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APPLICATION NUMBER:

022472Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

CLINICAL REVIEW and CDTL MEMO

Application Type	NDA class 2 resubmission
Application Number(s)	22,472
Priority or Standard	S
Submit Date(s)	15 Oct 2013
Received Date(s)	15 Oct 2013
PDUFA Goal Date	15 Apr 2014 – original 15 Jul 2014 – major amendment extension
Division / Office	DMEP/ODE2/OND
Reviewer Name(s)	Lisa B. Yanoff, M.D.
Review Completion Date	25 June 2014
Established Name	Technosphere insulin inhalation powder
(Proposed) Trade Name	Afrezza
Therapeutic Class	Inhaled insulin
Applicant	MannKind
Formulation(s)	Inhalation powder (pre-metered)
Dosing Regimen	Dose-titrated prandial inhalation
Indication(s)	The treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia.
Intended Population(s)	Adults with Diabetes Mellitus

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment	8
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.....	11
1.4	Recommendations for Postmarket Requirements and Commitments	11
2	INTRODUCTION AND REGULATORY BACKGROUND.....	13
2.1	Product Information.....	13
2.2	Tables of Currently Available Treatments for Proposed Indications	14
2.3	Availability of Proposed Active Ingredient in the United States	15
2.4	Important Safety Issues With Consideration to Related Drugs	15
2.5	Summary of Presubmission Regulatory Activity Related to Submission	16
2.6	Other Relevant Background Information	29
3	ETHICS AND GOOD CLINICAL PRACTICES	29
3.1	Submission Quality and Integrity.....	29
3.2	Compliance with Good Clinical Practices.....	29
3.3	Financial Disclosures.....	30
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	30
4.1	Chemistry Manufacturing and Controls/Device.....	30
4.2	Clinical Microbiology.....	31
4.3	Preclinical Pharmacology/Toxicology	31
4.4	Clinical Pharmacology	32
4.4.	Mechanism of Action	38
4.4.2	Pharmacodynamics.....	38
4.4.3	Pharmacokinetics.....	38
5	SOURCES OF CLINICAL DATA.....	39
5.1	Tables of Studies/Clinical Trials	39
5.2	Review Strategy.....	42
5.3	Discussion of Individual Studies/Clinical Trials.....	43
6	REVIEW OF EFFICACY.....	61
	Efficacy Summary.....	61
6.1	Indication	62
6.1.1	Methods	62
6.1.2	Demographics.....	62
6.1.3	Subject Disposition.....	68
6.1.4	Analysis of Efficacy Endpoint(s)	71
6.1.4.1.1	Analysis of Primary Efficacy Endpoint: Study 171 – Type 1 Diabetes	71

6.1.4.1.2	Analysis of Secondary Endpoints(s): Study 171 – Type 1 Diabetes	81
6.1.4.1.3	Other Endpoints: Study 171 – Type 1 Diabetes	82
6.1.4.1.4	Subpopulations: Study 171 – Type 1 Diabetes.....	82
6.1.4.2.1	Analysis of Primary Efficacy Endpoint: Study 175 – Type 2 Diabetes	82
6.1.4.2.2	Analysis of Secondary Endpoints(s): Study 175 – Type 2 Diabetes	85
6.1.4.2.3	Other Endpoints: Study 175 – Type 2 Diabetes	87
6.1.4.2.4	Subpopulations: Study 175 – Type 2 Diabetes.....	89
6.1.5	Analysis of Clinical Information Relevant to Dosing Recommendations	89
6.1.6	Discussion of Persistence of Efficacy and/or Tolerance Effects	89
6.1.7	Additional Efficacy Issues/Analyses	90
7	REVIEW OF SAFETY	90
	Safety Summary.....	90
7.1	Methods	91
7.1.1	Studies/Clinical Trials Used to Evaluate Safety.....	91
7.1.2	Categorization of Adverse Events.....	92
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	92
7.2	Adequacy of Safety Assessments	93
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	93
7.2.2	Explorations for Dose Response	97
7.2.3	Special Animal and/or In Vitro Testing	97
7.2.4	Routine Clinical Testing.....	97
7.2.5	Metabolic, Clearance, and Interaction Workup.....	97
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	97
7.3	Major Safety Results	97
7.3.1	Deaths	97
7.3.2	Nonfatal Serious Adverse Events	99
7.3.3	Dropouts and/or Discontinuations	109
7.3.4	Significant Adverse Events	117
7.3.5	Submission Specific Primary Safety Concerns	122
7.4	Supportive Safety Results.....	134
7.4.1	Common Adverse Events	134
7.4.2	Laboratory Findings	138
7.4.3	Vital Signs	138
7.4.4	Electrocardiograms (ECGs)	139
7.4.5	Special Safety Studies/Clinical Trials	139
7.4.6	Immunogenicity.....	143
7.5	Other Safety Explorations	143
7.5.1	Dose Dependency for Adverse Events	144
7.5.2	Time Dependency for Adverse Events.....	144
7.5.3	Drug-Demographic Interactions	144
7.5.4	Drug-Disease Interactions	144

7.5.5	Drug-Drug Interactions	144
7.6	Additional Safety Evaluations	144
7.6.1	Human Carcinogenicity.....	144
7.6.2	Human Reproduction and Pregnancy Data	144
7.6.3	Pediatrics and Assessment of Effects on Growth.....	144
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	145
7.7	Additional Submissions / Safety Issues	146
8	POSTMARKET EXPERIENCE.....	146
9	APPENDICES.....	147
9.1	Literature Review/References	174
9.2	Labeling Recommendations	174
9.3	Advisory Committee Meeting	174

Table of Tables

Table 1- HbA1c (%) results for the phase 2/3 trials in patients with type 1 diabetes.....	22
Table 2 - HbA1c (%) results for key phase 2/3 trials in type 2 diabetes	29
Table 3 – Pharmacokinetic and Biopharmaceutic Studies.....	39
Table 4 - Clinical Efficacy and Safety Studies	40
Table 5 - Afrezza TI Dose Conversion for the Gen2 Inhaler.....	44
Table 6 – Recommended Afrezza TI Dose Adjustments for Gen2	45
Table 7– Basal Insulin Titration Algorithm.....	53
Table 8 – Insulin Aspart Dosing Algorithm.....	54
Table 9 – Subject Demographics and Baseline Characteristics – Study 171.....	63
Table 10 – Summary of Basal Insulin Stratification (Randomized Population).....	66
Table 11 – Subject Demographics and Baseline Characteristics – Study 175.....	66
Table 12– Subject Disposition Study 171	69
Table 13– Subject Disposition Study 175.....	70
Table 14 – Trial 171 ANCOVA of Mean Change from Baseline in HbA1c (%) at Week 24, MMRM Model, FAS Population	73
Table 15 – Trial 009 ANCOVA of Mean Change from Baseline in HbA1c (%) at Week 52, ITT Population with LOCF	74
Table 16 - Study 171 – Sponsor’s Table of Average Daily Dose of Basal Insulin (IU/Day) Since Randomization by Time Periods (Safety Population).....	76
Table 17 - Study 171 - Average Daily Dose of Prandial Insulin since Randomization by Time Periods (Safety Population)	78
Table 18 – Study 171: Efficacy Results for HbA1c (%) by Sex.....	82
Table 19 – Study 175 - ANCOVA of Primary Endpoint – Change in HbA1c From Baseline to Week 24 -MMRM Analysis with FAS Population.....	83
Table 20 – Efficacy of Non-titratable Antidiabetes Drugs on a Background of Metformin or at Least Two Other Oral Antidiabetes Drugs	83
Table 21– Study 175 (T2DM): Responder Rate for HbA1c at Week 24.....	85
Table 22 – Study 175 (T2DM): Statistical Results for FPG (mg/dL).....	86
Table 23 – Study 175 (T2DM): Statistical Results for Body Weight (kg)	87
Table 24 – Overview of Clinical Safety Data for TI.....	91
Table 25 – Number of Subjects in Pooled, Controlled Phase 2/3 Clinical Studies	93
Table 26 – Demographic and Baseline Disease Characteristics of the T1DM Pooled Controlled Phase 2/3 Trials Safety Population of 2013 Resubmission.....	95
Table 27 – Demographic and Baseline Disease Characteristics of the T2DM Pooled Controlled Phase 2/3 Trials Safety Population of 2013 Resubmission.....	96
Table 28– Deaths Listing for TI and Comparator, Cutoff date 31 Jul 2013	98
Table 29 – Incidence of Serious Adverse Events by System Organ Class and Preferred Term for T1DM and T2DM Combined, Pooled Phase 2/3 Safety Population, 2013 Resubmission.....	100
Table 30 – Listing of Patients with Non-hypoglycemic Serious Adverse Events (SAEs) Occurring after Randomization in the Pooled Phase 2/3 Population since the 2010 Resubmission cutoff - T1DM and T2DM combined	106
Table 31 – SAEs During the Randomized Treatment Phase of Study 175.....	108

