer’s comment: This trial was not designed/ was underpowered to examine the difference in HbA1c between treatment groups. Consequently, the 95% CI is wide and statistical non-inferiority is not shown.**

Additional analyses related to the primary endpoint – Trial 101

Table 6.39 shows IMP doses achieved by subjects at the end of the trial.

**Table 6.39 – Trial 101 Mean Daily Doses of 3 Drugs at the End of the Treatment Period (Safety Population)**

	TI (U)	aspart (IU)	Lantus	
			TI (U)	Aspart (IU)
N	49	56	48	55
Mean	132	22	23	21
SD	68	7	12	7
95% CI	112 - 151	20 - 24	20 - 27	19 - 23

Source: Table 10, Trial 101 CSR

**Reviewer’s comment: The dose of Lantus in the TI group is slightly higher than in the insulin aspart group.**

#### 6.1.4.5 Analysis of the HbA1c Endpoint – Pulmonary Safety Trial 030

Change in HbA1c was measured as a secondary endpoint in trial 030. The Agency statistician believes that because of the study design the HbA1c endpoint would be of limited utility and likely not contribute to the overall impression of efficacy of TI, and therefore, did not analyze the efficacy data for this trial. The Sponsor’s results based on the ITT/LOCF population showed no difference between the two treatment groups for either T2DM or T1DM.

#### 6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy endpoints across some or all of the trials that are reviewed in this document are as follows

- Effect on Postprandial Glucose (PPG) Control

Meal challenges, standardized for each trial, were conducted to evaluate the postprandial glucose response to TI. Since the meal content and measurement parameters differed from trial to trial, none of the meal challenge related data were pooled. Variables examined included area under the PPG concentration-time curve ( $AUC_{\text{glucose}}$ ) which gives an overall assessment of glucose excursion over a defined time period, and/or 2-hour mean PPG values. The 2-hour mean PPG value is often used in clinical practice to either diagnose DM or to adjust prandial insulin medication.

- Fasting Plasma Glucose (FPG)

Fasting plasma glucose is a common secondary endpoint in DM trials. One of the methods of diagnosing DM is a FPG  $\geq 126$  mg/dL.

### 6.1.5.1 Secondary Endpoints - Placebo Controlled Trials T2DM

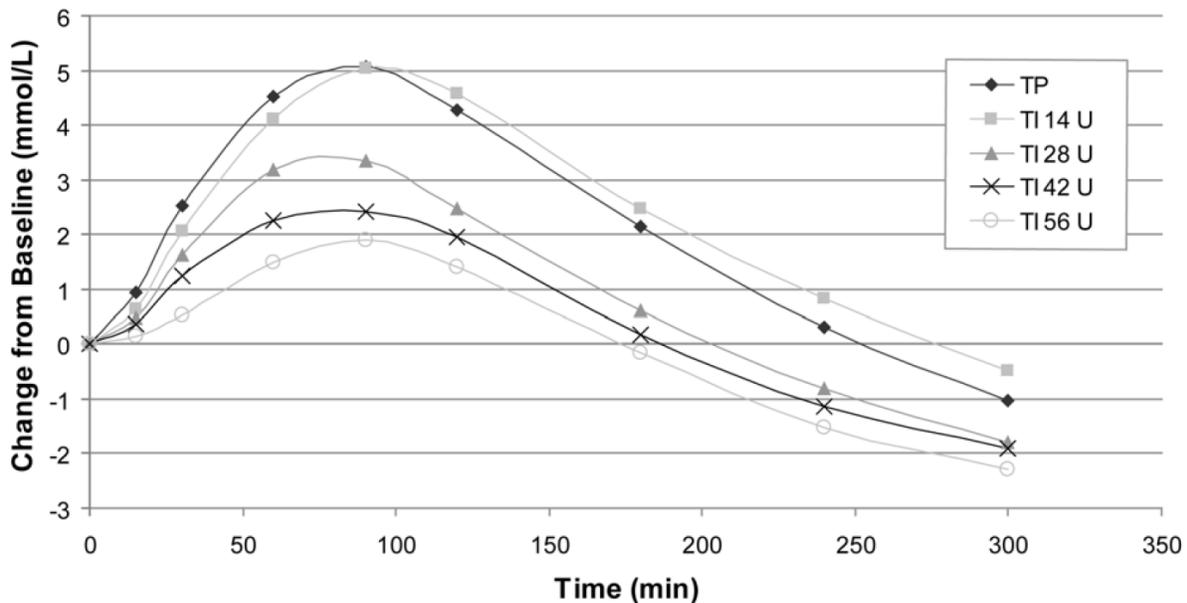
#### Effect on Postprandial Glucose Control - Trial 005

Although the Sponsor defined postprandial glucose control as a primary efficacy variable, this variable is reviewed here in the section on secondary endpoints.

#### Postprandial AUC<sub>glucose</sub> (0-300 minutes) After a Meal Challenge – Trial 005

Figure 6.10 shows postprandial changes in blood glucose at Visit 12 (week 17/study endpoint) collected at 0 minutes (fasting) through 300 minutes. There appears to be an early dose dependent effect of TI in reducing postprandial glucose excursions with less obvious dose-dependent effect at the later time points of the glucose excursions.

**Figure 6.10 – Trial 005 Postprandial Blood Glucose Values (0-300 Minutes) at Visit 12, ITT Population**



Source: Table 4, Trial 005 CSR

In an ANCOVA model including treatment group as the main effects and baseline  $AUC_{\text{glucose}}$  as a covariate, there was a statistically significant reduction in mean  $AUC_{\text{glucose}}$  between the three highest TI dosage groups and TP (placebo) from baseline to 11 weeks of treatment. (Table 6.40). P values were based on two-sample t-tests for comparison between TI and TP and included step-down procedures to reduce the likelihood of type 1 error.

Results were similar when a term for time adjusted Lantus exposure (TALE) was included in the ANCOVA model.

**Table 6.40 – Trial 005 ANCOVA of Change in  $AUC_{\text{glucose}}$  0-300 (min\*mg/dL) After 11 Weeks, ITT Population**

Treatment Group	N	Baseline value (raw mean) and (SD)	Final value (raw mean) and (SD)	Change from baseline  LS Mean	95% CI for the LS Mean change from baseline	Difference from TP LS Mean (Other-TP)	P value from t test with stepdown procedure
TP	40	69373.34 (19267.68)	63639.4 (14068.00)	-3353.56	-7814.87,1107.74		
TI 14 U	41	64491.34 (18161.65)	59616.2 (17197.54)	-5274.94	-9657.72,-892.16	-1921.37	0.5457 (stepdown procedure stops here)
TI 28 U	40	62005.31 (18480.84)	52640.8 (15558.74)	-11180	-15631, -6729.13	-7826.52	0.0156
TI 42 U	41	66056.37 (17656.71)	54961.5 (18056.64)	-10603	-14987, -6220.26	-7249.84	0.0232
TI 56 U	40	64036.69 (15084.44)	52044.7 (15357.54)	-12651	-17089, -8212.37	-9297.21	0.0040

Source: Sponsor's submission 17 Nov 2009

**Reviewer's comment: These results are consistent with the primary efficacy analysis, in that there is a statistically significant effect of TI vs. placebo (although not in the 14 U dose group in this analysis). Given that TI is a prandial insulin these results are not unexpected. Again, there appears to be little difference between the 42 U TI dose and the 56 U TI dose. This is possibly due to the trial design limitations.**

Effect on Fasting Plasma Glucose - Trial 005

There were mean decreases in FPG in all 5 treatment groups between Visit 5 (Baseline) and Visit 12 (study endpoint) (Table 6.41). None of the decreases in the TI groups were significantly different from the decrease in the TP group. Results were similar when time adjusted Lantus exposure (TALE) was included in the ANCOVA model.

**Table 6.41 – Trial 005 ANCOVA of Change in fasting plasma glucose (mg/dL) After 11 Weeks, ITT Population**

Treatment Group	N	Baseline value (raw mean) and (SD)	Final value (raw mean) and (SD)	Change from baseline LS Mean	95% CI for the LS Mean change from baseline	Difference from TP LS Mean (Other - TP)	P value from t test with stepdown procedure
TP	40	189.68 (57.31)	172.37 (46.79)	-12.0062	-25.3727, 1.3602		
TI 14 U	41	177.90 (52.54)	156.45 (46.62)	-23.5577	-36.7302, -10.385	-11.5515	0.2267
TI 28 U	40	177.91 (49.23)	159.43 (46.78)	-20.5855	-33.9215, -7.2495	-8.5793	0.3718
TI 42 U	41	179.44 (48.89)	176.27 (45.79)	-4.3075	-17.4759, 8.8609	7.6987	0.4197
TI 56 U	40	181.47 (49.20)	172.97 (47.61)	-8.3600	-21.6902, 4.9703	3.6462	0.7037 (stepdown procedure stops here)

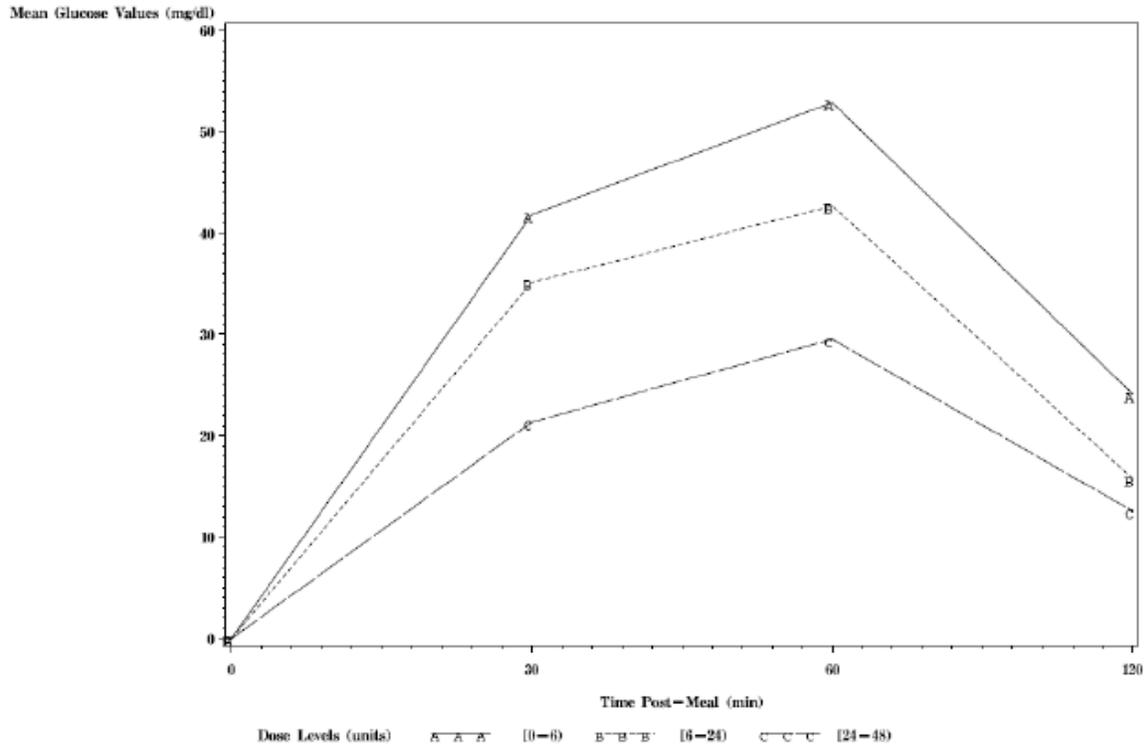
Source: Sponsor's submission 17 Nov 2009

**Reviewer's comment:** These results are consistent with what would be expected from a prandially dosed insulin such as TI and are consistent with the finding that there was no difference in Lantus exposure among the treatment groups because Lantus, the basal insulin in the treatment regimen, would be expected to affect fasting glucose to a greater extent than TI, a prandial insulin, would affect fasting glucose.

Effect on Postprandial Glucose Control - Trial 0008

The secondary objective of the study was to compare AUC<sub>0-120</sub> after the start of a meal challenge at Visits 3, 6, 8, and 9. The Time-0 corrected plasma glucose values by average dose categories during a standardized meal challenge test are shown in Figure 6.11.

**Figure 6.11 – Trial 0008 Mean Time 0-Corrected Laboratory Glucose Values by Weighted Average Dose Level Over Time, Post-meal (ITT Population)**



Source: Figure 7, Trial 0008 CSR

Postprandial glucose excursions showed a dose response. Subjects on the lowest dose of TI (6 U) had the highest increases from Time 0 in plasma glucose at 30, 60, and 120 minutes after ingesting the standardized meal (~50 mg/dL at 60 minutes), subjects on intermediate doses (6 to 24 U) had intermediate increases at all 3 time points (~40 mg/dL at 60 minutes), and subjects on the highest doses (24 to 48 U) had the smallest increases at all 3 time points (~30 mg/dL at 60 minutes).

In the ITT Population, glucose AUC<sub>0-120</sub> in the TI group decreased significantly from Baseline to Visit 9 ( $p < 0.0001$ ). In comparison, there was virtually no change seen in the TP group. Similar results were seen in the Primary Efficacy Population.

#### Effect on Fasting Plasma Glucose - Trial 0008

Fasting plasma glucose levels were measured during the standardized meal challenge test. At Week 12, mean FPG levels decreased by 11.57 (SD 38.59) mg/dL compared with baseline for the TI group as compared with a mean decrease of 7.53 (SD 46.21) mg/dL compared with

baseline for the TP group. These results were not affected by the subjects' ability to use Lantus as a rescue medication. Only 2 subjects received Lantus during the trial (one in each group).

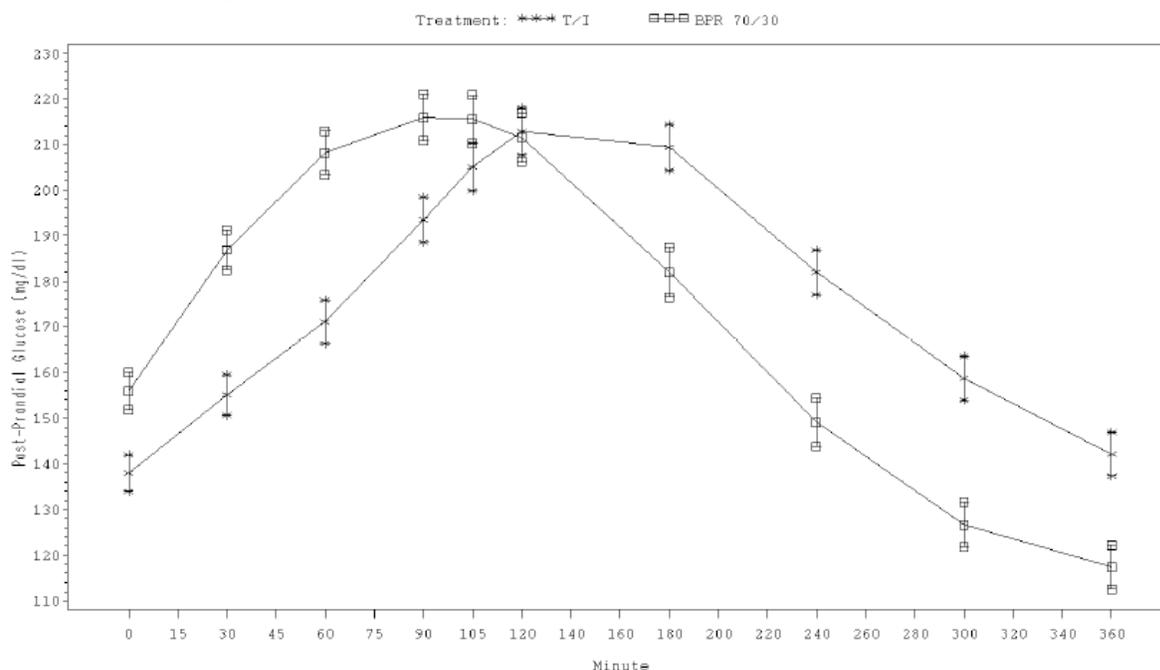
**Reviewer's comment: The decrease in FPG due to TI seen in the trial is not clinically important and not different from placebo, perhaps because TI Inhalation Powder is intended for use as prandial insulin and would be expected to affect PPG more than FPG.**

### 6.1.5.2 Secondary Endpoints – Long-Term Active Control Trial T2DM

#### Effect on Postprandial Glucose Control - Trial 102

Figure 6.12 shows glucose excursions during 360 minutes after a standardized meal challenge for the TI + insulin glargine group vs. the 70/30 mix group at Week 52 (study endpoint).

**Figure 6.12 – Trial 102 Postprandial Plasma Glucose (mg/dL) After a Meal Challenge at Week 52 (ITT Population)**



Source: Figure 6, Trial 102 CSR

Fasting glucose values (Time 0 of the meal challenge) were lower in the TI + glargine arm than in the 70/30 mix arm. The TI + glargine arm showed a slower rise in mean PPG and lower a 1-hour PPG value. At ~120 minutes post-dose, mean PPG values were similar for the TI + glargine

and 70/30 mix arms. At ~120 minutes post-dose, mean PPG values in the 70/30 mix arm began to drop towards baseline; the TI arm began a decline towards baseline at ~180 minutes. At the end of the meal challenge, the mean PPG value at 360 minutes in the TI group was similar to the baseline value. In the 70/30 mix group, the mean PPG value at 360 minutes was ~ 40 mg/dL below the baseline value at Time 0. The AUC<sub>0-360</sub> was comparable between groups (1076 and 1020 mg·hr/dL in the TI and 70/30 mix arms, respectively).

**Reviewer's comment: These data suggest that TI has a different PD profile than 70/30 insulin and support the Sponsor's assertion that the risk of hypoglycemia is lower with TI around 3 hours post-prandially because the TI group did not show the late negative glucose excursion (below baseline) that was seen in the 70/30 group. However, the 2-hour mean PPG value appears similar between treatment groups. It appears from the figure, though, that if the time 0 values had been similar, the TI group may have had a higher mean 2 hour PPG.**

#### Effect on Fasting Plasma Glucose - Trial 102

Mean FPG values observed at trial endpoint (Week 52) were higher than optimal in both treatment groups: 140 (SD 56) and 156 (SD 60) mg/dL in the TI + glargine and 70/30 mix arms, respectively. Basal insulin dosing was not optimized per the protocol dosing guidelines which required an increase in basal insulin when FPG values were > 110 mg/dL. The percentage of subjects with a recorded FPG < 110 mg/dL at Week 52 was 25% in the 70/30 mix arm and 36% in the TI + glargine arm.

**Reviewer's comment: These results are in keeping with the primary efficacy endpoint (HbA1c) analyses.**

Fasting plasma glucose values were obtained at clinic visits (i.e. not home glucose monitoring). The unadjusted mean changes from Baseline (Week 0) were -36 (SE 5) mg/dL in the TI + glargine arm and -18 (SE 4) mg/dL in the 70/30 mix arm in the ITT population. In an ANCOVA model including treatment group and site as fixed effects with baseline fasting plasma glucose as a covariate, the LS mean treatment difference was -18 mg d/L (SE 6) (95% CI -29 to -6, p=0.0029). Similar results were obtained for the PP population.

**Reviewer's comment: The clinical relevance of the greater reduction in FPG in the TI arm compared with the 70/30 mix arm is unclear. Since TI is a prandial insulin it would not be expected to show greater reductions in FPG than comparators would show. Additionally, the HbA1c change from baseline was numerically less in the TI + glargine group compared with the 70/30 mix arm. The difference might be related to the PD characteristics of 70/30 - with the intermediate-acting insulin, this insulin peaking about 6-8 hours after injection.**

### 6.1.5.3 Secondary Endpoints – Short/Intermediate Term Active Control Trials T2DM

#### Secondary Endpoints - Trial 014

There were no secondary endpoints for this trial reviewed.

#### Secondary Endpoints - Trial 103

##### Effect on Fasting Plasma Glucose - Trial 103

For this trial the secondary endpoint of fasting plasma glucose (FPG) was reviewed.

The change from Baseline (Week 0) to the endpoint of Treatment Period I (Week 12) for FPG is presented in Table 6.42. In the ITT Population, the mean change from Baseline was statistically significant only for the metformin + secretagogue arm. Similar results were obtained for the PP Population. There was no statistically significant difference between the groups in FPG change from Baseline.

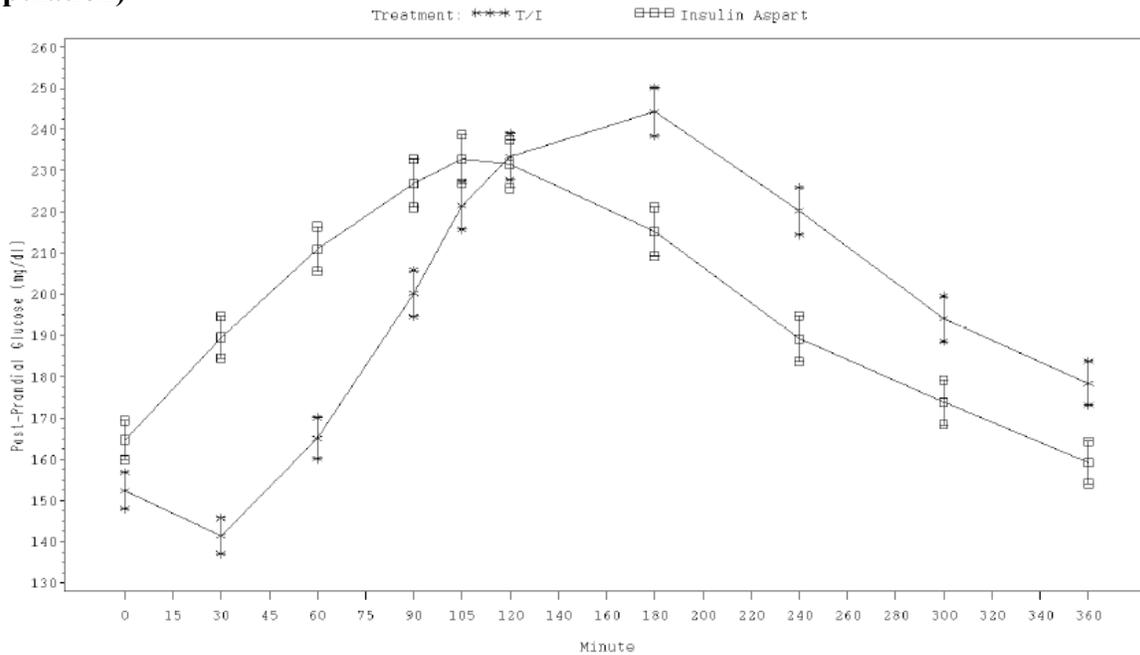
		Metformin + Secretagogue (MS)	TI + Metformin (TM)
Baseline (Week 0)	N	146	117
	Mean	198.3	184.5
	SD	48.4	46.3
Endpoint (Week 12)	N	146	117
	Mean	177.9	178.3
	SD	58.0	47.3
Change from Baseline	Mean	-20.3	-6.2
	SD	48.3	46.1
Within Group <sup>b</sup>	P value	0.0001	0.1478
Between Group <sup>a</sup>	P value	0.1440	
a - p values and estimates are derived from an ANCOVA model with treatment group and investigator site as class variables and baseline FPG as a covariate. b - p values are derived from a paired <i>t</i> test. Source: Table 30, Trial 103 CSR			

### 6.1.5.4 Secondary Endpoints – Active Control Trials T1DM

Effect on Postprandial Glucose Control - Trial 009

Figure 6.13 shows glucose excursions during 360 minutes after a standardized meal challenge for the TI + basal insulin group vs. the insulin aspart + basal insulin group at Week 52 (study endpoint).

**Figure 6.13 – Mean Postprandial Glucose (mg/dL) After a Meal Challenge at Week 52 (ITT Population)**



Source: Figure 5, Trial 009 CSR

Fasting glucose values (Time 0 of the meal challenge) were lower in the TI group than in the insulin aspart group. The TI group showed a slower rise in mean PPG and lower 1-hour PPG values. At ~120 minutes postdose, mean PPG values were similar between groups. At ~120 minutes postdose, mean PPG values in the insulin aspart group began to drop toward baseline; the TI arm began a decline towards baseline at ~180 minutes. The AUC<sub>0-360</sub> was comparable between treatment groups (1148 vs. 1133 mg·hr/dL).

**Reviewer’s comment: These results are similar to what was shown for trial 102.**

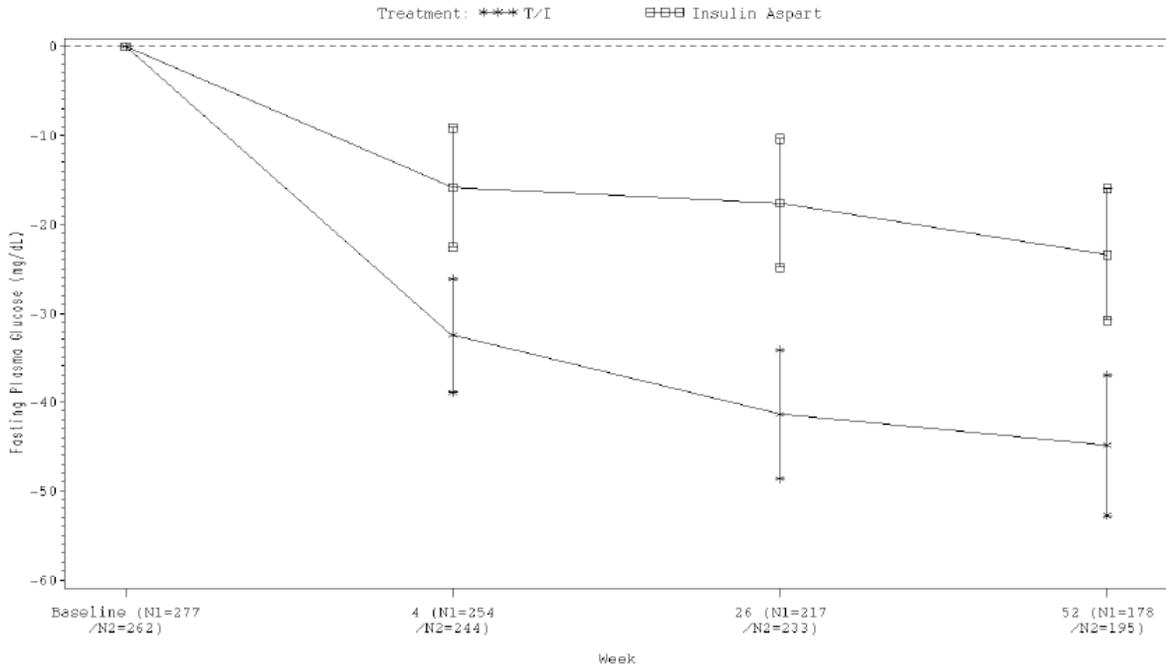
Effect on Fasting Plasma Glucose - Trial 009

Over the 52-week treatment period mean FPG levels decreased significantly in the TI group compared to FPG levels in the insulin aspart group (Table 6.43).

<b>Table 6.43 – Trial 009 ANCOVA of Treatment Difference in Change From Baseline in Fasting Plasma Glucose (mg/dL) at Week 52, ITT Population without LOCF</b>				
Time Point	Statistic	TI	Insulin Aspart	TI vs. Insulin Aspart
Baseline	N	178	195	
	Mean	185	185	
	SD	85.5	87	
	95% CI	172 - 198	172 - 197	
Week 52	N	178	195	
	Mean	140	161	
	SD	72	68	
	95% CI	129 - 151	152 - 171	
Change from Baseline to Week 52	N	178	195	
	LS Mean	-46.5	-25.7	-20.9
	SE	5.6	5.2	7.4
	95% CI	-57.5 – (-35.5)	-35.9 – (-15.4)	<b>-35.4 – (-6.3)</b> <b>P = 0.0052</b>
ANCOVA model included pooled site and treatment as fixed effects and baseline FPG value as covariate Source: Table 7.4.3.1, Trial 009 CSR				

Figure 6.14 shows that the mean fasting plasma glucose was still decreasing at the end of the 52 week trial.

**Figure 6.14 – Mean (SE) Change From Baseline in FPG (mg/dL) Over 52 Weeks (ITT Population)**



Source: Figure 4, Trial 009 CSR

**Reviewer’s comment:** These results are similar to trial 102, i.e. the reduction in HbA1c was lower in the TI treatment groups but the FPG reduction was higher in the TI treatment groups. The reason for these findings is unclear.

Secondary Endpoints - Trial 101

The trial’s secondary endpoint of change in HbA1c from Baseline to Week 12 was reviewed by the clinical reviewer in the primary efficacy endpoints section. No other secondary endpoints were reviewed for this trial.

6.1.6 Other Endpoints

Insulin therapy is often accompanied by the undesirable side effect of body weight gain. Therefore, the change in body weight from baseline to trial end was examined by the clinical reviewer in the two 52 week controlled trials (102 in T2DM and 009 in T1DM) and in trial 103, the phase 3 trial in T2DM.

Body Weight After 52 Weeks - Trial 102

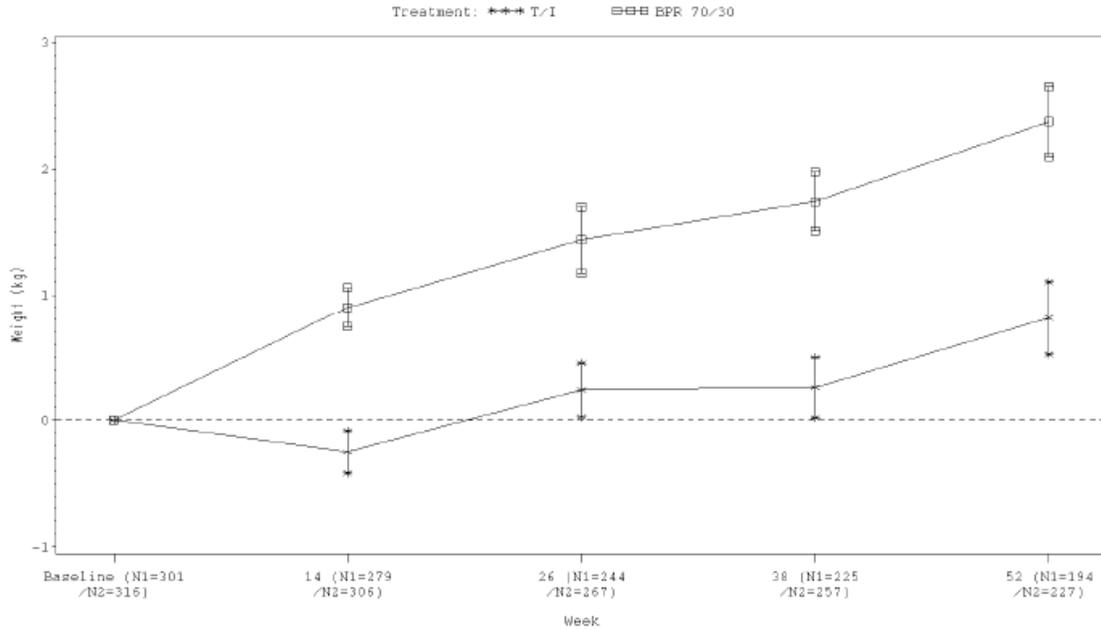
In an ANCOVA model including treatment group and pooled investigator site as fixed effects and baseline body weight as a covariate, there was a statistically significant difference in mean kilograms of body weight gained at the end of 52 weeks between the TI + insulin glargine group and the 70/30 insulin mix group in favor of TI (Table 6.44 without LOCF and Table 6.45 with LOCF). In the LOCF analysis, in the TI + glargine arm, subjects gained a LS Mean of 0.4 kg vs. 1.9 kg in the 70/30 mix arm ( $p < 0.0001$ ), with a treatment difference of -1.5 kg.

<b>Table 6.44 – Trial 102 ANCOVA of Change in Body Weight (kg) at Week 52, ITT Population</b>				
Time Point	Statistic	TI	70/30 Mix	TI vs. 70/30 Mix
Baseline	N	194	227	
	Mean	86.5	84.9	
	SD	17.0	17.4	
	95% CI	84.1 – 88.9	82.6 – 87.2	
Week 52	N	194	227	
	Mean	87.3	87.3	
	SD	17.3	18.0	
	95% CI	84.8 – 87.9	84.9 – 89.6	
Change from Baseline to Week 52	N	194	227	
	LS Mean	0.9	2.5	-1.6
	SE	0.3	0.3	0.41
	95% CI	0.3 – 1.5	1.9 – 3.0	-2.4 – (-0.9) p = 0.0002
ANCOVA model included pooled site and treatment as fixed effects and baseline body weight value as covariate Source: Table 28, Trial 102 CSR				

<b>Table 6.45 - Trial 102 ANCOVA of Change in Body Weight (kg) at Week 52, ITT Population with LOCF</b>				
Time Point	Statistic	TI	70/30 Mix	TI vs. 70/30 Mix
Baseline	N	279	308	
	Mean	88.0	85.7	
	SD	17.13	18.00	
	95% CI	(86.0,90.0)	(83.7,87.7)	
Week 52	N	279	308	
	Mean	88.5	87.6	
	SD	17.23	18.36	
	95% CI	(86.4,90.5)	(85.5,89.6)	
Change from Baseline to Week 52	N	279	308	
	LS Mean	0.4	1.9	-1.5
	SE	0.25	0.24	0.33
	95% CI	(-0.1,0.9)	(1.4,2.4)	(-2.1,-0.8)
	P-value			<.0001
Source: Sponsor's submission 22 Nov 2009				

The weight gain seen in both groups appears to occur gradually and subjects appear to be continuing to gain weight at week 52 (Figure 6.15).

**Figure 6.15 – Trial 102 Mean (SE) Change in Body Weight (kg) Over 52 Weeks (ITT Population)**



Source: Figure 8, Trial 102 CSR

Body Weight After 52 Weeks - Trial 009

In an ANCOVA model including treatment group and pooled investigator site as fixed effects and baseline body weight as a covariate, there was a statistically significant difference in mean kilograms of body weight gained at the end of 52 weeks between the TI + insulin glargine group and the insulin aspart + insulin glargine group in favor of TI (Table 6.46 without LOCF and Table 6.47 with LOCF). In the TI + glargine arm, subjects lost a LS Mean of 0.5 kg vs. a gain of 1.4 kg in the aspart + glargine arm ( $p < 0.0001$ ), with a treatment difference of -1.8 kg. Similar results were obtained with the ITT with LOCF Population.

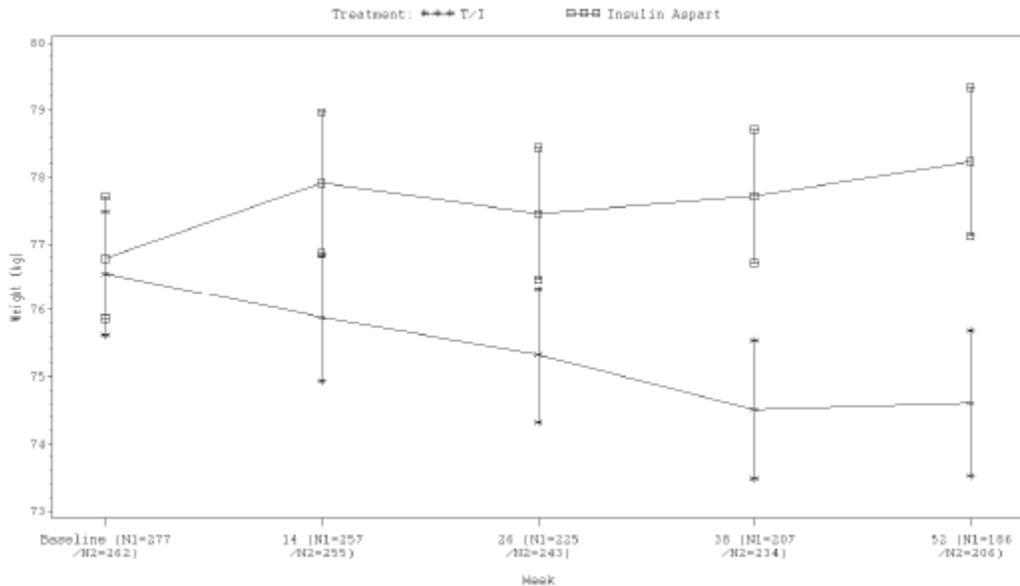
<b>Table 6.46 – Trial 009 ANCOVA of Change in Body Weight (kg) at Week 52, ITT Population</b>				
Time Point	Statistic	TI	Insulin Aspart	TI vs. Insulin Aspart
Baseline	N	186	206	
	Mean	75.1	76.9	
	SD	14.8	15.3	
	95% CI	72.9 – 77.2	74.8 – 79.0	
Week 52	N	186	206	
	Mean	74.6	78.2	
	SD	14.7	15.9	
	95% CI	72.5 – 76.7	76.1 – 80.4	
Change from Baseline to Week 52	N	186	206	
	LS Mean	-0.5	1.4	-1.8
	SE	0.3	0.3	0.4
	95% CI	-1.1 – 0.1	0.8 – 1.9	-2.7 – (-1.0) p=<0.0001
ANCOVA model included pooled site and treatment as fixed effects and baseline body weight value as covariate Source: Table 28, Trial 009 CSR				

<b>Table 6.47 - Trial 009 ANCOVA of Change in Body Weight (kg) at Week 52, ITT Population with LOCF</b>				
Time Point	Statistic	TI	Insulin Aspart	TI vs. Insulin Aspart
Baseline	N	260	257	
	Mean	76.5	76.9	
	SD	15.37	15.01	
	95% CI	(74.7,78.4)	(75.0,78.7)	
Week 52	N	260	257	
	Mean	76.0	78.1	
	SD	15.39	15.62	
	95% CI	(74.1,77.9)	(76.1,80.0)	
Change from Baseline to Week 52	N	260	257	
	LS Mean	-0.6	1.2	-1.8
	SE	0.25	0.25	0.35
	95% CI	(-1.1,-0.1)	(0.7,1.7)	(-2.5,-1.1)
	P-value			<.0001
Source: Sponsor's submission 22 Nov 2009				

Figure 6.16 shows the mean body weight change over the 52 week trial duration. The insulin aspart group appears to be still gaining weight at trial end. The TI group appears to be weight stable at trial end.

**Reviewer’s comment: Since glycemic control in the TI arm was inferior to the insulin aspart arm, some of the differential body weight change may be related to the differing glycemic control between groups.**

**Figure 6.16 – Trial 009 Mean (SE) Change in Body Weight (kg) Over 52 Weeks (ITT Population)**



Source: Figure 7, Trial 009 CSR

Body Weight After 12 Weeks - Trial 103

Table 6.48 presents the mean change from Baseline (Week 0) to Week 12 for the ITT Population by randomized treatment group. Note that this table includes the TI alone treatment arm. Treatment with TI alone or in combination with metformin, but not with metformin + secretagogue, was associated with statistically significant weight loss after 12 weeks of treatment. The difference between treatments was statistically significant for the comparison of TI + metformin versus metformin + secretagogue (p=0.0044) with a difference of -0.84 kg, and the comparison of TI + metformin versus TI alone (p=0.0284) with a difference of -0.67 kg. Similar results were obtained with the ITT with LOCF Population (Table 6.49).

**Table 6.48 – Trial 103 Mean Change from Baseline to Week 12 in Body Weight (kg) (ITT Population)**

		TI Alone	Metformin + Secretagogue (MS)	TI + Metformin (TM)
Baseline (Week 0)	N	135	153	123
	Mean	84.8	84.6	82.0
	SD	14.0	16.3	13.5
Endpoint (Week 12)	N	135	153	123
	Mean	84.2	84.2	80.9
	SD	13.5	16.5	13.1
Change from Baseline	Mean	-0.6	-0.4	-1.1
	SD	2.6	2.2	2.5
Between Group <sup>a</sup>	Comparison	TI vs. MS	TM vs. MS	TM vs. TI
	Estimate	-0.2	-0.8	-0.7
	P value	0.5493	0.0044	0.0284
Within Group <sup>b</sup>	P value	0.0125	0.0531	0.0001

a - p values and estimates are derived from an ANCOVA model with treatment group and investigator site as class variables and baseline body weight as a covariate.  
 b - p values are derived from a paired *t* test.

**Table 6.49 - Trial 103 Mean Change from Baseline to Week 12 in Body Weight (kg) (ITT Population with LOCF)**

		TI Alone	Metformin + Secretagogue (MS)	TI + Metformin (TM)
Baseline (Week 0)	N	177	162	169
	Mean	86.14	84.18	83.87
	SD	15.590	16.214	13.934
Endpoint (Week 12)	N	177	162	169
	Mean	85.51	83.81	82.79
	SD	15.075	16.423	13.580
Change from Baseline	Mean	-0.63	-0.38	-1.08
	SD	2.424	2.178	2.415
	LS Mean	-0.61	-0.39	-1.14
	SE of LS Mean	0.176	0.184	0.180
Within Group	P value	0.0006	0.0307	<0.0001
Between Group	Comparison	TI - MS	TM - MS	TM - TI
	Estimate	-0.21	-0.75	-0.54
	P value	0.4017	0.0035	0.0321

Source: Sponsor's submission 22 Nov 2009

**Reviewer's comment: Taken together, these data suggest that TI predisposes to less weight gain than other commonly used insulin therapies in both T1 and T2 DM and possibly**

**secretagogue therapy in T2DM (although the comparison was not statistically significant). Note, however, that these analyses do not adjust for glycemic control. The reason for this finding was not explored. One hypothesis is that less mild/moderate hypoglycemia with TI could lead to less food intake to cover low blood glucose levels which might in turn lead to less weight gain.**

### 6.1.7 Subpopulations

Please see Dr. Liu’s statistical review. Dr. Liu performed subgroup analyses on age, sex, and race for Studies 014, 102, 103, 009, and 101 individually, and found no significant interactions for those trials, except in Study 009, a significant treatment-by-sex was observed ( $p < 0.10$ ). Below is the table showing the difference between the 2 sexes. For males, the mean change from baseline at Week 52 was almost 0% (see table below and see Dr. Liu’s statistical efficacy review for details).