Table 32 – Adverse Events Leading to Dropout –T1DM – 2013 Resubmission	109
Table 33 - Adverse Events Leading to Dropout –T2DM – 2013 Resubmission	111
Table 34 – Lung Cancer Cases in Afrezza TI-Treated Patients.....	118
Table 35 –Lung Cancer in the Afrezza TI Program.....	119
Table 36 – Number of Reported Malignancies in Type 1 or Type 2 Subjects, Excluding Non-Melanoma Skin Malignancies (Pooled Safety Population)	125
Table 37 – Incidence of Potentially Immunogenic Adverse Events – T1DM and T2DM Combined (2013 Resubmission Safety Population)	127
Table 38 – Event Rates for Hypoglycemia Events – Study 171	130
Table 39 – Incidence of Hypoglycemia – Trial 171	132
Table 40 – Common Adverse Events (incidence >2% and occurring ≥0.5% more frequently with TI than comparator) in the phase 2/3 trials in patients with T1DM, excluding cough and hypoglycemia.....	134
Table 41 – Common Adverse Events (incidence >2% and occurring ≥0.5% more frequently with TI than comparator) in the main phase 3 trials in patients with T2DM, excluding cough and hypoglycemia.....	135
Table 42 - Common Adverse Events Occurring in ≥2% of Subjects in Trial 171, and Occurring More Frequently with TI than Comparator.....	136
Table 43 - Common Adverse Events Occurring in ≥2% of Subjects in Trial 175, and Occurring More Frequently with TI than Placebo, and all Events from the Respiratory, Thoracic, and Mediastinal Disorders System-Organ Class Occurring in ≥2% of Subjects.....	137
Table 44 - Common Adverse Reactions Patients with Type 2 Diabetes Mellitus (excluding Hypoglycemia) Treated with TI.....	137
Table 45 - Common Adverse Reactions Patients with Type 1 Diabetes Mellitus (excluding Hypoglycemia) Treated with TI.....	138
Table 46 – Serious Adverse Events in Trial 171	140
Table 47 – Adverse Events Leading to Discontinuation in Trial 171.....	141
Table 48 – Common Adverse Events Occurring in ≥2% of Subjects in Trial 171, Including MedTone arm.....	142
Table 49 - Deaths Listing ¹ for Afrezza TI and Comparator	152

Table of Figures

Figure 1 - Study 171 Schematic	52
Figure 2– Study 175 Schematic	59
Figure 3 – Study 171 - Primary Efficacy Endpoint: Observed Mean Change (SE) in HbA1c (%) from Screening to Week 28 by Randomized Treatment Group (FAS Population)	72
Figure 4 – Study 171 – Mean Daily “Basal” Insulin Dose Change from Baseline (SE) in IU/day over time (Safety Population) in Aspart and Afrezza TI Gen 2 Arms.....	75
Figure 5 – Study 171 – Mean (SE) Daily “Prandial” Insulin Dose Change from Baseline (IU/day) over time (Safety Population) in Aspart and Afrezza TI Gen 2 Arms.....	77
Figure 6 – Mean HbA1c Change over Time, Study 175	84
Figure 7 - Observed Mean (SE) of FPG Measurements over Time (FAS Population)	86
Figure 8 - Study 175 - Box Plots of Average Daily Dose of Prandial Insulin since Randomization by Time Periods (Safety Population)	88

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

For this NDA resubmission I recommend **approval** of Afrezza for the treatment of diabetes mellitus in adults. This is consistent with my recommendations for the first two review cycles.

For the current review cycle the major additional clinical data with which FDA was presented were:

- Two additional phase 3 trials – one in type 1 diabetes patients and one in type 2 diabetes patients that used the new inhaler device, the Gen2 device; one of these trials also provided a head-to-head comparison of pulmonary safety between the original device and the Gen2 device.
- Additional clinical pharmacology data assessing the question of the dose proportionality of Afrezza
- Two additional cases of lung cancer among Afrezza-treated patients

In my view, these new data support my original recommendation of approval, and they also form the basis of my recommendations for postmarketing requirements and commitments.

My recommendation also takes into consideration the overwhelming vote for approval from the voting participants of the Endocrinologic and Metabolic Advisory Committee (EMDAC) meeting held 1 Apr 2014 to discuss the Afrezza marketing application.

1.2 Risk Benefit Assessment

The risk benefit assessment for type 1 and type 2 diabetes was considered separately because the two diseases are distinct.

For type 2 diabetic subjects the potential benefits of Afrezza outweigh the risks. At the time of the original NDA review of Afrezza, for type 2 diabetic patients there was clear evidence of efficacy of Afrezza compared with placebo which, along with clinical pharmacology trials, provided evidence that Afrezza functions as exogenous insulin. In the current resubmission a new phase 3 placebo-controlled study of Afrezza in type 2 diabetes patients on a background of oral antidiabetes drugs showed that the placebo-adjusted decrease in HbA1c after 24 weeks was better than the reduction observed for placebo. The placebo-adjusted reduction was modest for an insulin product (approximately 0.4 percentage points in HbA1c) but the difference was statistically significant and there were no major trial conduct issues limiting confidence in the results.

In other type 2 diabetes trials (submitted with the original NDA), Afrezza generally provided numerically less glycemic control than comparator in the active-controlled trials. Afrezza plus a

long-acting injected insulin was statistically 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 lesser efficacy 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 diabetes patients, Afrezza appears to meet this requirement.

As I stated in my original NDA review, and voiced by the EMDAC, among type 2 diabetes 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.

The identified risks including pulmonary risks (acute bronchospasm in patients with chronic lung disease, decline in lung function over time) and a potential lung cancer risk can be mitigated through labeling and postmarketing required studies and risk management strategies.

For type 1 diabetes patients, the risk benefit assessment is more challenging. For type 1 patients, in the original NDA there was only one confirmatory efficacy trial. In this trial, Afrezza was inferior and statistically worse after 52 weeks of treatment than a standard-of-care intensive insulin regimen which consisted of basal/bolus subcutaneous insulin therapy. At that time, I argued that 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 require sufficient exogenous insulin. The observation that in a 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 the year while receiving a similar dose of basal insulin as the subcutaneous insulin comparator group, is evidence of the efficacy of Afrezza in the type 1 population.

In the current resubmission, a new phase 3 active-controlled study of Afrezza in type 1 diabetes patients in combination with basal insulin therapy showed that Afrezza was statistically worse than the comparator insulin after 24 weeks of treatment, although the prespecified non-inferiority margin was met. The results of this trial are largely consistent with the 52-week trial submitted with the original NDA. 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 targets, leading to difficulty in determining how efficacious Afrezza would be if optimally titrated. Furthermore, in the new phase 3 study there were significant missing data issues such that the degree of missing data for HbA1c at Week 24 raised issues on the reliability and confidence in the results. Nevertheless, as with the 52-week trial, the natural history of type 1 diabetes still plays a role in interpretation of the trial results.

Another consideration is that there is no conceivable physiologic reason why Afrezza should work as exogenous insulin for type 2 patients and not type 1 patients. In fact, type 1 patients tend to be less insulin resistant than type 2 patients and therefore, would be expected to be more sensitive to Afrezza than type 2 patients would be. The pivotal type 1 trial designs limited the comparison to injected basal/bolus insulin therapy to which Afrezza seems to be inferior for both type of diabetes. The important question faced by FDA is whether the relative loss in efficacy that will likely occur with Afrezza use (compared with subcutaneous prandial insulin use) is justified by the benefit of the alternative route of administration.

In the review of safety, in addition to the risks identified above, 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. If approved, the labeling for Afrezza should note the risk of diabetic ketoacidosis in Warnings and Precautions and should advise patients and prescribers that in risk situations for diabetic ketoacidosis, changing from Afrezza to subcutaneous insulin should be considered. I am also recommending a postmarketing required study to further investigate the less than dose-proportional pharmacodynamic response at higher doses of Afrezza observed in clinical pharmacology studies of Afrezza. Once available, these data could help health care providers to identify patients who may not be appropriate for Afrezza therapy, i.e. those requiring large doses of prandial insulin.

As noted above, a meeting of the EMDAC was convened to discuss the Afrezza application (see section 9 of this review). After considering the available data for Afrezza the EMDAC overwhelmingly voted to approve Afrezza for both type 1 and type 2 diabetes. The EMDAC acknowledged that Afrezza may not be appropriate for all diabetes patients but that there may be a group of patients, such as those with needle phobia, or impairments preventing the use of injectable therapies, who could benefit from Afrezza. It was clear from the EMDAC that the approval of Afrezza was highly supported. The EMDAC expressed concern about the potential lung cancer risk with Afrezza and recommended that this safety signal be addressed in postmarketing studies.

In the case of Afrezza, I believe it is reasonable to allow for a role of individual health care providers and patients to decide whether the relative loss in efficacy is outweighed by any relative benefit of inhaled vs. injected prandial insulin therapy (e.g. needle phobia). Therefore, my recommendation for approval in type 1 patients, is based on the provision that through labeling it will be shown that the inclusion of Afrezza as the prandial insulin in a basal/bolus regimen is less effective than injected basal/bolus therapy, and that patients 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., at risk for diabetic ketoacidosis).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I recommend that Afrezza should be approved with a Risk Evaluation and Mitigation Strategies (REMS).

The Division of Risk Management (DRISK) documents in detail the Agency decision regarding the need for a REMS (see review dated 24 Jun 2014). The internal discussion focused on the risk of acute bronchospasm in patients with chronic lung disease. We considered the possibility that use of Afrezza outside of a clinical trial scenario could result in patients with chronic lung disease using the drug and that the typical prescribers of Afrezza, likely Endocrinologists as well as Internists and other primary care providers, do not routinely need to consider lung function when prescribing insulin. Therefore, although including the risk of acute bronchospasm in patients with chronic lung disease is appropriate for a boxed warning, additional measures were thought to be needed to disseminate the risk message.

The REMS is mainly a communication plan REMS with goal of the REMS 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

At the time of this review, the REMS plans have been vetted within the Agency, with the Sponsor, and finalized. Please see Appendix 1 for full details of the REMS elements.

1.4 Recommendations for Postmarket Requirements and Commitments

My recommendations for postmarketing requirements and commitments are based on the safety issues identified during review of the application. In addition, there are postmarketing requirements recommended to satisfy the Pediatric Research Equity Act (PREA).

The potential risk of pulmonary malignancy – Because of its mode of action and because of the experience with Exubera (see section 2.4) and the small imbalance of lung cancer cases observed in the Afrezza development program there is a concern of a potential lung cancer risk with Afrezza. The available data discussed in this review (see section 7.3.4) do not demonstrate a clear risk association for lung cancer. However, concern remains because the data currently available may not be sufficient to clearly rule out an excess risk of lung cancer due to Afrezza use, in part, because of the long latency and relative rarity of malignancy events compared with other types of adverse events such as diabetic ketoacidosis and pulmonary function decline.

Therefore, the potential risk of lung cancer is best assessed in the postmarketing setting. The study designed to assess this potential risk should be a required, randomized, controlled clinical trial that is sufficiently large and of sufficient duration to evaluate the primary objective of comparing the incidence of pulmonary malignancy observed with Afrezza to a standard-of-care control group. A placebo-controlled trial was considered, but ultimately rejected given that patients will likely be able to discern Afrezza from placebo within days of monitoring their blood glucose levels. Therefore, for practicality reasons and to improve subject retention, an open label trial is recommended.

Although the clinical development program for Afrezza did not suggest an excess cardiovascular (CV) risk, the program was not designed adequately to assess CV risk. Therefore, I recommend that the long term outcomes trial designed to assess lung cancer risk 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). CV risk needn't be the primary objective of the outcomes trial. See section 7.3.5 for a detailed explanation of my rationale for this recommendation.

The risk of lung function decline over time –At the time of this review, only 2 years of pulmonary safety data are available for Afrezza. While the observed decline in FEV1 seems to be non-progressive, the long term effect of Afrezza on pulmonary function is unknown. This concern was also expressed by the EMDAC. Therefore, I recommend a postmarketing requirement to evaluate the long-term effect Afrezza on pulmonary function. The pulmonary reviewer states that a sub-study of the above recommended large outcomes trial to assess lung cancer risk, would be appropriate to address this safety concern and that a separate trial is not needed. I agree with this recommendation.

The risk of diabetic ketoacidosis (DKA) – An imbalance in DKA was observed in the Afrezza clinical trials (13 to 3) not favoring Afrezza; however, it is not clear from the data whether the use of Afrezza contributed to this imbalance or whether by chance, more patients randomized to Afrezza had infections, illness, or other issues predisposing to DKA. The clinical pharmacology reviewer concluded that in clinical studies, while an increase in Afrezza pharmacokinetics (PK) (e.g., insulin AUC) was dose proportional, increase in pharmacodynamics (PD) (i.e., GIRAUC₀₋₂₄₀) was less than dose proportional. The observed non-proportionality in dose-response for PD may affect the dosing titration – such that after a certain dose the incremental benefit in terms of PD will be minimal with increase in dose. It is possible that the near-maximal effect of Afrezza occurs in the clinically relevant dose range, and that this could confer a higher risk for DKA. It would be difficult to address the root cause of this safety concern with additional clinical trial data. Therefore, I favor requiring a dose-ranging pharmacokinetic/pharmacodynamic euglycemic glucose-clamp study to characterize the dose-response of Afrezza relative to subcutaneous insulin in patients with type 1 diabetes. At least three to four doses for each route of insulin administration should be selected to ensure both the linear and curvilinear portions of the dose-response curves are adequately captured and characterized. The study should compare the dose-response curves for Afrezza and subcutaneous insulin noting the dose at which the response becomes curvilinear for each. These data may impact labeling recommendations for dosing and

thereby mitigate the risk of DKA that has been observed with Afrezza. See also section 4.4 of this review.

Within subject variability study and risk of hypoglycemia - The within-subject variability of Afrezza was not studied in the clinical development program. Clinical implications of a high within-subject variability could be a less consistent therapeutic effect on a dose-to-dose and day-to-day basis which could lead to under- and/or over-dosing. While this is not an approvability issue, the within-subject variability should be assessed in a required post-marketing study. These data may impact labeling recommendations for glucose monitoring and thereby mitigate the risk of hypoglycemia, which has been observed with Afrezza.

The EMDAC raised a concern regarding the design of the Afrezza inhaler cap, that it could be inadvertently inhaled by patients. A postmarketing commitment study should also be included in the approval letter for the Sponsor to study the design of the inhaler cap in an effort to improve the design to prevent inadvertent inhalation of the cap.

PREA required studies - An open-label PK, and multiple-dose safety and tolerability dose-titration trial of Afrezza in pediatric patients ages 4 to 17 years (inclusive) with type 1 diabetes (Part 1), followed by a prospective, multicenter, open-label, randomized, controlled trial comparing the efficacy and safety of prandial Afrezza to prandial, subcutaneous, insulin aspart used in combination with subcutaneous basal insulin in pediatric patients 4 to 17 years old (inclusive) with type 1 or type 2 diabetes (Part 2). Part 2 of the trial should include a 4-week run-in phase and a 52-week randomized intervention phase.

At the time of this review, the postmarketing requirements and commitments have been vetted within the Agency, with the Sponsor, and finalized. Please see Appendix 2 for full details.

2 Introduction and Regulatory Background

2.1 Product Information

Afrezza is a drug-device combination product consisting of a dry powder formulation of recombinant regular human insulin [i.e., Technosphere Insulin (referred to in this review as TI)] and an inhaler device (i.e., Gen2 inhaler). In this review TI plus the inhaler is referred to as “Afrezza”, “TI”, or “Afrezza TI”. In this review “TP” or Technosphere placebo is the term used for placebo powder administered with the Gen 2 inhaler (or MedTone inhaler in older studies). Afrezza is intended to cover meal time insulin requirements for the treatment of adults with both type 1 (T1DM) and type 2 diabetes mellitus (T2DM).

Patients self-administer the insulin powder by oral inhalation. The insulin powder is pre-filled into cartridges packaged in blisters. Cartridges contain either 0.35 mg or 0.7 mg of insulin per cartridge. The patient uses the product by removing a cartridge from the blister package, inserting it into the inhaler, placing the inhaler in his/her mouth and inhaling the powder. The inhaler is breath-powered.

The 0.35 mg and 0.7 mg cartridge presentations have nominal fill weights of 3.3 mg and 6.7 mg of TI Inhalation Powder, respectively. In the current application the Sponsor states that ‘each milligram of TI Inhalation Powder contains 3 U of insulin’ and that this amount is the subcutaneously injected short-acting insulin equivalent.

Reviewer’s comment: In the early Afrezza development program including through the current phase 3 studies, what the Sponsor is now calling a 3 U Gen2 cartridge was called the 10 U Gen2 cartridge, and was stated to be equivalent to approximately 4 units of injected rapid-acting insulin. The 6.7 mg TI Inhalation power cartridge that the Sponsor is now calling the 6 U Gen2 cartridge, was previously called a 20 U Gen2 cartridge and was stated to be equivalent to approximately 8 units of injected rapid-acting insulin. This has implications for labeling with regard to dosing recommendations. I do not agree with this dosing regimen change (see section 4 – Clinical Pharmacology).