Study 009 –Efficacy Results for HbA1c by Sex

ITT	Change from Baseline at Week 52 : LS Mean $\pm$ SE (N)		Treatment Difference		
	TI + Lantus	Insulin aspart + Lantus	LS Mean (SE)	95% CI	p-value
Male	-0.00 $\pm$ 0.09 (146)	-0.47 $\pm$ 0.08 (136)	0.47 (0.12)	(0.23, 0.70)	0.0001
Female	-0.19 $\pm$ 0.09 (131)	-0.26 $\pm$ 0.09 (126)	0.07 (0.12)	(-0.17, 0.30)	0.58

In the Sponsor’s analyses, subject demographics including age, sex, race / ethnic group, region of treatment, duration of disease, and BMI were evaluated as pooled data. HbA1c analyses (change in baseline) for the following subpopulations were analyzed; the Sponsor concluded no meaningful differences in effect of TI on HbA1c in these subpopulations although some subgroups were too small to make meaningful comparisons:

Age Group

- 18 to 64 years
- 65 to 74 years
- $\geq 75$  years

Race / ethnic group

- Caucasian
- Hispanic
- Black / African American
- Asian
- Other

Sex

- Male
- Female

BMI Group

- < 20 kg/m<sup>2</sup>
- 20 to 25 kg/m<sup>2</sup>
- > 25 to 30 kg/m<sup>2</sup>
- > 30 to 35 kg/m<sup>2</sup>
- > 35 to 40 kg/m<sup>2</sup>
- > 40 kg/m<sup>2</sup>

Duration of Disease since Diabetes Diagnosis

- < 5 years
- ≥ 5 years

Region

- Eastern Europe
- Western Europe
- North America
- Latin America

The Sponsor's analysis of male vs. female using the pooled T1DM ITT Population showed that the mean change in HbA1c from Baseline for female subjects at 12 months was -0.29% and the mean change at 12 months for male subjects was -0.23%.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Patients with diabetes (both T1D and T2D) have varying insulin requirements that depend on many factors including the diabetes type, the degree of insulin resistance, diet, and the duration of their disease. In addition, dose requirements vary over time by individual. The Sponsor conducted two placebo-controlled trials in T2DM which demonstrated a significant placebo-adjusted reduction in HbA1c for TI. The clinical reviewer disagrees that these two trials have demonstrated a dose-response effect for the reasons described in previous sections. Therefore, clinical information relevant to dosing recommendations should be obtained from clinical pharmacology studies. The following summary of clinical pharmacology data relevant to dosing recommendations is obtained from the Sponsor's integrated summary of efficacy. Please see the clinical pharmacology review of Dr. Chung for the Agency's expert opinion on these data and conclusions.

In the TI clinical pharmacology program, doses ranging from 6 U to 100 U were studied. The bioavailability of insulin administered as TI is 18 to 24 % of RHI and RAA based on AUC<sub>0-240</sub> as assessed in 6 crossover studies. In addition, dose linearity and absorption was demonstrated: two 15 U cartridges and one 30 U cartridge of TI are bioequivalent for insulin (AUC<sub>0-360</sub> and C<sub>max</sub>) and FDKP (AUC<sub>0-480</sub>) as assessed in trial 116. TI produces rapid and high peak insulin concentrations that fall between the peak concentration times of iv insulin and sc RHI or RAA. The typical insulin t<sub>max</sub> administered as TI is approximately 14 minutes. The maximum insulin concentrations after administrations of 30 U of TI were 50 µU/mL to 70 µU/mL. These values are comparable to the mean maximum insulin concentrations found in healthy subjects (76 µU/mL) after a standardized meal. Insulin concentrations after TI administration approach

baseline within 3-4 hours. The glucose lowering activity of TI peaks within 39 to 56 minutes of administration and the timing of the peak is independent of dose.

For all patients, the ideal timing of TI administration was evaluated with respect to a meal (PDC-INS-0011). The greatest decreases in blood glucose were observed when TI was administered 10 minutes before or immediately before the meal. Administration 15 and 30 minutes after the start of the meal was not as effective. TI dosed 10 minutes before the meal was also associated with the greatest drop in glucose below baseline. Hence, to maximize postprandial glucose lowering and minimize the risk of hypoglycemia, dosing at the start of a meal is most appropriate. TI onset of action is faster than that of other prandial insulin. Some patients, such as those with delayed gastric emptying due to autonomic neuropathy or who have ingested meals with large fat content, may benefit from splitting the dose or administering the dose entirely or in part after the meal. The total dose per meal can be split before and after the meal when using more than one cartridge. After initiating TI therapy, dose adjustment may be required based on individual patient needs as is required with other glucose-lowering agents. Each patient should be titrated to their optimal TI dose based on blood glucose measurements.

Based upon these data, two scenarios were developed and tested in the Phase 3 Clinical trial program:

- Insulin naïve patients typically started on 15 U TI at each meal. The TI dose was titrated as appropriate to control blood sugar.
- Patients switching from sc insulin to TI used a transition ratio of 3 U TI for every one IU of sc RHI or RAA
  - For patients transitioning from insulin regimens that include short acting and / or longer or intermediate acting insulin, the starting TI dose was based on the total daily sc insulin dose. Patients replaced 50% of the total daily insulin dose with a corresponding dose of TI divided between main meals. Additional doses were taken to accommodate additional meals. The remaining 50% of the total dose of subcutaneous insulin was given as longer acting insulin.

### Dosing Recommendations Tested in Phase 3 Program

#### Insulin naïve patients

In Trial 103, TI was initiated with the following guidelines.

#### TI Dose Initiation:

The initial prandial TI dose was 15 U, administered immediately before the first mouthful of food at each meal, typically 3 times daily (could be 2-4 times/day).

#### TI Dose Titration:

##### General Considerations:

- Subsequently, prandial TI was titrated on the basis of self-blood glucose monitoring (SBGM) profiles, laboratory results and/or clinical findings;

- Titration beyond the starting dose began after 1 week, unless clinical signs indicate earlier titration,
- Dose titration decision-making was based principally on the 7-point capillary blood profiles (i.e., pre-prandially, 2-hour post-prandially and at bedtime)
- Target BG concentrations include
  - FPG, Pre-meal and bedtime BG concentrations < 110 mg/dL
  - 2-hour post-prandial BG concentrations < 140 mg/dL
- The maximum allowed prandial dose of TI was 90 U per meal, approximating 30 U of sc regular insulin or rapid-acting insulin analogs.
- For most patients, TI doses were likely to be the same for each meal. In some patients, however, different doses could be required for breakfast, lunch and dinner.

Specific Guidelines:

- TI dose titration for a particular meal was based on trends of at least 3 recent pre-prandial or bedtime SBGM profiles determined on 3 separate days (e.g., the 3 days of 7-point Capillary Blood Profiles):
  - *Pre-lunch* SBGM will determine *pre-breakfast* TI dose titrations
  - *Pre-dinner* SBGM will determine *pre-lunch* TI dose titrations
  - *Bedtime* SBGM will determine *pre-dinner* TI dose titrations
  - 2-hour post prandial SBGM could be used instead of the pre-meal SBGM

<b>Table 6.50 - Prandial TI Dosing Titration</b>	
<b>Pre-lunch, Pre-dinner or Bedtime SBGM Value Trends (At least 3 Recent Measurements on 3 Separate Days)</b>	<b>Prandial TI Titration at Preceding Meal (U/meal)</b>
≥ 110 mg/dL	Increase by 15 U
< 110 mg/dL and ≥ 80 mg/dl	No titration required
< 80 mg/dL	Reduce by 15 U
<b>Post-Prandial SBGM Trends (at least 3 recent measurements on 3 separate days)</b>	
≥ 140 mg/dL	Increase by 15 U
< 140 mg/dL and ≥ 80 mg/dL	No titration required
< 80 mg/dL	Reduce by 15 U

Patients already on sc insulin

In the Phase 3 clinical trial program, subjects with T2D or T1D who were transferred from prandial insulins to TI (trials 102, 009 and 030) used the following dosing schedule:

Insulin bioavailability following inhalation of TI was approximately 30% relative to sc insulin (estimate of bioavailability is rounded up from 24% for increased safety). TI was supplied in 15 U and 30U cartridge strengths.

- 15 Units was approximately 5 IU of sc regular insulin or rapid-acting analog insulins,

- 30 Units was approximately 10 IU of sc regular insulin or rapid-acting analog insulins, Patients replaced each unit of sc prandial insulin with 3 units of TI.
- The appropriate TI dose for a given meal was the nearest available dose of TI that was 3 times the current sc regular or rapid-acting insulin dose.
- The calculated TI starting meal dose was rounded *down* to the nearest 15 U, to avoid potential hypoglycemia.
- TI doses were adjusted in increments of 15 U, as needed, up to a maximum of 90 U per meal.

A subject could require 1 to 3 successive cartridges depending on the total dose of TI required for a meal.

Subjects who were on self-mix regimen (e.g., intermediate insulin [NPH, Lente, and Ultralente] + regular insulin or rapid-acting insulin analog) or a pre-mix regimen (e.g., Premix Analog 70/30) followed these procedures to calculate initial insulin dosages:

1. Determine the subject's pre-randomization total daily sc insulin dose.
2. Replace 50% of the total daily sc insulin dose with a corresponding daily TI dose. The remaining 50% of the total daily dose of sc insulin should be given as basal/long-acting insulin.
3. Calculate the daily TI dose in U by multiplying the 50% of the pre-randomization total daily dose by 3.
4. Divide the daily TI dose in U by the number of meals the subject eats (usually 2 – 3) to the starting TI dose for each meal.
5. Round the starting TI dose/meal *down* to the nearest 15 U (to avoid potential hypoglycemia). Doses of TI were subsequently adjusted in increments of 15 U, as needed, up to a maximum of 90 U per meal using the protocol guidelines as outline above.

Following these guidelines did not result in an increase in hypoglycemic events relative to comparator insulin regimens in the phase 3 program (see Ms. Mele's statistical review). Further, while in some trials glycemic control was not optimized, it appears to be due to lack of adherence to these titrations guidelines rather than inherently inappropriate guidelines. Therefore, the clinical reviewer generally agrees with the Sponsor's proposed dosing recommendations although they should be simplified for labeling.

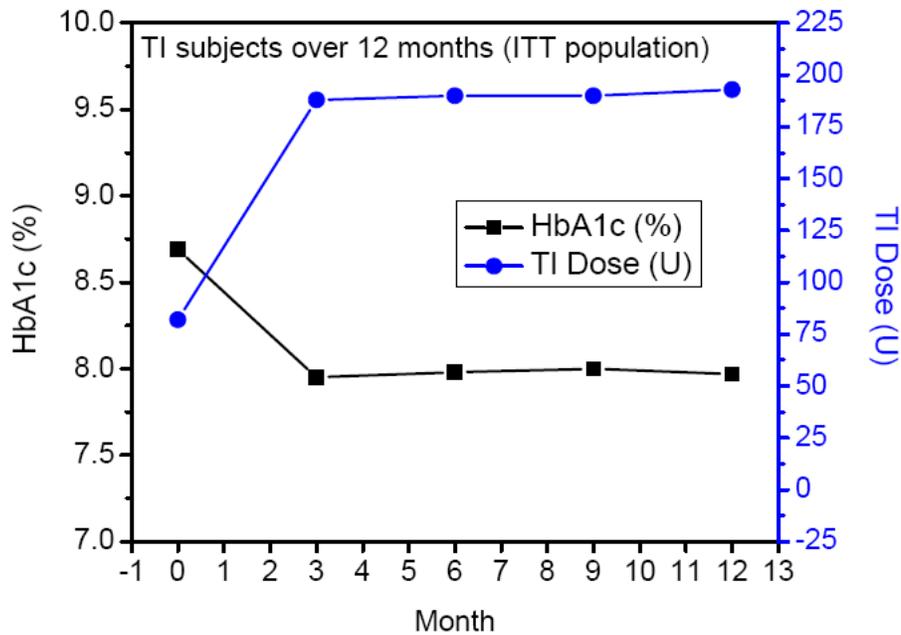
#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Based on results of the two 52 weeks trials (102 in T2DM and 009 in T1DM) persistence of efficacy has been demonstrated to at least 1 year. Based on the time-response profiles in the two long term studies there is no evidence of tolerance to TI.

In trial 102, improvements in HbA1c occurred after 3 months (Figure 6.17). The HbA1c improvements were sustained throughout the study on TI doses that reached a plateau at Month 3 and remained constant over the last 6 months of treatment. The sustained efficacy was not influenced by the basal insulin component of the treatment regimen because the mean daily

insulin glargine dose reached a plateau (~ 44 IU/day) between 3 and 6 months and did not increase significantly after that time.

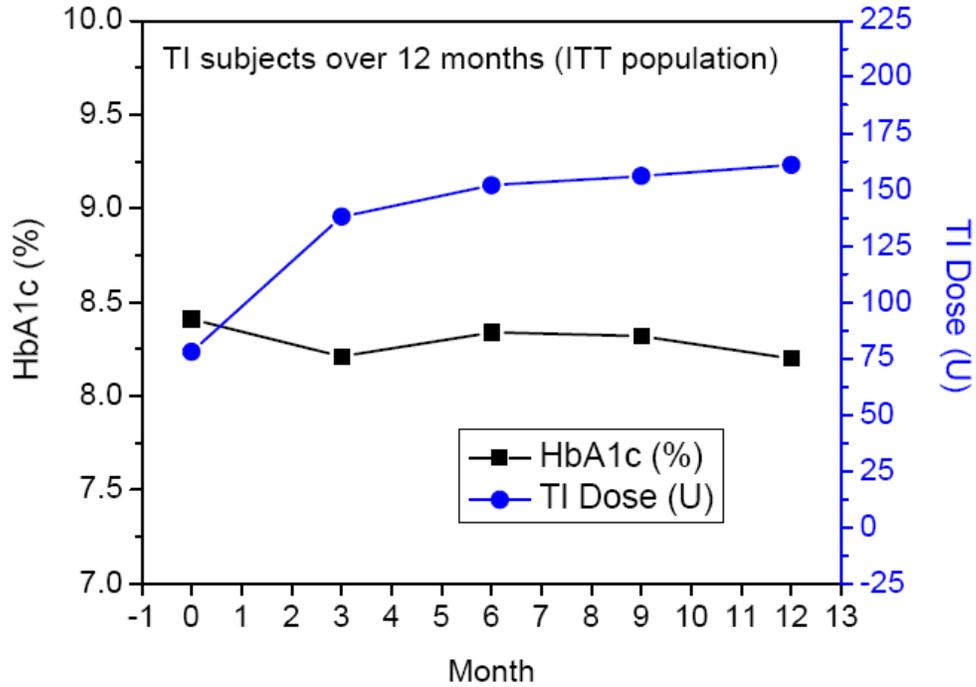
**Figure 6.17 – Trial 102 Mean Change in HbA1c vs. Mean Daily TI (U) Dose Over Time (ITT Population)**



Source: Figure 126, ISE

Persistence of efficacy comparable to that observed in subjects with T2D was seen in the type 1 population. In trial 009, the TI dose began to plateau at Month 6 and its effect on HbA1c was maintained over the subsequent 6 months (Figure 6.18). The sustained efficacy was not influenced by the basal insulin component of the treatment regimen because the mean daily insulin glargine dose reached a plateau by Month 2 (~33 IU/ day) and did not significantly increase after that time.

**Figure 6.18 – Trial 009 Mean Change in HbA1c vs. Mean Daily TI (U) Dose Over Time (ITT Population)**



Source: Figure 127, ISE

#### 6.1.10 Additional Efficacy Issues/Analyses

None

## 7 Review of Safety

### Safety Summary

Non-pulmonary safety is evaluated in this review. The major safety findings are as follows: There was no imbalance in the rate of deaths between TI-treated subjects and comparator-treated subjects. Among T2DM subjects there was no pattern of a single type of SAE that occurred with significantly greater frequency among TI-treated subjects than among comparator-treated subjects. Among T1DM subjects, there was a higher rate of DKA seen in TI-treated subjects vs. comparator-treated subjects. A review of the narratives for these cases of DKA did not suggest a commonality among the patients.

Premature discontinuation from clinical trials was higher among TI-treated subjects for both T2 and T1 populations. The reason for the imbalance was primarily due to withdrawals for adverse events and subjects withdrawing consent. More than half of the dropouts for adverse events were respiratory-related and are discussed in the pulmonary safety review. The higher rate of withdrawals for non-pulmonary adverse events is likely due to the open-label nature of the trial designs because an examination of the incidence rate of adverse events overall showed no difference between TI and comparators suggesting that subjects treated with TI were dropping out at a higher rate for essentially the same adverse events. Investigator verbatim terms for subjects who withdrew consent were reviewed by the Sponsor for all events and by the clinical reviewer for trials 102 and 009 (the pivotal efficacy trials) to determine if any miscoding occurred. There were essentially no subjects who were reclassified as having adverse events leading to withdrawal although several subjects were reclassified as withdrawing for a reason related to lack of efficacy.

Safety issues of interest reviewed in this document included hypoglycemia, cardiovascular events, neoplasms and immunogenicity. A statistical review of hypoglycemia was conducted by Joy Mele, one of the Agency's statisticians and should be considered the definitive analyses of hypoglycemia as there were methodological problems with the Sponsor's analyses. Overall, the rates of hypoglycemia were comparable between TI and insulin comparators except for in trial 102 where the rate of severe hypoglycemia was lower for TI. The hypoglycemia data should be interpreted in context of glycemic control. Analyses of cardiovascular safety were submitted by the Sponsor that included an independent blinded search of MedDRA system organ classes for all cardiac and vascular terminology. Although there were limitations to this analysis (discussed in this review) there was no concerning signal for cardiovascular risk suggested by the analysis. Neoplasms were examined in the TI program, with a special interest in bronchogenic carcinoma, because of the post-marketing reports of an increased rate of lung malignancy with use of Exubera. No safety signal for any type of malignancy neoplasm was seen in the TI clinical development program, although neoplasms were few and will require further evaluation in post-

marketing studies. In general, insulin antibodies increased to a greater extent among TI-treated subjects than comparator-treated subjects, although there appeared to be no clinical impact of these increased antibody levels.

Hypoglycemia and cough were the most common adverse events seen among TI-treated subjects in the phase 2/3 controlled clinical trials. Other common events included upper respiratory tract infection and nasopharyngitis which occurred at similar rates between TI and comparators. Review of laboratory results and vital signs revealed no statistically significant or clinically important differences between TI and comparators. A review of the thorough QT study is pending at the time of this review, but analysis of QTc interval shifts suggests no safety signal.

## **7.1 Methods**

### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

The data sources used in the safety assessment were adequate. In general, the Sponsor's methods were appropriate for the safety evaluation. A separate evaluation of hypoglycemia was performed by Ms. Mele, one of the Agency's statisticians.

Table 7.1 summarizes the safety database for TI. The trial number is listed; the reader can refer to Tables 5.1 and 5.2 for a description of each trial. The safety data for each study consist of all randomized subjects who received  $\geq 1$  dose of study drug. All safety data were presented according to the actual treatment the subjects received. The safety assessments and analyses include data available as of 15 Nov 2008. The 120 day safety update includes additional data available as of 31 May 2009. The 120 safety update is discussed in section 7.7.

Controlled safety/ efficacy trials	T1DM	2 Trials: 009 and 101
	T2DM	6 Trials: 005, 0008, 102, 014, 026, and 103
Controlled long-term safety trial	Combined T1DM and T2DM	030 – 2 year pulmonary safety trial
Uncontrolled long-term safety data	T2DM	010 – 4 years
Follow-up observational study	Combined T1DM and T2DM	126 – 2 months
Clinical Pharmacology	Healthy volunteers, T1DM and T2DM	25 studies: 0001, 0001A, 0001B, 0001C, 0002, 0002A, 0003, 0003A, 03B, 03B2, 0004, 0004A, 0006, 0007, 00011, 025, 110, 113, 114, 116, 122, 123, 129, 138, 104
Special Safety Clinical Pharmacology studies		131 (QT study), 017 (renal impairment), 111 (hepatic impairment), 016 (smokers), 015 (COPD), 112 (URI), 027 (asthma)
Terminated (asthma)	Combined T1DM and T2DM	105
Ongoing Trials	T1DM	117
	T2DM	118
Source, ISS		

### 7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA 7.1. The clinical reviewer compared investigator verbatim terms to the Sponsor’s preferred terms for all deaths, serious adverse events and events leading to dropout. The Sponsor’s MedDRA coding was appropriate.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Information for comparison of incidence of safety findings was obtained from the pooled controlled Phase 2 and Phase 3 study data. Pooling criteria were as follows: similarity of trial design and continuous exposure to Investigational Medicinal Product (IMP) for greater than 14 days with T1DM and T2DM patients pooled separately. In the pooling strategy, the numerator events and denominators for the selected studies were combined with no statistical weighting of studies.

The pooled analyses include data from all complete Phase 2/3 controlled trials including both type 1 and type 2 diabetes patients and that had database locks on or before the cutoff date of Nov. 15, 2008. The studies contributing to the pooled analysis are as follows:

- Trials included in the pooled Type 1 diabetes datasets were 009, 030, and 101.

- Trials included in the pooled Type 2 diabetes datasets were 005, 0008, 102, 014, 026, 030, and 103 (the first 3 months of data).

Non-pooled trials included all other trials in which subjects were exposed to TI (e.g. trials where subjects used empty MedTone inhalers were not included). The non-pooled studies included: clinical pharmacology trials with a treatment of less than or equal to 14 days; trial 010, a long-term, uncontrolled, open-label safety follow-up trial in subjects with type 2 diabetes; trial 126, a follow-up observational trial evaluating pulmonary function in subjects who were previously exposed to TI or comparator in trials 030, 103, 102 and 009 (subjects were not exposed to study drug during participation in this follow up trial); the nonrandomized observational period (Weeks 12 to 24) of trial 103; trial 014, for which only the first 6-month treatment period of the trial is included; trial 105, a trial with a duration > 14 days in subjects with asthma that was terminated because of very low enrollment (3 subjects randomized); and trial 104, a phase 2, non-pooled trial lasting less than 14 days.

**Reviewer’s comment: All of the FDA recommendations regarding safety assessments, pooling strategies and analysis methods appear to have been followed. The pooling strategy was consistent with that commonly used in drug development programs and is acceptable.**

Study Medications Contributing to Safety Analysis Groups

TI was generally tested in combination with other medications, and the comparator groups were often using multiple medications. Table 7.2 shows the study medication categories used by subjects in the pooled safety trials.

<b>Table 7.2 – Overview of Study Medications Contributing to Safety Analysis Groups</b>	
Study Medications Contributing to TI Group	Study Medications Contributing to Comparator Group
<b>Type 2 DM</b>	
TI + insulin glargine (trial 005) TI (± OAD ± insulin glargine) (trial 0008) TI + insulin glargine (trial 014) TI + OAD (trial 026) TI + usual care (trial 030) TI + insulin glargine (± OAD) (trial 102) TI ± metformin (trial 103)	TP + insulin glargine (trial 005) TP (± OA ± insulin glargine) (trial 0008) Insulin aspart + insulin glargine (trial 014) OADs (trial 026) Usual care (trial 030) Premix 70/30 insulin analog (± OAD) (trial 102) Metformin + secretagogue (trial 103)
<b>Type 1 DM</b>	
TI + insulin glargine (trial 009) TI + insulin glargine (trial 101) TI ± usual care (trial 030)	Insulin aspart + insulin glargine (trial 009) Insulin aspart + insulin glargine (trial 101) Usual care (trial 030)
Usual care: At the discretion of their physicians, subjects were to receive antidiabetes treatment (diet, exercise, OA, and/or insulin), according to established American Diabetes Association guidelines.	
Source: Table 5, Integrated Summary of Safety	

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### 7.2.1.1 Total number of subjects exposed to TI in all clinical trials (phases 1, 2, and 3)

#### Number of Subjects Exposed at Appropriate Durations

According to the February 2008 draft Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, the recommendation is that at least 2,500 subjects be exposed to the investigational product with at least 1,300 to 1,500 of these subjects exposed to the investigational product for 1 year or more and at least 300 to 500 subjects exposed to the investigational product for 18 months or more.

Table 7.3 shows the number of subjects exposed by defined duration combining the type 1 and type 2 diabetes populations as of the cutoff date for the 120-day safety update (31 May 2009). The table includes all subjects exposed to TI, i.e. includes studies of any phase

Disease Type	All Subjects Exposed to TI (n)	Mean/Median exposure time (days)	At least 3 months ( $\geq$ 80 days)	At least 6 months ( $\geq$ 165 days)	At least 12 months ( $\geq$ 330 days)	At least 18 months ( $\geq$ 510 days)	At least 24 months ( $\geq$ 660 days)
Type 1	857	233.8/114	514	400	355	135	112
Type 2	2160	323.4/169	1644	1258	844	567	498
Combined	3021	297.7/169	2160	1658	1199	702	610

Source: Sponsor's submission 11 Nov 2009

**Reviewer's comment: The development program meets the ICH guidelines for sample size for drugs developed to treat chronic, non-life-threatening conditions (at least 300-600 patients for six months, 100 for 12 months, total exposure of 1,500 patients. However, there are slightly fewer patients at the one year mark than is recommended in the DMED guidance. However, these are general recommendations, not requirements, and the number of patients exposed for at least 18 months is adequate. In addition, more than 600 TI-treated patients were exposed to study drug for at least 2 years.**

#### 7.2.1.2 Exposure in pooled controlled phase 2/3 trials safety population

Table 7.4 presents the overall exposure data for the combined pooled safety population. A total of 2409, 1945, and 114 type 1 or type 2 subjects in the TI, comparator, and TP groups were exposed to study medication, respectively, in controlled phase 2/3 TI clinical trials. Mean durations of exposure were  $275 \pm 237$ ,  $386 \pm 243$ , and  $81 \pm 27$  days in the TI, comparator, and TP groups, respectively. Approximately 60% of subjects who received TI did so for more than 3 months. The number of subjects with type 1 or type 2 diabetes exposed to TI for at least 1 year was 831/2409 (34%).

Exposure data are presented for T2DM and T1DM separately for the rest of this section.

<b>Table 7.4 – Number (Percentage) of Subjects Exposed by Defined Duration, Type 1 and Type 2 Diabetes (Safety Population – Pooled Controlled Phase 2/3 Trials)</b>			
Duration of Exposure (months)	TI n = 2409	Comparator n = 1944	TP n = 114
	n (%)	n (%)	n (%)
0 – 3	804 (33.4)	296 (15.2)	62 (54.4)
> 3 and up to 6	485 (20.1)	331 (17.0)	52 (45.6)
> 6 and up to 12	396 (16.4)	385 (19.8)	0
> 12 and up to 24	718 (29.8)	913 (47.0)	0
> 24	6 (0.2)	18 (0.9)	0
At least 6 months (>182 days)	1126 (46.7)	1318 (67.8)	0
At least 12 months (>365 days)	831 (34.5)	1044 (53.7)	0
At least 18 months (>547 days)	504 (20.9)	690 (35.5)	0
At least 24 months (>730 days)	7 (0.3)	18 (0.9)	0

Source: Table 14, ISS

#### 7.2.1.2.1 Exposure in the Type 2 DM pooled safety population

A total of 1795 and 114 subjects with T2DM in the TI and TP groups were exposed to study medication, respectively, in controlled phase 2/3 TI clinical trials (Table 7.5). Mean durations of exposure were  $259.2 \pm 237.9$  and  $81.4 \pm 27.4$  days in the TI and TP groups, respectively. Approximately 62.3% of subjects with type 2 diabetes were exposed to TI for more than 3 months. The number of subjects exposed to TI for at least 1 year was 535/1795 (29.8%).

**Table 7.5 – Number (Percentage) of Subjects Exposed to TI vs. Comparator by Defined Duration, Type 2 Diabetes (Safety Population – Pooled Controlled Phase 2/3 Trials)**

Duration of Exposure (months)	TI n = 1795 n (%)	Comparator n = 1345 n (%)	TP n = 114 n (%)
0 – 3	676 (37.7)	257 (19.1)	62 (54.4)
> 3 and up to 6	392 (21.8)	254 (18.9)	52 (45.6)
> 6 and up to 12	241 (13.4)	236 (17.5)	0
> 12 and up to 24	482 (26.9)	582 (43.3)	0
> 24	4 (0.2)	15 (1.1)	0
At least 6 months (>182 days)	731 (40.7)	835 (62.1)	0
At least 12 months (>365 days)	535 (29.8)	658 (48.9)	0
At least 18 months (>547 days)	373 (20.8)	480 (35.7)	0
At least 24 months (>730 days)	5 (0.3)	15 (1.1)	0

Source: Table 16, ISS

The majority (74%) of subjects with T2DM who received TI for any length of time received an average daily dose of 180 U or less (Table 7.6). The most common duration of TI treatment was 0 to 3 months in which 471/675 of subjects (70 %) received an average daily dose of 180 U or less. The recommended dose of TI in Phase 2/3 clinical trials was up to 90 U 3 times a day with meals and an additional dose if necessary. A small number of subjects received an average daily dose of more than 300 U of TI for various time periods.

**Table 7.6 – Number and Percent of T2DM Subjects Exposed to Defined Doses for Defined Durations (Safety Population – Pooled Controlled Phase 2/3 Trials)**

Exposure Duration (Months)	Average Daily Dose of TI (U)	Subjects Exposed to TI n (%)
Overall	≤ 60	428 (23.8)
	> 60 – 120	435 (24.2)
	> 120 – 180	449 (25.0)
	> 180 – 240	312 (17.4)
	> 240 – 300	151 (8.4)
	> 300	19 (1.1)
		<b>Total: 1794</b>
0-3	≤ 60	233 (13.0)
	> 60 – 120	158 (8.8)
	> 120 – 180	131 (7.3)
	> 180 – 240	111 (6.2)
	> 240 – 300	37 (2.1)
	> 300	5 (0.3)
		<b>Total: 675 (37.7)</b>
> 3- 6	≤ 60	166 (9.2)
	> 60 – 120	94 (5.2)
	> 120 – 180	88 (4.9)
	> 180 – 240	33 (1.8)
	> 240 – 300	10 (0.6)
	> 300	1 (0.1)
		<b>Total: 392 (21.8)</b>
> 6 - 12	≤ 60	9 (0.5)
	> 60 – 120	48 (2.7)
	> 120 – 180	48 (2.7)
	> 180 – 240	45 (2.5)
	> 240 – 300	36 (2.0)
	> 300	6 (0.3)
		<b>Total: 192 (10.7)</b>
> 12 -24	≤ 60	20 (1.1)
	> 60 – 120	132 (7.4)
	> 120 – 180	181 (10.1)
	> 180 – 240	123 (6.9)
	> 240 – 300	67 (3.7)
	> 300	7 (0.4)
		<b>Total:530 (29.6)</b>
> 24	≤ 60	0
	> 60 – 120	3 (0.2)
	> 120 – 180	1 (0.1)
	> 180 – 240	0
	> 240 – 300	1 (0.1)
	> 300	0
		<b>Total: 5 (0.4)</b>
An additional type 2 subject (MKC-TI-030/1990) did not have adequate dosing information and was excluded from this analysis.		
Source: Table 19, ISS		

Demographics for subjects with T2DM are shown in Table 7.7. There was a balance of men and women in the trials. The majority of subjects with type 2 diabetes in the controlled phase 2/3 TI clinical trials were Caucasian. The percentage of Black/African-American subjects was 4.9% and 4.6% in the TI and comparator groups, respectively. The mean age was roughly 56 years and mean BMI was 31 kg/m<sup>2</sup>.

	TI (n=1795)	Comparator (n=1345)	TP (n=114)
Sex			
• % Male	51 %	51 %	57 %
Race			
• Caucasian	81 %	80 %	80 %
• Black or African American	5 %	5 %	3 %
• Hispanic	10 %	10 %	12 %
• Asian	3 %	3 %	4 %
• Other	1 %	2 %	1 %
Age (years)			
• Mean (SD)	56 (9)	56 (9)	56 (10)
• Median	57	56	56
• Range	19 - 82	18 - 78	26 - 76
Age Group (years)			
• 18 – 64	83 %	84 %	79 %
• 64 – 74	16 %	15 %	19 %
• > 74	1 %	1 %	2 %
BMI (kg/m <sup>2</sup> )			
• Mean (SD)	31 (5)	31 (5)	31 (4)
• Median	31	31	30
• Range	15 - 56	19 - 64	21 - 39
Duration of Diabetes			
• Mean (SD)	10.8	11.4	7.8
• Median	9.5	10.1	7.4
• Range	0.6 – 44.6	0.3 – 52.3	1.6 – 18.2
Smoking History			
• Yes (%)	30 %	30 %	38 %
Source: ISS and Sponsor's submission 22 Nov 2009			

**Reviewer's comment: The subject demographics are essentially representative of the type 2 diabetic population in general allowing adequate safety assessments with one exception. The proportion of African American subjects in the safety population is notably lower than the proportion of African American diabetics in the U.S. population.**

#### 7.2.1.2.2 Exposure in the Type 1 DM pooled safety population

A total of 614 subjects with T1DM were exposed to TI in controlled phase 2/3 TI clinical trials with a mean duration of exposure of  $321.2 \pm 229.79$  days. The majority (51.8%) of subjects with T1DM were exposed to TI for up to 12 months (Table 7.8). The number of subjects exposed to TI for at least 1 year was 296/614 (48.2%).

<b>Table 7.8 – Number (Percentage) of Subjects Exposed by Defined Duration, Type 1 Diabetes (Safety Population – Pooled Controlled Phase 2/3 Trials)</b>		
Duration of Exposure (months)	TI n = 614	Comparator n = 599
	n (%)	n (%)
0 – 3	128 (20.8)	39 (6.5)
> 3 and up to 6	93 (15.1)	77 (12.9)
> 6 and up to 12	155 (25.2)	149 (24.9)
> 12 and up to 24	236 (38.4)	331 (55.3)
> 24	2 (0.3)	3 (0.5)
At least 6 months (>182 days)	395 (64.3)	483 (80.6)
At least 12 months (>365 days)	296 (48.2)	386 (64.4)
At least 18 months (>547 days)	131 (21.3)	210 (35.1)
At least 24 months (>730 days)	2 (0.3)	3 (0.5)

Source: Table 15, ISS

The majority (74.8%) of subjects with T1DM who received TI for any length of time received an average daily dose of 180 U or less (Table 7.9). The most common duration of TI treatment was >12 to 24 months in which 202 of the 293 subjects (68.9%) received an average daily dose of 180 U or less.

**Table 7.9 – Number and Percent of T1DM Subjects Exposed to Defined Doses for Defined Durations (Safety Population – Pooled Controlled Phase 2/3 Trials)**

Exposure Duration (Months)	Average Daily Dose of TI (U)	Subjects Exposed to TI n (%)
Overall	≤ 60	47 (7.7)
	> 60 – 120	223 (36.3)
	> 120 – 180	189 (30.8)
	> 180 – 240	103 (16.8)
	> 240 – 300	46 (7.5)
	> 300	5 (0.8)
		<b>Total: 613</b>
0-3	≤ 60	25 (4.1)
	> 60 – 120	55 (9.0)
	> 120 – 180	31 (5.0)
	> 180 – 240	15 (2.4)
	> 240 – 300	2 (0.3)
	> 300	0
		<b>Total: 128 (20.8)</b>
> 3- 6	≤ 60	10 (1.6)
	> 60 – 120	40 (6.5)
	> 120 – 180	28 (4.6)
	> 180 – 240	11 (1.8)
	> 240 – 300	4 (0.7)
	> 300	0
		<b>Total: 93 (15.2)</b>
> 6 - 12	≤ 60	4 (0.7)
	> 60 – 120	29 (4.7)
	> 120 – 180	34 (5.5)
	> 180 – 240	18 (2.9)
	> 240 – 300	10 (1.6)
	> 300	2 (0.3)
		<b>Total: 97 (15.7)</b>
> 12 -24	≤ 60	8 (1.3)
	> 60 – 120	98 (16.0)
	> 120 – 180	96 (15.6)
	> 180 – 240	58 (9.4)
	> 240 – 300	30 (4.9)
	> 300	3 (0.5)
		<b>Total: 293 (47.7)</b>
> 24	≤ 60	0
	> 60 – 120	1 (0.2)
	> 120 – 180	0
	> 180 – 240	1 (0.2)
	> 240 – 300	0
	> 300	0
		<b>Total: 2 (0.4)</b>
An additional type 1 subject (009/5029) did not have adequate dosing information and are excluded from this analysis.		
Source: Table 18, ISS, with correction from Sponsor's submission 22 Nov 2009		

Demographics for subjects with type 1 diabetes are shown in Table 7.10. The majority of subjects with type 1 diabetes in the controlled phase 2/3 TI clinical trials were Caucasian. The percentage of Black/African-American subjects was 3.7% and 3.3% in the TI and comparator groups, respectively. The majority of the subjects were 18 to 64 years of age, consistent with the demographics for T1DM in the population at large. The mean BMI in all treatment groups was around 26 mg/kg<sup>2</sup> which as expected, is leaner than the type 2 population.

<b>Table 7.10 – Demographic Characteristics of the T1DM Pooled Controlled Phase 2/3 Trials Safety Population</b>		
	TI (n=614)	Comparator (n=599)
Sex		
• % Male	52 %	53 %
Race		
• Caucasian	91 %	91 %
• Black or African American	4 %	3 %
• Hispanic	4 %	4 %
• Asian	1 %	1 %
• Other	1 %	1 %
Age (years)		
• Mean (SD)	38 (13)	38 (12)
• Median	38	38
• Range	18 - 69	18 - 76
Age Group (years)		
• 18 – 64	98 %	98.3 %
• 64 – 74	2 %	1.5 %
• > 74	0 %	0.2 %
BMI (kg/m <sup>2</sup> )		
• Mean (SD)	26 (4)	26 (4)
• Median	26	26
• Range	16 - 40	17 - 41
Duration of Diabetes		
• Mean (SD)	16.5	16.6
• Median	14.2	14.3
• Range	0.2 – 61.0	0.4 – 63.9
Smoking History		
• Yes (%)	24 %	24 %

Source: ISS and Sponsor's submission 22 Nov 2009

**Reviewer's comments: Exposure in the pooled controlled phase 2/3 trials is adequate for estimating and comparing incidence of safety variables.**

**Note that there was an error found in the total exposure table for Type 1 diabetics provided by the Sponsor. The clinical reviewer notified the Sponsor of this finding in an information request dated 10 Nov 2009. The Sponsor responded 22 Nov 2009 with an updated table**

**correcting the error. Since then, further inconsistencies in the numbers in the above tables have been noted but have not been reconciled at the time of this review. These are not likely to change the overall conclusions of this review and will be addressed in the cross discipline team leader memo.**

#### 7.2.2 Explorations for Dose Response

Hypoglycemia is an adverse event for which the risk is directly proportional to TI dose. Hypoglycemia is discussed in section 7.3.5.1 and in Ms. Mele's statistical safety review. Please see also Dr. Karimi-Shah's pulmonary safety review for a discussion of dose response for pulmonary safety.

#### 7.2.3 Special Animal and/or In Vitro Testing

There were no unusual preclinical signals or early clinical signals that warranted special animal or in vitro testing. The preclinical program appears to have encompassed the usual preclinical testing procedures and was adequate.

Due to the potential lung carcinogenicity signal with Exubera, the only approved (now withdrawn) inhaled insulin to date, the clinical reviewer notes that preclinical testing was adequate to explore the potential for lung and general carcinogenicity. Animal findings suggested that Technosphere insulin and Technosphere particles did not have carcinogenic potential. The carcinogenicity study findings were presented to ECAC on Sept 29th 2009 and ECAC concurred that these studies were adequate and were negative for carcinogenicity.

#### 7.2.4 Routine Clinical Testing

Routine testing of study subjects was adequate in the opinion of the clinical reviewer. Individual trials had scheduled routine clinical testing measurements at specified intervals but in all trials measurements were performed at least at baseline and study endpoint. Vital signs evaluated included weight, height, blood pressure (systolic and diastolic), temperature, radial pulse, respiratory rate, and waist circumference. BMI was calculated based on measurements of weight and height collected at baseline, and weight collected at post-baseline visits. Clinical laboratory measurements included comprehensive hematology and chemistry panels. ECGs were also performed routinely. Measurements of pulmonary safety are discussed in Dr. Karimi-Shah's pulmonary safety review.

## 7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to section 4.4 Clinical Pharmacology

## 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Exubera (NDA 21,868), the first inhaled insulin NDA, was approved by the FDA in January 2006, but then withdrawn from the market in October 2007 due to marketing reasons. Postmarketing information regarding the use of Exubera suggested a possible primary lung cancer signal. See section 2.2.

The Sponsor submitted an analysis of adverse events of neoplasm including primary lung malignancy. Since cancers usually take a long time to develop, the current TI database from the premarketing clinical development program with its limited duration cannot fully characterize the risk of neoplasm associated with use of TI; neoplasms may be better evaluated in postmarketing studies.

Concerns regarding lack of data due to certain exclusion criteria (renal and hepatic insufficiency, chronic lung disease, smokers), and lack of data in African Americans, have already been discussed. The adequacy of the extent of pulmonary safety data contained in the NDA is being assessed by the Division of Pulmonary and Allergy Drug Products.

## 7.2.7 Adequacy of Safety Assessments - Summary

In the opinion of the clinical reviewer, an adequate number of subjects were exposed to TI overall. The designs of the studies used in the pooled analyses (placebo- or open-label active-controlled trials) were generally adequate to answer critical questions, and potential class effects were evaluated. There were no problems suggested by pre-clinical data that were not evaluated. Adequacy of pulmonary safety assessments are discussed in the pulmonary safety review.

Limitations to the safety assessments include the following:

- African Americans were under-represented. Pulmonary function may be different in African American subjects vs. Caucasian subjects. Specifically, African Americans have been described to have lower normative values for baseline lung function than those seen in Caucasian Americans and Mexican-Americans (Hankinson, 1999). Therefore, the primary safety concern regarding the underrepresentation of African Americans is a pulmonary safety issue.
- Subjects with pertinent risk factors including a recent smoking history and/or chronic lung disease were not assessed in the clinical development program and may be considered relevant populations for postmarketing studies.

- Few patients in the clinical development program used doses of > 240 U TI. Notably, patients across trials generally were not titrated to goal, and therefore, safety may not have been adequately assessed for doses that will ultimately be used in the clinical setting when subjects are actually titrated to goal. However, the pulmonary review identified no dose response relationship to pulmonary function decline and there was no signal of other serious risk in the clinical development program that warrants further study in patients using higher TI doses.

## 7.3 Major Safety Results

### 7.3.1 Deaths

At the time of NDA submission a total of 16 subjects with type 1 or type 2 diabetes who participated in the TI program had died. Of the 16 subjects who died, 14 were included in the pooled database for the Phase 2/3 controlled trials. Of the 14 subjects who died in the pooled phase 2/3 controlled trials, 9/2409 (0.4%) received TI and 5/1944 (0.3%) received comparator. One other death occurred in a patient exposed to TI in the uncontrolled long term safety trial 010. One death occurred in a patient who had been in the comparator group in trial 014, and died during the follow up phase.

In the 120 day safety update submitted on 16 Jul 2009 (database lock 31 May 2009), four more deaths were reported for TI treated patients which had been received for patients enrolled in completed trials but after database lock. One of these deaths was reported in the controlled trial 102. The three remaining deaths were reported for subjects in the long term uncontrolled trial 010. All deaths were follow-ups of previously reported serious adverse events and occurred after subjects had completed trial participation and patients were no longer on study medication.

Table 7.11 summarizes deaths occurring in subjects treated with TI and Comparator.