The original Afrezza development program used the MedTone inhaler, not the Gen2 inhaler. MannKind switched to the to-be-marketed Gen2 inhaler in 2010 because they believe it is a smaller and simpler device. The Gen2 inhaler requires less TI inhalation powder to provide the same insulin exposure. Thus, a 10U Gen2 cartridge provides the same insulin exposure as a 15U MedTone cartridge. Likewise, a 20U Gen2 cartridge provides the same insulin exposure as a 30U MedTone cartridge. The studies submitted for the original NDA for Afrezza (and for the first resubmission) described in section 2.5 were conducted with the MedTone device.

2.2 Tables of Currently Available Treatments for Proposed Indications

Despite the number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an antidiabetic drug.

T2DM can be treated with a combination of proper diet, exercise, and one of a number classes of drugs, alone or in combination.

- Insulin and insulin analogues
- Sulfonylureas (SU)
- Biguanides
- Meglitinides
- Thiazolidinediones (TZDs)
- Inhibitors of alpha-glucosidase
- Analogues of Glucagon-like Peptide 1 (GLP-1)
- Synthetic analogues of human amylin
- Inhibitors of the enzyme dipeptidyl peptidase 4
- Bile acid sequestrants
- Dopamine agonists

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.

There are no currently available inhaled insulin therapies for diabetes. As is discussed in section 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 insulin therapy delivered by inhalation.

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. (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)) has been under review by the FDA Office of New Drug Quality Assessment (ONDQA).

2.4 Important Safety Issues With Consideration to Related Drugs

Lung Cancer Signal with Exubera

Exubera (Insulin Human [rDNA origin] Inhalation Powder) was approved by the FDA in January 2006 to improve glycemic control in adults with type 1 and type 2 diabetes. Exubera was later withdrawn by the sponsor (Pfizer) due to lower than expected sales. 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. At the time of the NDA filing in 2006, there was a known imbalance in lung cancers in Exubera-exposed participants in clinical trials.

To further assess lung cancer risk, the sponsor conducted a follow-up study (referred to as FUSE: An Observational Follow up Study of Patients Previously Enrolled in Exubera Controlled Clinical Trials) of participants who had been exposed to Exubera and comparison medications in pre-approval clinical trials and to standard of care after trial completion. In July 2012, FDA received the final study report for the FUSE Study. Significant imbalances in lung cancer mortality (6 cases in 12,605.9 Patient-Years (PYs) in the Exubera group and 2 cases in 11,802.5 PYs in the comparator group, Incidence Density Ratio: 2.81; 95% CI: 0.50-28.46) and lung

cancer incidence (12 cases in 11,180.7 PYs in the Exubera group and 3 cases in 10,467.9 PYs in the comparator group, IDR: 3.75; 95% CI: 1.01-20.68) were seen.

Because Afrezza also directly administers insulin into the lung, this safety concern with Exubera may be relevant to Afrezza and other inhaled insulin products.

Decline in Pulmonary Function with Exubera

Another safety concern identified in the Exubera program of relevance is that Exubera-treated patients had a greater mean reduction in forced expiratory volume in 1 second (FEV1) and in diffusing capacity of the lung for carbon monoxide (DLCO) 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 FEV1 or DLCO was <70% predicted. Discontinuation of Exubera was recommended if there was a confirmed decline in FEV1 \geq 20%.

Other Issues from the Exubera Clinical Development Program

- 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.
- Smokers had a 2-5-fold higher systemic insulin exposure compared to non-smokers

The Exubera program consisted of 7 phase 3 trials (two in T1DM and five in T2DM). 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.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Overview

The 2009 Original NDA for the TI Inhalation System was submitted to the FDA on 16 March 2009. This NDA included data for TI Inhalation Powder with the MedTone Inhaler.

FDA issued a Complete Response Letter (CRL) on 12 Mar 2010.

The 2010 Amendment was submitted to the FDA on 29 Jun 2010 in response to the CRL. In this amendment, the Gen2 inhaler replaced the MedTone Inhaler. To support this change the Sponsor submitted by in vitro device performance data and a clinical pharmacology study (MKC-TI- 142) intended to demonstrate bioequivalence between the two inhalers. Please see the Clinical Pharmacology review for comment on this study.

FDA issued a second CRL on 18 Jan 2011 citing the lack of meaningful information regarding patient use and robustness of the Gen2 inhaler and its impact on efficacy and safety in controlled Phase 3 clinical trials.

Phase 3 Protocols Reviewed since Last CRL

On 08 June 2011 MannKind submitted a draft protocol for MKC-TI-171 the planned pivotal Phase 3 study in Type 1 diabetes patients. On 10 August 2011 a Type C face-to-face meeting was held to discuss the planned, and minutes were provided to the Sponsor (dated 07 September 2011) reflecting the Agency’s feedback. On 17 Oct 2011 the Sponsor submitted the final version of protocol 171. On 24 Oct 2011 FDA emailed one final comment regarding the protocol to the Sponsor.

Table 4 below from the Sponsor’s submission summarizes the pre-submission regulatory activity.

Table 4. List of Key Regulatory Submissions and Communications

Date	Application	SN	Description
16 Mar 2009	NDA	0000	Original NDA 022472 Submission
16 July 2009	NDA	0006	120-Day Safety Update Submission
12 Mar 2010	NDA		Complete Response Letter from the FDA
12 May 2010	NDA	0044	Information package - Type C meeting End of Review
02 Jul 2012	NDA		FDA minutes - End of Review 1 meeting (9 Jun 2010)
29 Jun 2010	NDA	0045	2010 Amendment, including the 2010 Safety Update
18 Jan 2011	NDA		Complete Response – Second Cycle
16 Mar 2011	NDA	0060	Information package - Type C meeting End of Review Second Cycle
26 May 2011	NDA		FDA minutes - End of Review 2 meeting (4 May 2011)
07 Jul 2011	IND	0396	Information package - Type C meeting: Phase 3, T1DM study design review and dose escalation
07 Sep 2011	IND		FDA minutes - Type C meeting (10 Aug 2011): Phase 3, T1DM study design review and dose escalation
07 Jul 2011	IND	0397	Information package - Type C meeting Phase3, T2DM study design review and dose escalation
07 Sep 2011	IND		FDA minutes - Type C meeting (10Aug 2011): Phase3, T2DM study design review and dose escalation
01 Feb 2013	NDA	0073:	Information package - Type C (pre-submission) meeting
05 Mar 2013	NDA		FDA minutes - Type C meeting – Written Responses
20 Mar 2013	NDA		FDA: General Advice Letter

FDA = Food and Drug Administration; IND = Investigational New Drug Application; NDA = New Drug Application; T1DM = Type 1 Diabetes Mellitus; T2DM = Type 2 Diabetes Mellitus.

Summary of Clinical Review of Original NDA

Note: the majority of the following sections are paraphrased or verbatim text from Dr. Joffe's original NDA CDTL memo.

The original Afrezza NDA included three phase-3 efficacy and safety trials with duration of 6 months or greater. In these trials, insulin was delivered using a different device (*MedTone C inhaler*) than the device the applicant now seeks to market (Gen2 inhaler). One trial evaluated efficacy and safety in patients with type 1 diabetes and two trials in patients with type 2 diabetes. Afrezza in combination with basal insulin was observed to afford statistically and clinically worse glucose lowering than subcutaneous basal-bolus therapy in both type-1 and type-2 diabetes (i.e., treatment effect difference between arms excluded 'no difference' and did not exclude the pre-specified non-inferiority margin). Only one trial, the comparison of Afrezza plus glargine to NovoLog Mix 70/30, met its primary intended objective (i.e., excluding the pre-specified non-inferiority margin). However, the absence of a "glargine only" arm in this trial, to evaluate the independent contribution of Afrezza to the overall glucose lowering effect, confounds interpretability of the results.

Other trial conduct related issues confounding interpretability of the results were: inadequate optimization of background therapies, inadequate titration of control and intervention insulins, and insufficient time on intervention to assess the full effect of the intervention on HbA1c reduction. The efficacy results of pivotal and supportive trials and key findings from the Agency's reviews are summarized in greater detail in the sections immediately below.

Another efficacy related issue identified in the Afrezza program arose from the unexpected results of a dose response study in patients with T2DM (Study 005). Insulin is a titratable product and, in the clinical dosing range, increasing doses of insulin are expected to result in incremental glucose lowering. In this study, doses of insulin above 28 units did not result in incremental HbA1c lowering (see Table 2 below).