<b>Table 7.11 – Deaths Listing<sup>1</sup> for TI and Comparator, Cutoff date 31 May 2009</b>						
Trial/Patient Number	Age (years)	Sex	Diabetes Type	Total Daily Dose <sup>2</sup>	Time <sup>3</sup>	Description
<b>TI</b>						
MKC-TI-030/857/3469	59	M	1	180 U	479	Acute cardiovascular collapse
MKC-TI-030/458/3254	67	F	2	210 U	167	Bile duct cancer
MKC-TI-030/526/0539	60	F	2	90 U	109	Ischemic stroke and acute MI
MKC-TI-102/483/2524	56	M	2	210 U	217	Hemorrhagic stroke
MKC-TI-030/031/0237	55	F	2	90 U	67	Cardiac arrest
MKC-TI-030/162/0611	58	M	2	180 U	178	Multifactorial CVA
MKC-TI-102/523/2158	72	M	2	180 U	34	Ischemic heart disease
MKC-TI-102/488/2219	64	M	2	270 U	163	Acute MI
MKC-TI-102/508/2891	50	M	2	270 U	306	Sepsis
MKC-TI-010/409/1854	75	M	2	120 U	756	Acute MI
MKC-TI-102/067/2909	62	M	2	210 U	199	Neuroendocrine tumor
MKC-TI-010/407/3316	67	M	2	90 U	693	Bronchogenic carcinoma
MKC-TI-010/009/0246	73	M	2	270 U	520	Metastatic prostate CA
MKC-TI-010/403/2782	60	M	2	270 U	372	Metastatic pancreatic adenocarcinoma
<b>Comparator</b>						
MKC-TI-030/174/1783	50	M	1	SC insulin	261	Road traffic accident
MKC-TI-030/912/3282	56	M	2	OADs	603	Cardiac arrest
MKC-TI-030/537/0308	51	F	2	SC insulin	399	Acute coronary syndrome
MKC-TI-102/322/1772	68	F	2	SC insulin	76	Cardiac arrest
MKC-TI-014/534/678	74	F	2	SC insulin	167	Acute coronary syndrome
MKC-TI-014/524/074	72	M	2	SC insulin	298	Acute cardiac failure
<p>1 - Includes all deaths that occurred during drug exposure; or within 30 days following discontinuation from drug; or later but resulting from adverse events that had onset during drug exposure or had onset within 30 days following drug exposure</p> <p>2 – Last dose prior to discontinuation if on TI or type of therapy if on comparator</p> <p>3 – Days on treatment before death</p> <p>Key: U=Units Technosphere Insulin, SC=subcutaneous, OADs=oral antidiabetic drugs, MI= myocardial infarction, CVA=cerebrovascular accident, CA=cancer</p>						

### Deaths narratives

A brief summary of each death narrative for inhaled insulin group patients follows. Patients are identified by their study number, then their site number, then their patient ID number.

### Original NDA submission

#### Controlled phase 2/3 trials

MKC-TI-030/857/3469: A 59-yo Caucasian male in the Ukraine with type 1 DM received TI 60 U prandially TID and basal insulin 40 IU subcutaneous (sc) QD. The duration of treatment at the onset of the event was 479 days. Patient was found dead at his desk. Blood glucose on the scene was 90 mg/dL. Autopsy showed coronary atherosclerosis. The cause of death was listed as acute cardiovascular collapse.

MKC-TI-030/458/3254: A 67-yo Caucasian female in Poland with type 2 DM, received TI Inhalation 75 U prandially BID with the addition of 60 U QD day; and insulin glargine (Lantus) subcutaneous (sc) 16 IU QD. The duration of treatment at the onset of the event was 167 days. The patient was hospitalized for abdominal pain and diagnosed with cholangiocarcinoma. The patient died 5 months later while undergoing chemotherapy.

MKC-TI-030/526/0539: A 60-yo Caucasian female in Russia with type 2 DM complicated by retinopathy and neuropathy, HTN, received TI 30 U TID prandially and insulin isophane, human biosynthetic (Protaphan), 34 IU subcutaneous (sc) QD as basal coverage. The duration of treatment at the onset of event was 109 days. The patient was hospitalized with neurologic symptoms and diagnosed with acute ischemic stroke. EKG also noted acute MI. Patient died 8 days later.

MKC-TI-102/483/2524: A 56-yo multiracial male in Brazil with type 2 DM complicated by retinopathy, HTN, dyslipidemia received TI 75 U prandially at breakfast and lunch and 60 U at dinner and insulin glargine 50 IU subcutaneous (sc) QD. The duration of treatment at the onset of the event was 217 days. The subject's antidiabetic regimen also included metformin 850 mg po BID since 2001. Patient presented to hospital with hypertensive emergency and died of hemorrhagic stroke.

MKC-TI-030/031/0237: A 55-yo (year old) Caucasian female in the U.S. with type 2 DM received TI 30 U prandially TID. The subject's antidiabetic regimen also included metformin 1000 mg BID since 2001, glyburide 10 mg BID since 1990, and rosiglitazone 8 mg QD since 2005. The duration of treatment at the onset of the event was 67 days. The dose had been increased 45 days prior to the event. The patient experienced sudden cardiac arrest while on a bus and could not be resuscitated. Patient had known coronary artery disease. No autopsy was performed. Cause of death was listed as cardiac arrest.

MKC-TI-030/162/0611: A 58-yo Caucasian male in the U.S. with type 2 DM received TI 60 U TID prandially. Type of basal insulin not reported. The duration of treatment at the onset of the event was 178 days. The patient experience left sided hemiparesis and died in the hospital after progressive deterioration. According to the narrative the death certificate listed the cause of death as respiratory failure, CVA, congestive heart failure and diabetes mellitus type 2.

MKC-TI-102/523/2158: A 72-yo Caucasian male in Russia with type 2 DM and known coronary artery disease with history of previous MI received TI 60 U TID prandially and insulin glargine 35 IU subcutaneously daily. The duration of treatment at the onset of event was 34 days. The patient complained of chest pain and died at home. An autopsy reported the cause of death as coronary heart disease.

MKC-TI-102/488/2219: A 64-yo Caucasian male in Brazil with type 2 DM received TI 90 U prandially TID and insulin glargine 62 IU subcutaneously (sc). The duration of treatment at the onset of the event was 163 days. The patient was known to have arterial hypertension, surgery for peripheral arterial insufficiency, and dyslipidemia, but no history of previous MI. The patient experienced epigastric pain at home for 2 days and then collapsed. He was pronounced dead upon arrival to the hospital. Autopsy showed the cause of death to be acute MI.

MKC-TI-102/508/2981: A 50-yo Caucasian male in Russia with type 2 DM received TI 90 U prandially TID and insulin glargine 48 IU subcutaneous (sc) QD. The duration of treatment at the onset of the event was 306 days. The subject's antidiabetic regimen also included metformin 850 mg BID po since 2003. Patient admitted with fever and died of overwhelming sepsis likely from a gangrenous toe. No hypoglycemia occurred.

#### Uncontrolled, Long term safety study, on TI

MKC-TI-010/409/1854: A 75-yo Caucasian male in the Czech Republic with type 2 DM. TI 30 U was administered via inhalation QID. The duration of TI Inhalation Powder treatment at the onset of event was 756 days. The subject's antidiabetic regimen also included insulin glargine 24 IU sc QD and metformin 1.5 g TID. Illnesses present at the onset of the events and other relevant medical history included dyslipidemia, coronary artery disease with angina pectoris New York Heart Association Class I to II, hypertension, hyperuricemia, and chronic LBBB. The patient experienced acute dyspnea, diagnosed with acute MI at hospital; complicated hospital course. Patient died 12 days later of cardiac failure.

#### Deaths in the 120 day safety update

MKC-TI-102/067/2909: A 62-yo Caucasian male in Argentina with T2DM. TI 90 U at breakfast, 30 U at lunch and 90 U at dinner was administered between 07 Aug 2007 and 21 Dec 2007 when the subject was discontinued due an abnormal chest CT (this event was reported originally to the NDA as a discontinuation due to an adverse event) and was eventually diagnosed with biopsy proven neuroendocrine tumor with lung involvement. The subject died in [REDACTED] due to the neuroendocrine tumor.

(Note this patient is also discussed in section 7.6.1 Neoplasms) MKC-TI-010/407/3316: A 67-yo Caucasian male in the Czech Republic with T2DM. He received TI Inhalation Powder 45 U TID via inhalation starting on 22 Mar 2005 and was administered 30 U TID from 01 Nov 2005 to 13 Dec 2006. The subject's antidiabetic regimen also included glibenclamide and metformin. On 07 Dec 2006 while undergoing diagnostic tests for an anemia workup, he underwent a CT scan of the lungs, which showed two areas measuring 12 × 19 × 20 mm and 19 × 14 × 20 mm in segment S2 in the right side of the lungs which was eventually (Feb 2007) confirmed to be bronchogenic carcinoma non-small-cell (T4N2M0). The patient's medical history was notable for tobacco use (40 cigarettes per day for 20 years) until 1985.

MKC-TI-010/009/0246: 73-yo Caucasian male in the United States with T2DM treated with TI 90 U TID prandially starting 04 Aug 2004. The patient also used glargine since 20 Dec 2005. Patient was diagnosed with metastatic prostate cancer to the bone on 06 Jan 2006. The patient had a history of elevated PSA since 1993. The last dose of study drug was on 06 Jun 2006. The patient died on [REDACTED] (b) (6). Cause of death was metastatic prostate cancer to the bone.

MKC-TI-010/403/2782: A 60-yo Caucasian male in the Czech Republic with T2DM treated with TI 90 U TID from 20 Apr 2005 to 19 Apr 2006. The patient also took metformin. The patient began having nonspecific symptoms of dyspepsia and weight loss 10 Mar 2006 and was diagnosed with pancreatic CA on 27 Apr 2006 which resulted in discontinuation of TI. The patient died on [REDACTED] (b) (6) from metastatic adenocarcinoma of the pancreas.

### Discussion of deaths

There was no apparent imbalance in the number of patients who died among the pooled phase 2/3 safety population, although deaths were few.

Of all the patients exposed to TI who died during the clinical development program the majority were type 2 diabetics. There was one death of a type 1 diabetic who was a 59-yo male. More than half died from cardiovascular causes. Four of the five who died in the comparator groups died from cardiovascular events. Most diabetic patients die of cardiovascular disease, and the percentage of deaths which were due to cardiovascular disease during the study of this product is consistent with the usual incidence of cardiovascular death among diabetics. There do not appear to be any deaths that can be directly attributed to study treatment (such as death from diabetic ketoacidosis or hypoglycemia).

### 7.3.2 Non-fatal Serious Adverse Events

A non-fatal serious adverse event (SAE) was defined as any AE with an outcome that met any of the following criteria:

- was life-threatening (placed the trial subject at immediate risk of death)
- required inpatient hospitalization or prolongation of existing hospitalization

- resulted in a persistent or significant disability/incapacity
- was a congenital anomaly/birth defect
- was an important medical event, defined as those events that may not have been immediately life-threatening or resulted in death or hospitalization but may have been considered serious when based upon appropriate medical judgment, may have jeopardized the trial subject, and may have required medical or surgical intervention to prevent one of the outcomes listed previously

The clinical reviewer reviewed the narratives for all SAEs and presents narratives here in this review for the following:

- a. Unusual events or events of interest (e.g., pharyngeal abscess, selected pulmonary events)
- b. Events that are potentially associated with hypoglycemia (e.g. falls, seizures, accidents) but are not reported as hypoglycemic events
- c. Events that could be immune-related
- d. Diabetic ketoacidosis (DKA)

#### Non-fatal Serious Adverse Events (SAEs) in T2DM

Table 7.12 shows the raw incidence and the exposure-adjusted incidence rate of SAEs that occurred in any system organ class and preferred term in the T2DM pooled safety population. The incidence of SAEs in the respiratory tract in the TI group was higher than in the comparator group but was low overall. Pulmonary serious adverse events will be discussed separately in Dr. Karimi-Shah's review. Among Type 2 patients, no pattern emerged of a single type of serious adverse event, or grouping of serious adverse events, that occurred with significantly greater frequency among TI patients than among comparator patients.

**Table 7.12 - Incidence of Non-Fatal SAEs That Occurred in Any System Organ Class, Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 1795) (SYE = 1274)		Comparator (n = 1345) (SYE = 1369)		TP (n = 114) (SYE = 25)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
	Any SAE	114 (6.4)	[8.9]	106 (7.9)	[7.7]	2 (1.8)
Cardiac disorders	23 (1.3)	[1.8]	22 (1.6)	[1.6]	0	0
Coronary artery disease	5 (0.3)	[0.4]	3 (0.2)	[0.2]	0	0
Atrial fibrillation	3 (0.2)	[0.2]	3 (0.2)	[0.2]	0	0
Myocardial infarction	3 (0.2)	[0.2]	3 (0.2)	[0.2]	0	0
Coronary artery atherosclerosis	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Coronary artery occlusion	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Acute coronary syndrome	1 (0.1)	[0.1]	2 (0.1)	[0.1]	0	0
Angina unstable	1 (0.1)	[0.1]	2 (0.1)	[0.1]	0	0
Bundle branch block right	1 (0.1)	[0.1]	0	0	0	0
Cardiac failure	1 (0.1)	[0.1]	0	0	0	0
Cardiac failure chronic	1 (0.1)	[0.1]	0	0	0	0
Coronary artery stenosis	1 (0.1)	[0.1]	1 (0.1)	[0.1]	0	0
Ischemic cardiomyopathy	1 (0.1)	[0.1]	0	0	0	0
Myocardial ischemia	1 (0.1)	[0.1]	1 (0.1)	[0.1]	0	0
Pericarditis	1 (0.1)	[0.1]	0	0	0	0
Ventricular tachycardia	1 (0.1)	[0.1]	0	0	0	0
Angina pectoris	0	0	2 (0.1)	[0.1]	0	0
Atrial flutter	0	0	1 (0.1)	[0.1]	0	0
Bundle branch block left	0	0	1 (0.1)	[0.1]	0	0
Coronary artery insufficiency	0	0	2 (0.1)	[0.1]	0	0
Hypertensive heart disease	0	0	1 (0.1)	[0.1]	0	0
Supraventricular tachycardia	0	0	2 (0.1)	[0.1]	0	0
Infections and infestations	25 (1.4)	[2.0]	19 (1.4)	[1.4]	0	0
Diabetic gangrene	2 (0.1)	[0.2]	0	0	0	0
Furuncle	2 (0.1)	[0.2]	0	0	0	0
Pneumonia	2 (0.1)	[0.2]	4 (0.3)	[0.3]	0	0
Urinary tract infection	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Wound infection	2 (0.1)	[0.2]	0	0	0	0
Carbuncle	1 (0.1)	[0.1]	0	0	0	0
Cellulitis	1 (0.1)	[0.1]	3 (0.2)	[0.2]	0	0
Cellulitis streptococcal	1 (0.1)	[0.1]	0	0	0	0
Diabetic foot infection	1 (0.1)	[0.1]	0	0	0	0
Diverticulitis	1 (0.1)	[0.1]	0	0	0	0
Gastroenteritis viral	1 (0.1)	[0.1]	0	0	0	0
Hepatitis viral	1 (0.1)	[0.1]	0	0	0	0
Injection site cellulitis	1 (0.1)	[0.1]	0	0	0	0
Localized infection	1 (0.1)	[0.1]	0	0	0	0
Osteomyelitis	1 (0.1)	[0.1]	2 (0.1)	[0.1]	0	0
Otitis media acute	1 (0.1)	[0.1]	0	0	0	0
Parotitis	1 (0.1)	[0.1]	0	0	0	0
Perirectal abscess	1 (0.1)	[0.1]	0	0	0	0
Pulmonary tuberculosis	1 (0.1)	[0.1]	0	0	0	0

**Table 7.12 - Incidence of Non-Fatal SAEs That Occurred in Any System Organ Class, Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 1795) (SYE = 1274)		Comparator (n = 1345) (SYE = 1369)		TP (n = 114) (SYE = 25)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
	Pyelonephritis chronic	1 (0.1)	[0.1]	0	0	0
Rectal abscess	1 (0.1)	[0.1]	0	0	0	0
Upper respiratory tract infection	1 (0.1)	[0.1]	0	0	0	0
Appendicitis	0	0	4 (0.3)	[0.3]	0	0
Arthritis bacterial	0	0	1 (0.1)	[0.1]	0	0
Bacterial sepsis	0	0	1 (0.1)	[0.1]	0	0
Bronchitis	0	0	1 (0.1)	[0.1]	0	0
Gangrene	0	0	1 (0.1)	[0.1]	0	0
Infection	0	0	1 (0.1)	[0.1]	0	0
Postoperative infection	0	0	1 (0.1)	[0.1]	0	0
Pyelonephritis	0	0	2 (0.1)	[0.1]	0	0
Sepsis	0	0	1 (0.1)	[0.1]	0	0
Staphylococcal scalded skin syndrome	0	0	1 (0.1)	[0.1]	0	0
Subcutaneous abscess	0	0	1 (0.1)	[0.1]	0	0
Nervous system disorders	13 (0.7)	[1.0]	14 (1.0)	[1.0]	0	0
Loss of consciousness	4 (0.2)	[0.3]	3 (0.2)	[0.2]	0	0
Dizziness	2 (0.1)	[0.2]	0	0	0	0
Transient ischemic attack	2 (0.1)	[0.2]	0	0	0	0
Ataxia	1 (0.1)	[0.1]	0	0	0	0
Carotid artery stenosis	1 (0.1)	[0.1]	0	0	0	0
Encephalopathy	1 (0.1)	[0.1]	0	0	0	0
Third nerve paralysis	1 (0.1)	[0.1]	0	0	0	0
Multiple sclerosis	1 (0.1)	[0.1]	0	0	0	0
Cerebrovascular accident	0	0	5 (0.4)	[0.4]	0	0
Hypoglycemic coma	0	0	1 (0.1)	[0.1]	0	0
Ischemic stroke	0	0	1 (0.1)	[0.1]	0	0
Neuritis	0	0	1 (0.1)	[0.1]	0	0
Radiculitis lumbosacral	0	0	1 (0.1)	[0.1]	0	0
Sciatica	0	0	1 (0.1)	[0.1]	0	0
Syncope	0	0	1 (0.1)	[0.1]	0	0
Metabolism and nutrition disorders	12 (0.7)	[0.9]	19 (1.4)	[1.4]	0	0
Hypoglycemia	7 (0.4)	[0.5]	10 (0.7)	[0.7]	0	0
Hyperglycemia	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Dehydration	1 (0.1)	[0.1]	0	0	0	0
Diabetes mellitus inadequate control	1 (0.1)	[0.1]	4 (0.3)	[0.3]	0	0
Hypoglycemic seizure	1 (0.1)	[0.1]	0	0	0	0
Ketoacidosis	1 (0.1)	[0.1]	1 (0.1)	[0.1]	0	0
Diabetic complication	0	0	1 (0.1)	[0.1]	0	0
Diabetic ketoacidosis	0	0	1 (0.1)	[0.1]	0	0
Obesity	0	0	1 (0.1)	[0.1]	0	0
Gastrointestinal disorders	11 (0.6)	[0.9]	8 (0.6)	[0.6]	1 (0.9)	[4.0]
Pancreatitis acute	3 (0.2)	[0.2]	0	0	0	0
Abdominal hernia	1 (0.1)	[0.1]	0	0	0	0
Anal fistula	1 (0.1)	[0.1]	0	0	0	0

**Table 7.12 - Incidence of Non-Fatal SAEs That Occurred in Any System Organ Class, Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 1795) (SYE = 1274)		Comparator (n = 1345) (SYE = 1369)		TP (n = 114) (SYE = 25)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
	Colitis ulcerative	1 (0.1)	[0.1]	0	0	0
Constipation	1 (0.1)	[0.1]	0	0	0	0
Erosive esophagitis	1 (0.1)	[0.1]	0	0	0	0
Gastritis	1 (0.1)	[0.1]	1 (0.1)	[0.1]	0	0
Gastritis erosive	1 (0.1)	[0.1]	0	0	0	0
Gastrointestinal hemorrhage	1 (0.1)	[0.1]	0	0	0	0
Intestinal obstruction	1 (0.1)	[0.1]	0	0	0	0
Esophageal ulcer	1 (0.1)	[0.1]	0	0	0	0
Pancreatic cyst	1 (0.1)	[0.1]	0	0	0	0
Pancreatitis	1 (0.1)	[0.1]	0	0	0	0
Retroperitoneal hemorrhage	1 (0.1)	[0.1]	0	0	0	0
Benign colonic polyp	0	0	1 (0.1)	[0.1]	0	0
Gastric ulcer	0	0	1 (0.1)	[0.1]	0	0
Gastroduodenitis	0	0	1 (0.1)	[0.1]	0	0
Inguinal hernia, obstructive	0	0	0	0	1 (0.9)	[4.0]
Pancreatic necrosis	0	0	1 (0.1)	[0.1]	0	0
Pancreatitis chronic	0	0	1 (0.1)	[0.1]	0	0
Peritonitis	0	0	1 (0.1)	[0.1]	0	0
Small intestinal obstruction	0	0	1 (0.1)	[0.1]	0	0
Umbilical hernia	0	0	1 (0.1)	[0.1]	0	0
Musculoskeletal and connective tissue disorders	12 (0.7)	[0.9]	9 (0.7)	[0.7]	1 (0.9)	[4.0]
Osteoarthritis	3 (0.2)	[0.2]	1 (0.1)	[0.1]	0	0
Intervertebral disc degeneration	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Intervertebral disc protrusion	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Arthralgia	1 (0.1)	[0.1]	0	0	0	0
Back pain	1 (0.1)	[0.1]	2 (0.1)	[0.1]	0	0
Intervertebral disc disorder	1 (0.1)	[0.1]	0	0	0	0
Localized osteoarthritis	1 (0.1)	[0.1]	1 (0.1)	[0.1]	0	0
Musculoskeletal chest pain	1 (0.1)	[0.1]	0	0	0	0
Rheumatoid arthritis	1 (0.1)	[0.1]	0	0	0	0
Spinal osteoarthritis	1 (0.1)	[0.1]	1 (0.1)	[0.1]	0	0
Tenosynovitis	1 (0.1)	[0.1]	0	0	0	0
Arthritis	0	0	1 (0.1)	[0.1]	0	0
Bone pain	0	0	1 (0.1)	[0.1]	0	0
Osteochondrosis	0	0	1 (0.1)	[0.1]	0	0
Polyarthritits	0	0	0	0	1 (0.9)	[4.0]
Spondylosis	0	0	1 (0.1)	[0.1]	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (0.6)	[0.9]	9 (0.7)	[0.7]	0	0
Breast cancer	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Basal cell carcinoma	1 (0.1)	[0.1]	0	0	0	0
Benign salivary gland neoplasm	1 (0.1)	[0.1]	0	0	0	0
Breast cancer stage III	1 (0.1)	[0.1]	0	0	0	0
Gastrointestinal cancer metastatic	1 (0.1)	[0.1]	0	0	0	0

**Table 7.12 - Incidence of Non-Fatal SAEs That Occurred in Any System Organ Class, Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 1795) (SYE = 1274)		Comparator (n = 1345) (SYE = 1369)		TP (n = 114) (SYE = 25)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
	Ovarian epithelial cancer	1 (0.1)	[0.1]	0	0	0
Pituitary tumor benign	1 (0.1)	[0.1]	0	0	0	0
Prostate cancer	1 (0.1)	[0.1]	1 (0.1)	[0.1]	0	0
Prostate cancer metastatic	1 (0.1)	[0.1]	0	0	0	0
Uterine leiomyoma	1 (0.1)	[0.1]	2 (0.1)	[0.1]	0	0
Adrenal adenoma	0	0	1 (0.1)	[0.1]	0	0
Benign pancreatic neoplasm	0	0	1 (0.1)	[0.1]	0	0
Cervix carcinoma	0	0	1 (0.1)	[0.1]	0	0
Colon cancer	0	0	1 (0.1)	[0.1]	0	0
Pancreatic carcinoma	0	0	1 (0.1)	[0.1]	0	0
Rectal cancer	0	0	1 (0.1)	[0.1]	0	0
Hepatobiliary disorders	5 (0.3)	[0.4]	5 (0.4)	[0.4]	0	0
Cholecystitis	3 (0.2)	[0.2]	3 (0.2)	[0.2]	0	0
Cholecystitis acute	1 (0.1)	[0.1]	0	0	0	0
Hepatitis toxic	1 (0.1)	[0.1]	0	0	0	0
Cholelithiasis	0	0	3 (0.2)	[0.2]	0	0
Gallbladder disorder	0	0	1 (0.1)	[0.1]	0	0
Injury, poisoning and procedural complications	8 (0.4)	[0.6]	10 (0.7)	[0.7]	0	0
Facial bones fracture	2 (0.1)	[0.2]	0	0	0	0
Electric shock	1 (0.1)	[0.1]	0	0	0	0
Fall	1 (0.1)	[0.1]	5 (0.4)	[0.4]	0	0
Hand fracture	1 (0.1)	[0.1]	0	0	0	0
Injury	1 (0.1)	[0.1]	0	0	0	0
Limb injury	1 (0.1)	[0.1]	0	0	0	0
Meniscus lesion	1 (0.1)	[0.1]	0	0	0	0
Rib fracture	1 (0.1)	[0.1]	1 (0.1)	[0.1]	0	0
Road traffic accident	1 (0.1)	[0.1]	2 (0.1)	[0.1]	0	0
Ankle fracture	0	0	1 (0.1)	[0.1]	0	0
Brain contusion	0	0	1 (0.1)	[0.1]	0	0
Cerebral hemorrhage traumatic	0	0	1 (0.1)	[0.1]	0	0
Hip fracture	0	0	1 (0.1)	[0.1]	0	0
Lower limb fracture	0	0	1 (0.1)	[0.1]	0	0
Multiple fractures	0	0	1 (0.1)	[0.1]	0	0
Procedural complication	0	0	1 (0.1)	[0.1]	0	0
Spinal fracture	0	0	1 (0.1)	[0.1]	0	0
Upper limb fracture	0	0	1 (0.1)	[0.1]	0	0
Respiratory, thoracic and mediastinal disorders	5 (0.3)	[0.4]	2 (0.1)	[0.1]	0	0
Asthma	1 (0.1)	[0.1]	0	0	0	0
Atelectasis	1 (0.1)	[0.1]	0	0	0	0
Dyspnea	1 (0.1)	[0.1]	0	0	0	0
Orthopnea	1 (0.1)	[0.1]	0	0	0	0
Vocal cord polyp	1 (0.1)	[0.1]	0	0	0	0
Hydrothorax	0	0	1 (0.1)	[0.1]	0	0
Pulmonary edema	0	0	1 (0.1)	[0.1]	0	0

**Table 7.12 - Incidence of Non-Fatal SAEs That Occurred in Any System Organ Class, Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 1795) (SYE = 1274)		Comparator (n = 1345) (SYE = 1369)		TP (n = 114) (SYE = 25)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
	Vascular disorders	6 (0.3)	[0.5]	3 (0.2)	[0.2]	0
Aortic stenosis	2 (0.1)	[0.2]	0	0	0	0
Deep vein thrombosis	1 (0.1)	[0.1]	0	0	0	0
Hypertension	1 (0.1)	[0.1]	0	0	0	0
Hypertensive crisis	1 (0.1)	[0.1]	0	0	0	0
Hypotension	1 (0.1)	[0.1]	0	0	0	0
Atherosclerosis obliterans	0	0	1 (0.1)	[0.1]	0	0
Essential hypertension	0	0	1 (0.1)	[0.1]	0	0
Thrombosis	0	0	1 (0.1)	[0.1]	0	0
Eye disorders	5 (0.3)	[0.4]	2 (0.1)	[0.1]	0	0
Retinal detachment	3 (0.2)	[0.2]	0	0	0	0
Retinal disorder	1 (0.1)	[0.1]	0	0	0	0
Vitreous hemorrhage	1 (0.1)	[0.1]	0	0	0	0
Diabetic retinopathy	0	0	1 (0.1)	[0.1]	0	0
Eye hemorrhage	0	0	1 (0.1)	[0.1]	0	0
Glaucoma	0	0	1 (0.1)	[0.1]	0	0
Optic atrophy	0	0	1 (0.1)	[0.1]	0	0
Optic neuropathy	0	0	1 (0.1)	[0.1]	0	0
General disorders and administration site conditions	5 (0.3)	[0.4]	3 (0.2)	[0.2]	0	0
Chest pain	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Generalized edema	2 (0.1)	[0.2]	0	0	0	0
Edema peripheral	1 (0.1)	[0.1]	0	0	0	0
Non-cardiac chest pain	0	0	1 (0.1)	[0.1]	0	0
Pyrexia	0	0	1 (0.1)	[0.1]	0	0
Blood and lymphatic system disorders	2 (0.1)	[0.2]	2 (0.1)	[0.1]	0	0
Lymphadenopathy	1 (0.0)	[0.1]	0	0	0	0
Thrombocythemia	1 (0.0)	[0.1]	0	0	0	0
Anemia	0	0	1 (0.1)	[0.1]	0	0
Thrombocytopenia	0	0	1 (0.1)	[0.1]	0	0
Renal and urinary disorders	4 (0.2)	[0.3]	6 (0.4)	[0.4]	0	0
Hydronephrosis	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Renal failure acute	2 (0.1)	[0.2]	1 (0.1)	[0.1]	0	0
Calculus bladder	1 (0.1)	[0.1]	0	0	0	0
Nephrolithiasis	1 (0.1)	[0.1]	3 (0.2)	[0.2]	0	0
Calculus ureteric	0	0	1 (0.1)	[0.1]	0	0
Renal colic	0	0	1 (0.1)	[0.1]	0	0
Renal failure	0	0	1 (0.1)	[0.1]	0	0
Urethral stricture	0	0	1 (0.1)	[0.1]	0	0
Reproductive system and breast disorders	2 (0.1)	[0.2]	2 (0.1)	[0.1]	0	0
Benign prostatic hyperplasia	2 (0.1)	[0.2]	0	0	0	0
Adenomyosis	0	0	1 (0.1)	[0.0]	0	0
Uterine prolapse	0	0	1 (0.1)	[0.0]	0	0
Psychiatric disorders	2 (0.1)	[0.2]	0	0	0	0
Depression	1 (0.1)	[0.1]	0	0	0	0

**Table 7.12 - Incidence of Non-Fatal SAEs That Occurred in Any System Organ Class, Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 1795) (SYE = 1274)		Comparator (n = 1345) (SYE = 1369)		TP (n = 114) (SYE = 25)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
	Psychotic disorder	1 (0.1)	[0.1]	0	0	0
Skin and subcutaneous tissue disorders	2 (0.1)	[0.2]	2 (0.1)	[0.1]	0	0
Angioneurotic edema	1 (0.1)	[0.1]	0	0	0	0
Hyperhidrosis	1 (0.1)	[0.1]	0	0	0	0
Skin ulcer	0	0	1 (0.1)	[0.1]	0	0
Urticaria	0	0	1 (0.1)	[0.1]	0	0
Immune system disorders	1 (0.1)	[0.1]	0	0	0	0
Autoimmune disorder	1 (0.1)	[0.1]	0	0	0	0
Investigations	1 (0.1)	[0.1]	0	[0.0]	0	0
International normalized ratio increased	1 (0.1)	[0.1]	0	0	0	0
Ear and labyrinth disorders	0	0	1 (0.1)	[0.1]	0	0
Meniere's disease	0	0	1 (0.1)	[0.1]	0	0
Endocrine disorders	0	0	1 (0.1)	[0.1]	0	0
Hypothyroidism	0	0	1 (0.1)	[0.1]	0	0

AE = adverse event; SYE = subject-years exposure; TEAE = treatment-emergent AE; TP = Technosphere<sup>®</sup> Inhalation Powder.

Adverse events were coded using MedDRA (Version 7.1).

Each SOC includes the total number of subjects by SOC.

Each subject may be counted more than once in different preferred terms for each AE reported..

a: All serious TEAEs of loss of consciousness were associated with severe hypoglycemia.

Data Source: Table G.2.9.6.1.1 and G.2.9.6.1.3

### Selected SAE narratives for the pooled T2DM safety population

**Polyarthritis** MKC-TI-005/101/4920: A 67-year-old (yo) Caucasian type 2 diabetic female in Germany was hospitalized for polyarthritis 58 days after starting TI. The pain was located in the back, hands, shoulders, and knees and lasted for several days. There was no action taken with study treatment and the subject completed the trial.

**Pericarditis** MKC-TI-005 302/2981: A 56-yo Caucasian type 2 diabetic male in Bulgaria received TI and glargine. He was hospitalized for pericarditis 90 days after initiation of TI. No action was taken with study drug and the subject completed the trial.

**Multiple sclerosis** MKC-TI-030 048/1962: A 55-yo Caucasian male in the United States received TI and oral diabetic agents for the treatment of type 2 diabetes mellitus. TI 60 U TID was administered from 28 Jul 2006 to 05 Apr 2008. On [REDACTED]<sup>(b) (6)</sup>, the subject was hospitalized due to complaints of multiple falls and left lower extremity weakness with difficulty getting out of bed. MRI findings were consistent with demyelinating plaques. He was diagnosed

with new onset multiple sclerosis (MS), and was started on intravenous (IV) methylprednisolone (Solu-Medrol) with improvement in strength. The subject was withdrawn from the study.

**Pituitary tumor benign** (MKC-TI-030 095/0918: A 58-yo Caucasian male in the U.S. received TI 30 U BID and 15 U QD from [REDACTED] (b) (6) to [REDACTED] (b) (6). Other medications included pioglitazone and metformin. Duration of treatment at the onset of the event was 137 days. The patient was hospitalized with a severe headache on [REDACTED] (b) (6) and was diagnosed with a pituitary macroadenoma with apoplexy which was surgically removed. The subject recovered with sequelae on [REDACTED] (b) (6). The subject continued in the trial.

**Essential thrombocythemia** MKC-TI-030 508/1183: A 47-yo Caucasian female in Russia received TI 30 U TID and metformin 850 PO BID both started on 29 May 2006. Isophane insulin 18 to 20 IU subcutaneously BID was started on an unknown date in 2007. The duration of treatment at the onset of the event was 311 days. On [REDACTED] (b) (6), the subject was hospitalized for examination and treatment of unspecified diabetic complications. A high platelet count was noted. Bone marrow biopsy confirmed essential thrombocythemia. The patient was discontinued from the trial due to the development of myeloproliferative disorder.

**Pharyngeal abscess** MKC-TI-030 539/1292: A 58-yo Caucasian female in Russia was randomized to the TI group. She received the TP alone for training on 02 Jun 2006. A few hours after administration of TP she became ill with symptoms of throat pain and edema and was diagnosed with pharyngeal abscess. She recovered but withdrew from the study due to the SAE.

**Rheumatoid arthritis** MKC-TI-030 853/3356: A 69-year-old Caucasian female in the Ukraine received TI 30 U inhaled at breakfast and 45 U inhaled at lunch and dinner from 04 Oct 2006 to 02 Oct 2007; intermediate acting insulin was administered 26 IU subcutaneously (sc) at breakfast and 22 IU sc at dinner from 04 May 2006 onward, and metformin was administered 850 mg po BID was administered from 25 Oct 2006 onward. The duration of treatment at the onset of the event was 365 days. The subject was hospitalized for signs and symptoms consistent with rheumatoid arthritis. The subject withdrew from the study.

**Diabetic ketoacidosis** MKC-TI-030 907/2979: A 58-yo Caucasian female in Canada received TI 90 U TID from 12 Sep 2006 to 11 Feb 2008; insulin detemir (Levemir) 22 IU QAM subcutaneously (sc) and 42 IU sc QHS was administered from 28 Sep 2007 to 11 Feb 2008, and Metformin 500 mg po BID was administered from 2000 to 11 Feb 2008. The duration of treatment at the onset of the first event was 339 days. The subject experienced DKA related to a URI and noncompliance related to depression. She permanently discontinued TI and withdrew from the study.

**Reviewer's comment: DKA is very unusual in T2DM raising the question of whether this was truly a case of DKA or perhaps whether this patient actually has T1DM.**

**Facial fracture and possible seizure** MKC-TI-102 188/2450: A 60-yo Caucasian female in the United States received TI 15 U prandially TID from [REDACTED] (b) (6) onward. Insulin glargine 30 IU QD was administered subcutaneously (sc) from 30 Apr 2007 onward. Pioglitazone (Actos) 22.5

mg po QD was administered from 23 Jul 2007 onward. The duration of treatment at the onset of the event was 172 days. On [REDACTED] (b) (6), the subject experienced a fall at home in her living room, where she hit a window ledge with her left eye bone and lost consciousness. She was subsequently brought to the hospital. The subject stated she did not know why she fell; she thought she had a seizure but was unsure. Discharge diagnoses included syncope, status post fall, with probable seizure episode versus hypoglycemic episode. No blood glucose levels were reported. The event was not coded as hypoglycemia. The subject remained in the trial.

**Acute hepatitis (viral)** MKC-TI-102 247/1687: A 44-yo Caucasian male in the United States received TI 75 U TID and insulin glargine 50 IU QHS subcutaneously (sc) from 13 Dec 2006 onward. The duration of treatment at the onset of the event was 121 days. On 12 Apr 2007, the subject experienced acute hepatitis. He presented to the emergency room on [REDACTED] (b) (6) with nausea, vomiting, runny nose, diffuse myalgia, and arthralgia. He had a fever of 100.2. Alanine transaminase (ALT) was 1415, aspartate transaminase (AST) was 850, and alkaline phosphatase was 517. An Epstein-Barr virus serology was positive for viral capsid AB IgG and viral capsid AB IgM suggesting a recent infection. Acute viral hepatitis due to Epstein-Barr virus infection was the final diagnosis. On 23 Apr 2007, he followed up with his attending physician. Total protein was 7.8, albumin 4.0, A/G ratio 1.1, unconjugated bilirubin 1.0, total bilirubin 1.0, AST 59, ALT 325, and alkaline phosphatase 448. A hepatitis panel was negative for A, B, and C viruses.

**Toxic hepatitis** MKC-TI-030-3363: A 59-yo Caucasian male in Poland received TI and Lantus since 25 Sep 2006. On 14 Feb 2008, at day 506 of treatment the subject had an adverse event reported by the Investigator as toxic hepatitis due to intake of Chinese herbs. A medical history revealed that the subject had been taking several doses of the herbal preparation for weight loss. His GGT was 2288 IU/L (normal range 10-249 IU/L). He was subsequently hospitalized on [REDACTED] (b) (6) due to the event, however details of hospitalization were not provided. Additional liver enzymes confirming the diagnosis of toxic hepatitis were not reported by the Investigator. No action was taken with the study medications in response to the event. The event resolved on [REDACTED] (b) (6) and the subject was discharged from the hospital on the same date.

**Acute renal failure** MKC-TI-102 289/3066: A 69-yo Caucasian female in the United States received TI 15 U at breakfast, 45 U at lunch, and 90 U at dinner and Insulin glargine 22 IU at bedtime from [REDACTED] (b) (6) onward. The duration of treatment at the onset of the event was 254 days. On [REDACTED] (b) (6), the subject experienced shortness of breath, acute renal failure supratherapeutic INR, and urinary tract infection and was hospitalized. Creatinine was 4.1 mg/dL. The renal failure was attributed to lisinopril possibly in the setting of a gram-negative urinary tract infection. The subject did not discontinue from the trial.

**Autoimmune disorder** MKC-TI-102 507/2532: A 50-yo Caucasian female in the Ukraine received TI U TID from [REDACTED] (b) (6) onward. Insulin glargine (Lantus) 35 IU subcutaneously QD in the evening was administered from 22 Aug 2007 onward. The duration of treatment at the onset of the event was 155 days. On [REDACTED] (b) (6), the subject was diagnosed with an unspecified autoimmune disorder during a planned hospitalization that began on [REDACTED] (b) (6) due to deterioration in vertebral osteoarthritis since May 2007. The vertebral osteoarthritis began in

1980 with pain in the lumbar spine followed by intense headache, vertigo, with a history of multiple hospitalizations for this condition. On 30 Nov 2007, diagnostic results included a higher titer of anti-DNA antibodies and isolated lupus erythematosus (LE) cells. No other clinical manifestations of systemic lupus erythematosus (SLE) were found. The subject was hospitalized again on [REDACTED] (b) (6) for joint complaints. On 20 Mar 2008, results of an immunoassay included circulating immune complex 148 units, C-reactive protein 3.01 mg/dL, antibodies to cardiolipin IgG 32.5 GPL, and antibodies to cardiolipin IgM 21.2 MPL, LE cells negative, antibodies to DNA and rheumatoid factor both within normal limits. On 09 Jul 2008, during a follow-up, the subject's general condition was satisfactory, but pain and joint stiffness remained. The subject's medical history is notable for an erythematous rash on the skin of abdomen, chest, and neck, as well as swelling of the joints that occurred in 2004. The subject did not discontinue from the trial.

**Deep vein thrombosis** MKC-TI-103 484/1823: A 41-yo Black female in Brazil received TI 30 U TID since [REDACTED] (b) (6), and metformin 850 mg po TID since 01 Oct 2006. The duration of treatment for TI Inhalation Powder at the onset of the event was 87 days. On [REDACTED] (b) (6) the subject was hospitalized for a deep vein thrombosis. No etiology was identified and there is not enough information in the narrative to identify a cause. The subject did not discontinue due to this SAE.

**Fall/Ankle fracture** MKC-TI-103 852/2536: A 54-yo Caucasian female subject in Ukraine received TI TID (90 U with breakfast, 75 U with lunch and 60 U with supper) from 04 Jul 2007 to 08 Nov 2007 and 90 U at breakfast and lunch and 75 U at supper from 08 Nov 2007 to 10 Jan 2008, and metformin po BID (850 mg and 1850 mg) starting 04 Jul 2007. The duration of treatment at the onset of the first event was 141 days. On 21 Nov 2007, the subject fell down damaged stairs at home while on the way to work. There was no blood glucose measurement at the time and no loss of consciousness.

**Angioneurotic edema** MKC-TI-014 514/984: A female subject with history of allergy to insulin and multiple prior episodes of angioedema upon ingestion of apples, nuts, and pears. The adverse event occurred with the first dose of TI and the subject was discontinued from the study.

**Erosive esophagitis** MKC-TI-030 001/0600: A 57 yo Caucasian male in the U.S. received TI for 39 days before experiencing nausea and vomiting. He was hospitalized and found to have moderate erosive esophagitis on endoscopy. The subject recovered and resumed TI treatment as the investigator did not think the event was related to TI use, although an alternate causality was not found.

**Esophageal ulcer** MKC-TI-030 162/0465: A 55 yo Caucasian male in the U.S. while several months into TI treatment experienced recurrent acute pancreatitis with a prolonged medical course complicated by recurrent hospital admissions for surgical complications, infections and pancreatic cysts. The subject was found to have small esophageal ulcers on one of the later admissions that appears to be due to the complications related to pancreatitis/recurrent emesis and abdominal pain. The ulcers are most likely not directly related to TI inhalation.

Significant SAE narratives for trial 010 – uncontrolled safety trial not included in pooled safety data.

**Meningioma** MKC-TI-010 309/4411: A 61-yo Caucasian type 2 diabetic female in Bulgaria diagnosed with benign meningioma. The duration of treatment at the onset of the event was 729 days.

**Renal carcinoma** MKC-TI-010 403/2595: A 63-yo Caucasian type 2 diabetic male subject in the Czech Republic diagnosed with carcinoma in situ of the left kidney. The duration of treatment at the onset of the event was 548 days. The subject's antidiabetic regimen also included metformin and glimepiride.

**Syncope** MKC-TI-010 007/0215: A 52-yo Hispanic type 2 diabetic male in the United States received TI 60 U TID from 14 Jul 2004 onward. The duration of treatment at the onset of the event was 1193 days. The subject's antidiabetic regimen also included insulin glargine 45 IU subcutaneously (sc) QD, metformin 1000 mg po BID, and rosiglitazone 8 mg po QD. On 19 Oct 2007, the subject was at work on a conference call when he suddenly passed out and fell on the floor. The subject lost consciousness for approximately 3 to 4 minutes. He had no sweating, dizziness, or weakness and had not had syncopal episode before in his life. He did report that prior to this syncopal episode, he had some numbness and tingling in his right arm. He had never had a hypoglycemic episode. His blood glucose level that morning was reported to be 89. No reason for the syncopal episode was ever found.