The Afrezza inhaler used in these phase 2 and phase 3 clinical studies (*MedTone C inhaler*) was completely re-designed after the applicant received inhaler device related complaints (i.e., broken caps, broken spring float, broken mouth piece, difficulty in inserting and removing cartridge etc.). The new inhaler, called *MedTone D inhaler*, was found to have comparable drug delivery performance in *in vitro* studies. The sponsor compared pharmacokinetic profiles between inhaled insulin delivered using the old (*MedTone C inhaler*) and the new device (*MedTone D inhaler*) in a PK study. Inspection of the site where this study was performed revealed multiple deficiencies affecting reliability of the data for this study. As a result of the inspection, the applicant could not use data generated using the *MedTone C Inhaler* to market the new *MedTone D inhaler*.

Product related safety issues identified in the review included tolerability (e.g., cough, irritation, throat pain) and pulmonary safety concerns (e.g., bronchospasm, and pulmonary function

decline). These findings will be summarized in greater detail in the safety section of this document.

FDA issued a Complete Response letter on March 12, 2010, highlighting deficiencies related to efficacy, pulmonary safety and inhaler device related issues. Based on the efficacy results summarized above, FDA 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 established to reduce long-term complications of microvascular disease in both type 1 and 2 diabetes.*”

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 to market Afrezza using an entirely new device (Gen-2 inhaler). At the meeting, the sponsor asserted that *in vitro* device performance studies and a PK study demonstrated the Gen2 and *MedTone* devices resulted in comparable delivery of the Afrezza drug product. The applicant was of the opinion that these studies were sufficient to permit reliance on efficacy and safety data derived with the *MedTone C* device to support approval of the Gen2 inhaler device.

The FDA had no experience with which to judge the acceptability of this approach and asked the applicant to share full results of the *in-vitro* comparative performance data for review prior to re-submission of the application. The applicant did not and proceeded with submitting their Complete Response which included *in vitro* performance data for the new device, a PK study comparing single dose PK profiles of the new and old device and the result of a post-hoc analysis performed on an early-terminated trial in subjects with T1 DM using the *MedTone Device*.

A Complete Response on the re-submission was issued on 18 Jan 2011. The deficiencies were related to the lack of efficacy and safety data with the new device and to the inadequacy of reliance on *in vitro* performance and single dose clinical pharmacology data to support approval of the Gen2 device.

In its decision FDA considered the following:

- Insufficient experience with inhaled insulin products to determine whether observed *in-vitro* performance differences with the new inhaler (i.e., Gen2 inhaler) would impact clinical safety (e.g., hypoglycemia) and longer term efficacy (i.e., ≥ 6 months).
- Insufficient characterization of the factors that influence pulmonary specific safety issues to allow extrapolation of safety using *in vitro* data and systemic pharmacokinetic profiles.
- Lack of resolution of efficacy issues identified with the data derived with the *MedTone C inhaler*.
- Absence of long-term use information for the Gen2 inhaler to assess for potential patient use and device robustness issues.

The information needed to resolve the deficiencies included two randomized, controlled phase 3 trials with the Gen2 device, one in patients with T1DM and the other in patients with T2DM.

FDA requested that at least one of these trials should include a treatment group using the MedTone C inhaler so that a head-to-head comparison of the pulmonary safety data for the two devices could be obtained. FDA noted that these trials should be of sufficient duration to permit an adequate titration of study medication and that titration be followed by at least twelve weeks of relatively stable insulin doses to allow sufficient time for HbA1c to fully reflect the impact of the titration phase. FDA also noted these phase 3 trials with the Gen2 inhaler should ensure that appropriate titration of insulin doses occurs. For safety assessments, FDA asked for analysis of adverse events of interest in the Gen2 phase 3 trials including updated analyses of lung cancer cases, pulmonary safety (with pulmonary function testing), hypoglycemia, diabetic ketoacidosis, immunogenicity, eye events (given that there were numerically more cases of retinal detachment with Afrezza vs. comparator in the controlled phase 2/3 MedTone program), and device-related performance issues.

The following section summarizes the efficacy findings of pivotal (i.e., ≥ 6 mos.) and supportive (≥ 11 weeks) studies in type 1 and 2 diabetes mellitus submitted in the original NDA (*MedTone C inhaler*). Efficacy results were derived from FDA analyses of the submitted efficacy data.

Efficacy: Type 1 Diabetes (MedTone C inhaler Trials)

The sponsor conducted one 12-week phase 2 trial (Study 101) and one 52-week phase 3 trial (Study 009) in patients with T1DM. Both studies were open-label trials that compared pre-meal Afrezza TI vs. pre-meal insulin aspart in patients receiving insulin glargine at bedtime.

Study 009 (52-week, open-label trial of Afrezza TI + glargine vs. insulin aspart + glargine)

This randomized, open-label trial enrolled patients with inadequately-controlled (HbA1c $>7\%$ to $\leq 11\%$) T1DM. 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 and visits dedicated to insulin titration occurred 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 starting dose of Afrezza TI was based on the assumption that a 15 unit cartridge of Afrezza TI corresponds to 5 units of subcutaneous insulin. Afrezza 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%, an 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 Afrezza TI-treated patients and 76% of the aspart-treated patients completed the trial. This 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 Afrezza 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 Afrezza TI-treated patients and 1.4% of aspart-treated patients.

As shown in Table 1, Afrezza 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%. 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, Afrezza 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%).

There was a treatment-by-gender interaction in this trial ($p=0.01$), which was 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 Afrezza 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 Afrezza TI treatment arm and -0.3% in the insulin aspart treatment arm.

In the Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza TI corresponds to approximately 40 units of subcutaneous insulin). Therefore, the prandial insulins comprised approximately 50% of the total daily insulin dose. Because patients with T1DM would not be expected to achieve adequate glycemic control on glargine alone, it may be reasonable to conclude that Afrezza (which comprised ~50% of the

median total daily insulin dose) has demonstrated evidence of efficacy for some patients with T1DM.

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 Afrezza 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 1), 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 1). 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 Afrezza TI treatment group.

Table 1- HbA1c (%) results for the phase 2/3 trials in patients with type 1 diabetes

Study	N	Baseline ¹ mean ± SD	Change from baseline Adj. mean ± SE	Difference in adjusted mean change 95% CI	p-value
Study 009 (52-week phase 3 non-inferiority trial in type 1 diabetes)					
1-year data					
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		
26-week data (post-hoc)					
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		
Study 101 (12-week phase 2 trial in type 1 diabetes)					
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		

¹Baseline 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

Source: Adapted from Dr. Joffe's memo, Original NDA review

Efficacy: Type 2 Diabetes Mellitus (MedTone C Inhaler Trials):

The sponsor conducted six phase 2/3 trials in patients with T2DM, 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.

Note that the two phase 2 trials (studies 005 and 0008) used different formulations of Afrezza 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 Afrezza TI (14 units, 28 units, 42 units, and 56 units) to placebo (Technosphere particles without insulin also called “TP”) in patients with T2DM. Afrezza TI or TP 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 Afrezza 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 Afrezza 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 Afrezza TI treatment groups received 11 weeks of the randomized Afrezza TI dose. Instead, all patients randomized to Afrezza TI were initiated on 14 units that was force-titrated in weekly intervals by 14-unit increments to the goal Afrezza TI dose. Therefore, patients randomized to 56 units of Afrezza 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 Afrezza TI.

The placebo-corrected mean change in HbA1c was -0.5% with Afrezza TI 14 units and 0.7-0.8% with Afrezza TI 28-56 units, suggesting a plateau effect for pre-meal doses of Afrezza TI above 28 units (Table 2). 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 Afrezza TI vs. TP in patients with T2DM. All enrolled patients were taking a stable dose of at least one oral anti-diabetic medication for at least 3 months. Patients assigned to Afrezza TI started 6 units with meals that was then titrated in increments of 6 units up to a maximum permitted dose of 48 units with meals. As shown in Table 2, the mean placebo-corrected reduction in HbA1c with Afrezza TI was -0.4% (95% confidence interval -0.6, -0.1; $p < 0.01$). Of note, mean doses of Afrezza 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 Afrezza 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 Afrezza TI + glargine vs. insulin aspart + glargine)

This randomized, open-label, trial was conducted exclusively in Russia and compared 24-weeks of treatment with Afrezza TI + glargine vs. insulin aspart + glargine in patients with T2DM. 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 Afrezza TI ($n=151$) or insulin aspart ($n=158$). Afrezza 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 Afrezza TI and aspart occurred at the investigator's discretion based on clinic or home blood glucose monitoring data. Approximately 80% of Afrezza 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 Afrezza TI – with more than one-half of these due to cough – and 0% with aspart) and by patient withdrawal of consent (6% with Afrezza TI vs. 0% with aspart).

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%. FDA 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, the FDA statistical reviewer noted that this analysis was biased because it excluded 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, the FDA statistical reviewer noted that Afrezza 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 2). 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, Afrezza 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 Afrezza 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 Afrezza 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 may be 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 Afrezza TI and reduction of 1.3% with aspart) likely overestimates the treatment effect of Afrezza 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 Afrezza 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 Afrezza 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 Afrezza TI-treated patients and 33% of aspart-treated patients achieved HbA1c $\leq 7\%$.

At endpoint, the median Afrezza 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 Afrezza TI over-and-above the efficacy resulting from uptitration of the glargine dose.

Study 102 (52-week open-label trial of Afrezza TI + glargine vs. NovoLog Mix 70/30)

This multinational, randomized, open-label, trial compared 52 weeks of treatment with Afrezza TI + glargine vs. twice-daily NovoLog Mix 70/30 in patients with T2DM. 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 Afrezza TI, 50% of the total daily pre-randomization insulin dose was replaced with Afrezza TI and the remaining 50% was replaced by glargine. Afrezza 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 contained fasting and post-prandial glycemic goals for investigators to target, titration was only prioritized early during the trial. The protocol stated 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 was a 52-week trial, titration should have been optimized until Week 40 (3 months prior to the endpoint HbA1c measurement).

Approximately 65% of the Afrezza TI-treated patients and 72% of the NovoLog Mix 70/30-treated patients completed the trial. This differential dropout rate was predominantly driven by patient withdrawal of consent (11.1% of Afrezza 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 Afrezza 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 Afrezza TI-treated patients and 2.9% of NovoLog Mix 70/30-treated patients.

Afrezza 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. 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 Afrezza 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).

In the Afrezza 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 Afrezza 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 Afrezza 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 Afrezza TI group and 88 units in the NovoLog Mix 70/30 group. Therefore, it appears that non-inferiority of Afrezza TI + glargine to NovoLog Mix 70/30 was established in the setting of a higher prandial insulin dose in the Afrezza TI group 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 Afrezza TI and not by glargine.

Study 103 (12-week open-label trial of Afrezza TI vs. Afrezza TI+metformin vs. sulfonylurea+metformin)

This randomized, open-label trial enrolled patients with T2DM and inadequate glycemic control (HbA1c 7.5-11%) on a stable dose (no change within the preceding 6 weeks) of metformin (≥ 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 Afrezza TI + metformin (i.e., replacement of the insulin secretagogue with Afrezza TI; n=175) or Afrezza TI alone (i.e., discontinuation of the secretagogue and metformin and initiation of Afrezza TI; n=183). This treatment period was then followed by a 12-week non-randomized treatment period, which is not discussed in this document.

Patients randomized to a Afrezza TI-containing regimen started Afrezza 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 Afrezza TI to be fully reflected in the endpoint HbA1c measurement.

The completion rate for the 12-week treatment period was 68% with Afrezza TI+metformin, 73% for Afrezza 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 Afrezza TI+metformin, 12% with Afrezza TI alone, and 1.2% with secretagogue+metformin) and patient withdrawal of consent (7% with Afrezza TI+metformin, 7% with Afrezza TI alone, and 6% with secretagogue+metformin).

The primary objective was to show superiority of Afrezza TI+metformin vs. secretagogue+metformin with respect to change in HbA1c from baseline to Week 12. Substitution of Afrezza 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 Afrezza TI+metformin group compared to -0.8% in the secretagogue+metformin group. The sponsor did not specify a non-inferiority margin. However, the FDA statistical reviewer noted that Afrezza TI+metformin was 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) was also shown when the completers population was used.

Note that the Afrezza 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 Afrezza TI alone group, the median total daily Afrezza 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 Afrezza 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 Afrezza 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 Afrezza TI+metformin group had a lower median metformin dose (1700 mg) than the metformin+secretagogue group (2000 mg). In addition, the full effects of Afrezza 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 Afrezza TI+metformin to show superiority against metformin+secretagogue. Also, the trial should not have compared a newly prescribed Afrezza 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 Afrezza TI appear more favorable than it otherwise is. This may limit a conclusion of non-inferiority.

Table 2 summarizes the results of the efficacy studies in the type 2 diabetes population. Note that Afrezza TI provides numerically less glycemic control than comparator in the active-controlled trials.

Table 2 - HbA1c (%) results for key phase 2/3 trials in type 2 diabetes

Study	N	Baseline mean±SD	Change from baseline Adj. mean ± SE	Difference in adj. mean change with 95% CI	p-value
Study 005 (11-week phase 2, double-blind, placebo-controlled, forced-titration)					
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		
Study 0008 (12-week phase 2, double-blind, placebo-controlled)					
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		
Study 014 (24-week phase 3, open-label, with aspart + glargine comparator)					
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		
Study 102 (52-week phase 3, open-label with NovoLog Mix 70/30 comparator)					
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		
Study 103 (12-week phase 3, open-label comparison of TI + metformin to secretagogue + metformin)					
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) ¹	0.51
Secretagogue + metformin	162	8.9±0.9	-0.8±0.1		
¹ TI+metformin vs. secretagogue+metformin; study was designed to demonstrate superiority between these two treatment groups					

Source: Adapted from Dr. Joffe's memo, Original NDA review

2.6 Other Relevant Background Information

As this is the third review cycle for Afrezza, the reader can find full details of the initial review cycle in the original NDA reviews.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Submission quality and integrity was acceptable.

3.2 Compliance with Good Clinical Practices

According to the submission, all clinical procedures were conducted in compliance with regulations set forth by the FDA, International Conference on Harmonization (ICH), and other relevant regulatory authorities. Informed consent was obtained at Screening before any clinical study procedures were performed.

A consultation was requested on 3 Jan 2014 to the Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, Office of Scientific Investigations. Two clinical sites participating in the two studies supporting the resubmission of NDA 22472 were inspected. The conclusions were that the studies at both sites do appear to have been conducted in accordance with good clinical practices. The data generated by both sites appear acceptable in support of the respective indication.

3.3 Financial Disclosures

One investigator had reportable financial interests: (b) (6), M.D. was a sub-investigator for trial MKC-TI-171 study site (b) (6). He reported ownership of common stock in MannKind Corporation valued at over \$50,000. After the sub-investigator bought this stock he removed himself from contact with study patients, including medical and protocol decisions including insulin titration. Site (b) (6) enrolled (b) (6) subjects in trial 171.

The FDA statistician ran the primary efficacy analysis excluding data from site (b) (6). The results were almost the same as the results using the entire study population. Therefore, I conclude that the reportable financial interests of Dr. (b) (6) had no impact on the NDA for Afrezza.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Summaries of issues related to other review disciplines can be found in the original NDA CDTL memo. This review focuses on issues new to the third cycle resubmission.

Overview of Reviews Conducted by Other Review Disciplines for the Third Cycle Resubmission:

CMC – team review

Drug Product – Dr. Edwin Jao, ONDQA/Division III/Branch VIII

Drug Substance – Dr. Muthukumar Ramaswamy ONDQA/Division III/Branch VII

Device – Mr. Sugato De M.S., ODE/DAGID/ARDB/CDRH

Microbiology – Dr. Denise Miller, Microbiologist, OPS/NDMS

Nonclinical Pharmacology/Toxicology – Dr. Miyun Tsai-Turton, ODE2/DMEP

Clinical Pharmacology – Dr. Sang Chung, OCP/DCPII

4.1 Chemistry Manufacturing and Controls/Device

The review of Afrezza was conducted as a CMC team review. Dr. Jao's review pertains to limited parts of the NDA, i.e., the drug product except for biopharm and microbiology aspects of the submission. Dr. Jao recommended approval of the NDA (see review in DARRTS 30 Mar 2014).

Dr. Jao concluded that the Sponsor had adequately addressed the 4 CMC related comments listed in the CR letter. Dr. Jao states: In this submission the applicant has provided data to fully address these issues. In conclusion, all critical issues are considered resolved satisfactorily. Adequate controls and risk management are in place to provide assurance for the quality and purity of the drug product for its intended use.

During his review of the Gen2 inhaler device, Dr. Jao found that dropping the inhaler from, or shaking the inhalers in, vertical orientations demonstrated reductions in the emitted dose and fine particle fraction of APSD. For APSD there was reduction of the particles collected by as much as 16% below the lower limit of the acceptance criteria. Dr. Jao states “From CMC perspective, since the observed out of specification results were not derived from normal use, but rather, from misuse conditions, the potential risk of safety and efficacy implication is relatively low, and can be adequately mitigated through proper labeling.”

Reviewer’s comment: I agree with this Dr. Jao. This CMC concern will be addressed through labeling.