Serious Adverse Events (SAEs) in T1DM

Table 7.13 shows the raw incidence and the exposure-adjusted incidence of SAEs that occurred in any system organ class and preferred term in the T1DM pooled safety population. Under the category of nervous system disorders all events appear to be definitely or probably related to hypoglycemia. The incidence of SAEs in the respiratory tract in the TI group was higher than in the comparator group but was low overall. Pulmonary serious adverse events will be discussed separately in Dr. Karimi-Shah's review. Among Type 1 patients, no pattern emerged of a single type of serious adverse event, or grouping of serious adverse events, that occurred with greater frequency among TI patients than among comparator patients except for diabetic ketoacidosis (DKA) which occurred in 13 subjects in the TI group and 3 in the comparator group. This difference accounts for the slight imbalance in the Metabolism and nutrition disorders SOC. Review of the narratives for these cases suggests that most were due to infections. There was only one event of DKA due to improper use of the inhaler. In this subject, MKC-TI-009 495/1748, it is actually not clear from the narrative whether the subject actually had DKA or whether she had severe hyperglycemia. The subject was hospitalized however, suggesting DKA. One case was due to the patient stopping the subcutaneous basal insulin on her own accord without consulting with her physician. One case was related to an overdose of paracetamol and ensuing illness. The cases of DKA occurred as early as 3 days after start of TI treatment up to > 400 days after start of TI treatment with no temporal apparent pattern.

**Table 7.13 - Incidence of Non-Fatal SAEs in Type 1 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 614) (SYE = 540)		Comparator (n = 599) (SYE = 682)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Any SAE	78 (12.7)	[14.4]	74 (12.4)	[10.9]
Metabolism and nutrition disorders	55 (9.0)	[10.2]	47 (7.8)	[6.9]
Hypoglycemia	37 (6.0)	[6.9]	40 (6.7)	[5.9]
Diabetic ketoacidosis	10 (1.6)	[1.9]	3 (0.5)	[0.4]
Hypoglycemic seizure	3 (0.5)	[0.6]	4 (0.7)	[0.6]
Ketoacidosis	3 (0.5)	[0.6]	0	0
Hyperglycemia	2 (0.3)	[0.4]	1 (0.2)	[0.1]
Dehydration	1 (0.2)	[0.2]	0	0
Diabetes mellitus inadequate control	1 (0.2)	[0.2]	2 (0.3)	[0.3]
Ketosis	1 (0.2)	[0.2]	0	0
Metabolic syndrome	0	0	1 (0.2)	[0.1]
Nervous system disorders	12 (2.0)	[2.2]	9 (1.5)	[1.3]
Loss of consciousness <sup>a</sup>	11 (1.8)	[2.0]	8 (1.3)	[1.2]
Convulsion	1 (0.2)	[0.2]	0	0
Epilepsy	1 (0.2)	[0.2]	0	0
Hypoglycemic coma	0	0	1 (0.2)	[0.1]
Injury, poisoning and procedural complications	8 (1.3)	[1.5]	7 (1.2)	[1.0]
Accidental overdose	1 (0.2)	[0.2]	0	0
Ankle fracture	1 (0.2)	[0.2]	3 (0.5)	[0.4]
Concussion	1 (0.2)	[0.2]	1 (0.2)	[0.1]
Jaw fracture	1 (0.2)	[0.2]	0	0
Overdose	1 (0.2)	[0.2]	0	0
Patella fracture	1 (0.2)	[0.2]	0	0
Road traffic accident	1 (0.2)	[0.2]	2 (0.3)	[0.3]
Upper limb fracture	1 (0.2)	[0.2]	0	0
Femur fracture	0	0	1 (0.2)	[0.1]
Fibula fracture	0	0	1 (0.2)	[0.1]
Foot fracture	0	0	1 (0.2)	[0.1]
Hip fracture	0	0	1 (0.2)	[0.1]
Joint dislocation	0	0	1 (0.2)	[0.1]
Tendon rupture	0	0	1 (0.2)	[0.1]
Thoracic vertebral fracture	0	0	1 (0.2)	[0.1]
Cardiac disorders	4 (0.7)	[0.7]	6 (1.0)	[0.9]
Angina unstable	1 (0.2)	[0.2]	0	0
Cardiac failure congestive	1 (0.2)	[0.2]	0	0
Coronary artery disease	1 (0.2)	[0.2]	0	0
Myocardial infarction	1 (0.2)	[0.2]	1 (0.2)	[0.1]
Acute coronary syndrome	0	0	1 (0.2)	[0.1]
Acute myocardial infarction	0	0	1 (0.2)	[0.1]
Angina pectoris	0	0	1 (0.2)	[0.1]
Sinus tachycardia	0	0	1 (0.2)	[0.1]
Supraventricular tachycardia	0	0	1 (0.2)	[0.1]
Gastrointestinal disorders	4 (0.7)	[0.7]	7 (1.2)	[1.0]
Duodenal ulcer	1 (0.2)	[0.2]	0	0

**Table 7.13 - Incidence of Non-Fatal SAEs in Type 1 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 614) (SYE = 540)		Comparator (n = 599) (SYE = 682)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Gastric ulcer	1 (0.2)	[0.2]	0	0
Gastritis	1 (0.2)	[0.2]	1 (0.2)	[0.1]
Large intestine perforation	1 (0.2)	[0.2]	0	0
Pancreatitis acute	1 (0.2)	[0.2]	0	0
Vomiting	1 (0.2)	[0.2]	0	0
Abdominal discomfort	0	0	1 (0.2)	[0.1]
Abdominal pain	0	0	1 (0.2)	[0.1]
Abdominal pain upper	0	0	1 (0.2)	[0.1]
Gastrointestinal hemorrhage	0	0	1 (0.2)	[0.1]
Gastroesophageal reflux disease	0	0	2 (0.3)	[0.3]
Hematemesis	0	0	1 (0.2)	[0.1]
Hiatus hernia	0	0	1 (0.2)	[0.1]
Intestinal obstruction	0	0	1 (0.2)	[0.1]
Esophagitis	0	0	1 (0.2)	[0.1]
Hepatobiliary disorders	4 (0.7)	[0.7]	2 (0.3)	[0.3]
Cholelithiasis	2 (0.3)	[0.4]	0	0
Cholecystitis acute	1 (0.2)	[0.2]	0	0
Hepatotoxicity	1 (0.2)	[0.2]	0	0
Cholecystitis chronic	0	0	1 (0.2)	[0.1]
Hepatocellular damage	0	0	1 (0.2)	[0.1]
Infections and infestations	2 (0.3)	[0.4]	9 (1.5)	[1.3]
Appendicitis	1 (0.2)	[0.2]	0	0
Staphylococcal infection	1 (0.2)	[0.2]	0	0
Cellulitis	0	0	1 (0.2)	[0.1]
Gastroenteritis viral	0	0	1 (0.2)	[0.1]
Localized infection	0	0	1 (0.2)	[0.1]
Pelvic abscess	0	0	1 (0.2)	[0.1]
Pilonidal cyst	0	0	1 (0.2)	[0.1]
Pneumonia	0	0	1 (0.2)	[0.1]
Pulmonary tuberculosis	0	0	1 (0.2)	[0.1]
Rectal abscess	0	0	1 (0.2)	[0.1]
Tonsillitis	0	0	1 (0.2)	[0.1]
Musculoskeletal and connective tissue disorders	2 (0.3)	[0.4]	2 (0.3)	[0.3]
Rotator cuff syndrome	2 (0.3)	[0.4]	0	0
Intervertebral disc protrusion	0	0	2 (0.3)	[0.3]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (0.3)	[0.4]	1 (0.2)	[0.1]
Breast cancer	1 (0.2)	[0.2]	0	0
Prostate cancer	1 (0.2)	[0.2]	0	0
Uterine leiomyoma	0	0	1 (0.2)	[0.1]
Respiratory, thoracic and mediastinal disorders	2 (0.3)	[0.4]	0	0
Bronchial obstruction	1 (0.2)	[0.2]	0	0
Cough	1 (0.2)	[0.2]	0	0
Hemoptysis	1 (0.2)	[0.2]	0	0

**Table 7.13 - Incidence of Non-Fatal SAEs in Type 1 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 614) (SYE = 540)		Comparator (n = 599) (SYE = 682)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Reproductive system and breast disorders	1 (0.2)	[0.2]	0	0
Adenomyosis	1 (0.2)	[0.2]	0	0
Vascular disorders	0	0	1 (0.2)	[0.1]
Extremity necrosis	0	0	1 (0.2)	[0.1]
Blood and lymphatic system disorders	0	0	1 (0.2)	[0.1]
Pernicious anemia	0	0	1 (0.2)	[0.1]
Eye disorders	0	0	1 (0.2)	[0.1]
Eye hemorrhage	0	0	1 (0.2)	[0.1]
Investigations	0	0	1 (0.2)	[0.1]
Blood potassium increased	0	0	1 (0.2)	[0.1]
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.2)	[0.1]
Pregnancy	0	0	1 (0.2)	[0.1]
Psychiatric disorders	0	0	1 (0.2)	[0.1]
Suicide attempt	0	0	1 (0.2)	[0.1]

Note(s): Adverse events were coded using the MedDRA dictionary (Version 7.1).

Each SOC includes the total number of subjects by SOC.

Each subject may be counted more than once in different preferred terms for each AE reported..

SYE = Subject exposure in subject-years

- a. All but one of the TEAEs of loss of consciousness were associated with hypoglycemia. One subject (MKC-TI-030/2706) in the TI group had 2 TEAEs of loss of consciousness that were attributed to hypoglycemia and/or latent neurological disease. Data source: Table G.1.9.6.1.1 and G.1.9.6.1.3

### Type 1 diabetes narratives

**Colon cancer with hepatic metastasis** MKC-TI-009 186/1011: A 56-yo Caucasian male in the United States with type 1 diabetes mellitus was undergoing the screening phase of the trial and was not randomized into the study. Before he completed his screening visit he was diagnosed with metastatic colon cancer.

**Hemoptysis and cough** MKC-TI-009 237/1207: A 45-yo Caucasian female in the United States was receiving TI 90 U before breakfast, 60 U before lunch and before dinner, and insulin glargine 30 IU daily subcutaneously (sc). On day 121 of treatment the subject reported episodes of coughing up blood (without sputum) for approximately the past 2 weeks that usually occurred 20 minutes after every TI Inhalation Powder treatment. TI Inhalation Powder was interrupted and the subject was given a prescription for insulin lispro (Humalog) 3 to 6 IU before each meal and instructed to continue insulin glargine 30 IU daily. Chest x-ray showed no abnormalities and PFTs were essentially unchanged. The symptoms resolved 11 days later. The subject discontinued from the trial due to the SAE.

**Cerebral concussion** MKC-TI-009 505/2090: A 23-yo Caucasian male in Russia received TI 60 U at breakfast and 30 U at lunch and at dinner and insulin glargine 24 U QHS. The duration of treatment at the onset of the event was 205 days. The subject experienced a cerebral concussion after hitting his head on the steering wheel during a car accident. The subject experienced nausea and dizziness and lost consciousness for several minutes. The event was not recorded as a hypoglycemic event because the blood glucose that morning before the subject was driving was normal. However, there is no report of a blood glucose being measured on the scene of the accident. The subject restarted TI after hospital discharge.

**Seizure** MKC-TI-030 092/2391: A 49-yo Caucasian male in the United States received TI 30 U TID from 22 Aug 2006 and insulin glargine (Lantus) 55 IU QD subcutaneously (sc) from 03 Aug 2006. The duration of treatment at the onset of the event was 6 days. On the morning of 27 Aug 2006, the subject was walking and noticed that his left hand was twitching. The subject's companions stated that he appeared to have had a seizure as his body was twitching. The subject spontaneously awoke from the incident, lying on the ground. His blood glucose was 146 mg/dL that morning before breakfast. No hypoglycemia was documented. No cause for the seizure was found. The extent of the workup for seizure is not described in the narrative. The subject continued in the trial.

**Loss of consciousness/Epilepsy** MKC-TI-030 406/2706: A 45-yo Caucasian male in the Czech Republic received TI 30 U TID from 02 Sep to 18 Sep 2006 and then was increased to 45 U TID starting 19 Sep 2006. On 24 Sep the subject lost consciousness while driving and crashed into the car in front of him. He awoke on his own and drank cola prior to any emergency services arriving. He had not missed a meal. Hypoglycemia was never documented. In fact his blood glucose was 440 mg/dL on the scene. The subject remained in the trial. The subject apparently had a history of occasional loss of consciousness events prior to trial enrollment.

Cases of diabetic ketoacidosis (note: many of the narratives did not provide laboratory evidence of DKA).

**Diabetic ketoacidosis** MKC-TI-009 189/1283: A 33-yo African American female using TI Inhalation Powder 60 U TID and insulin glargine 30 IU QHS experienced headache, nausea, vomiting, and tachycardia without respiratory distress and was admitted to the hospital with DKA. The investigator reported that there were no missed doses of insulin. The duration of treatment at the onset of the event was 146 days. The subject discontinued the trial due to the SAE.

**Diabetic ketoacidosis** MKC-TI-009 229/1931: A 35-yo Caucasian male in the U.S. receiving TI 90 U at breakfast, 60 U at lunch, 60 U at dinner, and 15 U PRN, and insulin glargine 11 IU QHS hospitalized with DKA likely due to a viral illness associated with vomiting. The blood glucose was 700 mg/dL on admission. The subject reported not taking any insulin for three days after the illness began, before the hospital admission. The duration of treatment at the onset of the event was 346 days.

**Diabetic ketoacidosis** MKC-TI-009 118/1546: A 42-yo African American male received TI 60 U at breakfast, 45 U at lunch, and 60 U at dinner. The insulin glargine dose was 28 IU in the morning and 14 IU at bedtime. The duration of treatment at the onset of the event was 205 days. On 12 Jul 2007, after eating some fish, the subject experienced nausea and vomiting and was found confused and disoriented in his apartment. The subject was living alone and was not appropriately hydrated during acute illness. Subsequently he was taken to the hospital and was diagnosed with diabetic ketoacidosis (DKA) with a pH of 7.16 and a blood glucose level of 888 mg/dL. The subject recovered and did not discontinue from the trial.

**Diabetic ketoacidosis** MKC-TI-009 313/1683: A 22-yo Caucasian male in Poland received TI 60 U at breakfast, 45 U at lunch, and 90 U at dinner, and insulin glargine 23 IU QHS. The duration of treatment at the onset of the event was 260 days. At a routine trial visit, the subject was noted to have elevated blood glucose, nausea and vomiting and tachypnea. The subject was hospitalized with confirmed DKA with a pH of 7.23 and blood glucose > 500 mg/dL. A precipitating cause was described as “dietary mistake”. TI was restarted upon discharge at the same dosing prior the event. The subject completed the trial.

**Diabetic ketoacidosis** MKC-TI-009 484/2303: A 26-yo Caucasian female in Brazil received TI 30 U at breakfast, 90 U at lunch, and 75 U at dinner, and insulin glargine 38 IU QHS. The duration of treatment at the onset of event was 362 days. The subject was hospitalized with DKA [(nausea and abdominal pain associated with excess food intake and a missed dose of “insulin” (not clear if TI or basal insulin)]. The investigator noted that in the discharge summary the pH at the time of admission was reported to be 7.11. The subject recovered in one day and did not discontinue from the trial.

**Diabetic ketoacidosis** MKC-TI-009 486/2242: A 23-yo Caucasian male in Brazil received TI 90 U at breakfast, 90 U at lunch, and 90 U at dinner, and insulin glargine 48 IU QHS. The duration of treatment at the onset of event was 265 days. The subject was hospitalized with DKA likely related to gastroenterocolitis associated with nausea, diarrhea and vomiting. The pH on admission was 7.35 with blood glucose of 511 mg/dL. Ketones were 2+. The subject recovered after one dose of bolus 10 IU rapid acting insulin subcutaneously; no changes were made with respect to study drugs, and the subject did not discontinue from the trial.

**Ketoacidosis** MKC-TI-009 495/1748: A 23-yo female Caucasian in Poland was started on TI Inhalation Powder 15 U TID plus 22 IU of insulin glargine (Lantus) at bedtime. On the day of study entry the subject experienced hyperglycemia (up to 380 mg/dL) and was hospitalized. It was presumed due to inappropriate use of the inhaler. Although the subject was hospitalized the narrative states that there was no evidence of metabolic acidosis so whether or not this was DKA is not clear. The patient was retrained on the use of the inhaler and completed the trial.

**Reviewer’s comment: This is likely not a true case of DKA.**

**Diabetic ketoacidosis** MKC-TI-009 181/1522: A 19-yo African American female received TI 30 U TID starting [REDACTED]<sup>(b) (6)</sup>. The subject received insulin glargine 35 IU subcutaneously at bedtime which was administered starting 20 Dec 2006. The duration of treatment at the onset of

event was 3 days. On [REDACTED] <sup>(b) (6)</sup>, the subject presented to the emergency room (ER) with symptoms of nausea and vomiting for 2 days. The subject was found to have a buttock abscess, and urinary tract infection, and was in DKA with a pH of 7.05 and blood glucose of 400 mg/dL. The patient's HbA1c was found to be 17.9%. The subject withdrew consent from the study after hospital discharge.

**Reviewer's comment: This patient had a HbA1c of close to 18% three days after starting TI. Clearly she should not have been enrolled in the clinical trial, i.e. she did not meet the inclusion criteria for HbA1c. This patient presumably has a history of non-adherence to her insulin regimen (hence the extremely high HbA1c) and this behavior likely contributed to her episode of DKA.**

**Diabetic ketoacidosis** MKC-TI-030 029/2970: A 29-yo Caucasian female in the United States received TI 60 U at breakfast and 75 U at lunch and dinner starting 07 Sep 2006 and subcutaneous insulin glargine (Lantus) 46 IU QD starting 1999. The duration of treatment at the onset of the event was 56 days. The subject was hospitalized with DKA. She admitted to stopping her basal insulin. She did not indicate that she thought she could get all the insulin she needs from TI so it is unclear why she stopped the basal insulin. The medical history notes that the subject had a history of prior hospitalizations for DKA and a history of depression. She did not discontinue from the trial.

**Diabetic ketoacidosis** MKC-TI-030 406/3031: A 24-yo Caucasian female in the Czech Republic received TI 75 U at breakfast and lunch, 90 U at dinner, and 15 U at other unspecified time from 03 Jul 2007 to 12 Nov 2007. Insulin glargine was administered sc 26 IU QD from 03 Jul 2007 onward. The duration of treatment at the onset of the first event was 421 days. On 13 Nov 2007, the subject experienced diabetic ketoacidosis (DKA) likely due to gastritis. She had another episode of DKA on 25 Feb 2008 associated with acute pancreatitis. She recovered and did not discontinue from the trial for these SAEs.

**Diabetic ketoacidosis and hepatotoxicity due to paracetamol overdose** MKC-TI-030 461/2708: A 42-yo Caucasian female in Poland received TI 30 U TID from 22 Jan 2007 to 02 Feb 2008. Insulin glargine was administered 18 IU QD from 13 Aug 2007 onward. The duration of treatment at the onset of the first event was 372 days. She recovered and did not discontinue from the trial for these SAEs.

**Diabetic ketoacidosis** MKC-TI-030 858/2805: A 31-yo Caucasian female in the Ukraine received TI 30 U TID from 04 Sep 2006 to 15 May 2007 was hospitalized with DKA associated with acute cholecystitis. She recovered and did not discontinue from the trial for this SAE.

**Diabetic ketoacidosis** MKC-TI-030 912/3493: A 19-yo Caucasian female in Canada received TI 60 U TID from 02 Oct 2006 to 07 Nov 2006, and insulin isophane injection (NPH insulin) 22 IU QD subcutaneously (sc) at bedtime starting in year 2000 onward. Duration of treatment at the onset of the event was 33 days. The subject had DKA related to influenza. She recovered but discontinued TI due to the event.

## Discussion of SAEs

Overall, there was a higher rate of DKA among T1DM subjects in the TI group vs. the comparator insulin group. The rate of DKA in the TI group was 2.5 per 100 patient years. To put this finding into context, a recent estimate of the rate of DKA seen in T1DM patients is shown below in this table from a 2009 publication from the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. The rate of DKA seen in TI-treated subjects in the TI clinical development program appears to be consistent with rates of DKA observed in these cohorts.

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### 7.3.3 Dropouts and/or Discontinuations

Dropouts for individual trials are discussed in section 6.

Subjects who withdrew consent were reviewed by the Sponsor and misclassifications were identified and re-classified as appropriate (e.g., to discontinuation due to an AE) prior to programmatic generation of tables and files. Of note, in the Russian Federation, it was not permissible to ask subjects for a reason for withdrawing consent.

#### 7.3.3.1 Overall Profile of Dropouts - Combined Type 1 and Type 2 Population

Disposition of subjects including dropouts by trial is discussed in the efficacy review. Table 7.14 shows the disposition for the type 1 and type 2 diabetic combined population in the pooled phase 2/3 clinical trials:

**Table 7.14 – Disposition of Subjects With T1 or T2DM (Safety Population - Pooled Controlled Phase 2/3 Trials)**

	Comparator				
	TI	TP	Other insulin	Non-insulin	All Comparator
	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized	2453	108			1978
Safety Population	2409	114	1541	403	1944
Completed 24 weeks	1539 (63.9)	0	1208 (78.4)	281 (67.9)	1489 (76.6)
Prematurely Discontinued	870 (36.1)	21 (18.4)	333 (21.6)	122 (30.3)	455 (23.4)
• Adverse Event	185 (7.7)	2 (1.8)	22 (1.4)	5 (1.2)	27 (1.4)
• Protocol Violation	50 (2.1)	3 (2.6)	24 (1.6)	5 (1.2)	29 (1.5)
• Subject Withdrew Consent	380 (15.8)	11 (9.6)	162 (10.5)	69 (17.1)	231 (11.9)
• Subject Died	8 (0.3)	0	5 (0.3)	0	5 (0.3)
• Physician Decision	64 (2.7)	1 (0.9)	16 (1.0)	6 (1.5)	22 (1.1)
• Lost to Follow-up	69 (2.9)	0	78 (5.1)	33 (8.2)	111 (5.7)
• Other	113 (4.7)	4 (3.5)	26 (1.7)	4 (1.0)	30 (1.5)
• Unknown	1 (0.0)	0	0	0	0

Source: Table 8, ISS

A total of 2409 subjects with type 1 or type 2 diabetes mellitus received treatment with TI Inhalation Powder in the pooled controlled phase 2/3 clinical trials. A total of 1944 subjects received comparator treatment, with 1541 of these 1944 subjects receiving other (non-TI) insulin treatment and 403 receiving oral agents only. An additional 114 subjects with type 2 diabetes received only Technosphere Powder (TP).

The incidence of discontinuation for any reason from the trials was 870/2409 (36.1%) in the TI group and 455/1944 (23.4%) in all comparator groups combined. The incidence of discontinuation from treatment with TP was 21/114 (18.4%). The most common reason for discontinuation in all treatment groups was withdrawal of consent, with 380/2409 (15.8%), 231/1944 (11.9%), and 11/114 (9.6%) of subjects in the TI, comparator, and TP groups discontinuing for that reason. The incidence of discontinuation for adverse events was 185/2409 (7.7%) in the TI group versus 27/1944 (1.4%) in the comparator group.

A total of 69 patients were lost to follow-up: As defined by the Sponsor’s guidelines, documented efforts were made to contact each subject, including 3 telephone calls and 2 certified letters. An Investigator deemed a subject lost to follow-up when attempts to contact subjects were exhausted.

**Reviewer’s comment: The imbalance in dropout rates is discussed for each diabetes type separately in the next sections.**

### 7.3.3.2 Overall Profile of Dropouts - Type 2 Population

The overall profile of dropouts among the type 2 population is shown in table 7.15. The incidence of discontinuation for any reason from the trials was 629/1795 (35.0%) in the TI group and 331/1345 (24.6%) in the comparator group. The incidence of discontinuation for TP-treated subjects was 21/114 (18.4%). The most common reason for discontinuation in all treatment groups was withdrawal of consent, with 251/1745 (14.0%), 173/1345 (12.9%), and 11/114 (9.6%) of subjects in the TI, comparator, and TP groups discontinuing for that reason. The incidence of discontinuation for adverse events, including laboratory abnormalities, was 142/1795 (7.9%) in the TI group versus 24/1345 (1.8%) in the comparator group.

**Table 7.15 - Disposition of Subjects With Type 2 Diabetes Mellitus (Safety Population – Pooled Controlled Phase 2/3 Trials)**

	TI n (%)	TP n (%)	Comparator		
			Other insulin n (%)	Non-insulin n (%)	All n (%)
Randomized subjects	1829	108	NA	NA	1363
Safety population	1795	114	953	392	1345
Completed study treatment	1166 (65.0)	0	733 (77.8)	281 (69.7)	1014 (75.4)
Prematurely discontinued	629 (35.0)	21 (18.4)	214 (22.2)	117 (29.8)	331 (24.6)
Reasons for discontinuation from study					
Adverse events <sup>a, b</sup>	142 (7.9)	2 (1.8)	19 (2.0)	5 (1.3)	24 (1.8)
Protocol violation	37 (2.1)	3 (2.6)	8 (0.8)	5 (1.3)	13 (1.0)
Subject withdrew consent	251 (14.0)	11 (9.6)	106 (11.1)	67 (17.1)	173 (12.9)
Subject died	7 (0.4)	0	4 (0.4)	0	4 (0.3)
Investigator decision	42 (2.3)	1 (0.9)	9 (0.9)	6 (1.5)	15 (1.1)
Lost to follow-up	53 (3.0)	0	53 (5.6)	30 (7.7)	83 (6.2)
Other	97 (5.4)	4 (3.5)	15 (1.6)	4 (1.0)	19 (1.4)
Unknown	0	0	0	0	0

NA = Not applicable; TI = Technosphere<sup>®</sup> Insulin; TP = Technosphere<sup>®</sup> Powder.

Including laboratory abnormalities.

<sup>b</sup> Includes subjects who were recorded on the subject summary page as discontinuing because of adverse events, but did not have TEAEs recorded as leading to discontinuation from the trial. Those subjects, by site number/study number/subject number, are: TI subjects 066/MKC-TI-030/0299, 066/MKC-TI-030/1053, 162/MKC-TI-030/3058, 176/MKC-TI-102/1498, 227/MKC-TI-103/1309, 346/MKC-TI-103/1789, 486/MKC-TI-103/2249, 523/MKC-TI-014/016, 530/MKC-TI-014/804, 861/MKC-TI-103/2281; TP subjects 019/PDC-INS-0008/374; other insulin subjects 089/MKC-TI-030/1283, 161/MKC-TI-030/3398, 188/MKC-TI-102/1338, 214/MKC-TI-102/1126, 321/MKC-TI-102/1653, 860/MKC-TI-030/2627; noninsulin subjects: 895/MKC-TI-103/2263, 069/MKC-TI-030/1198.

Note: Percentages are based on the total number of subjects in the Safety Population in each treatment group.

Data source: Table G.2.1.

Observations of note regarding reasons for discontinuation among Type 2 diabetics include:

- Premature discontinuation was more common among TI patients than among all other patient groups, although this difference was smallest when TI was compared to non-insulin therapies

- The reason for this imbalance seems to be primarily due to the reasons of “adverse events including laboratory abnormalities” and “subject withdrew consent”
- The large number of patients for whom consent was withdrawn is less of a concern than it is with type 1 diabetics because there was a relatively similar rate among patient groups.
- There were a few subjects who were recorded on the subject summary page as discontinuing because of adverse events, but did not have TEAEs recorded as leading to discontinuation from the trial (see superscript b in Table 7.15). These subjects do not appear to be clustered in any one site (which could have implied poor data integrity at that site).

### 7.3.3.3 Overall Profile of Dropouts - Type 1 Population

The overall profile of dropouts among the type 1 population is shown in table 7.16. The incidence of discontinuation for any reason from the trial was 241/614 (39.3%) in the TI group and 124/599 (20.7%) in all comparator groups combined. The incidence of discontinuations due to adverse events, including laboratory abnormalities, was 43/614 subjects (7.0%) in the TI group versus 3/599 subjects (0.5%) in the comparator group.

<b>Table 7.16 – Disposition of Subjects with T1DM (Safety Population - Pooled Controlled Phase 2/3 Trials)</b>		
	TI n (%)	Comparator n (%)
Randomized	624	615
Safety Population	614	599
Completed 24 weeks	373 (60.7)	475 (79.3)
Prematurely Discontinued	241 (39.3)	124 (20.7)
• Adverse Event	43 (7.0)	3 (0.5)
• Protocol Violation	13 (2.1)	16 (2.7)
• Subject Withdrew Consent	129 (21.0)	58 (9.7)
• Subject Died	1 (0.2)	1 (0.2)
• Physician Decision	22 (3.6)	7 (1.2)
• Lost to Follow-up	16 (2.6)	28 (4.7)
• Other	16 (2.6)	11 (1.8)
• Unknown	1 (0.2)	0

Source: Table 9 ISS

Observations of note regarding reasons for discontinuation among Type 1 diabetics include:

- Premature discontinuation was more common among TI patients
- The reason for this imbalance seems to be primary due to the reasons of “adverse events including laboratory abnormalities” and “subject withdrew consent”
- There is an imbalance in the incidence of discontinuation for adverse events between the groups.

- The large number of patients for whom consent was withdrawn is of concern, because it raises the question of whether some of these patients actually dropped out for adverse events, particularly because the proportion of patients who withdrew consent was not balanced across treatment groups. However, the Sponsor reexamined all narratives for patients who discontinued for these reasons and reclassified them if the narrative suggested an adverse event. The clinical reviewer confirmed these reanalyses for the one year trials (102 and 009). These are discussed in the context of these individual trials in section 6.

#### 7.3.3.2 Discontinuations due to SAEs:

Table 7.17 shows discontinuations due to serious adverse events among type 2 diabetic subjects in the pooled phase 2/3 safety population. Table 7.18 shows discontinuations due to serious adverse events among type 1 diabetic subjects in the pooled phase 2/3 safety population.

Among type 2 subjects, the rate of discontinuation for SAEs was higher in the TI group than in the comparator group, though these events appear to be evenly distributed across many system organ classes and preferred terms.

Among type 1 subjects, the rate of discontinuation for SAEs was higher in the TI group than in the comparator group. There was a higher rate of discontinuations coded under the system organ class of “Metabolism and nutrition disorders” and “Respiratory, thoracic and mediastinal disorders” in the TI group that account for this imbalance. These are expected adverse events with use of an unfamiliar insulin product with a pulmonary route of administration. The higher rate of diabetic ketoacidosis among type 1 subjects was discussed previously. Note that in many cases these events of diabetic ketoacidosis did not lead to discontinuation from trials. In addition, there are small numbers of SAEs leading to discontinuation, which limit conclusions. For example, 1 more event with comparator and 1 less event with TI would essentially eradicate these imbalances across SOCs.

**Table 7.17 - Incidence of Non-Fatal SAEs Leading to Discontinuation from Trial in Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI		Comparator	
	(n = 1795)		(n = 1345)	
	(SYE = 1274)		(SYE = 1369)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Any SAE	23 (1.3)	[1.8]	12 (0.9)	[0.9]
Blood and lymphatic system disorders	0	0	2 (0.1)	[0.1]
Anemia	0	0	1 (0.1)	[0.1]
Thrombocytopenia	0	0	1 (0.1)	[0.1]
Cardiac disorders	6 (0.3)	[0.5]	3 (0.2)	[0.2]
Acute coronary syndrome	1 (0.1)	[0.1]	0	0
Cardiac failure	1 (0.1)	[0.1]	0	0
Cardiac failure chronic	1 (0.1)	[0.1]	0	0
Coronary artery disease	1 (0.1)	[0.1]	0	0
Myocardial infarction	1 (0.1)	[0.1]	1 (0.1)	[0.1]
Myocardial ischemia	1 (0.1)	[0.1]	0	0
Angina pectoris	0	0	1 (0.1)	[0.1]
Atrial fibrillation	0	0	1 (0.1)	[0.1]
Coronary artery occlusion	0	0	1 (0.1)	[0.1]
Eye disorders	1 (0.1)	[0.1]	0	0
Retinal disorder	1 (0.1)	[0.1]	0	0
Infections and infestations	5 (0.3)	[0.4]	1 (0.1)	[0.1]
Diabetic foot infection	1 (0.1)	[0.1]	0	0
Diabetic gangrene	1 (0.1)	[0.1]	0	0
Localized infection	1 (0.1)	[0.1]	0	0
Pneumonia	1 (0.1)	[0.1]	1 (0.1)	[0.1]
Pulmonary tuberculosis	1 (0.1)	[0.1]	0	0
Upper respiratory tract infection	1 (0.1)	[0.1]	0	0
Injury, poisoning and procedural complications	1 (0.1)	[0.1]	3 (0.2)	[0.2]
Hand fracture	1 (0.1)	[0.1]	0	0
Fall	0	0	1 (0.1)	[0.1]
Hip fracture	0	0	1 (0.1)	[0.1]
Rib fracture	0	0	1 (0.1)	[0.1]
Road traffic accident	0	0	1 (0.1)	[0.1]
Metabolism and nutrition disorders	3 (0.2)	[0.2]	3 (0.2)	[0.2]
Dehydration	1 (0.1)	[0.1]	0	0
Diabetes mellitus inadequate control	1 (0.1)	[0.1]	0	0
Hyperglycemia	1 (0.1)	[0.1]	0	0
Ketoacidosis	1 (0.1)	[0.1]	0	0
Hypoglycemia	0	0	2 (0.1)	[0.1]
Obesity	0	0	1 (0.1)	[0.1]
Musculoskeletal and connective tissue disorders	1 (0.1)	[0.1]	1 (0.1)	[0.1]
Rheumatoid arthritis	1 (0.1)	[0.1]	0	0

**Table 7.17 - Incidence of Non-Fatal SAEs Leading to Discontinuation from Trial in Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI		Comparator	
	(n = 1795)		(n = 1345)	
	(SYE = 1274)		(SYE = 1369)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Bone pain	0	0	1 (0.1)	[0.1]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (0.2)	[0.2]	1 (0.1)	[0.1]
Breast cancer stage III	1 (0.1)	[0.1]	0	0
Ovarian epithelial cancer	1 (0.1)	[0.1]	0	0
Pituitary tumor benign	1 (0.1)	[0.1]	0	0
Pancreatic carcinoma	0	0	1 (0.1)	[0.1]
Nervous system disorders	3 (0.2)	[0.2]	1 (0.1)	[0.1]
Third nerve paralysis	1 (0.1)	[0.1]	0	0
Loss of consciousness	1 (0.1)	[0.1]	1 (0.1)	[0.1]
Multiple sclerosis	1 (0.1)	[0.1]	0	0
Psychiatric disorders	2 (0.1)	[0.2]	0	0
Depression	1 (0.1)	[0.1]	0	0
Psychotic disorder	1 (0.1)	[0.1]	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.1)	[0.1]	1 (0.1)	[0.1]
Asthma	1 (0.1)	[0.1]	0	0
Hydrothorax	0	0	1 (0.1)	[0.1]
Skin and subcutaneous tissue disorders	1 (0.1)	[0.1]	0	0
Angioneurotic edema	1 (0.1)	[0.1]	0	0
Vascular disorders	0	0	1 (0.1)	[0.1]
Thrombosis	0	0	1 (0.1)	[0.1]

AE = adverse event; SYE = subject-years exposure; TEAE = treatment-emergent AE.

Each SOC includes the total number of subjects by SOC.

Each subject may be counted more than once in different preferred terms for each AE reported.

Data Source: Table G.2.9.7.1.1 and G.2.9.7.1.3

**Table 7.18 -Incidence of Non-Fatal SAEs Leading to Discontinuation in Type 1 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

	TI		Comparator	
	(n = 614)		(n = 599)	
	(SYE = 540)		(SYE = 682)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Any SAE leading to discontinuation	8 (1.3)	[1.5]	3 (0.5)	[0.4]
Cardiac disorders	1 (0.2)	[0.2]	0	0
Cardiac failure congestive	1 (0.2)	[0.2]	0	0
Infections and infestations	0	0	1 (0.2)	[0.1]
Pulmonary tuberculosis	0	0	1 (0.2)	[0.1]
Metabolism and nutrition disorders	4 (0.7)	[0.7]	1 (0.2)	[0.1]
Diabetic ketoacidosis	1 (0.2)	[0.2]	0	0
Hyperglycemia	1 (0.2)	[0.2]	0	0
Hypoglycemia	1 (0.2)	[0.2]	0	0
Hypoglycemic seizure	1 (0.2)	[0.2]	0	0
Ketosis	1 (0.2)	[0.2]	0	0
Metabolic syndrome <sup>a</sup>	0	0	1 (0.2)	[0.1]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.2)	[0.2]	0	0
Breast cancer	1 (0.2)	[0.2]	0	0
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.2)	[0.1]
Pregnancy	0	0	1 (0.2)	[0.1]
Respiratory, thoracic and mediastinal disorders	2 (0.3)	[0.4]	0	0
Bronchial obstruction	1 (0.2)	[0.2]	0	0
Cough	1 (0.2)	[0.2]	0	0
Hemoptysis	1 (0.2)	[0.2]	0	0

<sup>a</sup> Review of this subjects’ narrative by the clinical reviewer suggests this subject actually discontinued for hospitalization due to fever

AE = adverse event; SYE = subject-years exposure; TEAE = treatment-emergent AE.

Each SOC includes the total number of subjects by SOC.

Each subject may be counted more than once in different preferred terms for each AE reported.

Data Source: Table G.1.9.7.1.1 and G.1.9.7.1.3

### 7.3.3.3 Discontinuations due to all AEs:

There was a higher rate of discontinuations due to all adverse events (note these include serious adverse events as well which results in a representation of some data from Table 7.17) among TI treated T2DM subjects compared with Comparator treated subjects (Table 7.19). More than half of the discontinuations due to adverse events among TI treated patients were respiratory-related. However, the absolute percentage of patients discontinuing due to a respiratory event was

relatively low (4 %) considering that TI is an inhaled insulin and was being compared to non-inhaled therapies.

The adverse events leading to discontinuation among type 2 subjects did not seem to cluster in any one system organ class, except in the SOC of respiratory events as expected. The Sponsor suggests that the discontinuations were biased against TI stemming from the open-label design. Subjects or investigators would be more likely to opt for discontinuing from a trial for a medical reason when they are on an experimental therapy than when they are using their usual regimen or an approved medication. Evidence for this assumption is that the overall rate of adverse events was similar between TI and Comparator treated patients.

A similar pattern was seen for type 1 diabetic subjects (Table 7.20) with the addition of the increased rate of discontinuation for diabetic ketoacidosis that was already discussed.

**Table 7.19 - Incidence of TEAEs Leading to Discontinuation from Trial in Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI		Comparator	
	(n = 1795)		(n = 1345)	
	(SYE = 1274)		(SYE = 1369)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Any TEAE leading to discontinuation	142 (7.9)	[11.1]	20 (1.5)	[1.5]
Blood and lymphatic system disorders	1 (0.1)	[0.1]	2 (0.1)	[0.1]
Lymphadenopathy	1 (0.1)	[0.1]	0	0
Anemia	0	0	1 (0.1)	[0.1]
Thrombocytopenia	0	0	1 (0.1)	[0.1]
Cardiac disorders	13 (0.7)	[1.0]	4 (0.3)	[0.3]
Myocardial ischemia	3 (0.2)	[0.2]	0	0
Acute myocardial infarction	2 (0.1)	[0.2]	0	0
Acute coronary syndrome	1 (0.1)	[0.1]	0	0
Angina pectoris	1 (0.1)	[0.1]	1 (0.1)	[0.1]
Cardiac failure	1 (0.1)	[0.1]	0	0
Cardiac failure acute	1 (0.1)	[0.1]	0	0
Cardiac failure chronic	1 (0.1)	[0.1]	0	0
Coronary artery atherosclerosis	1 (0.1)	[0.1]	0	0
Coronary artery disease	1 (0.1)	[0.1]	0	0
Hypertensive cardiomyopathy	1 (0.1)	[0.1]	0	0
Myocardial infarction	1 (0.1)	[0.1]	1 (0.1)	[0.1]
Palpitations	1 (0.1)	[0.1]	0	0
Tachycardia	1 (0.1)	[0.1]	0	0
Atrial fibrillation	0	0	1 (0.1)	[0.1]
Cardiac arrest	0	0	1 (0.1)	[0.1]
Coronary artery occlusion	0	0	1 (0.1)	[0.1]
Eye disorders	1 (0.1)	[0.1]	1 (0.1)	[0.1]
Retinal disorder	1 (0.1)	[0.1]	0	0
Retinopathy hemorrhagic	0	0	1 (0.1)	[0.1]
Gastrointestinal disorders	5 (0.3)	[0.4]	0	0
Constipation	1 (0.1)	[0.1]	0	0
Duodenal ulcer hemorrhage	1 (0.1)	[0.1]	0	0
Nausea	1 (0.1)	[0.1]	0	0
Pancreatitis	1 (0.1)	[0.1]	0	0
Toothache	1 (0.1)	[0.1]	0	0
General disorders and administration site conditions	11 (0.6)	[0.9]	0	0
Chest discomfort	3 (0.2)	[0.2]	0	0
Asthenia	2 (0.1)	[0.2]	0	0
Chest pain	2 (0.1)	[0.2]	0	0
Fatigue	2 (0.1)	[0.2]	0	0
Performance status decreased	1 (0.1)	[0.1]	0	0
Pyrexia	1 (0.1)	[0.1]	0	0
Immune system disorders	3 (0.2)	[0.2]	0	0

**Table 7.19 - Incidence of TEAEs Leading to Discontinuation from Trial in Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI		Comparator	
	(n = 1795)		(n = 1345)	
	(SYE = 1274)		(SYE = 1369)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Hypersensitivity	2 (0.1)	[0.2]	0	0
Drug hypersensitivity	1 (0.1)	[0.1]	0	0
Infections and infestations	15 (0.8)	[1.2]	1 (0.1)	[0.1]
Bronchitis	4 (0.2)	[0.3]	0	0
Upper respiratory tract infection	3 (0.2)	[0.2]	0	0
Gangrene	2 (0.1)	[0.2]	0	0
Pneumonia	2 (0.1)	[0.2]	1 (0.1)	[0.1]
Bronchitis acute	1 (0.1)	[0.1]	0	0
Bronchitis chronic	1 (0.1)	[0.1]	0	0
Diabetic foot infection	1 (0.1)	[0.1]	0	0
Diabetic gangrene	1 (0.1)	[0.1]	0	0
Endocarditis	1 (0.1)	[0.1]	0	0
Localized infection	1 (0.1)	[0.1]	0	0
Pharyngitis	1 (0.1)	[0.1]	0	0
Pulmonary tuberculosis	1 (0.1)	[0.1]	0	0
Staphylococcal sepsis	1 (0.1)	[0.1]	0	0
Injury, poisoning and procedural complications	1 (0.1)	[0.1]	3 (0.2)	[0.2]
Hand fracture	1 (0.1)	[0.1]	0	0
Fall	0	0	1 (0.1)	[0.1]
Hip fracture	0	0	1 (0.1)	[0.1]
Rib fracture	0	0	1 (0.1)	[0.1]
Road traffic accident	0	0	1 (0.1)	[0.1]
Investigations	5 (0.3)	[0.4]	0	0
Alanine aminotransferase increased	1 (0.1)	[0.1]	0	0
Blood creatine phosphokinase increased	1 (0.1)	[0.1]	0	0
Carcinoembryonic antigen increased	1 (0.1)	[0.1]	0	0
Gamma-glutamyltransferase increased	1 (0.1)	[0.1]	0	0
Pulmonary function test abnormal	1 (0.1)	[0.1]	0	0
Pulmonary function test decreased	1 (0.1)	[0.1]	0	0
Metabolism and nutrition disorders	15 (0.8)	[1.2]	6 (0.4)	[0.4]
Hyperglycemia	10 (0.6)	[0.8]	1 (0.1)	[0.1]
Diabetes mellitus inadequate control	2 (0.1)	[0.2]	0	0
Dehydration	1 (0.1)	[0.1]	0	0
Diabetes mellitus	1 (0.1)	[0.1]	0	0
Hypoglycemic seizure	1 (0.1)	[0.1]	0	0
Ketoacidosis	1 (0.1)	[0.1]	0	0
Hypoglycemia	0	0	4 (0.3)	[0.3]

**Table 7.19 - Incidence of TEAEs Leading to Discontinuation from Trial in Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI		Comparator	
	(n = 1795)		(n = 1345)	
	(SYE = 1274)		(SYE = 1369)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Obesity	0	0	1 (0.1)	[0.1]
Musculoskeletal and connective tissue disorders	2 (0.1)	[0.2]	1 (0.1)	[0.1]
Intervertebral disc protrusion	1 (0.1)	[0.1]	0	0
Rheumatoid arthritis	1 (0.1)	[0.1]	0	0
Bone pain	0	0	1 (0.1)	[0.1]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	4 (0.2)	[0.3]	1 (0.1)	[0.1]
Bile duct cancer	1 (0.1)	[0.1]	0	0
Breast cancer stage III	1 (0.1)	[0.1]	0	0
Ovarian epithelial cancer	1 (0.1)	[0.1]	0	0
Pituitary tumor benign	1 (0.1)	[0.1]	0	0
Pancreatic carcinoma	0	0	1 (0.1)	[0.1]
Nervous system disorders	14 (0.8)	[1.1]	3 (0.2)	[0.2]
Headache	4 (0.2)	[0.3]	0	0
Cerebral atherosclerosis	1 (0.1)	[0.1]	0	0
Encephalitis	1 (0.1)	[0.1]	0	0
Hemorrhagic stroke	1 (0.1)	[0.1]	0	0
Hypoaesthesia	1 (0.1)	[0.1]	0	0
Third nerve paralysis	1 (0.1)	[0.1]	0	0
Ischemic stroke	1 (0.1)	[0.1]	0	0
Loss of consciousness	1 (0.1)	[0.1]	1 (0.1)	[0.1]
Multiple sclerosis	1 (0.1)	[0.1]	0	0
Psychomotor hyperactivity	1 (0.1)	[0.1]	0	0
Syncope	1 (0.1)	[0.1]	0	0
Diabetic neuropathy	0	0	1 (0.1)	[0.1]
Facial palsy	0	0	1 (0.1)	[0.1]
Psychiatric disorders	2 (0.1)	[0.2]	0	0
Depression	1 (0.1)	[0.1]	0	0
Psychotic disorder	1 (0.1)	[0.1]	0	0
Alcoholism	0	0	1 (0.1)	[0.1]
Respiratory, thoracic and mediastinal disorders	74 (4.1)	[5.8]	1 (0.1)	[0.1]
Cough	47 (2.6)	[3.7]	0	0
Dyspnea	8 (0.4)	[0.6]	0	0
Throat irritation	4 (0.2)	[0.3]	0	0
Asthma	1 (0.1)	[0.1]	0	0
Bronchial hyperactivity	1 (0.1)	[0.1]	0	0
Bronchospasm	1 (0.1)	[0.1]	0	0
Wheezing	1 (0.1)	[0.1]	0	0

**Table 7.19 - Incidence of TEAEs Leading to Discontinuation from Trial in Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI		Comparator	
	(n = 1795)		(n = 1345)	
	(SYE = 1274)		(SYE = 1369)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Allergic pharyngitis	1 (0.1)	[0.1]	0	0
Asphyxia	1 (0.1)	[0.1]	0	0
Increased upper airway secretion	1 (0.1)	[0.1]	0	0
Laryngospasm	1 (0.1)	[0.1]	0	0
Lung cyst benign	1 (0.1)	[0.1]	0	0
Lung disorder	1 (0.1)	[0.1]	0	0
Painful respiration	1 (0.1)	[0.1]	0	0
Pharyngolaryngeal pain	1 (0.1)	[0.1]	0	0
Pulmonary congestion	1 (0.1)	[0.1]	0	0
Pulmonary edema	1 (0.1)	[0.1]	0	0
Respiratory tract congestion	1 (0.1)	[0.1]	0	0
Respiratory tract irritation	1 (0.1)	[0.1]	0	0
Rhonchi	1 (0.1)	[0.1]	0	0
Throat tightness	1 (0.1)	[0.1]	0	0
Hydrothorax	0	0	1 (0.1)	[0.1]
Skin and subcutaneous tissue disorders	3 (0.2)	[0.1]	0	0
Angioneurotic edema	1 (0.1)	[0.1]	0	0
Hyperhidrosis	1 (0.1)	[0.1]	0	0
Pruritis generalized	1 (0.1)	[0.1]	0	0
Surgical and medical procedures	1 (0.1)	[0.1]	0	0
Tooth extraction	1 (0.1)	[0.1]	0	0
Vascular disorders	1 (0.1)	[0.1]	2 (0.1)	[0.1]
Aortic atherosclerosis	1 (0.1)	[0.1]	0	0
Diabetic vascular disorder	0	0	1 (0.1)	[0.1]
Thrombosis	0	0	1 (0.1)	[0.1]

AE = adverse event; SYE = subject-years exposure; TEAE = treatment-emergent AE.

Each SOC includes the total number of subjects by SOC.

Each subject may be counted more than once in different preferred terms for each AE reported.

Source: Table 37, ISS

Case narratives:

Chest discomfort Subject MKC-TI-030/073/0328: A 54 yo Asian female in the U.S. was administered 30 U TI at breakfast, 15 U at lunch and 30 U at dinner at this dose for approximately 4 months prior to trial discontinuation. The subject reported tightness of the chest from 18 days into the trial until discontinuation 6 months later. No treatment was given for the event. There is no report of whether the chest tightness resolved after the subject discontinued TI.

Chest discomfort: Subject MKC-TI-030/080/0101: A 46 yo Caucasian male in the U.S. was administered 30 U TI three times daily along with UC treatment and reported stinging in his chest and coughing which prompted him to discontinue from the trial 36 days after initiation of TI. The events resolved after TI was stopped.

Chest discomfort: Subject MKC-TI-030/158/0360: A 57 yo Caucasian male in the U.S. received TI at doses up to 60 U TID prandially. The subject reported “heaviness in the chest” 22 days after initiation of TI. The subject discontinued the trial on the same day as the report of the event. No follow up information was given about the subject.

Bronchospasm: Subject MKC-TI-102 603/2260: A 37 yo Hispanic male in Mexico received TI starting in April 2007. In July 2007 the subject reported cough, pharyngitis, and bronchospasm. The narrative states that no treatment was given and the subject continued in the trial until October 2007 when he developed influenza and he was discontinued from the trial due to bronchospasm.

Wheezing: Subject MKC-TI-030/081/0528: A 65 yo Caucasian male in the U.S. received TI 30 U TID with meals along with UC treatment and reported wheezing 46 days after initiation of TI. No treatment was given for the event which resolved spontaneously. The subject was withdrawn from the study.

Laryngospasm: Subject MKC-TI-030/169/0948: A 67 yo Caucasian male in the U.S. received TI up to 45 U TID prandially. On the day of initiation of TI treatment the subject reported “laryngospasm” but no details are given in the narrative except that no treatment was given for the event and that the subject also experienced heartburn that was treated with rabeprazole. The laryngospasm was reported as resolved approximately 3 weeks later.

Asthma: Subject MKC-TI-030/5251836: A 50 yo Caucasian male in Russia experienced “asthma” after one day of TI treatment. There are no other details provided except that no treatment was given for the event.

Asthma: Subject MKC-TI-102 375/3007: A 49 yo Hispanic female in Mexico received TI for 196 days when she had an event of ‘asthma’ treated with budesonide, ipratropio, and salbutamol. The event was considered not resolved and the subject withdrew from the study.

Throat tightness/wheezing: Subject MKC-TI-102 102/3016: A 48 yo Caucasian male in the U.S. received TI for 112 days when he experienced an upper respiratory infection associated with wheezing and throat tightening. The subject was treated with Ciprofloxacin.

Bronchial hyperactivity Subject MKC-TI-102 603/1607: A 63 yo Hispanic female in Mexico received TI for 71 days when she experienced “bronchial hyperactivity” (no other clinical details given). She was treated with budesonide, ciprofloxacin, and Combivent. The event was not resolved and the subject withdrew from the study.

Bronchial hyperactivity: Subject MKC-TI-102 483/2784: A 65 yo female from Brazil received TI for 115 days when she experienced “bronchial hyperactivity” (no other clinical details). She was treated with Alenia, Combivent, and prednisone. The event was considered not resolved and she was withdrawn from the study.

**Some of the cases above could possibly represent unmasking of previously undiagnosed asthma.**

Hypersensitivity: Subject MKC-TI-030/537/0154: A 64 yo Caucasian female in Russia received TI 30 U with breakfast and 15 U with lunch and dinner. Two days after treatment the subject experienced an “allergic event” for which no treatment was given and caused the subject to discontinue from the trial. The subject had a history of drug hypersensitivity resulting in urticaria. The subject was given salbutamol suggesting a respiratory component to the event but it is not clear if the salbutamol was given at the time of the event or before the event.

Drug hypersensitivity: Subject MKC-TI-005 311/3469: A 60 yo Caucasian male in Bulgaria received TP (not TI) for 2 days during the run in phase of the protocol. The subject had a history of cold-induced urticaria at trial entry. Two days after starting TP the subject experienced canker sores on the mouth and laryngeal mucosa and urticaria on the fingertips. The subject was withdrawn from the study and not rechallenged. Note: the subject never received TI

Drug hypersensitivity: Subject MKC-TI-102 208/1169: A 59 yo Caucasian male in the U.S. received TI for one day when he experienced throat irritation, pain and itching that was considered hypersensitivity to TI. No treatment was given for the event. The subject withdrew from the trial. The medical history for the subject says he had a history of “hypersensitivity”, allergic rhinitis, and asthma.

**Reviewer’s comment: Subjects with asthma should not have been included in the trial.**

Alanine aminotransferase increased/Gamma-glutamyltransferase increased: Subject MKC-TI-103 603/1901. A 56 yo Hispanic female in Mexico had screening liver tests on 28 Mar 2007 which showed an ALT of 19 U/L (reference range 0-30 U/L) and a GGT of 45 U/L (reference range 6-32 U/L). On 09 Apr 2007 she was going to be started on TI and then was found to have an ALT of 39 U/L and a GGT of 282 U/L at the 09 Apr 2007 visit, prior to being dosed with TI. The subject discontinued treatment on 24 Apr 2007. At the follow up visit on 26 Apr 2007 the ALT was 19 U/L and the GGT was 68 U/L.

**Table 7.20 -Incidence of TEAEs Leading to Discontinuation in Type 1 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

	TI		Comparator	
	(n = 614)		(n = 599)	
	(SYE = 540)		(SYE = 682)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Any TEAE leading to discontinuation	43 (7.0)	[8.0]	4 (0.7)	[0.6]
Respiratory, thoracic and mediastinal disorders	26 (4.2)	[4.8]	0	0
Cough	19 (3.1)	[3.5]	0	0
Dyspnea	2 (0.3)	[0.4]	0	0
Asthma	1 (0.2)	[0.2]	0	0
Bronchial obstruction	1 (0.2)	[0.2]	0	0
Hemoptysis	1 (0.2)	[0.2]	0	0
Productive cough	1 (0.2)	[0.2]	0	0
Respiratory disorder	1 (0.2)	[0.2]	0	0
Respiratory tract congestion	1 (0.2)	[0.2]	0	0
Upper respiratory tract congestion	1 (0.2)	[0.2]	0	0
Metabolism and nutrition disorders	7 (1.1)	[1.3]	1 (0.2)	[0.1]
Hyperglycemia	3 (0.5)	[0.6]	0	0
Hypoglycemia	2 (0.3)	[0.4]	0	0
Diabetes mellitus inadequate control	1 (0.2)	[0.2]	0	0
Diabetic ketoacidosis	1 (0.2)	[0.2]	0	0
Hypoglycemia seizure	1 (0.2)	[0.2]	0	0
Ketosis	1 (0.2)	[0.2]	0	0
Metabolic syndrome <sup>a</sup>	0	0	1 (0.2)	[0.1]
Cardiac disorders	3 (0.5)	[0.6]	0	0
Angina pectoris	1 (0.2)	[0.2]	0	0
Cardiac failure congestive	1 (0.2)	[0.2]	0	0
Palpitations	1 (0.2)	[0.2]	0	0
General disorders and administration site conditions	3 (0.5)	[0.6]	0	0
Chest discomfort	1 (0.2)	[0.2]	0	0
Chest pain	1 (0.2)	[0.2]	0	0
Fatigue	1 (0.2)	[0.2]	0	0
Infections and infestations	3 (0.5)	[0.6]	1 (0.2)	[0.1]
Bronchitis	1 (0.2)	[0.2]	0	0
Sinusitis	1 (0.2)	[0.2]	0	0
Upper respiratory tract infection	1 (0.2)	[0.2]	0	0
Pulmonary tuberculosis	0	0	1 (0.2)	[0.1]
Investigations	3 (0.5)	[0.6]	0	0
Pulmonary function test decreased	1 (0.2)	[0.2]	0	0
Weight decreased	1 (0.2)	[0.2]	0	0
Weight increased	1 (0.2)	[0.2]	0	0
Gastrointestinal disorders	2 (0.3)	[0.4]	0	0
Dry mouth	1 (0.2)	[0.2]	0	0
Dyspepsia	1 (0.2)	[0.2]	0	0

**Table 7.20 -Incidence of TEAEs Leading to Discontinuation in Type 1 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

	TI		Comparator	
	(n = 614)		(n = 599)	
	(SYE = 540)		(SYE = 682)	
Halitosis	1 (0.2)	[0.2]	0	0
Stomach discomfort	1 (0.2)	[0.2]	0	0
Vomiting	1 (0.2)	[0.2]	0	0
Nervous system disorders	2 (0.3)	[0.4]	0	0
Headache	2 (0.3)	[0.4]	0	0
Vascular disorders	2 (0.3)	[0.4]	0	0
Aortic calcification	1 (0.2)	[0.2]	0	0
Circulatory collapse	1 (0.2)	[0.2]	0	0
Eye disorders	1 (0.2)	[0.2]	0	0
Vision blurred	1 (0.2)	[0.2]	0	0
Musculoskeletal and connective tissue disorders	1 (0.2)	[0.2]	0	0
Musculoskeletal chest pain	1 (0.2)	[0.2]	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.2)	[0.2]	0	0
Breast cancer	1 (0.2)	[0.2]	0	0
Psychiatric disorders	1 (0.2)	[0.2]	0	0
Depression	1 (0.2)	[0.2]	0	0
Injury, poisoning and procedural complications	0	0	1 (0.2)	[0.1]
Head injury	0	0	1 (0.2)	[0.1]
Road traffic accident	0	0	1 (0.2)	[0.1]
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.2)	[0.1]
Pregnancy	0	0	1 (0.2)	[0.1]

<sup>a</sup> Review of this subjects’s narrative by the clinical reviewer suggests this subject actually discontinued for hospitalization due to fever

AE = adverse event; SYE = subject-years exposure; TEAE = treatment-emergent AE.

Each SOC includes the total number of subjects by SOC.

Each subject may be counted more than once in different preferred terms for each AE reported.

Source: Table 36, ISS

Case narratives:

Asthma: Subject MKC-TI-009/229/1866: A 57 yo Caucasian male in the U.S. received TI 45 U three times daily with meals, with 34 IU of Lantus once daily. The event occurred 165 days after the onset of TI treatment. The narrative reports that the subject had no history of asthma but the investigator verbatim term for the reason for discontinuation was “exacerbation of asthma.” The patient was reported, however, to have “sleep apnea syndrome.” There are no clinical details of the event provided in the narrative.

Asthma, bronchitis, bronchospasm, cough, hemoptysis, wheezing (multiple preferred terms)  
Subject MKC-TI-009 186/1064: A 66 yo Caucasian female in the U.S. received TI for 231 days before the event(s). The subject experienced these events listed simultaneously (i.e. all of these preferred terms appear to be related to one event). The subject was treated with Proventil and Xopenex and withdrawn from the trial due to these events.

**Reviewer's comment: It is not clear how this subject is included in the table above because some of these preferred terms are not listed in the table.**

**Reviewer's comment: Overall, the higher rate of discontinuations due to non-pulmonary adverse events (pulmonary events are discussed in the pulmonary safety review) is not of major concern because of the lack of concentration in any one system organ class and the observation that the overall rate of adverse events is similar between treatment groups. These observations suggest that the higher rate of discontinuation due to adverse events seen among TI-treated subjects may, at least partly, be due to the open-label trial design. An alternate (though unlikely) explanation is that when TI caused AEs, it did so with greater severity than did comparator, and that increased severity resulted in an increased rate of discontinuations due to AEs.**

7.3.3.4 Explorations for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions, and drug-drug interactions related to dropouts

Analysis of demographic data (age, sex and race) for permanent discontinuations revealed few differences by demography. The only difference noted in the disposition by age, sex and race was the difference in the completers by sex, with more male subjects having early discontinuations in both treatment groups and both diabetes types; this finding did not seem to be influenced by the proportion of discontinuations due to adverse events, which was comparable between sexes in both diabetes types. Caveats to these conclusions are that the applicant's specified age ranges were 18-64 years, 65-74 years, and 75 years or older. Most patients were in the 18-64 age-group. Therefore, no meaningful comparisons regarding disposition by age are possible given that most subjects were included in the same age group. Also, the diabetes population was predominantly Caucasian (approximately 90%), thus the comparison with other races in terms of disposition is of limited value.

#### 7.3.4 Significant Adverse Events

Significant adverse events are those that are discussed in section 7.3.5.

### 7.3.5 Submission Specific Primary Safety Concerns

#### 7.3.5.1 Hypoglycemia

Hypoglycemia is a submission specific primary safety concern and is discussed in detail in this section. Hypoglycemia serious adverse events and hypoglycemia events leading to discontinuation are discussed in previous sections. Please, also, see Ms. Joy Mele's statistical review of hypoglycemia.

Hypoglycemia is a significant limiting factor in the glycemic management of diabetes, especially with subcutaneous insulin products. Although reducing blood glucose levels to target may help prevent microvascular complications of diabetes, the risk of hypoglycemia is generally increased with tighter glycemic goals. Severe hypoglycemia can be associated with higher rates of accidents, injuries and other acute serious adverse events and sometimes death. Fear of hypoglycemia can also inhibit patients and clinicians from titrating insulin to appropriate goals. Therefore, a new insulin therapy that is shown to be effectively non-inferior, but not superior, to already approved treatments also should not increase the risk of hypoglycemia beyond that seen with the comparators. Historically, the rates and therefore implications of hypoglycemia among type 1 and type 2 diabetics are different and therefore are analyzed and reviewed separately in this document.

The Sponsor stated that clinical pharmacology data in the TI development program suggested that TI might have a lower risk of hypoglycemia than subcutaneous injected short acting or regular human insulin (intermediate acting) because of its pharmacokinetic profile of rapid action. The implication of this PK profile is that TI delivers insulin during the time when postprandial glucose excursions occur and not beyond, and is, therefore, theoretically less likely to cause hypoglycemia.

#### Definitions of hypoglycemia:

Over the development of the Phase 1 through Phase 3 trials of TI, definitions for hypoglycemic events were modified somewhat. The Sponsor states that the definitions of severe hypoglycemia were consistent during the entire Phase 3 program.

**Reviewer's comment: As is shown in the following section, the definitions of severe hypoglycemia seem to vary from trial to trial, inconsistent with the sponsor's claim that the definitions were consistent across the Phase 3 program.**

Type 2 Diabetes:

**Trials 005, 0008, 014, and 026**

Mild/moderate hypoglycemia: Blood glucose level < 63 mg/dL or hypoglycemia-like symptoms that disappear with appropriate caloric intake. In the case of hypoglycemia symptoms, the Investigator (or the subject, in 026) was to confirm the hypoglycemia event with a blood glucose reading and record the blood glucose value.

Severe hypoglycemia: Events that require glucagon injections, glucose infusions, or assistance to the subject by a third party because of impaired consciousness, inability to cognate or irrational behavior.

### **Trials 030, 102, and 103**

Mild/moderate hypoglycemia: Hypoglycemia-like symptoms and a blood glucose measurement of < 63 mg/dL; OR in the absence of a blood glucose measurement, hypoglycemia-like symptoms that are relieved with carbohydrate intake or self-administered glucagon injections; OR any blood glucose measurement of  $\leq 49$  mg/dL and > 36 mg/dL with or without symptoms.

Severe hypoglycemia: Blood glucose concentration  $\leq 36$  mg/dL or when all 3 of the following occurred simultaneously - subject requires the assistance of another person; AND subject exhibits at least 1 cognitive neurological symptom; AND measured blood glucose is < 49 mg/dL, or, in the absence of a blood glucose measurement, clinical symptoms are reversed by oral carbohydrates, sc glucagon or intravenous glucose administration.

Type 1 Diabetes:

### **Trials 009 and 030**

Mild/moderate hypoglycemia: Hypoglycemia-like symptoms and a blood glucose measurement of  $\leq 63$  mg/dL; OR in the absence of a blood glucose measurement, hypoglycemia-like symptoms that are relieved with carbohydrate intake or self-administered glucagon injections; OR any blood glucose measurement of  $\leq 49$  mg/dL and > 36 mg/dL with or without symptoms.

Severe hypoglycemia: Blood glucose concentration  $\leq 36$  mg/dL or when all 3 of the following occurred simultaneously - subject requires the assistance of another person; AND subject exhibits at least 1 cognitive neurological symptom; AND measured blood glucose is  $\leq 49$  mg/dL, or, in the absence of a blood glucose measurement, clinical symptoms are reversed by oral carbohydrates, sc glucagon or intravenous glucose administration.

### **Trial 101**

Mild/moderate hypoglycemia: Blood glucose level < 63 mg/dL or symptoms which correlated with known hypoglycemic symptoms and which disappeared with appropriate caloric intake.

Severe hypoglycemia: A hypoglycemic episode that required glucagon injections, glucose infusions, or help by a third party due to impaired consciousness, impaired cognition, or irrational behavior.

Although the definitions of severe hypoglycemia differed from trial to trial, for the purposes of the pooled analyses the sponsor defined severe hypoglycemia as follows:

1. the subject requiring the assistance of another person, and
2. the presence of at least 1 cognitive neurological symptom (memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, seizure, or loss of consciousness), and
3. blood glucose was  $\leq 49$  mg/dL, or in the absence of a blood glucose measurement, those subjects whose clinical symptoms were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose administration.

Or –

any blood glucose value  $\leq 36$  mg/dL

In addition, at the pre-NDA meeting the FDA requested a separate analysis based on each criterion of the definition of clinically severe hypoglycemia listed above (except any BG value less than or equal to 36 mg/dL.) The Sponsor conducted a retrospective review of all hypoglycemia narratives in order to provide these separate analyses.

Data from non-pooled trials are not included in overall comparisons of incidence and event rates that are presented in the following sections.

It should be noted that some trials excluded patients who had had two or more severe hypoglycemic episodes within the six months prior to study entry. Thus, the study did not include patients with a known predisposition to frequent severe hypoglycemia.

#### 7.3.5.1.1 Hypoglycemia in Type 2 Diabetes

Seven trials contributed data to the pooled phase 2/3 hypoglycemia analysis. Three of the type 2 diabetes trials did not have an insulin product in the comparator arm. Table 7.21 shows trials with insulin and non-insulin comparator arms.

<b>Table 7.21 – Pooled Type 2 Diabetes Trials for Hypoglycemia Analyses</b>			
Trial	TI Group	Comparator Group Insulin vs. no insulin	Comparator Treatment
102	TI + insulin glargine	Insulin	Premix analog 70/30
014	TI + insulin glargine	Insulin	Insulin aspart + insulin glargine
030 <sup>a</sup>	TI + UC including insulin	Insulin	UC including insulin
103	TI + metformin or TI alone	Non-insulin	Metformin + secretagogue
030	TI + UC including insulin	Non-insulin	UC without insulin
026	TI + UC (OADs)	Non-insulin	UC without insulin
<sup>a</sup> Trial included both subjects taking insulin and not taking insulin UC=usual care; OAD=oral antidiabetic drug Source: Sponsor’s statistical analysis plan			

In all of the Sponsor’s analyses, non-insulin using comparator groups had lower rates of both mild/moderate and severe hypoglycemia than TI groups. Therefore, only analyses of TI vs. insulin comparator groups are shown.

In part because the definitions of severe hypoglycemia differed among trials, the Agency statistician, Ms. Mele, analyzed severe hypoglycemia separately for each trial. Results showed that all trials had similar rates of severe hypoglycemia between TI arms and insulin comparator groups except for trial 102 in which the rate of severe hypoglycemia was lower for the TI group vs. the insulin comparator group. Rates of total hypoglycemia were lower in TI groups than in insulin comparator groups for trials 102 and 014. Please see Ms. Mele’s review for further details.

**Reviewer’s comment: The clinical reviewer agrees with the Agency statistician, that the pooling strategy for hypoglycemia analyses is not ideal, because definitions differed among trials. Also, comparators differ among trials and each type of comparator may have a different rate of hypoglycemia. In addition, efficacy results differed, for example, in trial 014 TI+glargine was statistically worse in terms of efficacy than insulin aspart+glargine so more hypoglycemia would be expected in the comparator group. For these reasons emphasis should be placed on Ms. Mele’s analyses of hypoglycemia, which can be found in detail in her review. The Sponsor’s analyses are provided below for completeness.**

The Sponsor’s analyses were performed on the pooled phase 2/3 safety population for all trials, although as stated above only the analyses of TI vs. insulin comparator are shown because of the consistent results for comparisons with non-insulin therapies). The overall incidence (number of subjects with at least 1 event/total number of subjects in the analysis population) of hypoglycemia in all pooled type 2 subjects is shown in Table 7.22. [Note that in this analysis subjects with more than one event are counted only once. However, a secondary analysis performed by the Sponsor based on event days (i.e. the days when subjects reported an event) showed similar results (data not shown)]. Results were in favor of TI for total and mild/moderate hypoglycemia when compared with subjects in the insulin comparator group. In the Sponsor’s analyses severe hypoglycemia rates were also in favor of TI. However, these are

being driven by events of blood glucose  $\leq 49$  mg/dL and  $\leq 36$  mg/dL rather than by events requiring assistance. The frequency of hypoglycemic events (event rate per 100 subject-months) type 2 diabetes pooled trials were also calculated by the Sponsor and results were similar to analyses based on overall incidence.

**Table 7.22 – Incidence of Hypoglycemia Events – Type 2 Diabetes, Pooled Phase 2/3 Safety Population (excluding data on non-insulin comparators)**

	TI N=1795	Insulin Comparator N=972
Total hypoglycemia events	570 (31.8%)	467 (49.6%)
Odds ratio	0.466	
p value	<0.0001	
Event rate (per 100 subject months)	23.87	38.78
Mild/moderate hypoglycemia events	567 (31.6%)	465 (49.4%)
Odds ratio	0.466	
p value	<0.0001	
Event rate (per 100 subject months)	23.16	37.32
Severe hypoglycemia events	50 (2.8%)	71 (7.5%)
Odds ratio	0.359	
p value	<0.0001	
Event rate (per 100 subject months)	0.66	1.37
Events requiring assistance	9 (0.9%)	10 (1.3%)
Odds ratio	0.721	
p value	0.4787	
Event rate (per 100 subject months)	0.08	0.12
Events with cognitive neurological symptoms	7 (0.7%)	13 (1.7%)
Odds ratio	0.429	
p value	0.0724	
Event rate (per 100 subject months)	0.05	0.16
Events with blood glucose $\leq 49$ mg/dL	301 (16.8%)	270 (28.7%)
Odds ratio	0.501	
p value	<0.0001	
Event rate (per 100 subject months)	6.79	11.20
Events with blood glucose $\leq 36$ mg/dL	47 (2.6%)	70 (7.4%)
Odds ratio	0.372	
p value	<0.0001	
Event rate (per 100 subject months)	0.63	1.33
p values are based on logistic regression with terms for treatment and pooled site		
Source: Table 3, Comprehensive Integrated Review of Hypoglycemia		

**Reviewer’s comment: The Sponsor’s results are consistent with the Agency’s results if severe hypoglycemia is defined as an event requiring assistance.**

Severe hypoglycemia event rates over time were examined in the type 2 diabetes pooled trials. The greatest number of severe hypoglycemic events occurred during the Month 0 to 3 period for subjects in the TI and Insulin groups, when the subjects were titrating their medication doses and tended to decrease over time for both treatment groups.

### Hypoglycemic Events Related to Mealtimes - Type 2 Diabetes Pooled Trials:

The Sponsor performed analyses of the number of hypoglycemic events versus relationship to mealtimes using the pooled phase 2/3 safety population. The event rates were similar for TI-treated subjects for non-severe hypoglycemic events compared with the insulin-treated population (5 vs. 7 events/100 subject-months respectively) within one hour before a meal and at 0 to 2 hours after a meal (6 vs. 7 events/100 subject-months respectively). The event rates were slightly lower for TI-treated subjects for non-severe hypoglycemic events compared with the insulin-treated group at > 2 to 4 hours after a meal (3 vs. 10 events/100 subject-months, respectively), and at > 4 hours after a meal (4 vs. 9 events/100 subject-months, respectively). For severe hypoglycemic events the numbers were too small to calculate meaningful event rates.

**Reviewer's comment: The PK profile of TI suggests that the largest difference between the rates of hypoglycemia between the TI group and the Insulin group should be > 2 hours post meal which does seem to be the case based on the above data.**

Additionally, based on home glucose monitoring there was no obvious trend in hypoglycemic events by time of day (morning, afternoon, evening, late night).

### Relationship of TI Exposure with Hypoglycemia - Type 2 Diabetes Pooled Trials:

As previously discussed there was a trend towards decreasing numbers of hypoglycemic events over time for all subjects. Subject reporting severe hypoglycemic events were analyzed for possible relationships to extended study medication exposure (> 1 year on study drug) versus shorter study medication exposure (< 1 year on study drug). Both shorter-term and longer-term medication exposure in these trials led to similar associations between hypoglycemic events and treatment groups.

**Reviewer's comment: These data presented above suggest that there is not an increased risk of hypoglycemic events with prolonged exposure to TI.**

### Hypoglycemic Event Rates Among Subjects Reaching Glycemic Targets - Type 2 Diabetes Pooled Trials:

Because the risk of hypoglycemia increases with more intensive glycemic control, the event rates of hypoglycemia were examined by end-of-trial HbA1c goals ( $\leq 6.5$ ,  $\leq 7.0$ , and  $\leq 8.0\%$ ) (Table 7.23). The rate of mild/moderate hypoglycemia was numerically lower in the TI group for all three glycemic targets compared with the insulin comparator group. For severe hypoglycemia, the event rates are low and comparable among groups. However, the definition of severe hypoglycemia used in these analyses was the Sponsor's combined definition rather than just events requiring assistance.

<b>Table 7.23 – Hypoglycemia Event Rates by End of Trial HbA1c Responders – T2DM Pooled Safety Population</b>		
	TI N=1795	Insulin Comparator N=972
<b>HbA1c ≤ 6.5%</b>		
Mild/moderate events		
Number (%) subjects with events	60 (52.6)	65 (77.4)
Number of events	413	747
Event rate (per 100 subject-months)	31.23	66.35
Severe events		
Number (%) subjects with events	7 (6.1)	8 (9.5)
Number of events	10	8
Event rate (per 100 subject-months)	0.76	0.71
<b>HbA1c ≤ 7%</b>		
Mild/moderate events		
Number (%) subjects with events	167 (53.4)	133 (65.8)
Number of events	1178	1442
Event rate (per 100 subject-months)	35.25	52.35
Severe events		
Number (%) subjects with events	16 (5.1)	18 (8.9)
Number of events	33	24
Event rate (per 100 subject-months)	0.99	0.87
<b>HbA1c ≤ 8%</b>		
Mild/Moderate events		
Number (%) subjects with events	349 (42.7)	281 (58.2)
Number of events	2287	3121
Event rate (per 100 subject-months)	28.43	47.76
Severe events		
Number (%) subjects with events	30 (3.7)	43 (8.9)
Number of events	55	79
Event rate (per 100 subject-months)	0.68	1.21
Source: Table 23 Comprehensive Integrated Review of Hypoglycemia		

**Reviewer’s comment:** These data suggest that in conditions of comparable glycemic control among type 2 diabetics, the risk of mild/moderate hypoglycemia is lower with TI treatment than subcutaneous insulin treatment and the risk of severe hypoglycemia is comparable for TI vs. subcutaneous insulin therapy. However, since most hypoglycemia occurred early in the trials, it is not certain that analysis of end-of-trial HbA1c target is truly a reflection of hypoglycemia in relation to glycemic control.

Conclusions Hypoglycemia in Type 2 Diabetes:

Conclusions regarding hypoglycemia in type 2 diabetes should be based on the Agency’s analyses for reasons described above. Overall, patients with Type 2 diabetes appear to have a lower risk of mild/moderate hypoglycemia when using TI + basal subcutaneous insulin vs. subcutaneous insulin. The risk of severe hypoglycemia is comparable between TI treated patients and comparator insulin treated patients except for in trial 102 where TI treated patients had a lower risk of severe hypoglycemia than comparator insulin treated patients.

#### 7.3.5.1.2 Hypoglycemia in Type 1 Diabetes

Three type 1 diabetes trials were included in the pooled phase 2/3 safety population. For analysis of the pooled type 1 diabetes trials, the comparator groups (insulin aspart and “usual care” subjects) are combined into one Comparator population. Subjects treated with insulin aspart participated in either trial 009 or 101, while the “usual care” subjects participated in trial 030.

The Sponsor’s analyses were performed on the pooled phase 2/3 safety population. The overall incidence (number of subjects with at least 1 event/total number of subjects in the analysis population) of hypoglycemia in all pooled type 1 subjects is shown in Table 7.24. The incidence rates appear comparable between treatment groups for all analyses. Although the p values are <0.05 for some analyses, the analyses were not adjusted for multiple comparisons and the event rates suggest no difference between treatment groups.

	TI N=614	Insulin Comparator N=599
<b>Table 7.24 – Incidence of Hypoglycemia Events – Type 1 Diabetes, Pooled Phase 2/3 Safety Population</b>		
Total hypoglycemia events	466 (75.9%)	485 (81.0%)
Odds ratio	0.749	
p value	0.0413	
Event rate (per 100 subject months)	138.6	124.06
Mild/moderate hypoglycemia events	464 (75.6%)	484 (80.8%)
Odds ratio	0.743	
p value	0.0354	
Event rate (per 100 subject months)	133.16	117.74
Severe hypoglycemia events	149 (24.3%)	165 (27.5%)
Odds ratio	0.826	
p value	0.1576	
Event rate (per 100 subject months)	5.16	6.03
Events requiring assistance	22 (3.9%)	18 (3.3%)
Odds ratio	1.193	
p value	0.5862	
Event rate (per 100 subject months)	0.46	0.39
Events with cognitive neurological symptoms	29 (5.2%)	16 (2.9%)
Odds ratio	1.799	
p value	0.0644	
Event rate (per 100 subject months)	0.79	0.23
Events with blood glucose ≤ 49 mg/dL	383 (62.4%)	396 (66.1%)
Odds ratio	0.862	
p value	0.2308	
Event rate (per 100 subject months)	50.36	44.89
Events with blood glucose ≤ 36 mg/dL	145 (23.6%)	157 (26.2%)
Odds ratio	0.904	
p value	0.4260	
Event rate (per 100 subject months)	4.89	5.74
p values are based on logistic regression with terms for treatment, region, and baseline HbA1c		
Source: Table 25, Comprehensive Integrated Review of Hypoglycemia		

As with the type 2 diabetes analyses, the Agency statistician, Ms. Mele, analyzed hypoglycemia separately for each trial. Results showed that all type 1 diabetes trials had similar rates of severe hypoglycemia between TI arms and insulin comparator groups. The rate of total hypoglycemia was lower in TI group than in insulin comparator group for trial 009, although TI was not non-inferior to comparator in trial 009.

Similar to the type 2 diabetes program, the greatest number of severe and non-severe hypoglycemic events occurred during the Month 0 to 3 period for subjects in the TI and Comparator groups, when the subjects were titrating their medication doses, and decreased over time for both treatment groups.

Hypoglycemic Events Related to Mealtimes - Type 1 Diabetes Pooled Trials:

The Sponsor performed analyses of the number of hypoglycemic events versus relationship to mealtimes using the pooled phase 2/3 safety population. The event rates in the 2 groups were very low and had no obvious relationship with mealtimes. More severe hypoglycemic events were reported within one hour before a meal than for other time points for both treatment groups.

The Sponsor also reported the number of hypoglycemic events vs. time of day (morning, afternoon, evening, and late night) during the first four weeks of treatment based on home glucose monitoring. Event rates for mild/moderate and severe hypoglycemia were numerically higher for both groups (TI and comparator) in the morning compared with other times of day, but otherwise there was no pattern to hypoglycemic event rates vs. time of day.

#### Relationship of TI Exposure with Hypoglycemia - Type 1 Diabetes Pooled Trials:

As previously discussed there was a trend towards decreasing numbers of hypoglycemic events over time for all subjects. Subject reported severe hypoglycemic events were analyzed for possible relationships to extended study medication exposure (> 1 year on study drug) versus shorter study medication exposure (< 1 year on study drug) and no effect of treatment duration on hypoglycemia event rates was found.

#### Hypoglycemic Event Rates Among Subjects Reaching Glycemic Targets - Type 1 Diabetes Pooled Trials:

Because the risk of hypoglycemia increases with more intensive glycemic control, the event rates of hypoglycemia were examined by HbA1c goals ( $\leq 6.5$ ,  $\leq 7.0$ , and  $\leq 8.0\%$ ) (Table 7.25). For mild/moderate hypoglycemia, the event rate for subjects who reached all three treatment target categories was numerically higher among TI treated patients than among comparator treated patients. The opposite was seen for severe hypoglycemic event rates, where the event rate for TI treated patients was numerically lower than for comparator treated patients in all three treatment target categories, although the numbers were small and are probably statistically equivalent.

<b>Table 7.25 – Hypoglycemia Event Rates by End of Trial HbA1c Responders – T1DM Pooled Safety Population</b>		
	TI N=614	Insulin Comparator N=599
<b>HbA1c ≤ 6.5%</b>		
Mild/moderate events		
Number (%) subjects with events	24 (88.9)	24 (77.4)
Number of events	875	665
Event rate (per 100 subject-months)	224.76	142.09
Severe events		
Number (%) subjects with events	16 (59.3)	9 (29.0)
Number of events	31	40
Event rate (per 100 subject-months)	7.96	8.55
<b>HbA1c ≤ 7%</b>		
Mild/moderate events		
Number (%) subjects with events	61 (87.1)	74 (86.0)
Number of events	1754	2093
Event rate (per 100 subject-months)	189.77	171.67
Severe events		
Number (%) subjects with events	29 (41.4)	26 (30.2)
Number of events	76	105
Event rate (per 100 subject-months)	8.22	8.61
<b>HbA1c ≤ 8%</b>		
Mild/Moderate events		
Number (%) subjects with events	217 (85.8)	255 (85.6)
Number of events	5431	6256
Event rate (per 100 subject-months)	178.19	149.77
Severe events		
Number (%) subjects with events	79 (31.2)	91 (30.5)
Number of events	191	305
Event rate (per 100 subject-months)	6.27	7.30
Source: Table 38 Comprehensive Integrated Review of Hypoglycemia		

**Reviewer’s comment:** It is unclear why the rate of mild/moderate hypoglycemia was more prevalent among TI treated patients in conditions of comparable glycemic control than among comparator treated patients given that Ms. Mele’s analyses of individual trials showed no excess risk of mild/moderate hypoglycemia among TI treated subjects, but it is reassuring to note that in the Sponsor’s analyses the rate of severe hypoglycemia is roughly comparable between treatment groups. As described above, end-of-treatment HbA1c may not be the best reflection of hypoglycemia in relation to glycemic control.

Conclusions Hypoglycemia in Type 1 Diabetes:

These data suggest that the risk of hypoglycemia among type 1 diabetic subjects is similar for TI vs. comparator insulins. Conclusions regarding hypoglycemia in type 1 diabetes should be based on the Agency’s analyses for reasons described above. Please see Ms. Mele’s review for details.

7.3.5.2 Cardiovascular safety

Because the product under review in this application is an insulin, it is not expected to follow the recommendations of the Agency's 2008 "Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" that makes recommendations about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

Nonetheless, the Sponsor submitted an analysis of cardiovascular safety which evaluated cardiovascular events identified through an independent blinded MedDRA search strategy. In the Sponsor's analysis, multiple MedDRA system organ classes were inspected for all cardiac and/or vascular terminology including:

- Cardiac disorders
- General and administration site conditions
- Nervous system disorders
- Surgical and medical procedures
- Vascular disorders

**Reviewer's comment: Caveats to this analysis include the observation that the Sponsor did not include terms from Investigations such as ECG-related preferred terms and Creatine Kinase-related preferred terms and that subjects who had had a myocardial infarction or stroke within the preceding 6 months of screening for trials were not enrolled based on exclusion criteria which could "de-enrich" the study population for at-risk subjects.**

The incidence of any cardiovascular TEAE in subjects with type 1 and type 2 diabetes was comparable between treatment groups with 198/2409 subjects (8.2%, incidence rate =10.9 per 100 SYE) in the TI group and 171/1944 subjects (8.8%, incidence rate = 8.3 per 100 SYE) in the comparator group (Table 7.26). Each subject is counted only once per system organ class and preferred term, and may be counted more than once in different preferred terms.

This analysis should not be considered a "MACE" (major adverse cardiovascular events) analysis because the analysis included such terms representing arrhythmias, cardiac valvular disorders, and venous diseases among others, which are not considered MACE endpoints.

However, the number of subjects with ischemic events (e.g., angina pectoris, angina unstable, myocardial infarction, and myocardial ischemia) was low and similar between treatment groups suggesting no evidence in the phase 2/3 program of excess cardiovascular risk.