Dr. Ramaswamy reviewed the drug substance for the resubmission. The drug substance is human insulin (recombinant). Its manufacturing and controls information are provided in DMF (b) (4) “The NDA resubmission contains updated CMC information on a testing site (name change) and revision to drug substance specification (i.e., commits to performing microbial examination (USP <61>), zinc content (NMT 1.0%, USP<591>) and high molecular weight proteins tests instead of relying on vendor CoA). From CMC reviewer perspective, the proposed are acceptable.”

Sugato De conducted the device review for the Gen2 device. Mr. De concluded that the Sponsor has adequately validated the proposed drug-device combination product in terms of *in vitro* performance and stability and has no approvability issues.

4.2 Clinical Microbiology

Dr. Miller recommended approval of Afrezza. She also recommended approval during the first cycle. There was no first resubmission microbiology review. There was no change in the quality microbiology release specifications, the drug product is tested for microbial limits according to USP <61> and <62>.

4.3 Preclinical Pharmacology/Toxicology

Dr. Tsai-Turton recommended approval of Afrezza. Please see Dr. Joffe’s original CDTL memo for a full summary of the nonclinical findings from the original review cycle. As summarized by Dr. Davis-Bruno for the EMDAC briefing materials:

“The pharmacology and toxicology of insulin has been established over the last 90 years. Therefore the supporting nonclinical data for Afrezza have focused on the novel components of

the inhalational Technosphere delivery system. A complete nonclinical development program of repeat-dose, genetic, reproductive/developmental, local tolerance, sensitization, immune toxicology and carcinogenicity studies have been performed. The results of these studies have suggested some potential for pulmonary irritation with Afrezza at maximum clinical exposures (99 mg Afrezza=TI =88.6 mg Technosphere + 10.4 mg insulin). This is based on minimal to mild respiratory irritation observed in rats and dogs following chronic exposure to Technosphere by inhalation at ≤ 2 -fold higher exposures in animals relative to therapeutic exposure at the maximum clinical dose (99 mg Afrezza). These findings in test species did not have any functional significance on respiratory function. The respiratory irritation appeared to recover with discontinuation of Technosphere inhalation in animals. Evidence of pulmonary inflammation was not observed following chronic inhalational administration in rats and dogs, including lifetime exposure in rat. No evidence of lung neoplasia or pre-neoplastic signals was present in a lifetime rat carcinogenicity study or in a 6-month transgenic mouse carcinogenicity study following Afrezza exposure.”

The current resubmission included:

- 1) assessment of Proliferating Cell Nuclear Antigen (PCNA) evaluation of lung tissues from the 26 week rat inhalation toxicology study and the 39 week dog inhalation toxicology study. Dr. Tsai-Turton found no concerns with the submitted data.
- 2) updated safety margin based on FDKP exposure data obtained from a new clinical study (MKC-TI-176) with the Gen2 Inhaler. In the original NDA, human FDKP exposures used to calculating safety margins were determined using data from clinical studies with the MedTone Inhaler. For the resubmission human trials were conducted with the Gen2 Inhaler. The Gen2 Inhaler produced human FDKP exposure values that were higher than when using the MedTone Inhaler since the Gen2 Inhaler delivers powder more efficiently than the MedTone Inhaler. Dr. Tsai-Turton concluded that based on the comparability across devices and adjustment for maximum human dose the safety margins calculated across devices are similar. Therefore the initial labeling comments from the Dec 18, 2009 Pharm/Tox Supervisory Memo are valid.
- 3) a new study to qualify insulin related compounds present at $>^{(b)(4)}$ % (MKC-PC-2010-0042) and presumably adjust specification limits for these impurities. Dr. Tsai-Turton found the results of this study acceptable. Note that Dr. Jao from CMC also reviewed these data and concurred that they are acceptable.

4.4 Clinical Pharmacology

Dr. Sang from the Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCPII) recommends approval of Afrezza stipulated with dosing recommendations and recommended postmarketing requirements.

The current resubmission included the following new studies:

1. MKC-TI-176 - biopharmaceutics study conducted with the Gen2 inhaler.
2. MKC-TI-177 - Insulin PK and PD study in T1D subjects (n=12) comparing Gen2 delivered Afrezza insulin (20 U) with insulin lispro (8 U, rapid acting analog (RAA)).

Key review issues

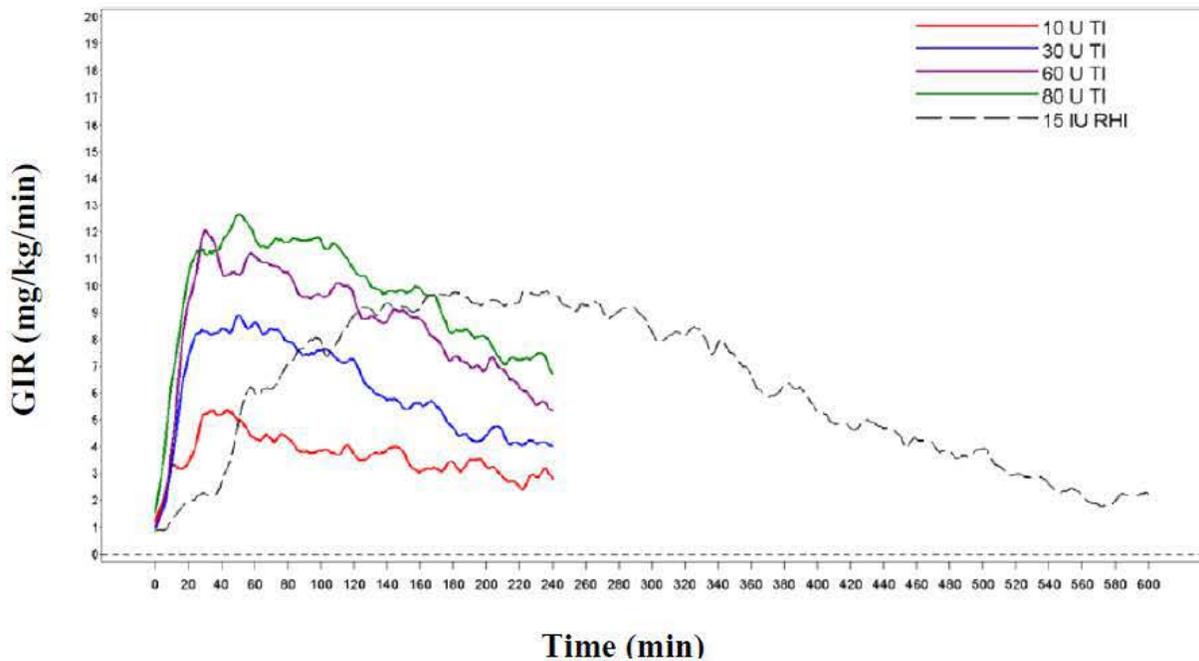
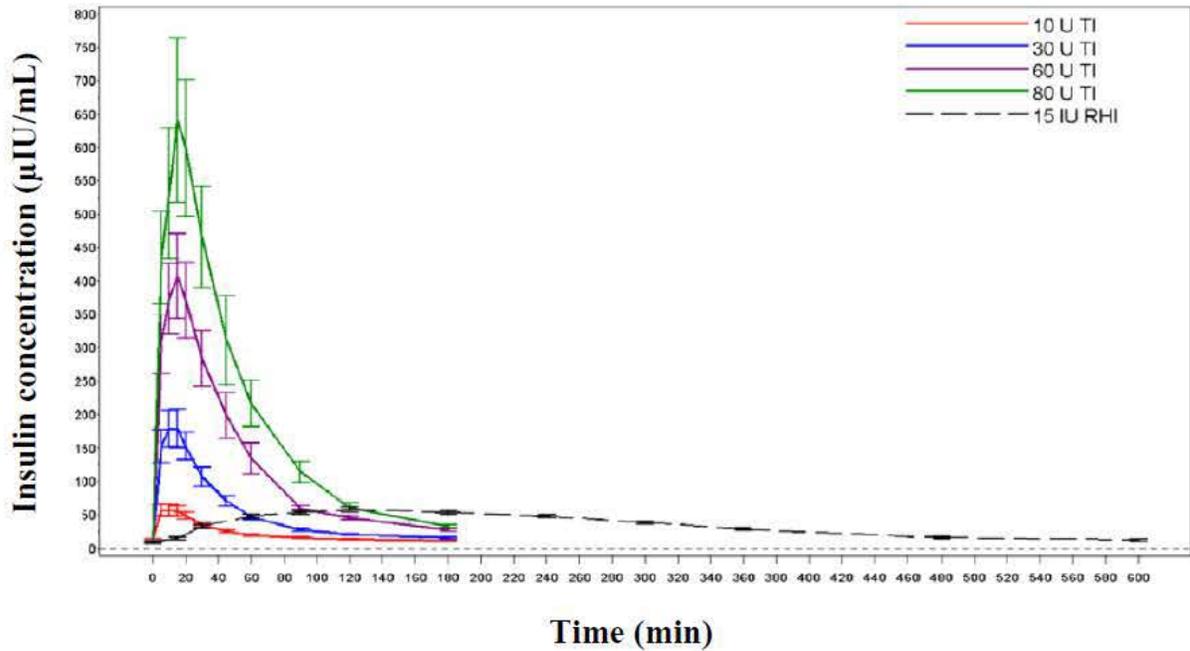
Dose proportionality