**Table 7.26 – Incidence of Cardiovascular TEAEs in Type 1 or Type 2 Subjects (Safety Population – Pooled Phase 2/3 Trials)**

System Organ Class Preferred Term	TI (n = 2409) (SYE = 1814)		Comparator (n = 1944) (SYE = 2051)		TP (n = 114) (SYE = 25)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Any cardiovascular TEAE	198 (8.2)	[10.9]	171 (8.8)	[8.3]	4 (3.5)	[16.0]
Cardiac disorders	79 (3.3)	[4.4]	73 (3.8)	[3.6]	1 (0.9)	[4.0]
Coronary artery disease	10 (0.4)	[0.6]	9 (0.5)	[0.4]	0	0
Angina pectoris	6 (0.2)	[0.3]	6 (0.3)	[0.3]	0	0
Atrial fibrillation	6 (0.2)	[0.3]	4 (0.2)	[0.2]	0	0
Myocardial ischemia	6 (0.2)	[0.3]	5 (0.3)	[0.2]	1 (0.9)	[4.0]
Tachycardia	5 (0.2)	[0.3]	5 (0.3)	[0.2]	0	0
Cardiac failure	4 (0.2)	[0.2]	1 (0.1)	[0.0]	0	0
Coronary artery atherosclerosis	4 (0.2)	[0.2]	3 (0.2)	[0.1]	0	0
Myocardial infarction	4 (0.2)	[0.2]	6 (0.3)	[0.3]	0	0
Palpitations	4 (0.2)	[0.2]	2 (0.1)	[0.1]	0	0
Angina unstable	3 (0.1)	[0.2]	2 (0.1)	[0.1]	0	0
Bradycardia	3 (0.1)	[0.2]	1 (0.1)	[0.0]	0	0
Cardiac failure congestive	3 (0.1)	[0.2]	1 (0.1)	[0.0]	0	0
Ischemic cardiomyopathy	3 (0.1)	[0.2]	0	0	0	0
Ventricular hypertrophy	3 (0.1)	[0.2]	3 (0.2)	[0.1]	0	0
Acute myocardial infarction	2 (0.1)	[0.1]	1 (0.1)	[0.0]	0	0
Bundle branch block right	2 (0.1)	[0.1]	0	0	0	0
Cardiomegaly	2 (0.1)	[0.1]	1 (0.1)	[0.0]	0	0
Cardiomyopathy	2 (0.1)	[0.1]	3 (0.2)	[0.1]	0	0
Coronary artery occlusion	2 (0.1)	[0.1]	1 (0.1)	[0.0]	0	0
Mitral valve incompetence	2 (0.1)	[0.1]	2 (0.1)	[0.1]	0	0
Sinus tachycardia	2 (0.1)	[0.1]	5 (0.3)	[0.2]	0	0
Tricuspid valve incompetence	2 (0.1)	[0.1]	0	0	0	0
Ventricular extrasystoles	2 (0.1)	[0.1]	1 (0.1)	[0.0]	0	0
Acute coronary syndrome	1 (0.0)	[0.1]	3 (0.2)	[0.1]	0	0
Age indeterminate myocardial infarction	1 (0.0)	[0.1]	1 (0.1)	[0.0]	0	0
Aortic valve sclerosis	1 (0.0)	[0.1]	0	0	0	0
Atrioventricular block first degree	1 (0.0)	[0.1]	1 (0.1)	[0.0]	0	0
Bundle branch block left	1 (0.0)	[0.1]	2 (0.1)	[0.1]	0	0
Cardiac arrest	1 (0.0)	[0.1]	2 (0.1)	[0.1]	0	0
Cardiac failure acute	1 (0.0)	[0.1]	0	0	0	0
Cardiac failure chronic	1 (0.0)	[0.1]	0	0	0	0
Cardiac flutter	1 (0.0)	[0.1]	0	0	0	0
Cardiac valve disease	1 (0.0)	[0.1]	0	0	0	0
Conduction disorder	1 (0.0)	[0.1]	0	0	0	0
Coronary artery stenosis	1 (0.0)	[0.1]	1 (0.1)	[0.0]	0	0
Extrasystoles	1 (0.0)	[0.1]	0	0	0	0
Hypertensive cardiomyopathy	1 (0.0)	[0.1]	0	0	0	0
Intracardiac thrombus	1 (0.0)	[0.1]	0	0	0	0
Pericarditis	1 (0.0)	[0.1]	0	0	0	0
Sinus arrhythmia	1 (0.0)	[0.1]	0	0	0	0
Sinus bradycardia	1 (0.0)	[0.1]	0	0	0	0

**Table 7.26 – Continued from previous page**

System Organ Class Preferred Term	TI (n = 2409) (SYE = 1814)		Comparator (n = 1944) (SYE = 2051)		TP (n = 114) (SYE = 25)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Supraventricular extrasystoles	1 (0.0)	[0.1]	1 (0.1)	[0.0]	0	0
Ventricular arrhythmia	1 (0.0)	[0.1]	0	0	0	0
Ventricular tachycardia	1 (0.0)	[0.1]	0	0	0	0
Aortic valve incompetence	0	0	1 (0.1)	[0.0]	0	0
Arrhythmia	0	0	1 (0.1)	[0.0]	0	0
Atrial flutter	0	0	1 (0.1)	[0.0]	0	0
Bifascicular block	0	0	1 (0.1)	[0.0]	0	0
Cardiac discomfort	0	0	1 (0.1)	[0.0]	0	0
Coronary artery insufficiency	0	0	2 (0.1)	[0.1]	0	0
Diastolic dysfunction	0	0	1 (0.1)	[0.0]	0	0
Hypertensive heart disease	0	0	1 (0.1)	[0.0]	0	0
Mitral valve prolapse	0	0	1 (0.1)	[0.0]	0	0
Supraventricular tachycardia	0	0	3 (0.2)	[0.1]	0	0
General disorders and administration site conditions	25 (1.0)	[1.4]	12 (0.6)	[0.6]	1 (0.9)	[4.0]
Chest pain	22 (0.9)	[1.2]	9 (0.5)	[0.4]	1 (0.9)	[4.0]
Non-cardiac chest pain	4 (0.2)	[0.2]	3 (0.2)	[0.1]	0	0
Axillary pain	1 (0.0)	[0.1]	0	0	0	0
Vascular disorders	116 (4.8)	[6.4]	97 (5.0)	[4.7]	2 (1.8)	[8.0]
Hypertension	70 (2.9)	[3.9]	68 (3.5)	[3.3]	1 (0.9)	[4.0]
Angiopathy	4 (0.2)	[0.2]	1 (0.1)	[0.0]	0	0
Flushing	4 (0.2)	[0.2]	1 (0.1)	[0.0]	0	0
Hypertensive crisis	4 (0.2)	[0.2]	4 (0.2)	[0.2]	0	0
Hypotension	4 (0.2)	[0.2]	2 (0.1)	[0.1]	0	0
Aortic stenosis	3 (0.1)	[0.2]	0	0	0	0
Orthostatic hypotension	3 (0.1)	[0.2]	0	0	0	0
Varicose vein	3 (0.1)	[0.2]	1 (0.1)	[0.0]	0	0
Hematoma	2 (0.1)	[0.1]	2 (0.1)	[0.1]	0	0
Hyperemia	2 (0.1)	[0.1]	0	0	0	0
Peripheral coldness	2 (0.1)	[0.1]	0	0	0	0
Phlebitis	2 (0.1)	[0.1]	2 (0.1)	[0.1]	0	0
Thrombophlebitis	2 (0.1)	[0.1]	0	0	1 (0.9)	[4.0]
Thrombophlebitis superficial	2 (0.1)	[0.1]	0	0	0	0
Aortic aneurysm	1 (0.0)	[0.1]	0	0	0	0
Aortic atherosclerosis	1 (0.0)	[0.1]	0	0	0	0
Aortic calcification	1 (0.0)	[0.1]	0	0	0	0
Arterial insufficiency	1 (0.0)	[0.1]	0	0	0	0
Atherosclerosis	1 (0.0)	[0.1]	0	0	0	0
Circulatory collapse	1 (0.0)	[0.1]	0	0	0	0
Deep vein thrombosis	1 (0.0)	[0.1]	1 (0.1)	[0.0]	0	0
Diabetic macroangiopathy	1 (0.0)	[0.1]	0	0	0	0
Hot flush	1 (0.0)	[0.1]	1 (0.1)	[0.0]	0	0

**Table 7.26 – Continued from previous page**

System Organ Class Preferred Term	TI (n = 2409) (SYE = 1814)		Comparator (n = 1944) (SYE = 2051)		TP (n = 114) (SYE = 25)	
	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]	n (%)	[per 100 SYE]
Intermittent claudication	1 (0.0)	[0.1]	1 (0.1)	[0.0]	0	0
Peripheral vascular disorder	1 (0.0)	[0.1]	0	0	0	0
Phlebothrombosis	1 (0.0)	[0.1]	1 (0.1)	[0.0]	0	0
Raynaud's phenomenon	1 (0.0)	[0.1]	0	0	0	0
Thrombosis	1 (0.0)	[0.1]	1 (0.1)	[0.0]	0	0
Varicophlebitis	1 (0.0)	[0.1]	0	0	0	0
Arterial disorder	0	0	2 (0.1)	[0.1]	0	0
Atherosclerosis obliterans	0	0	2 (0.1)	[0.1]	0	0
Essential hypertension	0	0	2 (0.1)	[0.1]	0	0
Extremity necrosis	0	0	1 (0.1)	[0.0]	0	0
Hypertensive angiopathy	0	0	1 (0.1)	[0.0]	0	0
Ischemia	0	0	1 (0.1)	[0.0]	0	0
Petechiae	0	0	1 (0.1)	[0.0]	0	0
Venous insufficiency	0	0	1 (0.1)	[0.0]	0	0
Venous stasis	0	0	1 (0.1)	[0.0]	0	0

AE = adverse event; TEAE = treatment-emergent AE.  
 Displayed TEAEs were identified by a MedDRA search strategy.  
 Each SOC includes the total number of subjects by SOC.  
 Each patient may be counted more than once in different preferred terms for each AE reported.  
 Source: Table 53, ISS

### 7.3.5.3 Device Safety issues:

Device safety issues are addressed by Dr. Melanie Choe from the Center for Devices and Radiologic Health, and by Dr. Alan Schroeder in his CMC review. Dr. Choe stated that “if the devices performed to specifications despite the complaints with the model C inhaler, and no adverse events were observed, as reported, the lack of direct comparison [i.e. validation of various improvements in Model D] should not be the subject of disapproval. The evaluation of clinical data should determine whether the device malfunction/misuses were factors in the safety and efficacy of the subject product.”

Based on evaluation of the clinical data by the clinical reviewer there appear to be only sporadic malfunction/misuse issues that were factors in the safety of the product. One subject (MKC-TI-009-455/1972) experienced hyperglycemia considered device-related and associated with a reported malfunction of the device (broken cap), the hyperglycemia resolved and did not result in discontinuation. The subject described in the SAE section (MKC-TI-009 495/1748) was hospitalized for presumed inappropriate use of the inhaler, not a device malfunction. The patient was retrained on the use of the inhaler and completed the trial.

Hyperglycemia may have several device-related causes, e.g., insufficient dose titration or failure of the device to deliver the intended dose, either due to malfunction or incorrect handling. In order to further investigate this, for all subjects who reported a TEAE of hyperglycemia, the device complaint records were reviewed by the Sponsor and analyses provided, to identify any subject who had also reported a device failure. This was done without consideration for timing of the respective reports.

Only 10 TEAEs of hyperglycemia in the clinical development program were found to originate from subjects treated with TI who reported device complaints of broken caps at any time. As breakage of the cap was a relatively common complaint for the MedTone Inhaler prior to hinge reinforcement in the commercial model (i.e. the change from Model C to Model D), this does not necessarily imply a causal relationship, but such a relationship cannot be excluded.

**Reviewer's comment: While a small number of subjects did apparently experience hyperglycemia due to broken cap issues which should be obsolete with the Model D inhaler, these small numbers of device issues cannot entirely account for the higher rate of hyperglycemia/lack of efficacy in the TI groups in the clinical trials.**

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

#### 7.4.1.1 Eliciting adverse events data in the development program

Protocols specified that all observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to study drug, were to be recorded as adverse events. Sources of AEs include data from physical examinations, laboratory results, ECGs, and information volunteered by patients during or between visits. Medical conditions present before the first dose of study drug were categorized as AEs if the disorder worsened after initiating study drug. The Sponsor asked investigators to evaluate each AE for severity, seriousness, relationship to study drug, duration, and action taken. Study personnel were instructed to follow each AE until resolution with assessments at each visit or more frequently, if needed.

#### 7.4.1.2 Incidence of common adverse events

This section reviews common AEs, defined as AEs occurring in >2% of patients in any treatment group. This frequency cutoff of >2% is inherently arbitrary, but is often used across pharmaceutical companies and across drug classes.

In the controlled phase 2/3 studies, in the T2DM population the most common adverse event was hypoglycemia for both TI and Comparator (Table 7.27). According to the raw incidence the rate of hypoglycemia is comparable between the TI and Comparator groups. However, the exposure-adjusted incidence (events per 100 subject-year exposure) of hypoglycemia is 44.7 for TI vs. 38.3 for Comparator.

**Reviewer's comment: Because of the differential dropout rate between TI and Comparator arms in many of the studies the subject-year exposure for Comparator is higher than for TI even though the number of patients for Comparator is fewer than for TI. Therefore, the difference in raw incidence compared with exposure-adjusted incidence of hypoglycemia could be due to the finding that hypoglycemic events tended to occur early in trials. This possibility is being discussed with the Agency's statistical team and will be incorporated into the cross discipline team leader memo.**

Cough was seen more frequently in the TI group relative to Comparator.

**Table 7.27 – Common AEs (Occurring in  $\geq 2\%$  of Either Treatment Group)  
 Raw and Exposure-Adjusted Incidence by Preferred Term – T2DM Pooled Controlled  
 Phase 2/3 Safety Population**

Preferred Term	TI (N=1795) SYE=1274		Comparator (n=1345) SYE=1369		TP (n=114) SYE=25	
	N (%)	per 100 SYE	N (%)	per 100 SYE	N (%)	per 100 SYE
Any AE	1275 (71.0)	100.1	958 (71.2)	70.0	73 (64.0)	292
Hypoglycemia	570 (31.8)	44.7	524 (39.0)	38.3	30 (26.3)	120
Cough	463 (25.8)	36.3	73 (5.4)	5.3	21 (18.4)	84.0
Upper respiratory infection	151 (8.4)	11.9	131 (9.7)	9.6	9 (7.9)	36.0
Nasopharyngitis	123 (6.9)	9.7	85 (6.3)	6.2	16 (14.0)	64.0
Hypertension	59 (3.3)	4.6	57 (4.2)	4.2	1 (0.9)	4.0
Headache	54 (3.0)	4.2	23 (1.7)	1.7	3 (2.6)	12.0
Influenza	52 (2.9)	4.1	48 (3.6)	3.5	0	0
Diarrhea	44 (2.5)	3.5	29 (2.2)	2.1	1 (0.9)	4.0
Arthralgia	43 (2.4)	3.4	38 (2.8)	2.8	0	0
Throat irritation	43 (2.4)	3.4	1 (0.1)	0.1	2 (1.8)	8.0
Productive cough	42 (2.3)	3.3	11 (0.8)	0.8	3 (2.6)	12.0
Fatigue	39 (2.2)	3.1	8 (0.6)	0.6	1 (0.9)	4.0
Bronchitis	37 (2.1)	2.9	19 (1.4)	1.4	2 (1.8)	8.0
Back pain	36 (2.0)	2.8	28 (2.1)	2.0	0	0
Nausea	36 (2.0)	2.8	14 (1.0)	1.0	1 (0.9)	4.0
Edema peripheral	34 (1.9)	2.7	28 (2.1)	2.0	0	0
Pharyngolaryngeal pain	33 (1.8)	2.6	11 (.8)	0.8	4 (3.5)	16.0
Urinary tract infection	31 (1.7)	2.4	37 (2.8)	2.7	0	0
Sinusitis	30 (1.7)	2.4	28 (2.1)	2.0	1 (0.9)	4.0
Diabetic retinopathy	26 (1.4)	2.0	31 (2.3)	2.3	0	0

Source: Table 48, ISS, Table G.2.9.2.1.1, Table G.2.9.2.1.3

**Reviewer’s comment: Because of few numbers in the TP groups the exposure adjusted incidence information is not comparable to that seen with TI and Comparator and should not be considered in estimating incidence of adverse events with TI. TP data should not be included in labeling.**

In the controlled phase 2/3 studies, in the T1DM population the most common adverse event was hypoglycemia for both TI and Comparator (Table 7.28). The discussion of the implications of evaluating adverse event rates using raw incidence or exposure-adjusted incidence in the T2DM population applies to the T1DM population as well.

Cough was seen more frequently in the TI group relative to Comparator. The common AEs observed in the T1DM population are similar to those seen in the T2DM population. One notable exception is that hyperglycemia occurred in 2.6% of the T1DM population but < 2 % of the T2DM population, and therefore, hyperglycemia is not listed in table 7.27.

**Table 7.28 – Common AEs (Occurring in  $\geq 2\%$  of Either Treatment Group)  
 Raw and Exposure-Adjusted Incidence by Preferred Term – T1DM Pooled Controlled  
 Phase 2/3 Safety Population**

Preferred Term	TI (N=614) SYE=540		Comparator (n=599) SYE=682	
	N (%)	per 100 SYE	N (%)	per 100 SYE
Any AE	544 (88.6)	100.7	539 (90.0)	79.0
Hypoglycemia	466 (75.9)	86.3	36 (81.0)	71.1
Cough	179 (29.2)	33.1	89 (6.0)	5.3
Upper respiratory infection	85 (13.8)	15.7	89 (14.9)	13.0
Nasopharyngitis	61 (9.9)	11.3	70 (11.7)	10.3
Influenza	34 (5.5)	6.3	37 (6.2)	5.4
Headache	33 (5.4)	6.1	19 (3.2)	2.8
Pulmonary function test decreased	27 (4.4)	5.0	8 (1.3)	1.2
Pharyngolaryngeal pain	23 (3.7)	4.3	9 (1.5)	1.3
Arthralgia	17 (2.8)	3.1	17 (2.8)	2.5
Hyperglycemia	16 (2.6)	3.0	9 (1.5)	1.3
Urinary tract infection	15 (2.4)	2.8	12 (2.0)	1.8
Productive cough	14 (2.3)	2.6	5 (0.8)	0.7
Sinusitis	13 (2.1)	2.4	16 (2.7)	2.3
Pain in extremity	6 (1.0)	NA	12 (2.0)	NA

Source: Table 47, ISS, Table G.1.9.2.2.3, Table G.1.9.2.2.1

## 7.4.2 Laboratory Findings

### 7.4.2.1 Overview of laboratory testing in the development program

### 7.4.2.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled Phase 2 and Phase 3 studies were used for comparisons of laboratory change and abnormalities between inhaled insulin and comparator(s).

### 7.4.2.3 Standard analyses and explorations of laboratory data

#### 7.4.2.3.1 Analyses focused on measures of central tendency

The following tables list mean changes from baseline in safety laboratory data for type 2 and type 1 diabetes, (Tables 7.29 and 7.30, respectively). Mean changes in hematology values over time in subjects with type 2 and type 1 diabetes were small and not notably different among the treatment groups in the controlled Phase 2/3 trials. MCH, MCH (pg) and MCV are part of the hematology panel; but these parameters were only measured in trial 103; therefore, analyses of these variables are only included in the type 2 diabetes table.

**Table 7.29 – Mean Changes in Laboratory Parameters from Baseline to Last Measurement in Type 2 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

Lab Category	Lab Test	Units	TI			Comparator			TP		
			N	Base-line Mean (SD)	Mean change from baseline (SD)	N	Base-line Mean (SD)	Mean change from baseline (SD)	N	Base-line Mean (SD)	Mean change from baseline (SD)
Hematology	Basophils	%	1044	0.3 (0.2)	0 (0.3)	640	0.3 (0.3)	0 (0.3)	104	0.3 (0.2)	0 (0.3)
	Eosinophils	%	1044	2.7 (2.6)	0.3 (2.7)	640	2.5 (2.5)	0.1 (2.6)	104	2.9 (2.0)	0.3 (1.6)
	MCH	pg	325	30.4 (1.7)	0 (0.8)	162	30.2 (2.0)	0 (0.7)	ND	ND	ND
	MCH		325	331.5 (11.3)	-0.6 (11.0)	162	332.5 (11.8)	-1.2 (10.3)	ND	ND	ND
	MCV	fL	325	91.7 (5.1)	0.2 (3.3)	162	90.9 (5.7)	0.3 (3.1)	ND	ND	ND
	Erythrocytes	10 <sup>6</sup> /μL	1477	4.7 (0.4)	-0.1 (0.3)	1184	4.8 (0.4)	-0.1 (0.3)	104	4.7 (0.4)	0 (0.3)
	Hematocrit	%	1477	43.7 (4.1)	-1.1 (3.0)	1184	44.2 (4.4)	-2.1 (3.2)	104	41.4 (3.4)	0.4 (3.3)
	Hemoglobin	g/dL	1576	14.3 (1.3)	-0.1 (0.8)	1240	14.3 (1.4)	-0.3 (0.9)	104	14.1 (1.3)	0 (1.1)
	Leukocytes	10 <sup>9</sup> /L	1477	6.8 (1.8)	0 (1.5)	1184	6.9 (1.8)	0 (1.5)	104	6.8 (1.7)	-0.1 (1.1)
	Lymphocytes	%	1044	31.8 (8.4)	-0.9 (8.3)	640	31.9 (8.1)	-0.2 (8.6)	104	30.4 (7.7)	0.2 (7.6)
	Monocytes	%	1044	5.8 (2.2)	0.1 (2.4)	640	5.9 (2.3)	-0.2 (2.4)	104	5.9 (2.3)	-0.1 (1.8)
	Neutrophils	%	1044	59.3 (9.4)	0.5 (9.7)	640	59.3 (9.2)	0.2 (10.4)	104	60.5 (8.9)	-0.3 (8.9)
	Platelets	10 <sup>9</sup> /L	1467	249 (61.5)	0.8 (36.9)	1179	252 (63.7)	2.9 (40.1)	104	251 (65.2)	-3.8 (32.1)
Liver Function	ALT	U/L	1542	27.8 (15.4)	-2.2 (12.9)	1215	26.2 (12.9)	0 (16.2)	104	30.3 (13.5)	-2.8 (11.1)
	AST	U/L	1542	22.6 (9.7)	0.1 (10.9)	1215	21.7 (8.4)	1.3 (11.6)	104	24.3 (9.8)	-0.7 (9.9)
	Alkaline Phosphatase	U/L	1541	80.5 (24.7)	-1.7 (16.7)	1214	81.4 (24.8)	-3.4 (18.0)	104	76.6 (27.5)	1.2 (11.5)
	Albumin	g/dL	1541	4.4 (0.3)	-0.1 (0.3)	1215	4.4 (0.3)	0 (0.2)	104	4.4 (0.3)	-0.1 (0.2)

	GGT	U/L	1298	37.2 (39.7)	0.1 (62.3)	1200	35.7 (62.8)	-1.1 (57.5)	59	27.3 (20.7)	1.5 (6.9)
	Total Protein	g/dL	1541	7.4 (0.4)	-0.1 (0.4)	1215	7.4 (0.5)	-0.1 (0.4)	104	7.3 (0.5)	-0.1 (0.4)
	Total Bilirubin	mg/dL	1537	0.5 (0.3)	0 (0.2)	1213	0.5 (0.3)	0 (0.4)	104	0.6 (0.4)	0 (0.2)
	Direct bilirubin	mg/dL	438	0.1 (0.1)	0 (0.1)	514	0.1 (0.1)	0 (0.1)	ND	ND	ND
Renal	BUN	mg/dL	1541	16.8 (5.1)	0.3 (4.2)	1215	16.8 (5.0)	0.8 (4.9)	104	16.4 (4.4)	0.5 (3.9)
	Creatinine	mg/dL	1542	0.9 (0.2)	0 (0.1)	1215	0.9 (0.2)	0 (0.1)	104	1 (0.2)	0 (0.1)
Chem-istry	Sodium	meq/L	1542	140.2 (3.1)	0 (3.3)	1215	140.1 (3.2)	0 (3.1)	104	140.2 (2.5)	0.9 (2.8)
	Chloride	mmol/L	1542	102.5 (3.0)	0.5 (3.1)	1214	102.3 (3.1)	0.6 (3.0)	104	103 (2.6)	0.8 (2.8)
	Bicarbonate	meq/L	1100	23.6 (2.9)	0.1 (3.0)	1045	24 (2.8)	-0.1 (2.7)	ND	ND	ND
	Potassium	meq/L	1542	4.5 (0.4)	-0.1 (0.5)	1214	4.5 (0.4)	0 (0.5)	104	4.5 (0.4)	0 (0.6)
	Magnesium	mg/dL	605	2 (0.2)	0 (0.2)	470	2 (0.2)	0 (0.2)	ND	ND	ND
	Calcium	mg/dL	1542	9.6 (0.5)	0 (0.6)	1214	9.5 (0.5)	0 (0.5)	104	9.5 (0.7)	0 (0.7)
	Phosphate	mg/dL	1486	3.7 (0.5)	0 (0.6)	1215	3.7 (0.6)	0 (0.6)	45	3.6 (0.5)	0.2 (0.6)
	Creatine Kinase	U/L	1098	132.1 (107.2)	13.1 (229.6)	1045	128.2 (92.1)	20.7 (228.2)	ND	ND	ND
	LDH	U/L	1099	170.7 (36.6)	7.1 (40.5)	1045	170.2 (37.7)	5.1 (46.1)	ND	ND	ND
	Uric acid	mg/dL	1048	5.1 (1.4)	0 (1.0)	640	4.9 (1.4)	0.2 (0.9)	104	5.5 (1.4)	-0.1 (0.8)
Lipids	Total cholesterol	mg/dL	1203	201.7 (49.6)	-4 (39.4)	1053	201.2 (48.5)	-3.7 (44.3)	95	195.2 (39.1)	-7.8 (32.0)
	HDL cholesterol	mg/dL	1202	51.3 (13.6)	-1.3 (8.6)	1052	52.3 (14.6)	-2.5 (8.7)	95	46.6 (9.5)	0.6 (5.8)
	LDL cholesterol	mg/dL	1160	112.8 (38.8)	0 (32.9)	1027	112.5 (39.6)	-0.6 (32.0)	86	110.9 (34.1)	-1.1 (27.2)
	Triglycerides	mg/dL	1203	199.4 (182.5)	-16 (144.8)	1053	194.3 (194.8)	-2.8 (298.1)	95	220.1 (147.5)	-42.3 (119.7)
Urinalysis	Albumin/creatinine ratio	mg/g Cr	956	85.5 (312.0)	5.4 (203.1)	676	94.2 (283.7)	18.5 (270.5)	97	55 (198.6)	3.4 (78.5)

ND = Not done

Source: Sponsor's Tables 33 and 39, Appendix 4 Integrated Summary of Safety

**Table 7.30 – Mean Changes in Laboratory Parameters from Baseline to Last Measurement in Type 1 Subjects (Safety Population – Pooled Controlled Phase 2/3 Trials)**

Lab Category	Lab Test	Units	TI			Comparator		
			N	Baseline Mean (SD)	Mean change from baseline (SD)	N	Baseline Mean (SD)	Mean change from baseline (SD)
Hema-	Basophils	%	315	0.4 (0.3)	0 (0.3)	315	0.4 (0.3)	0 (0.3)

tology								
	Eosinophils	%	315	2.8 (2.5)	0.7 (2.4)	315	2.8 (2.1)	0.1 (2.2)
	MCH	pg	ND	ND	ND	ND	ND	ND
	MCH		ND	ND	ND	ND	ND	ND
	MCV	fl	ND	ND	ND	ND	ND	ND
	Erythrocytes	10 <sup>6</sup> /μL	466	4.8 (0.5)	-0.1 (0.3)	543	4.8 (0.5)	-0.1 (0.3)
	Hematocrit	%	466	43.8 (4.4)	-1.5 (3.0)	543	44.1 (4.4)	-1.9 (3.1)
	Hemoglobin	g/dL	510	14.3 (1.4)	-0.2 (0.8)	565	14.4 (1.4)	-0.3 (0.8)
	Leukocytes	10 <sup>9</sup> /L	466	6.3 (1.6)	-0.2 (1.5)	543	6.2 (1.6)	-0.1 (1.4)
	Lymphocytes	%	315	30.8 (8.2)	0.1 (9.6)	315	31.7 (8.1)	-0.1 (7.9)
	Monocytes	%	315	6.5 (2.3)	-0.3 (2.4)	315	6.7 (2.3)	-0.7 (2.3)
	Neutrophils	%	315	59.5 (9.5)	-0.4 (11.3)	315	58.4 (9.4)	0.7 (9.6)
	Platelets	10 <sup>9</sup> /L	462	266.5 (62.8)	-2.2 (39.6)	539	262.9 (58.9)	-1.5 (38.8)
Liver Function	ALT	U/L	493	21.5 (11.8)	1.3 (15.3)	557	20.8 (10.1)	0.3 (11.5)
	AST	U/L	493	20.7 (9.0)	1.7 (14.9)	557	21.1 (9.1)	0.6 (10.2)
	Alkaline Phosphatase	U/L	492	82.4 (28.2)	-4.4 (15.2)	557	80 (24.3)	-3.6 (14.1)
	Albumin	g/dL	493	4.4 (0.3)	0 (0.3)	557	4.4 (0.3)	-0.1 (0.3)
	GGT	U/L	493	23.6 (33.0)	1.1 (18.7)	557	20.9 (21.2)	1.6 (35.0)
	Total Protein	g/dL	493	7.3 (0.4)	0 (0.4)	557	7.3 (0.5)	-0.1 (0.4)
	Total Bilirubin	mg/dL	493	0.6 (0.4)	0 (0.3)	557	0.6 (0.3)	0 (0.2)
	Direct bilirubin	mg/dL	158	0.2 (0.1)	0 (0.1)	216	0.2 (0.1)	0 (0.1)
Renal	BUN	mg/dL	493	15.4 (4.5)	0.2 (3.9)	557	15.5 (4.5)	0.6 (4.4)
	Creatinine	mg/dL	493	0.9 (0.2)	0 (0.1)	557	0.9 (0.2)	0 (0.1)
Chemistry	Sodium	meq/L	493	139.7 (3.1)	0.1 (3.6)	557	140 (3.1)	-0.2 (3.3)
	Chloride	mmol/L	493	102.1 (2.8)	0.6 (3.2)	557	102.4 (2.8)	0.8 (3.1)
	Bicarbonate	meq/L	440	25 (2.5)	0 (2.7)	501	25.1 (2.5)	-0.4 (2.7)
	Potassium	meq/L	492	4.5 (0.4)	-0.2 (0.5)	557	4.5 (0.5)	-0.1 (0.5)
	Magnesium	mg/dL	262	2 (0.2)	0 (0.2)	259	2 (0.2)	0 (0.2)
	Calcium	mg/dL	492	9.5 (0.4)	0 (0.5)	557	9.5 (0.4)	0 (0.4)
	Phosphate	mg/dL	493	3.7 (0.7)	0.1 (0.8)	557	3.7 (0.7)	0 (0.8)
	Creatinine Kinase	U/L	440	147.8 (371.3)	-11.7 (425.5)	501	136 (166.1)	-6.3 (170.8)
	LDH	U/L	440	164.8 (31.5)	13.3 (91.9)	501	165.6 (29.9)	5.7 (31.2)
	Uric acid	mg/dL	315	4 (1.1)	-0.1 (0.7)	315	3.9 (1.1)	0 (0.7)
Lipids	Total cholesterol	mg/dL	493	188 (36.8)	-3.1 (27.4)	557	188.4 (39.3)	-3.0 (27.3)
	HDL cholesterol	mg/dL	492	65.2 (16.5)	-3.4 (10.0)	557	64.5 (15.9)	-2.8 (10.6)
	LDL cholesterol	mg/dL	492	103.7 (31.0)	0.2 (22.5)	557	105.4 (33.7)	-0.8 (22.8)
	Triglycerides	mg/dL	493	95.3 (61.8)	1.8 (54.7)	557	94.2 (62.7)	2.0 (49.9)

Source: Sponsor's Tables 32 and 38, Appendix 4 Integrated Summary of Safety

#### 7.4.2.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.31 shows the number and percent of subjects with shifts from normal to abnormal from baseline to last measurement in type 2 subjects and Table 7.32 shows these data for the type 1 diabetes population. MCH, MCH (pg) and MCV are part of the hematology panel; but these

parameters were only done in trial 103; therefore, analyses of these variables are only included in the type 2 diabetes table.

There were no meaningful differences between the TI group and the comparator group for shifts in any of the laboratory variables at last measurement in type 2 subjects or type 1 subjects in the controlled Phase 2/3 trials.

<b>Table 7.31 – Number and Percent of Subjects With Shifts Above and Below the Normal Reference Range from Baseline to Last Measurement in Type 2 Subjects (Pooled Controlled Phase 2/3 Trials)</b>												
Lab Category	Lab Test	Units	Last Visit Value	TI Baseline Value			Comparator Baseline Value			TP Baseline Value		
				Below Normal	Normal	Above Normal	Below Normal	Normal	Above Normal	Below Normal	Normal	Above Normal
Hematology	Basophils	%	Below	0	0	0	0	0	0	0	0	0
			Above	0	1 (0.1)	0	0	1 (0.2)	0	0	1 (1.0)	0
	Eosinophils	%	Below	0	0	0	0	0	0	0	0	0
			Above	0	46(4.4)	36(3.4)	0	35 (5.5)	10(1.6)	0	5(4.8)	6 (5.8)
	MCH	pg	Below	9 (2.8)	2 (0.6)	0	3 (1.9)	1 (0.6)	0	ND	ND	ND
			Above	0	3 (0.9)	3 (0.9)	0	1 (0.6)	3 (1.9)	ND	ND	ND
	MCH	-	Below	33 (10.2)	40 (12.3)	0	15(9.3)	20 (12.3)	0	ND	ND	ND
			Above	0	1 (0.3)	0	0	0	0	ND	ND	ND
	MCV	fl	Below	7 (2.2)	3 (0.9)	0	2 (1.2)	1 (0.6)	0	ND	ND	ND
			Above	0	10 (3.1)	10 (3.1)	0	6 (3.7)	7 (4.3)	ND	ND	ND
	Erythrocytes	10 <sup>6</sup> /μL	Below	182 (12.3)	132 (8.9)	0	134 (11.3)	134 (11.3)	0	19 (18.3)	6 (5.8)	0
			Above	0	1 (0.1)	3 (0.2)	0	0	2 (0.2)	0	0	0
	Hematocrit	%	Below	29 (2.0)	46 (3.1)	0	19 (1.6)	59 (5.0)	0	9 (8.8)	3 (2.9)	0
			Above	0	7 (0.5)	1 (0.1)	0	2 (0.2)	4 (0.3)	0	0	0
	Hemoglobin	g/dL	Below	144 (9.2)	112 (7.1)	0	119 (9.6)	118 (9.5)	0	9 (8.7)	6 (5.8)	0
			Above	0	6 (0.4)	3 (0.2)	1 (0.1)	2 (0.2)	3 (0.2)	0	0	0
	Leukocytes	10 <sup>9</sup> /L	Below	29 (2.0)	47 (3.2)	0	20 (1.7)	36 (3.0)	0	5 (4.8)	4 (3.8)	0
			Above	0	27 (1.8)	7 (0.5)	0	18 (1.5)	6 (0.5)	0	0	1 (1.0)
	Lymphocytes	%	Below	107 (10.2)	118 (11.3)	3 (0.3)	59 (9.2)	75 (11.7)	2 (0.3)	8 (7.7)	3 (2.9)	0
			Above	1 (0.1)	34 (3.3)	19 (1.8)	4 (0.6)	27 (4.2)	9 (1.4)	0	2 (1.9)	0
	Monocytes	%	Below	3 (0.3)	12 (1.1)	0	1 (0.2)	6 (0.9)	0	4 (3.8)	3 (2.9)	0
			Above	0	35 (3.4)	8 (0.8)	0	15 (2.3)	6 (0.9)	0	0	2 (1.9)
	Neutrophils	%	Below	55 (5.3)	61 (5.8)	10 (1.0)	33 (5.2)	43 (6.7)	13 (2.0)	2 (1.9)	2 (1.9)	1 (1.0)
			Above	6 (0.6)	122 (11.7)	143 (13.7)	5 (0.8)	81 (12.7)	90 (14.1)	0	4 (3.8)	10 (9.6)
	Platelets	10 <sup>9</sup> /L	Below	19 (1.3)	19 (1.3)	0	17 (1.4)	12 (1.0)	0	0	4 (3.8)	0
			Above	0	4 (0.3)	3 (0.2)	0	6 (0.5)	3 (0.3)	0	0	1 (1.0)
Liver Function	ALT	U/L	Below	0	0	0	0	0	0	0	0	0
			Above	0	92 (6.0)	166 (10.8)	0	92 (7.6)	115 (9.5)	0	2 (1.9)	6 (5.8)
	AST	U/L	Below	0	0	0	0	0	0	0	0	0
			Above	0	51 (3.3)	46 (3.0)	0	52 (4.3)	45 (3.7)	0	2 (1.9)	3 (2.9)

Clinical Review  
 Lisa B. Yanoff, M.D.  
 NDA 22,472 N 000  
 Afrezza (Technosphere Human Insulin Inhalation Powder)

	Alkaline Phosphatase	U/L	Below	0	5 (0.3)	0	1 (0.1)	0	0	1 (1.0)	0	0
			Above	0	33 (2.1)	46 (3.0)	0	24 (2.0)	33 (2.7)	0	0	2 (1.9)
	Albumin	g/dL	Below	1 (0.1)	2 (0.1)	0	0	1 (0.1)	0	0	0	0
			Above	0	9 (0.6)	1 (0.1)	0	0	0	0	0	0
	GGT	U/L	Below	3 (0.2)	6 (0.5)	0	8 (0.7)	5 (0.4)	0	0	0	0
			Above	0	54 (4.2)	252 (19.5)	1 (0.1)	64 (5.3)	191 (15.9)	0	2 (3.4)	5 (8.5)
	Total Protein	g/dL	Below	1 (0.1)	7 (0.5)	0	3 (0.2)	11 (0.9)	0	0	0	0
			Above	0	6 (0.5)	3 (0.2)	0	8 (0.7)	6 (0.5)	0	0	0
	Total Bilirubin	mg/dL	Below	0	1 (0.1)	0	0	0	0	1 (1.0)	1 (1.0)	0
			Above	0	32 (2.1)	22 (1.4)	0	17 (1.4)	20 (1.6)	0	0	1 (1.0)
	Direct bilirubin	mg/dL	Below	0	0	0	0	0	0	ND	ND	ND
			Above	0	8 (1.6)	8 (1.6)	0	15 (2.6)	9 (1.6)	ND	ND	ND
Renal	BUN	mg/dL	Below	9 (0.6)	21 (1.4)	0	8 (0.7)	15 (1.2)	1 (0.1)	0	1 (1.0)	0
			Above	1 (0.1)	83 (5.4)	63 (4.1)	0	92 (7.6)	47 (3.9)	0	8 (7.7)	7 (6.7)
	Creatinine	mg/dL	Below	0	0	0	0	0	0	0	0	0
			Above	0	62 (4.0)	123 (8.0)	0	58 (4.8)	119 (9.8)	0	5 (4.8)	2 (1.9)
Chemistry	Sodium	meq/L	Below	3 (0.2)	14 (0.9)	0	1 (0.1)	12 (1.0)	0	0	1 (1.0)	0
			Above	0	14 (0.9)	3 (0.2)	0	21 (1.7)	6 (0.5)	0	1 (1.0)	0
	Chloride	mmol/L	Below	2 (0.1)	9 (0.6)	0	3 (0.2)	7 (0.6)	0	0	1 (1.0)	0
			Above	0	16 (1.0)	2 (0.1)	0	18 (1.5)	4 (0.3)	0	0	0
	Bicarbonate	meq/L	Below	113 (10.3)	130 (11.8)	0	84 (8.0)	115 (11.0)	0	ND	ND	ND
			Above	0	0	0	0	0	0	ND	ND	ND
	Potassium	meq/L	Below	4 (0.3)	10 (0.6)	0	0	1 (0.1)	0	0	0	0
			Above	0	46 (3.0)	11 (0.7)	0	49 (4.0)	11 (0.9)	0	3 (2.9)	0
	Magnesium	mg/dL	Below	5 (0.8)	10 (1.7)	0	2 (0.4)	6 (1.3)	0	ND	ND	ND
			Above	0	1 (0.2)	1 (0.2)	0	1 (0.2)	0	ND	ND	ND
	Calcium	mg/dL	Below	1 (0.1)	14 (0.9)	0	1 (0.1)	2 (0.2)	0	0	3 (2.9)	0
			Above	0	4 (0.3)	2 (0.1)	0	4 (0.3)	0	0	0	1 (1.0)
	Phosphate	mg/dL	Below	3 (0.2)	20 (1.3)	0	1 (0.1)	21 (1.7)	0	0	1 (2.2)	0
			Above	0	38 (2.6)	3 (0.2)	0	39 (3.2)	7 (0.6)	0	1 (2.2)	0
	Creatinine Kinase	U/L	Below	3 (0.3)	9 (0.8)	0	1 (0.1)	6 (0.6)	0	ND	ND	ND
			Above	0	49 (4.5)	50 (4.6)	0	54 (5.2)	42 (4.0)	ND	ND	ND
	LDH	U/L	Below	3 (0.3)	1 (0.1)	0	1 (0.1)	2 (0.2)	0	ND	ND	ND
			Above	0	65 (5.9)	18 (1.6)	0	49 (4.7)	8 (0.8)	ND	ND	ND
	Uric acid	mg/dL	Below	28 (2.7)	18 (1.7)	0	12 (1.9)	10 (1.6)	0	4 (3.8)	3 (2.9)	0
			Above	0	65 (6.2)	86 (8.2)	0	44 (6.9)	58 (9.1)	0	2 (1.9)	6 (5.8)
Lipids	Total cholesterol	mg/dL	Below	0	1 (0.1)	0	0	0	0	1 (1.1)	0	0
			Above	0	123 (10.2)	238 (19.8)	0	107 (10.2)	222 (21.1)	0	9 (9.5)	17 (17.9)
	HDL cholesterol	mg/dL	Below	33 (2.7)	49 (4.1)	1 (0.1)	25 (2.4)	57 (5.4)	0	8 (8.4)	3 (3.2)	0
			Above	0	30 (2.5)	72 (6.0)	0	27 (2.6)	77 (7.3)	0	3 (3.2)	1 (1.1)
	LDL cholesterol	mg/dL	Below	76 (6.6)	62 (5.3)	4 (0.3)	62 (6.0)	72 (7.0)	8 (0.8)	1 (1.2)	1 (1.2)	0
			Above	4 (0.3)	91 (7.8)	91 (7.8)	4 (0.4)	77 (7.5)	108 (10.5)	0	8 (9.3)	6 (7.0)

	Tri-glycerides	mg/dL	Below Above	15 (1.2) 0	23 (1.9) 93 (7.7)	0 289 (24.0)	12 (1.1) 1 (0.1)	23 (2.2) 93 (8.8)	0 228(21.7) 0	0 0	1 (1.1) 5 (5.3)	0 24 (25.3)
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ND = Not done or no data

Source: Sponsor's Tables 36 and 42, Integrated Summary of Safety

**Table 7.32 – Number and Percent of Subjects With Shifts Above and Below the Normal Reference Range from Baseline to Last Measurement in Type 1 Subjects (Pooled Controlled Phase 2/3 Trials)**

Lab Category	Lab Test	Units	Last Visit Value	TI (n=614) Baseline Value			Comparator (n=599) Baseline Value		
				Below Normal	Normal	Above Normal	Below Normal	Normal	Above Normal
Hematology	Basophils	%	Below	ND	ND	ND	ND	ND	ND
			Above						
	Eosinophils	%	Below	0	0	0	0	0	0
			Above	0	34(10.8)	14 (4.4)	0	14 (4.4)	12 (3.8)
	MCH	pg	Below	ND	ND	ND	ND	ND	ND
			Above						
	MCH	-	Below	ND	ND	ND	ND	ND	ND
			Above						
	MCV	fl	Below	ND	ND	ND	ND	ND	ND
			Above						
	Erythrocytes	10 <sup>6</sup> /μL	Below	42 (9.0)	61(13.1)	0	61(11.2)	63(11.6)	0
			Above	0	0	2 (0.4)	0	0	0
	Hematocrit	%	Below	5 (1.1)	20 (4.3)	0	7 (1.3)	14 (2.6)	0
			Above	0	2 (0.4)	0	0	2 (0.4)	0
	Hemoglobin	g/dL	Below	41 (8.0)	37 (7.3)	0	34 (6.0)	53 (9.4)	0
			Above	0	0	1 (0.2)	0	1 (0.2)	0
	Leukocytes	10 <sup>9</sup> /L	Below	20 (4.3)	25 (5.4)	0	16 (2.9)	24 (4.4)	0
			Above	0	2 (0.4)	0	0	4 (0.7)	1 (0.2)
	Lymphocytes	%	Below	31 (9.8)	49(15.6)	1 (0.3)	28 (8.9)	38(12.1)	0
			Above	3 (1.0)	12 (3.8)	2 (0.6)	0	14 (4.4)	10 (3.2)
	Monocytes	%	Below	0	2 (0.6)	0	1 (0.3)	3 (1.0)	0
			Above	1 (0.3)	12 (3.8)	4 (1.3)	0	10 (3.2)	7 (2.2)
	Neutrophils	%	Below	23 (7.3)	31 (9.8)	6 (1.9)	29 (9.2)	21 (6.7)	2 (0.6)
			Above	6 (1.9)	50(15.9)	35(11.1)	2 (0.6)	52(16.5)	39(12.4)
	Platelets	10 <sup>9</sup> /L	Below	0	2 (0.4)	0	2 (0.4)	5 (0.9)	0
			Above	0	5 (1.1)	1 (0.2)	0	2 (0.4)	1 (0.2)
Liver Function	ALT	U/L	Below	0	0	0	0	0	0
			Above	0	26 (5.3)	22 (4.5)	0	26 (4.7)	17 (3.1)
	AST	U/L	Below	0	0	0	0	0	0
			Above	0	22 (4.5)	9 (1.8)	0	20 (3.6)	6 (1.1)
	Alkaline Phosphatase	U/L	Below	0	0	0	0	0	0
			Above	0	2 (0.4)	14 (2.8)	0	8 (1.4)	15 (2.7)
	Albumin	g/dL	Below	1 (0.2)	0	0	1 (0.2)	0	0
			Above	0	2 (0.4)	0	0	1 (0.2)	0

	GGT	U/L	Below	10 (2.0)	11 (2.2)	0	6 (1.1)	7 (1.3)	0
			Above	0	14 (2.8)	28 (5.7)	0	16 (2.9)	29 (5.2)
	Total Protein	g/dL	Below	1 (0.2)	7 (1.4)	0	2 (0.4)	7 (1.3)	0
			Above	0	5 (1.0)	0	0	2 (0.4)	1 (0.2)
	Total Bilirubin	mg/dL	Below	0	0	0	0	0	0
			Above	0	7 (1.4)	21 (4.3)	0	13 (2.3)	18 (3.2)
	Direct bilirubin	mg/dL	Below	0	0	0	0	0	0
			Above	0	5 (2.8)	13 (7.3)	0	9 (3.7)	10 (4.1)
Renal	BUN	mg/dL	Below	8 (1.6)	15 (3.0)	0	6 (1.1)	22 (3.9)	0
			Above	0	13 (2.6)	8 (1.6)	1 (0.2)	34 (6.1)	10 (1.8)
	Creatinine	mg/dL	Below	0	0	0	0	0	0
			Above	0	17 (3.4)	27 (5.5)	0	16 (2.9)	28 (5.0)
Chemistry	Sodium	meq/L	Below	0	3 (0.6)	0	1 (0.2)	1 (0.2)	0
			Above	0	7 (1.4)	1 (0.2)	0	5 (0.9)	3 (0.5)
	Chloride	mmol/L	Below	1 (0.2)	5 (1.0)	0	2 (0.4)	1 (0.2)	0
			Above	0	10 (2.0)	1 (0.2)	0	10 (1.8)	2 (0.4)
	Bicarbonate	meq/L	Below	6 (1.4)	24 (5.5)	0	16 (3.2)	44 (8.8)	0
			Above	0	1 (0.2)	0	0	0	0
	Potassium	meq/L	Below	0	4 (0.8)	0	0	0	0
			Above	0	12 (2.4)	9 (1.8)	0	17 (3.1)	10 (1.8)
	Magnesium	mg/dL	Below	0	1 (0.4)	0	0	0	0
			Above	0	0	0	0	0	0
	Calcium	mg/dL	Below	0	1 (0.2)	0	0	2 (0.4)	0
			Above	0	0	0	0	0	0
	Phosphate	mg/dL	Below	1 (0.2)	5 (1.0)	0	0	19 (3.4)	0
			Above	2 (0.4)	22 (4.5)	4 (0.8)	2 (0.4)	15 (2.7)	2 (0.4)
	Creatinine Kinase	U/L	Below	2 (0.5)	2 (0.5)	0	1 (0.2)	0	0
			Above	0	23 (5.2)	21 (4.8)	0	23 (4.6)	8 (1.6)
	LDH	U/L	Below	0	0	0	0	1 (0.2)	0
			Above	0	21 (4.8)	4 (0.9)	0	20 (4.0)	5 (1.0)
	Uric acid	mg/dL	Below	21 (6.7)	23 (7.3)	0	22 (7.0)	21 (6.7)	0
			Above	0	1 (0.3)	5 (1.6)	0	3 (1.0)	1 (0.3)
Lipids	Total cholesterol	mg/dL	Below	0	0	0	0	0	0
			Above	0	31 (6.3)	46 (9.3)	0	34 (6.1)	55 (9.9)
	HDL cholesterol	mg/dL	Below	2 (0.4)	5 (1.0)	0	3 (0.5)	6 (1.1)	0
			Above	0	23 (4.7)	130 (26.4)	0	28 (5.0)	130 (23.3)
	LDL cholesterol	mg/dL	Below	31 (6.3)	25 (5.1)	0	34 (6.1)	23 (4.1)	0
			Above	0	12 (2.4)	15 (3.0)	0	14 (2.5)	21 (3.8)
	Triglycerides	mg/dL	Below	29 (5.9)	48 (9.7)	0	37 (6.6)	47 (8.4)	0
			Above	0	28 (5.7)	26 (5.3)	0	28 (5.0)	26 (4.7)

ND = Not done or no data

Source: Sponsor's Tables 35 and 41, Integrated Summary of Safety

### Clinically important shifts

Because of small numbers, clinically important (as defined below) laboratory result analyses were combined for type 1 and type 2 subjects.

The Sponsor defined clinical importance for hematology variables as follows:

- Hemoglobin decrease  $> 2$  g/dL AND absolute value  $< 9.0$  g/dL
- Hematocrit absolute value  $< 27$  or  $> 55\%$
- Red blood cell count absolute value  $< 3.0$  OR  $> 6.8 \times 10^6/\mu\text{L}$
- White blood cell count absolute value  $< 3.0$  or  $> 12.0 \times 10^9/\text{L}$
- Eosinophils increase  $\geq 100\%$  AND absolute value  $> 0.7 \times 10^9/\text{L}$
- Lymphocytes decrease  $\geq 33\%$  AND absolute value  $< 0.8 \times 10^9/\text{L}$
- Neutrophils increase  $\geq 100\%$  OR absolute value  $> 9.0 \times 10^9/\text{L}$ ; decrease  $\geq 33\%$  OR absolute value  $< 1.4 \times 10^9/\text{L}$
- Platelets increase  $\geq 50\%$  AND absolute value  $> 750 \times 10^9/\text{L}$ ; decrease  $\geq 50\%$  AND absolute value  $< 130 \times 10^9/\text{L}$

Table 7.33 shows the number and percent of type 1 or type 2 diabetic subjects with clinically important (as defined by the Sponsor) hematology values at any time during the trial after baseline for the safety population. The treatment groups have comparable rates of “clinically important” hematology values.

<b>Table 7.33 - Number and Percent of T2DM or T1DM Subjects who had “Clinically Important” Hematology Values at Any Time During the Trial After Baseline (Pooled Safety Population)</b>			
	TI N=2409	Comparator N=1944	TP N=114
Laboratory Parameter	n/N (%)	n/N (%)	n/N (%)
Erythrocytes	4/1994 (0.2)	1/1730 (0.1)	1/104 (1.0)
Hematocrit	3/1994 (0.2)	10/1730 (0.6)	1/104 (1.0)
Hemoglobin	1/2087 (0.0)	1/1808 (0.1)	1/104 (1.0)
Leukocytes	37/1944 (1.9)	30/1730 (1.7)	1/104 (1.0)
Platelets	5/1937 (0.3)	8/1727 (0.5)	0/104

Source: Table3 61, ISS

The Sponsor defined clinical importance for chemistry variables as follows:

- Albumin decrease  $\geq 1.0$  g/dL AND absolute value  $< 2.5$  g/dL
- Alkaline Phosphatase increase  $\geq 100\%$  AND absolute value  $> 250$  U/L
- ALT/AST increase  $\geq 100\%$  AND absolute value  $> 3 \times \text{ULN}$
- Bicarbonate –increase  $> 5$  mmol/L AND absolute value  $> 35$  mmol/L or decrease  $> 5$  mmol/L AND absolute value  $< 17$  mmol/L
- BUN increase  $\geq 50\%$  AND absolute value  $> 50$  mg/dL
- Calcium –increase  $\geq 2.0$  mg/dL AND absolute value  $> 11$  mg/dL or decrease  $\geq 1.5$  mg/dL AND absolute value  $< 7.0$  mg/dL
- CPK absolute value  $> 1000$  IU/L
- Creatinine increase  $\geq 50\%$  AND absolute value  $> 2.0$  mg/dL

- Phosphorus - increase  $\geq 2.5$  mg/dL AND absolute value  $> 6.0$  mg/dL or decrease  $\geq 1.0$  mg/dL AND absolute value  $< 2.0$  mg/dL
- Lactate Dehydrogenase increase  $\geq 100\%$  AND absolute value  $> 750$  IU/L
- Magnesium absolute value  $< 1$  or  $> 3$  mEq/L
- Potassium - increase  $\geq 0.8$  mmol/L AND absolute value  $> 5.5$  mmol/L or decrease  $\geq 0.8$  mmol/L AND absolute value  $< 3.0$  mmol/L
- Sodium - increase  $\geq 10$  mmol/L AND absolute value  $> 150$  mmol/L or decrease  $\geq 10$  mmol/L AND absolute value  $< 120$  mmol/L
- Fasting Triglycerides increase  $\geq 200\%$  OR absolute value  $> 600$  mg/dL
- Total Bilirubin increase  $\geq 100\%$  AND absolute value  $> 3$  mg/dL
- Uric acid increase  $\geq 50\%$  AND absolute value  $> 10.0$  mg/dL
- Chloride absolute value  $< 90$  or  $> 120$  mEq/L
- Cholesterol increase  $\geq 100\%$  AND absolute value  $> 300$  mg/dL
- Total Protein absolute value  $< 4$  or  $> 12$  g/dL

The number and percent of type 1 or type 2 subjects who had clinical chemistry values that met clinically important criteria were small and essentially balanced among the treatment groups in the controlled Phase 2/3 trials as shown in Table 7.34.

**Table 7.34 - Number and Percent of T2DM or T1DM Subjects who had “Clinically Important” Chemistry Values at Any Time During the Trial After Baseline (Pooled Safety Population)**

	TI N=2409	Comparator N=1944	TP N=114
Laboratory Parameter	n/N (%)	n/N (%)	n/N (%)
ALT	9/2035 (0.4)	6/1773 (0.3)	0/104
Alkaline Phosphatase	1/2034 (0.0)	2/1773 (0.1)	0/104
AST	7/2035 (0.3)	4/1773 (0.2)	0/104
Bicarbonate	7/1540 (0.5)	8/1547 (0.5)	0/1
Bilirubin	0/2035	2/1773 (0.1)	0/104
Blood urea nitrogen	0/2035	1/1773 (0.1)	0/104
Calcium	7/2034 (0.3)	4/1773 (0.2)	0/104
Chloride	3/2035 (0.1)	3/1773 (0.2)	0/104
Cholesterol	4/1696 (0.2)	2/1611 (0.1)	0/95
Creatine kinase	11/1540 (0.7)	15/1547 (1.0)	0/0
Creatinine	1/2036 (0.0)	2/1773 (0.1)	0/104
Lactate dehydrogenase	2/1540 (0.1)	0/1547	0/0
Phosphate	3/1980 (0.2)	10/1773 (0.6)	0/45
Potassium	42/2034 (2.1)	40/1773 (2.3)	1/104 (91.0)
Sodium	1/2035 (0.0)	2/1773 (0.1)	0/104
Uric acid	1/1363 (0.1)	0/955	0/104

Source: Table 64, ISS

#### 7.4.2.3.3 Marked outliers and dropouts for laboratory abnormalities

Discontinuations were discussed in section 7.3.3. Briefly, only one subject with type 2 diabetes, who was in the control arm in trial 102, discontinued due to a hematologic abnormality. None of the subjects who received at least one dose of TI discontinued treatment because of a chemistry laboratory abnormality including liver function tests and creatinine. Three patients who discontinued during the run-in period and were using only TP discontinued due to elevated liver enzymes.

At the Agency's request (30 Oct 2009) additional analyses of liver (ALT and total bilirubin) and renal function (creatinine) laboratory tests were performed by the Sponsor focusing on marked outliers (Table 7.35). The rate of significant outliers is comparable among groups. The clinical reviewer reviewed all case narratives for TI treated subjects with ALT > 5 X ULN, total bilirubin > 5 X ULN, and serum creatinine > 2 X ULN. All narratives suggested alternative causes of the laboratory abnormalities. Most of these cases included patients who already had elevated values at baseline or had single elevated values during the trial which resolved spontaneously.

**Table 7.35 – Number and Percentages of Subjects Meeting Various Lab Cutpoints – T1DM and T2DM Subjects Combined – Pooled Safety Population**

Cutpoints	TI N=2409 n (%)	TP N=114 n (%)	Other Insulin N=1541 n (%)	Comparator Non-insulin N=403 n (%)	All Comparator N=1944 n (%)
ALT (U/L)					
> ULN and ≤ 3 X ULN	759 (31.5)	20 (17.5)	448 (29.1)	143 (35.5)	591 (30.4)
> 3 X ULN and ≤ 5 X ULN	24 (1.0)	1 (0.9)	14 (0.9)	3 (0.7)	17 (0.9)
> 5 X ULN and ≤ 10 X ULN	4 (0.2)	0	2 (0.1)	1 (0.2)	3 (0.2)
> 10 X ULN	0	0	1 (0.1)	0	1 (0.1)
Total Bilirubin (mg/dL)					
> ULN and ≤ 2 X ULN	206 (8.6)	5 (4.4)	120 (7.8)	15 (3.7)	135 (6.9)
> 2 X ULN and ≤ 5 X ULN	14 (0.6)	0	14 (0.9)	0	14 (0.7)
> 5 X ULN and ≤ 10 X ULN	0	0	1 (0.1)	0	1 (0.1)
> 10 X ULN	0	0	1 (0.1)	0	1 (0.1)
Serum Creatinine (mg/dL)					
> ULN and ≤ 1.5 X ULN	506 (21.0)	14 (12.3)	382 (24.8)	86 (21.3)	468 (24.1)
> 1.5 X ULN and ≤ 2 X ULN	26 (1.1)	0	27 (1.8)	2 (0.5)	29 (1.5)
> 2 X ULN	6 (0.2)	0	4 (0.3)	1 (0.2)	5 (0.3)

Source: Sponsor's submission 10 Nov 2009

In the information request from the Agency on 30 Oct 2009, the Sponsor was also requested to provide information for patients in their phase 2/3 database as well as in their entire development program to date for the following parameters: subjects with ALT > 3X ULN and total bilirubin > 2X ULN and alkaline phosphatase < 2.5 X ULN (Hy's Law chemistry) and subjects who met the criteria: ALT > 3X ULN and total bilirubin > 2x ULN (regardless of alkaline phosphatase). The Sponsor responded with information from their phase 2/3 program but reported that it would be

extremely labor intensive to provide these data for their entire development program and that they would need more time to complete the request.

In the phase 2/3 program, there were no patients who met the parameter of Hy's Law chemistry. There was one patient who met the parameter of ALT >3X ULN and total bilirubin >2x ULN (regardless of alkaline phosphatase). This patient, MKC-TI-102-2603, was randomized to comparator treatment (70/30 Novolog mix) and developed pancreatic cancer during the trial.

Based on these reassuring findings in the phase 2/3 program, the Sponsor was informed that providing the data for their entire development program was not necessary.

#### 7.4.2.4 Additional analyses and explorations of laboratory data

Because there were no clinically meaningful differences between TI and comparator groups for laboratory abnormalities in controlled Phase 2/3 trials, explorations for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions, and drug-drug interactions were not conducted.

### 7.4.3 Vital Signs

#### 7.4.3.1 Overview of vital signs testing in the development program

Vital signs were measured at baseline and at end of study or time of study discontinuation. Vital signs evaluated included weight, height, blood pressure (systolic and diastolic), temperature, radial pulse, respiratory rate, and waist circumference. BMI was calculated based on measurements of weight and height collected at baseline, and weight collected at post-baseline visits. BMI is discussed in section 6 with efficacy parameters.

#### 7.4.3.2 Selection of studies and analyses for overall drug/control comparisons

The clinical reviewer used the controlled Phase 2 and Phase 3 populations for comparisons of frequencies of vital signs abnormalities.

#### 7.4.3.3 Standard analyses and explorations of vital signs data

##### 7.4.3.3.1 Analyses focused on measures of central tendency

## Type 2 Diabetes

No clinically meaningful changes in any of the vital signs variables occurred either within or between treatment groups in subjects with type 2 diabetes in the controlled phase 2/3 trials. Mean changes in vital signs were small and similar in both treatment groups. Mean changes tended to be larger at month 24 when fewer TI subjects had available data. Changes in specific variables are summarized below.

- *Temperature*: there were no changes from baseline in mean or median temperature at any time point in either the TI group or in the comparator group.
- *Systolic blood pressure*: there were decreases in systolic blood pressure at all time points from month 3 to month 18 in the TI group. Mean changes ranged from -0.7 mmHg at month 6 to -1.3 mmHg at month 18. There were similar changes in the comparator group. At month 24, there was a mean increase in systolic blood pressure of 1.2 mmHg in the TI group, and a 1.0 mmHg mean decrease in the comparator group. However, only 137 of 1795 randomized TI subjects had data at this time point, and no other time point showed an increase in SBP.
- *Diastolic blood pressure*: there were decreases in systolic blood pressure at all time points in the TI group. Mean changes ranged from -0.8 mmHg at month 3 to -2.8 mmHg at month 24. There were similar, but somewhat smaller, changes in diastolic blood pressure in the comparator group.
- *Pulse rate*: there were no meaningful variations in either mean or median pulse rates in either treatment group. The largest change was an increase of 1.3 beats/min in mean pulse rate in the comparator group at month 18.
- *Respiratory rate*: Respiratory rate did not change meaningfully in either treatment group. The largest change was a mean increase of 0.6 breaths/min in the TI group at month 24.

## Type 1 Diabetes

No clinically meaningful changes in any of the vital signs variables occurred either within or between treatment groups in subjects with type 1 diabetes and were similar among the treatment groups in the controlled phase 2/3 trials. Mean changes in vital signs were small and similar in both treatment groups. Mean changes tended to be larger at month 24 when fewer TI subjects had available data. Changes in specific variables are summarized below.

- *Temperature*: there were no changes from baseline in mean or median temperature at any time point in either treatment group.
- *Systolic blood pressure*: there were mean decreases in systolic blood pressure at all time points from month 3 to month 18 in the TI group. Mean changes ranged from -1.3 mmHg at month 3 to -2.7 mmHg at month 6. There were similar but smaller changes in the comparator group.
- *Diastolic blood pressure*: there were decreases in diastolic blood pressure at all time points from month 3 to month 18 in the TI group. Mean changes ranged from -0.7 mmHg at month 12 to -1.5 mmHg at month 18. There were similar changes in the comparator group.
- *Pulse rate*: In the TI group, pulse rate varied from a mean decrease of 0.6 beats/min at month 6 to a mean increase of 0.9 beats/minute at month 18. Changes in the comparator group varied similarly.

- *Respiratory rate*: Respiratory rate did not vary meaningfully in either treatment group. Mean changes in respiratory rate were  $\leq 1$  breath/minute at all time points.

#### 7.4.3.3.2 Analyses focused on outliers or shifts from normal to abnormal

Because there were no concerning signals in the analyses of central tendency including analyses of means, medians, and ranges of vital sign values, analyses focusing on shifts from normal to abnormal were not performed.

#### 7.4.3.3.3 Marked outliers and dropouts for vital sign abnormalities

The Sponsor did not submit analyses of vital signs outliers.

#### 7.4.3.4 Additional analyses and explorations of vital signs data

Because there were no significant differences between TI and comparator groups for vital signs in controlled Phase 2/3 trials, explorations for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions, and drug-drug interactions were not conducted.

### 7.4.4 Electrocardiograms (ECGs)

#### 7.4.4.1 Overview of ECG testing in the development program

12-lead ECG assessments included PR interval, QRS complex, QT interval, heart rate, and QTc interval. Only the QTc interval, calculated by the Sponsor, using the Fridericia formula ( $QTc = QT/RR^{1/3} = QT*HR$  [in seconds]<sup>1/3</sup>), are presented in the tables.

A copy of the tracing was added to the CRF which was blinded to treatment group allocation. PR, QRS, QT, and QTc intervals and heart rate were recorded on the ECG page of the CRF. ECG results were reviewed by investigators and were classified by investigators on the CRF as “Normal,” “Abnormal Not Clinically Significant,” or “Abnormal Clinically Significant.”

**Reviewer’s comment: Because the investigator decision of “not clinically significant” or “clinically significant” can be subjective, the clinical reviewer chose to present only “normal” vs. “abnormal” results in the table below.**

7.4.4.2 Shift table presenting abnormality status change from baseline to post-baseline time points.

Overall, no consistent signal of an effect on ECG findings was observed in combined population of subjects with type 1 or type 2 diabetes. No significant difference over time was found between groups in new ECG findings (Table 7.36).

<b>Table 7.36 - Number and Percent of Type 1 or Type 2 Subjects With Shifts in ECG Findings, Excluding QTc Interval, from Baseline to On Treatment (Safety Population – Pooled Controlled Phase 2/3 Trials)</b>							
		TI Baseline Value		Comparator Baseline Value		TP Baseline Value	
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Month 3	Normal	225 (48)	34 (7.2)	70 (27.8)	22 (8.7)	49 (55.1)	8 (9.0)
	Abnormal	33 (7.0)	177 (37.7)	18 (7.1)	149 (59.1)	9 (10.1)	23 (25.8)
Last Measurement	Normal	753 (50.8)	154 (10.4)	714 (47.9)	166 (11.1)	49 (55.1)	8 (9.0)
	Abnormal	150 (10.1)	426 (28.7)	177 (11.8)	434 (29.2)	9 (10.1)	23 (25.8)

Source: Table 69, ISS

7.4.4.3 Shift table presenting QTc interval prolongation from baseline to post-baseline time points.

No evidence of risk of QT prolongation was found in shifts from baseline in QTc intervals or in the percent of subjects who had increases in QTc interval of greater than 30 or 60 msec (Table 7.37)

**Table 7.37 - QTc Interval Prolongation Shifts From Baseline Measurement in Type 1 or Type 2 Subjects (Safety Population - Pooled Controlled Phase 2/3 Trials)**

		TI Baseline					Comparator Baseline				
Time Point	Change (msec)	N	≤ 450	>450-480	>480-500	>500	N	≤ 450	>450-480	>480-500	>500
			n (%)	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	n (%)
Month 3	≤ 450	468	432 (92.3)	16 (3.4)	0	1 (0.2)	253	244 (96.4)	1 (0.4)	0	0
	>450-480		8 (1.7)	9 (1.9)	1 (0.2)	0		5 (2.0)	1 (0.4)	0	0
	>480-500		1 (0.2)	0	0	0		0	0	0	0
	>500		0	0	0	0		2 (0.8)	0	0	0
	Last measurement	1485	1381 (93.0)	41 (2.8)	5 (0.3)	3 (0.2)	1502	1423 (94.7)	30 (2.0)	2 (0.1)	2 (0.1)
	>450-480		25 (1.7)	17 (1.1)	1 (0.1)	0		25 (1.7)	10 (0.7)	1 (0.1)	1 (0.1)
	>480-500		4 (0.3)	4 (0.3)	1 (0.1)	0		3 (0.2)	0	1 (0.1)	0
	>500		3 (0.2)	0	0	0		3 (0.2)	0	1 (0.1)	0

Source: Table 70, ISS

#### 7.4.5 Special Safety Studies/Clinical Trials

Other special safety studies included in this NDA include pulmonary function tests, chest x-rays, and high-resolution computerized tomography of the chest for pulmonary safety. Please see Dr. Karimi-Shah’s pulmonary safety review for evaluation of these data.

##### 7.4.5.1 Thorough QT Study

Protocol MKC-T-131 entitled “A Phase 1, randomized, double-blind, cross-over, placebo- and active-controlled cardiac safety study of therapeutic and suprathreshold doses of fumaric acid diethyl fumarate (FDM) administered as Technosphere® Inhalation Powder in healthy subjects” was performed to determine if a suprathreshold dose of TP (therefore, essentially examining the excipient FDM) would prolong the mean QT/QTc interval, as measured by the maximum change in time-matched, placebo-subtracted, individualized corrected QT (QTcI) for the suprathreshold dose of T Inhalation Powder, where the upper bound of the 95% 1-sided CI on the day of treatment for the suprathreshold dose versus placebo was not to exceed 10 ms.

**Reviewer’s comment: The adequacy of the thorough QT study design including whether the “suprathreshold dose” was adequate will be addressed in the QT study consult which**

**is pending at the time of this review. The Sponsor's summary of the QT study is provided below.**

Time-matched analysis of the placebo-corrected mean QTcI change from baseline revealed that the upper 95% confidence bound (1-sided) was below the 10-ms threshold at all time points in the suprathereapeutic and therapeutic treatment groups and confirmed that the moxifloxacin treatment group met the assay sensitivity criteria (ie, mean difference of moxifloxacin and placebo > 5 ms) at 7 time points. Time-averaged analysis of the placebo-corrected mean QTcI change from baseline for the suprathereapeutic (40 mg) and therapeutic (20 mg) doses of T Inhalation Powder (-0.3 ms and -0.5 ms, respectively) showed no significant effect of FDKP on QTc. Assay sensitivity was reached in that the placebo-corrected mean QTcI change from baseline for moxifloxacin was 5.5 ms (expected, 5 ms to 10 ms). Mean change from baseline for placebo was -3.5 ms, showing that the study was well conducted and that background QTc variability was controlled.

#### 7.4.6 Immunogenicity

Insulin antibodies (IABs) have been found in both non-diabetics without previous exposure to insulin and in diabetic patients treated with insulin, with predominant occurrence found in the latter (Stoeber, 2004). IAB production appears to be greater with inhaled insulin products than with subcutaneously administered insulin products (Heise, 2005) although the higher IAB titers have not been shown to be associated with adverse clinical consequences. Nevertheless, theoretical clinical concerns about the implications of these increased IAB levels led to special assessment of immunogenicity in the TI development program.

Of note, across the Exubera development program, greater increases occurred in insulin antibody levels, as reflected by insulin binding activity, for patients taking inhaled insulin than for patients taking either subcutaneous insulin alone or oral agents alone.

The Sponsor performed an integrated analysis of IABs with the following objectives:

- To examine IAB levels and changes in such levels over time during clinical trials of TI in patients with type 1 and type 2 diabetes, respectively
- To compare changes in IAB levels from baseline between treatment groups receiving TI or comparator
- To evaluate the clinical significance of the potential effects of insulin antibodies associated with TI
- To investigate the reversibility of the changes in IAB levels and the potential effects after discontinuation of TI (extension trial MKC-TI-126 was used for this purpose)
- To examine the development of insulin antibodies in relation to prior insulin use or the presence of insulin antibodies at trial entry for patients with type 2 diabetes.

Trials contributing qualitative IAB data were:

Type 2DM: 005, 102, 014, 026, and 030 presented individually and pooled

Type 1DM: 009, 101, and 030 presented individually and pooled

Extension trials: 010 and 126 presented individually

Methodology: The IAB radioimmunoassay utilized in all clinical trials (except trial 0008 which used a qualitative radioimmunoassay) was conducted by [REDACTED] (b) (4). In all cases, the class of antibody that was measured is IgG. The units for IAB measurement were Kronus units/mL.

### Analysis of Insulin Antibodies in T2DM

Different comparators were used in the various trials. Therefore, this evaluation was based primarily on the individual trial results with the pooled analysis results presented as secondary support. Key points of the IAB analysis results are presented by trial below, followed by the pooled results. Measurements below quantifiable limit (BQL, 1.6 U/mL) were reported as 0.8 U/mL.

Trial 005: Insulin antibodies were measured at Visit 1 (Baseline) and Visit 12 (Week 17). The highest mean levels of insulin antibodies were observed in subjects randomized to TI 42 U and 56 U (the two highest doses in the trial).

Trial 102: IAB levels were evaluated at baseline and Weeks 14, 26, 38, and 52. Mean and median changes from baseline to Week 52 in IAB levels were higher in the TI group than in the 70/30 mix group (Table 7.38). Subjects treated with TI experienced an increase in mean and median IAB levels that was apparent by Week 14 of treatment; the median change from baseline in the TI group was 3.7 U/mL at Week 14 versus 1.7 U/mL in the 70/30 mix group. The mean and median levels continued to rise in the TI group and appeared to reach a peak at Weeks 26 to 38, followed by a small decline thereafter. At Week 52, the median change from baseline in IAB level was 6.6 Kronus U/mL in the TI group versus 3.0 Kronus U/mL in the 70/30 mix group.

**Table 7.38 – Trial 102 Mean and Median Changes From Baseline in Insulin Antibodies (U/mL) Throughout the Trial (Safety Population)**

Time Point	Statistic	TI N=323		70/30 Novolog Mix N=331	
		Reported Value	Change from Baseline	Reported Value	Change from Baseline
Baseline	n	300		309	
	Mean	10.8		11.6	
	SD	16.7		18.8	
	Median	6.1		5.6	
	Range	0.8 – 138.6		0.8 - 141.3	
Week 14	n	265	245	300	282
	Mean	29.1	19.1	16.8	5.3
	SD	41.2	36.8	26.1	19.0
	Median	10.5	3.7	7.8	1.7
	Range	0.8 – 195.1	-60.5 – 184.6	0.8 – 190.8	-56.2 – 169.7
Week 26	n	233	217	268	254
	Mean	32.9	22.9	17.4	6.7
	SD	42.1	37.4	25.8	19.6
	Median	14.2	6.7	8.9	2.6
	Range	0.8 – 190.0	-61.3 – 172.1	0.8 – 190.5	-43.9 – 179.8
Week 38	n	216	198	251	237
	Mean	32.9	22.7	17.0	6.7
	SD	39.2	35.1	23.0	17.0
	Median	15.9	8.3	9.7	3.3
	Range	0.8 – 178.8	-61.1 – 160.1	1.7 – 151.9	-49.0 – 126.0
Week 52	n	194	179	227	213
	Mean	29.2	19.7	18.1	7.1
	SD	35.6	35.0	27.5	20.2
	Median	14.2	6.6	8.7	3.0
	Range	0.8 – 183.8	-60.5 – 159.5	1.6 – 197.3	-70.2 – 136.8

Source: Table 15, ISS: CIR IAB

In trial 102, 4 subjects had insulin antibodies in the 95<sup>th</sup> percentile of subjects with insulin antibodies in the TI clinical development program and also experienced SAEs (retinal detachment, 1 T1-treated subject; ischemic cardiomyopathy, 1 T1-treated subject; fall, rib fracture, and bone pain, 1 70/30 Novolog mix-treated subject; and viral gastroenteritis and dizziness, 1 T1-treated subject). None of the SAEs had any apparent relationship with IAB titers and all subjects completed the trial with acceptable glycemic control.

Trial 014: Insulin antibodies were measured at Visit 5 (Baseline) and Visit 13 (treatment endpoint); no inferential statistics were employed. Results are shown in Table 7.39. The levels of insulin antibodies increased over time in TI-treated subjects but not in the insulin aspart-treated subjects. The median values were not provided by the Sponsor.

Visit Number	Statistic	TI (N=151)	Insulin Aspart (n=158)
Visit 5	n	148	157
	Mean (SD)	21.2 (36.8)	18.2 (28.2)
	Range	0.8 – 310.2	1.8 – 200.0
Visit 13	n	123	152
	Mean (SD)	71.3 (130.3)	18.8 (23.3)
	Range	2.2 – 1000.0	1.8 – 167.8

Source: Table 16, ISS, CIR IAB

Trial 103: Trial 103 compared TI to oral agents. Median changes from baseline to Week 12 in IAB levels were small in all subjects during Treatment Period I (12 weeks of treatment) but higher in the TI alone and TI + metformin groups compared with the metformin + sulfonylurea group (Table 7.40).

Visit/Statistic	TI Alone N=131	Metformin + Secretagogue N=147	TI + Metformin N=121
<b>Baseline</b>			
Mean (SD)	3.5 (1.8)	3.7 (2.4)	3.5 (1.9)
Median	3.1	3.1	3.1
Range	1.6 – 9.2	1.6 – 21.3	1.6 – 13.0
<b>Week 12</b>			
Mean (SD)	7.4 (16.6)	3.9 (2.5)	7.3 (13.0)
Median	4.1	3.3	3.8
Range	1.6 – 175.7	1.6 – 21.4	1.6 – 116.9
<b>Change from baseline</b>			
Mean (SD)	3.9 (16.6)	0.19 (1.8)	3.7 (13.0)
Median	0.8	0	0.2
Range	-4.2 – 172.7	-5.2 – 5.8	-4.0 – 114.0

Source: Table 17, ISS CIR IAB

Trial 026: Insulin antibodies were measured at Visit 1 (Baseline) and Visit 10 (treatment endpoint); no inferential statistics were employed. The mean levels of insulin antibodies did not increase over the course of this trial in the control group but did increase in the TI group (Table 7.41).

**Reviewer’s comment:** The median values appear more comparable across groups and the standard deviations are large in the TI treatment groups suggesting a wide range of antibody responses among TI-treated subjects.

In the TI group, post-baseline IAB concentrations of 20 U/mL or greater were reported for 5 subjects (6.7%), of whom 2 subjects had concentrations greater than 60 U/mL. In comparison, no subjects in the control group had a post-baseline IAB concentration of greater than 20 U/mL. The clinical reviewer examined HbA1c changes over time for the subjects with the two highest

antibody titers. Subject 103/site 507 had a baseline titer of 10.7 and a week 10 titer of 124.0. Subject 261/site 515 had a baseline titer of 6.4 and a week 10 titer of 66.6. Both subjects improved HbA1c from baseline to visit 10 (baseline 11.8/week 10 8.7/change -3.1% and baseline 10.1/week 10 8.3/change -1.8%, respectively) suggesting no adverse effect on glycemic control from high IAB titers.

<b>Table 7.41 – Trial 026 Change from Baseline in IABs (U/mL) (Safety Population)</b>			
Visit Number	Statistic	TI (N=75)	Control (n=15)
Visit 1	n	74	14
	Mean (SD)	6.1 (2.3)	4.9 (2.6)
	Median	6.1	5.0
Visit 10	n	69	14
	Mean (SD)	10.2 (16.2)	6.0 (3.2)
	Median	6.8	5.8
Source: Table 18, ISS, CIR IAB			

Trial 030: Insulin antibodies were measured in subjects with diabetes at Visits 1, 3, 4, 5, 6 and 7 (0, 3, 6, 12, 18, and 24 months) during the trial. The change in IAB levels over the time course of the trial was analyzed. Insulin antibodies increased significantly over the first 6 months in the trial, peaking around 18 months (Table 7.42); values were relatively stable from 6 months to 2 years. Mean and median changes from Baseline to last measurement in IAB levels were higher in the TI group than in the UC group. Note that the UC group includes insulin users and non-insulin users. Therefore, a more appropriate comparison would have been TI vs. comparator insulin users.

**Table 7.42 – Trial 030 T2DM Subjects Mean and Median Changes From Baseline in Insulin Antibodies (U/mL) Throughout the Trial (Safety Population)**

Time Point	Statistic	TI N=656		Usual Care N=678	
		Reported Value	Change from Baseline	Reported Value	Change from Baseline
Baseline	n	652		671	
	Mean (SD)	6.7 (13.5)		6.5 (13.8)	
	Median	4.0		3.7	
Month 3	n	527	527	573	573
	Mean	14.1 (51.5)	7.9 (47.5)	6.6 (20.7)	0.3 (15.6)
	Median	3.7	0	3.2	-0.4
Month 6	n	473	473	546	546
	Mean	21.0 (72.0)	14.8 (67.1)	7.3 (22.5)	0.58 (16.6)
	Median	4.6	0.4	2.9	-0.7
Month 12	n	414	414	505	505
	Mean	19.3 (63.7)	13.1 (58.3)	7.3 (18.6)	0.4 (13.9)
	Median	5.7	1.5	3.6	0
Month 18	n	351	351	454	454
	Mean	26.8 (82.1)	20.4 (77.3)	11.2 (23.6)	4.4 (21.2)
	Median	10.1	5.3	7.1	2.7
Month 24	n	133	133	454	454
	Mean	18.6 (61.6)	14.5 (60.4)	11.6 (24.0)	4.9 (21.8)
	Median	7.9	4.6	7.1	2.5
Last measurement	n	530	530	595	595
	Mean	23.2 (76.2)	17.1 (72.1)	10.1 (21.4)	3.6 (19.5)
	Median	7.5	3.3	6.3	1.8

Source: Table 8.9.1.2, trial 030 tables

Pooled T2DM analyses:

Tables 7.43 and 7.44 summarize IABs for T2DM Subjects by whether they were insulin-using or non-insulin-using at trial entry using Phase 2/3 pooled data for T2DM trials. Recall that the UC group is exposed to either insulin or non-insulin therapies or both. The tables summarize the data by comparator. Mean increases in IAB for TI-treated subjects were generally greater than for subjects in any other comparison group, although this pattern was not seen for non-insulin users at baseline where SC insulin resulted in greater increases in IAB than did TI. In subjects who had been exposed to insulin prior to TI administration, the baseline values were slightly but consistently higher across all of the treatment groups. Their increases appeared to be of the same magnitude though compared with those without prior insulin exposure. One exception is that among subjects who were non-insulin using at trial entry, treatment with SC insulin appeared to result in a greater increase in IABs than treatment with TI did, although there were only 24 patients in the SC group, which limits conclusions. However, the largest mean increases were seen in the insulin using groups at trial entry group exposed to TI and SC insulin. The largest median change was seen in the non-insulin using at trial entry group exposed to SC insulin.

**Table 7.43 – Summary Statistics of IABs (U/mL) for T2DM Subjects who were Insulin-Using at Trial Entry (Pooled Safety Population)**

	TI N=861		TP N=12		SC N=462		UC N=395		OAD N=5	
	IAB Value	Change from Baseline	IAB Value	Change from Baseline	IAB Value	Change from Baseline	IAB Value	Change from Baseline	IAB Value	Change from Baseline
<b>Baseline</b>										
n	689		12		286		392		5	
Mean	9.3		8.1		12.0		8.4		3.5	
SD	16.7		15.3		19.4		17.6		2.2	
Median	5.1		3.6		5.8		4.6		3.1	
Range	0.8 – 200.0		1.8 – 56.6		0.8 – 141.3		0.8 – 182.6		0.8 – 6.9	
<b>Endpoint</b>										
n	763	593	12	12	449	275	356	353	5	5
Mean	39.8	24.2	6.6	-1.5	18.6	7.1	12.4	3.5	4.4	0.8
SD	90.9	76.1	6.3	9.3	26.0	21.3	27.6	23.9	2.3	1.5
Median	11.2	4.4	4.8	1.0	9.8	2.8	7.1	1.6	4.8	0.6
Range	0.8 – 1000.0	-197.4 – 862.6	2.8 – 25.9	-30.7 – 3.9	1.8 – 197.3	-70.2 – 136.8	0.8 – 387.6	-147.4 – 351.3	0.8 – 6.8	-1.0 – 2.8

Source: Table 20, ISS CIR IAB

**Table 7.44 – Summary Statistics of IABs (U/mL) for T2DM Subjects who were Non-Insulin-Using at Trial Entry (Pooled Safety Population)**

	TI N=872		TP N=41		SC N=24		UC N=298		OAD N=161	
	IAB Value	Change from Baseline	IAB Value	Change from Baseline	IAB Value	Change from Baseline	IAB Value	Change from Baseline	IAB Value	Change from Baseline
<b>Baseline</b>										
n	855		40		23		293		158	
Mean	4.2		4.3		5.5		3.8		3.6	
SD	3.8		2.5		3.9		3.2		2.5	
Median	3.6		4.0		4.6		3.0		3.2	
Range	0.8 – 77.2		0.8 – 12.0		0.8 – 15.5		0.8 – 19.5		0.8 – 21.3	
<b>Endpoint</b>										
n	773	759	33	32	21	20	260	256	148	145
Mean	9.5	5.3	4.6	0.2	14.2	8.8	7.2	3.4	3.8	0.1
SD	25.1	23.4	2.4	1.0	12.4	12.1	10.5	10.4	2.6	2.0
Median	5.0	1.0	4.2	0.2	12.0	5.1	5.4	1.8	3.3	0
Range	0.8 – 434.8	-10.4 – 382.6	0.8 – 12.0	-2.7 – 1.9	1.6 – 53.9	-3.2 – 49.9	0.8 – 145.6	-14.6 – 140.7	0.8 – 21.4	-5.6 – 5.8

Source: Table 21, ISS CIR IAB

Extension Trial:

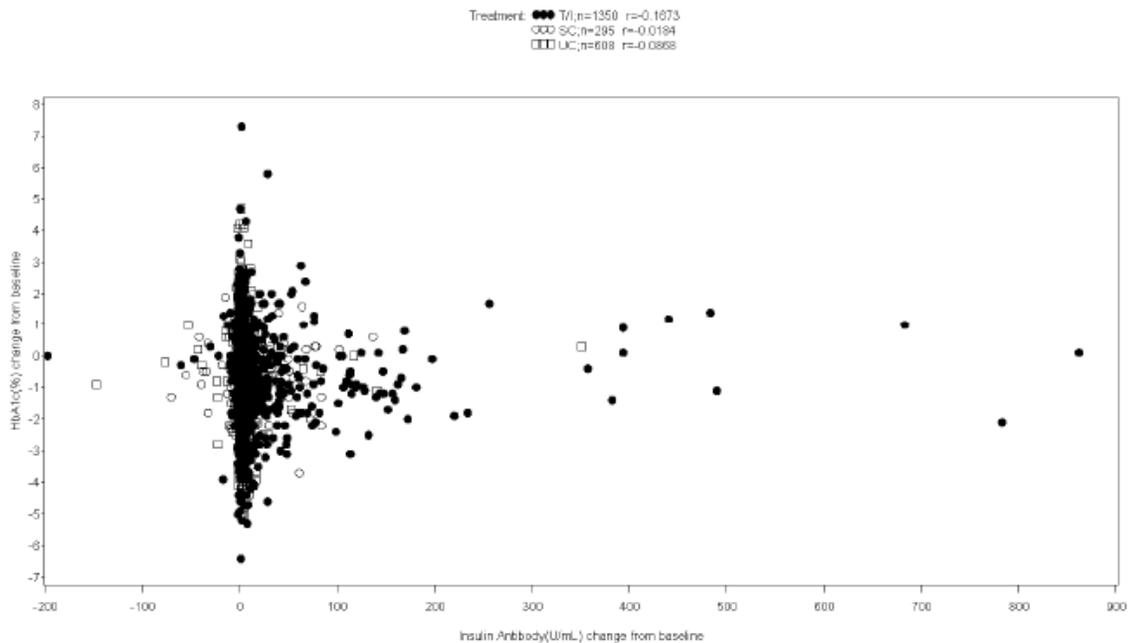
Trial 126: Trial 126 followed subjects who were previously enrolled in trials 102, 009, 103 and 030 (both T2DM and T1DM subjects) for two months after trial discontinuation to determine what happens to IAB titers after treatment with TI is discontinued. In general, the mean and median IAB levels declined over the 3-month period after TI was discontinued. For the majority of subjects in the ex-TI group, the decline was larger during the first month after discontinuation of TI, and IAB levels continued to decline at three months post-TI.

For subjects in trial 126 who were previously on TI, approximately 70% were within  $\pm 25$  Kronos units of their baseline at the last measurement, whereas approximately 90% on comparator were within the same range.

Clinical impact analyses in T2DM:

In subjects with T2DM, there was no association between IAB levels or changes in IAB levels and change from baseline in HbA1c for either the individual trial data or the pooled data (Figure 7.1). Also apparent in this figure is that subjects with outlier values for IAB levels ( $> 200$  U/mL) do not have a discernable relationship between IAB level and change in HbA1c. Similar results were seen for comparisons between IAB levels and change from baseline in fasting plasma glucose values, and IAB levels and end of trial insulin doses administered.

**Figure 7.1 – Correlation between Changes in IABs (U/mL) and HbA1c (%) at End of Trial for T2DM Subjects (Pooled Phase 2/3 Controlled T2DM Safety Population)**



Source: Figure 11, ISS CIR IAB

Relationship between AEs and IAB titers in T2DM:

The association between IAB levels and pulmonary function tests is explored in the separate Pulmonary Safety Review.

Hypoglycemia – In general the rate of severe hypoglycemia was comparable between TI and sc insulin even though IAB levels were higher among TI treated patients.

Allergic Adverse Events - All allergic AEs were evaluated for a relationship to insulin antibodies. There were 4 subjects who had immune system disorders, all classified as allergic AEs secondary to seasonal or environmental allergies but not related to administration of insulin, either TI or SC. In subjects who had allergic AEs, the titers of insulin antibodies remained constant across the trials, except for one subject, whose antibody titers rose significantly over time, peaking at 18 months. This subject's immune AE was a worsening of seasonal allergies. There was one SAEs related to an immune or allergic AE (the subject with angioneurotic edema who received one dose of TI and then discontinued from the trial), The subject had a history of allergy to insulin. Insulin antibodies did not appear to be more prevalent in subjects who experienced an SAE compared with subjects who did not experience an SAE.

#### Analyses of Subjects with Highest Observed IAB Levels in T2DM:

High antibody titers are defined as those titers in the upper 95<sup>th</sup> or higher percentiles of the maximum post-baseline IAB levels during the treatment period. Since TI was associated with the highest levels of antibodies and oral hypoglycemic agents were associated with the lowest antibody titers, the 95<sup>th</sup> percentile or higher *within* each group (TI, TP, insulin using, non-insulin using) was compared with the 5<sup>th</sup> percentile *within* each group.

As shown in Table 7.45, treatment-emergent AEs were slightly higher in the 95<sup>th</sup> percentile group for both the TI and insulin groups compared with the 5<sup>th</sup> percentile groups, AEs and SAEs were higher in 95<sup>th</sup> percentile group for both the TI and insulin groups compared with the 5<sup>th</sup> percentile groups, whereas the AEs leading to discontinuation were lower in the 95<sup>th</sup> percentile group. The observed pattern does not appear to be clinically meaningful because one would expect a higher rate of discontinuation due to AEs along with the observed higher AE rates among 95<sup>th</sup> percentile subjects. However, it is reassuring that the TI group and the sc insulin group show the same pattern, i.e. the same apparent relationship between IAB levels and adverse events.

**Table 7.45 – Statistics of Highest Observed Insulin Antibodies and Clinical Events for T2DM Subjects (Pooled T2DM Safety Population)**

Clinical Event	95 <sup>th</sup> Percentile Subjects				5 <sup>th</sup> Percentile Subjects			
	TI N=77	TP N=3	Insulin N=45	Non- Insulin N=18	TI N=90	TP N=3	Insulin N=49	Non- Insulin N=39
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least one hypoglycemic event	39 (50.6)	0	27 (60.0)	4 (22.2)	15 (16.7)	0	14 (28.6)	4 (10.3)
Hypoglycemic event rate (per 100 subject-months)	4.6	0	4.8	1.1	4.2	0	2.8	1.8
Number of subjects with at least one severe hypoglycemic event	3 (3.9)	0	4 (8.9)	0	0	0	3 (6.1)	0
Severe hypoglycemic event rate (per 100 subject-months)	0.4	0	0.7	0	0	0	0	0
TEAE	62 (80.5)	1 (33.3)	38 (84.4)	13 (72.2)	58 (64.4)	1 (33.3)	32 (65.3)	21 (53.8)
SAE	17 (22.1)	0	14 (31.3)	1 (5.6)	4 (4.4)	0	8 (16.3)	3 (7.7)
AE leading to discontinuation	14 (18.2)	0	4 (8.9)	1 (5.6)	44 (48.9)	0	20 (40.8)	7 (17.9)

Source: Table 24, ISS CIR IAB

**Reviewer’s comment: Small sample sizes in these subgroups limit interpretation of the data.**

Analysis of Insulin Antibodies in T1DM

Different comparators were used in the various trials. Therefore, this evaluation was based primarily on the individual trial results with the pooled analysis results presented as secondary support. Key points of the IAB analysis results are presented by trial below, followed by the pooled results. Measurements below quantifiable limit (BQL, 1.6 U/mL) were reported as 0.8 U/mL.

Trial 009:

Insulin antibodies levels were collected at baseline and Weeks 14, 26, 38, and 52 and are presented in Table 7.46. Mean and median changes from Baseline (Week 0) to Week 52 in IAB levels were higher in the TI group than in the insulin aspart group. Mean and median changes from baseline increased through Week 38 and declined slightly thereafter in the TI group.

**Table 7.46 – Trial 009 Mean and Median Changes From Baseline in Insulin Antibodies (U/mL) Throughout the Trial (Safety Population)**

Time Point	Statistic	TI N=293		Insulin Aspart N=272	
		Reported Value	Change from Baseline	Reported Value	Change from Baseline
Baseline	n	280		259	
	Mean	14.0		13.1	
	SD	21.3		19.2	
	Median	7.1		6.6	
	Range	0.8 – 187.0		0.8 – 125.7	
Week 14	n	235	226	255	243
	Mean	45.7	34.7	15.9	2.0
	SD	49.1	44.1	24.5	20.6
	Median	22.7	14.4	7.6	0.3
	Range	0.8 – 197.3	-29.0 – 188.4	0.8 – 176.4	-75.4 – 153.4
Week 26	n	200	195	237	227
	Mean	58.2	48.6	13.8	-0.7
	SD	51.2	48.3	19.2	15.5
	Median	39.4	33.7	8.1	0.6
	Range	0.8 – 199.5	-42.6 – 189.9	-42.6 – 189.9	-91.7 – 67.7
Week 38	n	183	179	232	222
	Mean	66.3	56.2	14.0	-0.31
	SD	65.1	59.7	18.2	17.3
	Median	50.3	43.8	9.1	1.1
	Range	0.8 – 548.0	-41.1 – 466.4	0.8 – 158.7	-91.6 – 109.4
Week 52	n	167	164	203	193
	Mean	61.3	49.2	12.7	-1.62
	SD	54.3	48.9	16.8	18.1
	Median	43.8	35.7	8.7	1.1
	Range	1.9 – 195.0	-38.4 – 189.3	0.8 – 192.4	-96.0 – 101.7

Source: Table 2, ISS: CIR IAB

One subject in the TI group had an IAB titer of 548 U/mL at Visit 10 (Week 38) (baseline value, 81.6 U/mL). None of the other subjects had values at any time during the trial of more than 199 U/mL. The subject had no unusual PFT, AE, or hypoglycemia findings and had improved glycemic control by the end of the trial, with the Hb1Ac dropping from 8.3% at Baseline (Week 0) to 7.4% at Visit 12 (Week 52). The daily TI dose at the time of the high titer result was 15 U at breakfast, 30 U at mid-day, and 30 U in the evening.

Trial 101: Insulin antibodies were collected at Visit 1, Visit 8, Visit 9, and Visit 10. Results for Visit 1 (Baseline/Week -4) and Visit 10 (Week 12) are presented in Table 7.47. The median concentration of insulin antibodies at baseline was similar in the 2 treatment groups. By the end of the trial (Visit 10), the median concentration increased more than 4-fold in the TI group, whereas the median concentration increased 1.5-fold in the SC group.

<b>Table 7.47 – Trial 101 Change from Baseline in IABs (U/mL) (Safety Population)</b>			
Visit Number	Statistic	TI (N=54)	Insulin Aspart (n=56)
Visit 1 (Week -4)	n	54	56
	Mean (SD)	17.0 (16.0)	25.7 (44.1)
	Median	11.8	11.4
Visit 10 (Week 12)	n	49	55
	Mean (SD)	99.8 (144.7)	34.1 (54.1)
	Median	49.3	15.2
Source: Table 18, ISS, CIR IAB			

Trial 030: Insulin antibodies were measured in subjects with diabetes at Visits 1, 3, 4, 5, 6 and 7 (0, 3, 6, 12, 18, and 24 months) during the trial. The change in IAB levels over the time course of the trial was analyzed (Table 7.48). Insulin antibodies increased significantly over the first 6 months in the trial, peaking around 18 months; values were relatively stable from 6 months to 2 years. Mean and median changes from Baseline to last measurement in IAB levels were higher in the TI group than in the UC group of patients with T1DM.

**Table 7.48 – Trial 030 T1DM Subjects Mean and Median Changes From Baseline in Insulin Antibodies (U/mL) Throughout the Trial (Safety Population)**

Time Point	Statistic	TI N=267		Usual Care N=271	
		Reported Value	Change from Baseline	Reported Value	Change from Baseline
Baseline	n	262		268	
	Mean (SD)	15.9 (32.7)		13.4 (29.8)	
	Median	6.1		6.7	
Month 3	n	188	188	240	240
	Mean	61.6 (102.8)	44.8 (86.2)	12.5 (25.6)	-1.28 (17.2)
	Median	15.5	7.9	5.2	-0.7
Month 6	n	164	164	237	237
	Mean	88.0 (126.2)	70.5 (112.4)	12.8 (34.4)	-0.8 (22.4)
	Median	34.9	20.3	4.9	-1.5
Month 12	n	144	144	220	220
	Mean	86.4 (146.7)	68.5 (132.5)	12.2 (25.2)	-1.9 (21.2)
	Median	26.1	16.7	5.5	-1.3
Month 18	n	131	131	205	205
	Mean	111.6 (180.8)	93.4 (168.1)	17.0 (26.9)	2.4 (21.7)
	Median	36.3	25.9	9.6	3.0
Month 24	n	44	44	191	191
	Mean	71.6 (114.6)	51.2 (97.5)	16.8 (28.6)	3.1 (25.7)
	Median	26.2	14.3	9.1	2.5
Last measurement	n	190	190	249	249
	Mean	94.4 (155.1)	77.7 (143.7)	15.2 (25.6)	1.7 (24.3)
	Median	30.5	20.9	8.6	1.8

Source: Table 3, ISS CIR IAB

Pooled T1DM analyses: Mean IAB levels increased from baseline to endpoint in both treatment groups, with peak average values occurring at Visit 6 (18 months). Increases from baseline to study endpoint for TI were greater than for the comparison group (Table 7.49). Increases for TI treated subjects with type 1 diabetes from baseline to study endpoint were much greater than those found in TI treated subjects with type 2 diabetes.

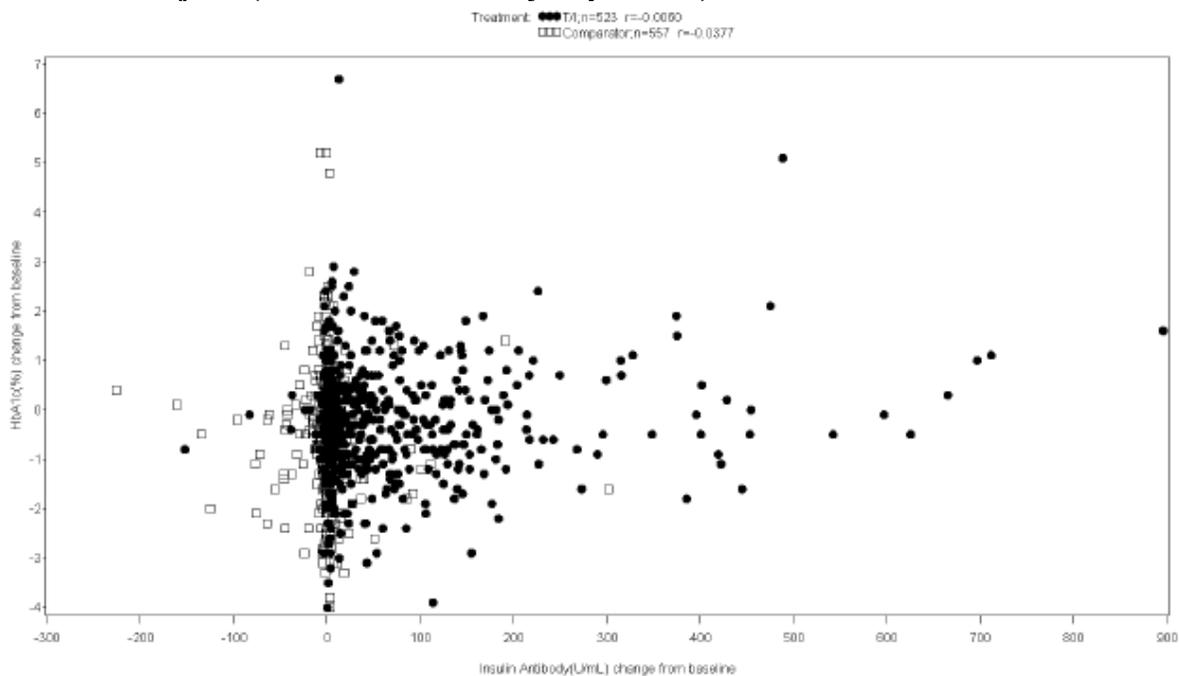
**Reviewer’s comment:** The reason for the higher rate of IAB formation among T1DM subjects compared with T2DM subjects was not explored in the TI clinical development program. One possibility is that T1DM patients, due to the nature of their disease, are predisposed to antibody formation in general compared with subjects with a non-immune-related etiology for their diabetes (i.e. type 2 patients). Another possibility is that T1DM subjects have a “pool” of IABs from prior insulin exposure that are elicited by TI exposure.

<b>Table 7.49 –Pooled T1DM Safety Population Change from Baseline in IABs (U/mL)</b>				
	TI (N=614)		Comparator (n=599)	
Visit /Statistic	Reported Value	Change from Baseline	Reported Value	Change from Baseline
<b>Baseline</b>				
n	599		584	
Mean (SD)	16.7 (36.2)		14.8 (28.7)	
Median	7.1		6.9	
Range	0.8 – 531.1		0.8 – 373.5	
<b>Endpoint</b>				
n	537	523	570	557
Mean (SD)	85.7 (127.9)	69.5 (114.9)	15.8 (26.8)	0.9 (26.7)
Median	35.8	25.9	9.1	1.3
Range	0.8 – 933.2	-152.0 – 896.5	0.8 – 308.4	-255.8 – 302.0
Source: Table 5, ISS, CIR IAB				

Clinical impact analyses in T1DM:

Similar to the analyses performed with T2DM subjects, there was no association between IAB levels or changes in IAB levels and change from baseline in HbA1c for either the individual trial data or the pooled data (Figure 7.2). Also apparent in this figure is that subjects with outlier values for IAB levels (> 200 U/mL) do not have a discernable relationship between IAB level and change in HbA1c. Similar results were seen for comparisons between IAB levels and change from baseline in fasting plasma glucose values, and IAB levels and end of trial insulin doses administered.

**Figure 7.2 – Correlation between Changes in IABs (U/mL) and HbA1c (%) at End of Trial for T1DM Subjects (Pooled T1DM Safety Population)**



Source: Figure 2, ISS CIR IAB

#### Relationship between AEs and IAB titers in T1DM:

The association between IAB levels and pulmonary function tests is explored in the separate Pulmonary Safety Review.

Hypoglycemia – In general the rate of severe hypoglycemia was comparable between TI and sc insulin even though IAB levels were higher among TI treated patients.

All allergic AEs were evaluated for a relationship to insulin antibodies. In subjects with type 1 diabetes, there were no allergic AEs or SAEs reported.

#### Analyses of Subjects with Highest Observed IAB Levels in T1DM:

High antibody titers are defined as those titers in the upper 95th or higher percentiles of the maximum post-baseline IAB levels during the treatment period. Since TI was associated with higher levels of antibodies than sc insulin was, the 95<sup>th</sup> percentile or higher *within* each group (TI vs. sc insulin) was compared with the 5<sup>th</sup> percentile *within* each group.

As shown in Table 7.50, the incidences of treatment-emergent AEs and SAEs were slightly higher in the 95<sup>th</sup> percentile group for both the TI and insulin groups compared with the 5<sup>th</sup> percentile groups, whereas the AEs leading to discontinuation were lower in the 95<sup>th</sup> percentile group. The observed pattern does not appear to be clinically meaningful because one would

expect a higher rate of discontinuation due to AEs along with the observed higher AE rates among 95<sup>th</sup> percentile subjects. This is the same pattern seen among T2DM subjects. As stated in the T2DM section, it is reassuring that the TI group and the sc insulin group show the same pattern, i.e. the same apparent relationship between IAB levels and adverse events. Therefore, it can be concluded that high titer IABs due to TI do not cause a disproportionately increased rate of adverse events compared with high titer IABs resulting from subcutaneous insulin therapy.

<b>Table 7.50 – Statistics of Highest Observed Insulin Antibodies and Clinical Events for T2DM Subjects (Pooled T2DM Safety Population)</b>				
Clinical Event	95 <sup>th</sup> Percentile Subjects		5 <sup>th</sup> Percentile Subjects	
	TI N=27 n (%)	SC Insulin N=29 n (%)	TI N=29 n (%)	SC Insulin N=31 n (%)
Number of subjects with at least one hypoglycemic event	23 (85.2)	25 (86.2)	16 (55.1)	26 (83.9)
Hypoglycemic event rate (per 100 subject-months)	62.5	60.0	110.8	84.6
Number of subjects with at least one severe hypoglycemic event	7 (25.9)	8 (27.6)	3 (10.3)	8 (25.8)
Severe hypoglycemic event rate (per 100 subject-months)	19.0	19.2	20.8	26.0
TEAE	25 (92.6)	28 (96.6)	25 (86.2)	27 (87.1)
SAE	13 (48.1)	15 (51.7)	11 (37.9)	11 (35.5)
AE leading to discontinuation	7 (25.9)	2 (6.9)	22 (75.9)	11 (35.5)
Source: Table 13, ISS CIR IAB				

**Reviewer’s comment: Again, small sample sizes in these subgroups limit interpretation of the data.**

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Evaluation of dose dependency for adverse events is difficult for the TI development program because of methodological reasons. As discussed previously, patients with diabetes (both T1D and T2D) have varying insulin requirements that depend on many factors including the diabetes type, the degree of insulin resistance, diet, and the duration of their disease. In addition, dose requirements vary over time by individual. Therefore, the dose of TI was individually titrated for the majority of the phase 2/3 clinical trials, and analyses based on dose would reflect post-randomization modification of study medication, in essence permitting comparisons based on non- (or no-longer-) randomized study populations. Further, at least for type 2 diabetes, as the

disease progresses, beta cell failure occurs with progressive loss of endogenous insulin secretion and increasing requirement for drug therapy, and eventually for increasing insulin requirement. A higher insulin requirement may be a reflection of duration of disease, which is in turn associated with aging; either duration of disease or aging could be associated with an increased incidence of many adverse events.

Only one phase 2/3 trial used forced dose titration of TI (trial 005) which could permit an exploration of adverse event dose dependency in a randomized population. Examination of common ( $\geq 4\%$ ) treatment emergent adverse events in this trial did not suggest dose dependency (Table 7.51)

<b>SOC/PT</b>	<b>TP (N = 46)</b>	<b>TI 14U (N = 45)</b>	<b>TI 28U (N = 46)</b>	<b>TI 42U (N = 45)</b>	<b>TI 56 (N = 45)</b>	<b>TI Total (N = 181)</b>
All TEAE	14	15	20	15	16	66
<b>Gastrointestinal Disorders</b>	2 (4.3)	2 (4.4)	2 (4.3)	5 (11.1)	2 (4.4)	11(6.1)
Constipation	—	—	—	2(4.4)	—	2(1.1)
<b>General Disorders and Administrative Site Conditions</b>	2 (4.3)	4 (8.9)	4 (8.7)	3 (6.7)	3 (6.7)	14(7.7)
Influenza-like illness	1 (2.2)	1 (2.2)	2 (4.3)	1 (2.2)	1 (2.2)	5 (2.8)
Fatigue	—	2 (4.4)	1 (2.2)	—	—	3 (1.7)
Pyrexia	—	—	2 (4.3)	—	—	2 (1.1)
<b>Infections and Infestations</b>	12 (26.1)	8 (17.8)	12 (26.1)	8 (17.8)	10 (22.2)	38 (21.0)
Nasopharyngitis	4 (8.7)	3 (6.7)	5 (10.9)	4 (8.9)	4 (8.9)	16(8.8)
Upper respiratory tract infection	4 (8.7)	2 (4.4)	3 (6.5)	1 (2.2)	1 (2.2)	7 (3.9)
Urinary tract infection	—	1 (2.2)	3 (6.5)	—	—	4 (2.2)
Bronchitis	2(4.3)	—	—	1(2.2)	1(2.2)	2(1.1)
Bronchitis acute	—	1(2.2)	—	—	2 (4.4)	3 (1.7)
<b>Musculoskeletal and Connective Tissue Disorders</b>	1 (2.2)	2 (4.4)	2 (4.3)	1 (2.2)	3 (6.7)	8 (4.4)
Muscle cramp	—	—	2 (4.3)	—	—	2 (1.1)
<b>Nervous System Disorders</b>	1 (2.2)	1 (2.2)	5 (10.9)	4 (8.9)	3 (6.7)	13(7.2)
Headache	1 (2.2)	—	1 (2.2)	3 (6.7)	2 (4.4)	6 (3.3)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>	3 (6.5)	1 (2.2)	3 (6.5)	2 (4.4)	2 (4.4)	8 (4.4)
Pharyngolaryngeal pain	1 (2.2)	1 (2.2)	2 (4.3)	—	1 (2.2)	4 (2.2)
<b>Vascular Disorders</b>	2 (4.3)	2 (4.4)	2 (4.3)	2 (4.4)	2 (4.4)	8 (4.4)
Hypertension	1 (2.2)	1 (2.2)	—	2 (4.4)	1 (2.2)	4 (2.2)

N = number of subjects. Data Source: Table 5.3.1 and Appendix 2, Listing 43.

Dose dependency for pulmonary events in which there is a baseline measurement (such as pulmonary function tests) might be useful in order to compare the change in pulmonary function over time as a function of TI dose.

### 7.5.2 Time Dependency for Adverse Events

Time dependency for hypoglycemic events is discussed in section 7.3.5.1. Time dependency for pulmonary events is explored in the pulmonary safety review. There were no other adverse events that warranted exploration for dose dependency in the clinical development program.

### 7.5.3 Drug-Demographic Interactions

#### Age

The Sponsor performed exploratory analyses of the frequency of all TEAEs for TI-treated subjects vs. comparator-treated subjects based on subject age group (18-64 years, 65-74 years, and > 75 years). There were no important differences in percent of TEAEs reported between TI and comparator in the pooled safety population based on subject age group. In addition, the older age groups did not have an increased risk of TEAEs; there is no evidence in these exploratory analyses that the risk of TEAEs in TI-treated subjects is related to age.

#### Sex

For the combined population of type 1 and type 2 subjects with diabetes, the percent of subjects reporting TEAEs was similar for men (74.1%) and women (77.0%) receiving TI.

#### Race

All-causality TEAEs were reported in similar numbers of subjects in the TI and comparator groups in the Caucasian, Black-African American and Hispanic populations. The incidence of all-causality TEAEs was 73.7% (n = 1484) and 76.5% (n = 1245) of TI and comparator-treated subjects in the Caucasian population, 86.5% (n= 96) and 78.0% (n = 64) of subjects in the Black African-American population, 85.0% (n = 175) and 84.5% (n = 142) of the Hispanic population, and 86.0% (n = 43) and 60.5% (n = 23) of the Asian population. The slightly higher rates of TEAEs among the TI-treated Black-African American subjects and Asian subjects stemmed from AEs distributed across many system organ classes and preferred terms, and the low numbers of events limit conclusions.

The following populations were not included in the Clinical Development program:

- Pediatric subjects
- Pregnant or lactating women

#### 7.5.4 Drug-Disease Interactions

The following were studied only in studies of short duration (less than 14 consecutive days), with mostly single administration:

- Active smokers
- Subjects with underlying lung disease such as asthma and COPD
- Subjects with renal insufficiency
- Subjects with hepatic insufficiency

For the combined population of subjects with type 1 and type 2 diabetes, approximately 1% of subjects in each treatment group had renal impairment [defined as having a creatinine between the normal value based on the laboratory reference range and an upper value (inclusive) arbitrarily set by the Sponsor (1.8 mg/dL for women and 2.0 mg/dL for men)]. The incidence of any particular TEAE was too low to allow meaningful comparisons between treatment groups.

#### Diabetes Complications

Subjects with severe diabetic complications were excluded from phase 2/3 clinical trials (history of: blindness from grade III or IV diabetic retinopathy, renal failure requiring dialysis or transplantation, amputation of limbs or digits related to diabetic vasculopathy or foot ulcers). The Sponsor provided analyses of subjects by reported baseline diabetic neuropathy, nephropathy, and retinopathy status and there did not appear to be a relationship between these diabetic complications and the incidence of adverse events.

#### Baseline HbA1c%

The Sponsor reported that adverse events were reviewed by level of baseline HbA1c and that no difference was detected in the distribution of AEs within or between TI and comparator as a function of baseline HbA1c level. However, the data for these analyses were not provided and could not be confirmed by the clinical reviewer.

#### 7.5.5 Drug-Drug Interactions

Specific drug-drug interactions were evaluated in clinical pharmacology trials.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

#### Neoplasms

Because of the post-marketing cases of lung cancer associated with Exubera which led to the Exubera product labeling changes, malignant (based on pathology findings) neoplasms were examined as an AE of interest for TI.

In the phase 2/3 controlled trials, 12/2409 subjects (0.5%) with type 1 or type 2 diabetes in the TI group and 7/1944 subjects (0.4%) in the comparator group reported malignant neoplasms (Table 7.52). When only regarding events with a latency of  $\geq 90$  days, the incidence of malignancies remained similar: 10/2409 subjects (0.4%) in TI and 5/1944 subjects in comparators (0.3%). Most malignancies were reported in the 2-year pulmonary safety trial 030. There were no primary lung malignancies in the pooled phase 2/3 safety population as of the cutoff date of November 2008. There was one case in a TI-treated subject of a neuroendocrine tumor with lung involvement (Oat cell cancer).

<b>Table 7.52 – Number of Reported Malignancies in Type 1 or Type 2 Subjects, Excluding Non-Melanoma Skin Malignancies (Pooled Safety Population)</b>				
	All Malignancies		Malignancies with Latency $\geq 90$ days	
	TI (N=2409)	Comparator (N=1944)	TI (N=2409)	Comparator (N=1944)
Breast cancer	4	2	4	2
Colon cancer	1	1	1	1
Ovarian epithelial cancer	1		1	
Bile duct cancer	1			
Prostate cancer	3	1	2	1
Cervix carcinoma		1		1
Rectal cancer		1		
Metastatic gastric cancer	1		1	
Pancreatic carcinoma		1		
Neuroendocrine tumor (lung involvement)	1		1	
Total	12	7	10	5

Source: Table 56, ISS

**Reviewer’s comment: There were few reported neoplasms in the pooled phase 2/3 controlled trials making comparisons difficult. There is no clustering of events by tumor site.**

Pulmonary high resolution computed tomography (HRCT) was performed in select trials for pulmonary safety evaluation. These revealed “neoplasms” that could not be coded as benign or malignant at the time of event reporting. These events are discussed in Dr. Karimi-Shah’s pulmonary safety review.

Neoplasms in uncontrolled and other non-pooled trials:

The only uncontrolled trial with reports of neoplasms in TI-treated subjects was trial 010. Over the course of the trial, there were 7 malignancies and 6 benign neoplasms reported in 13 out of 229 subjects.

There was one case of a reported primary lung malignancy in a patient enrolled in the uncontrolled extension trial 010. The case narrative is provided below.

Subject 407/3316, is a 66-year-old (age at entry into trial) male in the Czech Republic who received TI Inhalation Powder 45 U TID via inhalation starting on 22 Mar 2005 and was administered at 30 U TID from 01 Nov 2005 to 13 Dec 2006. The subject’s antidiabetic regimen also included glibenclamide and metformin. On 07 Dec 2006 while undergoing diagnostic tests for an anemia workup, he underwent a CT scan of the lungs, which showed two areas measuring 12 × 19 × 20 mm and 19 × 14 × 20 mm in segment S2 in the right side of the lungs which was eventually confirmed to be bronchogenic carcinoma non-small-cell (T4N2M0). The patient’s medical history was notable for tobacco use (40 cigarettes per day for 20 years) until 1985. Information about this patient submitted in the 120 day safety update revealed that the patient eventually died from bronchogenic carcinoma in (b) (6)

The other malignancies in the uncontrolled trial 101 were not clustered into any one type and included renal cell, pancreatic, prostate, colon, skin and hematologic cancers.

Because of the limited number of cases of malignancy in the clinical development program the Sponsor presented an analysis of the incidence rate of malignant neoplasms in the TI clinical development program compared to the expected rate using epidemiologic information from the NCI/Surveillance Epidemiology End Results database (SEER). The rates seen in the TI development program were similar to expected rates for a similar but untreated population.

Discussion of malignancies: Overall, there were few events to be able to make meaningful comparisons between TI treated patients and controls in the TI development program. Lung malignancies are the primary concern with use of TI and there was only one case of bronchogenic carcinoma in the TI development program. The sponsor argues that in pre-clinical studies, including a 2-year carcinogenicity study in rats and a 6-month study in transgenic mice, there has been no evidence of carcinogenicity (please see Dr. Tsai-Turton’s pharm tox review for a discussion of pre-clinical studies and carcinogenicity. In this program, TP without insulin was studied for carcinogenicity potential). Combining the non-clinical data, the SEER data, and the

malignancy rates in the clinical development program, there does not appear to be a malignancy signal for TI. However, because of the limited timeframe of the TI clinical development program and because of postmarketing data suggesting a relationship between Exubera and lung malignancy evaluating for risk of malignant neoplasms of the lung should be a focus of postmarketing studies of TI.

### 7.6.2 Human Reproduction and Pregnancy Data

Eleven pregnancies were reported during the clinical development program; 3 of the subjects were not receiving study medication at the time of the pregnancy diagnosis and 2 of the subjects were nondiabetic subjects not exposed to study treatment in trial 030. Of the remaining 6 subjects, 4 subjects received comparator treatment (2 subjects received usual care and 2 received insulin aspart + insulin glargine). Two of the 11 pregnancies reported occurred in the TI group; 1 of these 2 pregnancies occurred in the spouse of a male TI-treated subject.

One subject (237/1388) randomized to TI in trial 102 became pregnant after an exposure to TI of 277 days; she was withdrawn from the trial. The outcome of the pregnancy was unknown despite attempts from the investigator to obtain follow-up information. One spousal pregnancy was reported by a subject treated with TI (Trial 030, subject 052/273); the subject had been treated for 528 days. The spouse experienced a normal spontaneous vaginal delivery, producing a healthy female baby at 40 weeks age of gestation (7 pounds 4 ounces, 20.5 inches in length).

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Human pediatric studies were not performed prior to submission of this NDA, nor have they been initiated at the time of this review. Pediatric subjects will be postmarketing requirements under the Pediatric Research Equity Act.

The Sponsor requested a partial waiver of pediatric assessment for age birth to (b) (4) of age for reasons that the product would be ineffective or unsafe in this age group. The Sponsor requested a deferral of pediatric assessment for ages (b) (4) to up to 17 years because additional safety data from adults are needed.

The Sponsor's justification is as follows:

(b) (4)

(b) (4)

The sponsor has submitted a pediatric assessment plan

(b) (4)

The Pediatric Review Committee (PeRC) meeting was held to discuss the appropriateness of the sponsor's proposed pediatric assessment plan on 05 Nov 2009. In general, the committee concluded that the plan was acceptable except for the upper age limit of the waiver request and the length of the major pediatric safety and efficacy trial.

(b) (4)

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The abuse potential of inhaled insulin was not evaluated by the applicant. Recreational abuse of insulin is unlikely, as it is not known to induce pleasurable effects generally associated with drugs of abuse. In general, accidental overdose of insulin results in hypoglycemia which can lead to neurological compromise, seizures, and occasionally death. No intentional or accidental overdose of inhaled insulin occurred during the drug development program.

## 7.7 Additional Submissions

The 120 day safety update was submitted on 16 July 2009. There was no new information that changes the general safety assessment of the original NDA. The submission contained updated safety information as of a cutoff date of 31 May 2009. As discussed in section 7.3.1, in the 120 day safety update four more deaths were reported for TI treated patients which had been received for patients enrolled in completed trials but after database lock. One of these deaths was reported in the controlled trial 102. The three remaining deaths were reported for subjects in the long term uncontrolled trial 010. All deaths were follow-ups of previously reported serious adverse events and occurred after subjects had completed trial participation and patients were no longer on study medication. Otherwise, the only reported safety information from completed clinical trials was updates of previous adverse events reports and some reclassification of adverse events (for example, reclassifying an event of severe hypoglycemia to non-severe hypoglycemia that did not change the overall safety conclusions of this review).

### New clinical trials:

In completed Phase 1 Study MKC-T-140, “An open-label, randomized, crossover, two-part study in healthy, normal volunteers to assess the safety, tolerability, pharmacokinetics, and inhalation parameters of Technosphere® Inhalation Powder as delivered by the Gen2A Inhaler compared to the MedTone® Inhaler Model C”, 30 healthy subjects were treated with TP (placebo). Safety analyses for this trial had not occurred at the time of this update. There were no reports of SAEs, deaths, or discontinuations due to treatment-emergent adverse events (TEAE).

In completed Phase 1 Study MKC-TI-141, “A single-center, open-label, randomized, crossover design trial in healthy normal volunteers to assess the relative bioavailability of Technosphere® Insulin Inhalation Powder as delivered by the Gen2B Inhaler (test inhaler) as compared to the MedTone® Inhaler Model C (reference inhaler),” 48 healthy subjects were randomized and trained with TP, and 45 were treated with TI. Safety analyses for this trial had not occurred at the time of this update. There were no reports of SAEs, deaths, or discontinuations due to TEAEs as of 31 May 2009.

In completed Phase 2 Study MKC-TI-118, (a randomized, open-label, 3-way crossover trial with 9 visits for each completed subject to compare the effect of Technosphere® Insulin Inhalation Powder, insulin lispro, and Exubera® on endogenous glucose production after a meal challenge and during a euglycemic glucose clamp procedure in subjects with type 2 diabetes), 30 subjects with type 2 diabetes were treated with TI. Safety analyses for this trial had not occurred at the time of this update. There were no reports of SAEs, deaths, or discontinuations due to TEAEs as of 31 May 2009.

In ongoing Phase 2 Study MKC-TI-119, (a single-center, open-label, pharmacodynamic trial to evaluate the effect of Technosphere® Insulin Inhalation Powder on postprandial glucose levels in subjects with type 1 and type 2 diabetes mellitus ingesting meals with varied carbohydrate content over 15 weeks of treatment), 8 subjects were treated with TI (5 subjects with type 1 diabetes and 3 with type 2 diabetes). There is no comparator arm in this trial. Safety analyses for

this trial had not occurred at the time of this update. There have been no reports of SAEs, deaths, or discontinuations due to TEAEs as of 31 May 2009.

In the ongoing Phase 3 study MKC-TI-117, A multi-center, open-label, randomized, controlled clinical trial evaluating the efficacy and safety of Technosphere® Insulin Inhalation Powder in combination with Lantus® (insulin glargine) versus Humalog® (insulin lispro) in combination with glargine in subjects with type 1 diabetes over a 16-week treatment period; 71 subjects have been enrolled with 8 discontinuations thus far. Complete safety analyses for this ongoing trial had not occurred at the time of this update. There were no reports of SAEs or deaths as of 31 May 2009. One subject (Subject 023/0005) treated with Technosphere® Insulin Inhalation Powder discontinued due to a non-serious TEAE of dyspnea which was of mild severity and resolved within 3 days of onset without medication.

The Phase 3 study MKC-TI-134 is an evaluation of the use of Afrezza in subjects with underlying lung disease. The data safety monitoring board (DSMB) meeting for MKC-TI-134 for subjects with underlying lung disease (asthma and chronic obstructive pulmonary disease [COPD]) was held on 12 May 2009. Based on review of the data from Technosphere® Insulin Inhalation Powder clinical pharmacology studies in a small number of subjects with diagnosed asthma or COPD, the DSMB was concerned about the potential risks for acute bronchoconstriction and pulmonary exacerbations associated with TI in this subpopulation of patients. During a follow up meeting on 28 May 2009, the DSMB recommended that MannKind suspend screening and enrollment in the trial in order to further determine how subjects with asthma and COPD should be evaluated. On 29 May 2009, all Investigators and the FDA were notified of MannKind Corporation's decision to suspend enrollment in trial MKC-TI-134 based on the recommendation of the DSMB. No subjects had been randomized to any study treatment at the time enrollment was suspended. The Sponsor, along with agreement from the Agency, has modified the inclusion criteria of the protocol to enhance subject safety.

The Phase 3 study MKC-TI-139 (Patient transfer program for transitioning from Exubera® (insulin human [rDNA origin]) Inhalation Powder to Technosphere® Insulin (insulin human [rDNA origin]) Inhalation Powder over a 24-month period) has enrolled 4 subjects as of the cutoff date of this update. No deaths, adverse events, or discontinuations have been reported for these four subjects.

## 8 Postmarket Experience

Not applicable as this product is not marketed in any country.

## 9 Appendices

### 9.1 Literature Review/References

Cryer PE, Childs BP. Negotiating the barrier of hypoglycemia in diabetes. *Diabetes Spectrum*. 2002; 15:20-7.

Kubiak T, Hermanns N, Schreckling HJ, Kulzer B, Haak T. Assessment of hypoglycemia awareness using continuous glucose monitoring. *Diabet Med*. 2004;21:487-90.

U.K. Hypoglycemia Study Group. Risk of hypoglycemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;50:1140-1147.

Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, Band MM, Reekie G, Leese GP; DARTS/MEMO Collaboration. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabet Med*. 2005; Jun 22(6):749-55.

National Cancer Institute Surveillance Epidemiology End Result database (SEER).  
<http://www.seer.cancer.gov/>

Stoever JA, Palmer JP. Inhaled insulin and insulin antibodies: a new twist to an old debate. *Diabetes Technol Ther* 2002;4(2):157-61.

Heise T, Bott S, Tusek C, Stephan JA, Kawabata T, Finco-Kent D, Liu C, Krasner A. The effect of antibodies on the metabolic action of inhaled and subcutaneous insulin. A prospective randomized pharmacodynamic study. *Diabetes Care* 2005;28:2161-9.

Goldstein D, Parker K, England J, et al. Clinical application of the glycosylated hemoglobin. *Diabetes*. 1982; 31: 70-8.

Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31: 1-11.

Nathan DM, Singer DE, Hurxthal K, Goodson JD. The clinical information value of the glycosylated hemoglobin assay. *N Engl J Med*. 1984; 310: 341-6.

The Facts about HbA1c from  
<http://www.aace.com/public/awareness/stateofdiabetes/FactsAboutA1C.pdf>

UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998; 352: 837-53.

UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*; 1998; 352: 854-65.

Welchol Prescribing Information, revised January, 2008

College of American Pathologists. Glycohemoglobin survey. 1999. Northfield, IL: College of American Pathologists; 1999 (Set GH-2).

Cycloset Prescribing Information, revised April, 2009

Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993; 329: 977-86.

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type I diabetes. *N Engl J Med*. 2005; 353: 2643-53.

Holman RR, Farmer AJ, Davies MJ, et al. for the 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med*. 2009; 361:1736-47.

Modern-Day Clinical Course of Type 1 Diabetes Mellitus After 30 Years' Duration. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005). *Arch Intern Med*. 2009; 169 (14):1307-1316.

Hankinson J et al 1999. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 159(1):179-87

## **9.2 Labeling Recommendations**

Labeling recommendations are contained throughout this review. A line-by-line labeling review will be performed separately.

## **9.3 Advisory Committee Meeting**

There was no advisory committee meeting for this NDA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	INSULIN HUMAN (RDNA ORIG)INH POWDER

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/s/

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LISA B YANOFF  
12/24/2009

HYLTON V JOFFE  
12/24/2009  
Please see CDTL memorandum.