MKC-TI-176 is the only biopharmaceutics study conducted since the second cycle 2010 resubmission. This study was conducted after advice from FDA as follows:

Since the May 4, 2011 End-of-Review meeting, FDA has held additional internal discussions with senior managers regarding the clinical development program of Afrezza with the Gen2 device. We note that in your original NDA application, a dose-response with higher insulin doses administered via the Model C device was not observed in the placebo-controlled Study 005. The overall short trial duration and design limiting duration of use at higher doses may have contributed to the lack of a dose-response; however, we are unaware of a similarly conducted study involving the Gen2 device which can ensure us that with increasing doses of insulin administered via this new device, greater efficacy can be achieved. Has Mannkind conducted a clinical study with the Gen2 device proposed for marketing that establishes a dose-response with escalating doses of insulin? (End of Review meeting 04 May 2011, minutes dated 26 May 2011; type C meeting 10 Aug 2011).

The Sponsor conducted MKC-TI-176 as a dose-ranging study and to demonstrate dose proportionality at higher doses (up to 80U) delivered as combinations of 10U and 20U cartridges. The relative bioavailability of insulin from each dose was determined by comparison to 15U regular human insulin administered by subcutaneous (SC) injection.

Study MKC-TI-176 was conducted in healthy subjects with the new Gen2 device. It was a randomized, five-way cross-over euglycemic clamp study (n=32) in which four doses of Afrezza (10, 30, 60, and 80 U) were compared with one dose of SC regular human insulin (15 U). In this study both PK and PD were assessed (see figure below).



Although, in the dose range tested, increase in PK (i.e., insulin AUC shown in the top panel) appears dose proportional, increase in PD (i.e., GIRAUC₀₋₂₄₀ shown in the bottom panel) was less than dose proportional. The clinical pharmacology reviewer noted that the PD response for each exposure quartile (representing 12.5% intervals) demonstrated that with an increase in

median insulin AUC_{0-180} exposure from 7466 to 35261 $\mu\text{IU}/\text{mL} \cdot \text{min}$ (i.e., about 6.6 fold increase), median $AUC_{GIR_{0-240}}$ only increased from 1542 to 2188 (i.e., 1.4 fold).

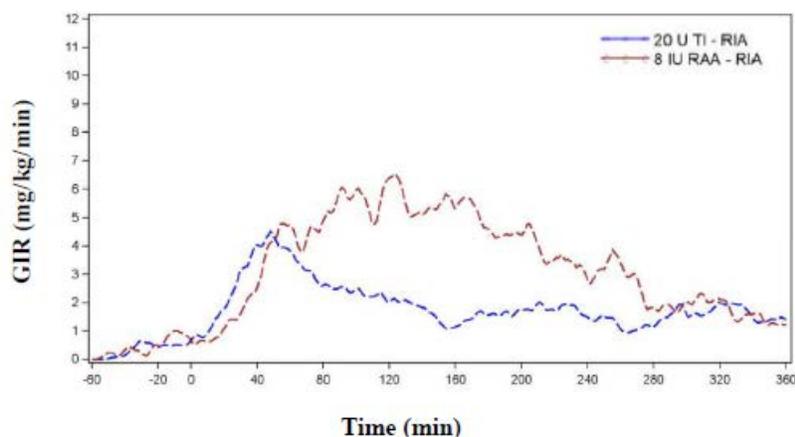
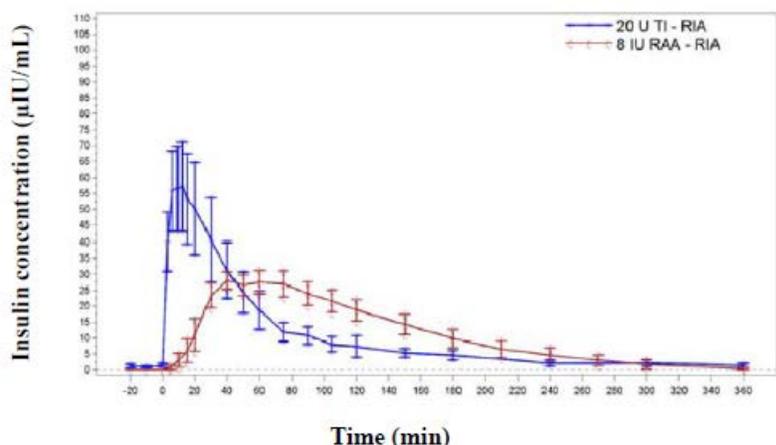
Dr. Chung also found problematic that only one dose of comparator injected insulin was studied, making it difficult to draw conclusions about dose proportionality of Afrezza compared to subcutaneous insulin. Exploratory modeling and a simulation exercise was performed to predict the dose-response profiles for Afrezza vs. SC regular human insulin (see Figure 9 on Page 23 of the Clinical Pharmacology review), which indicates that Afrezza reaches to the point of diminishing return early, i.e. by about 75 to 100 U of Afrezza dose (SC equivalent dose of 30-40 units), relative to SC insulin (for which point of diminishing return occurs by about 200 IU dose).

Dr. Chung stated “With the information submitted in this application, OCP was not able to evaluate if the dose-response relationship for Afrezza insulin parallels to that observed for SC insulin. OCP recommends that further information on dose-response relationship for Afrezza relative to SC insulin be collected in post-marketing studies.”

Reviewer’s comment: I agree with the Clinical Pharmacology reviewer that the less-than dose proportional nature of the Afrezza PD effect and the modeling data that suggest Afrezza reaches the point of diminishing return early relative to subcutaneous insulin have important clinical implications. Patients requiring high doses of Afrezza could be at risk for diabetic ketoacidosis due to nearing maximal effect in the clinically relevant dose range. Because of the safety signal of diabetic ketoacidosis observed in the Afrezza clinical trials, the dose-response profile of Afrezza relative to subcutaneously administered insulin should be further evaluated in a post-marketing required study.

PK and PD of Afrezza compared to rapid acting insulin analog

Insulin PK and PD were also assessed in a crossover euglycemic clamp study (Study MKC-TI-177) in T1D subjects (n=12) comparing Gen2 delivered Afrezza insulin (20 U) with insulin lispro (8 U, rapid acting analog (RAA)). Time profiles for insulin concentrations (upper panel) and glucose infusion rate (lower panel) are shown in the Figure below which is sourced from Dr. Chung’s review.



Dr. Chung made the observation that in this study PD effect (GIR-time profile) for Afrezza does not mirror the PK (time-concentration) profile, i.e., although insulin C_{max} for Afrezza is almost double the C_{max} for RAA, GIR_{max} for Afrezza is lower than RAA.

Reviewer's comment: These data do not support the Sponsor's claim that Afrezza is an 'ultra-rapid' acting insulin, with faster onset of action than rapid acting insulin analog. The PK profile suggests a rapid absorption, but as noted by Dr. Chung, the PD effect does not mirror the PK profile. This finding should be noted in labeling.

Dosing regimen

The Sponsor is proposing that the dosing regimen include Afrezza cartridges 3 U and 6 U. The following figure is taken from the proposed Afrezza labeling.

Injected Mealtime Insulin Dose	AFREZZA® Dose	# of 3 unit (blue) cartridges needed	# of 6 unit (green) cartridges needed
up to 3 units	3 units		
4-6 units	6 units		
7-9 units	9 units		
10-12 units	12 units		
13-15 units	15 units		
16-18 units	18 units		

As noted in section 2 of this review, in the early Afrezza development program including through the current phase 3 studies, what the Sponsor is now calling a 3 U Gen 2 cartridge was called the 10 U Gen2 cartridge, and was stated to be equivalent to approximately 4 units of injected rapid-acting insulin. The 6.7 mg TI Inhalation power cartridge that the Sponsor is now calling the 6 U Gen2 cartridge, was previously called a 20 U Gen2 cartridge and was stated to be equivalent to approximately 8 units of injected rapid-acting insulin. However, the proposed dosing regimen and the dosing conversion factors are different than that tested in Phase 3 trials evaluating the Gen2 device, which were as follows: “a conversion factor approximating a 10 U cartridge with 4 units of regular human insulin was utilized. Similarly, a 20 U cartridge approximated 8 units of regular human insulin.” Therefore, we have no direct clinical experience with the Sponsor’s proposed dosing regimen.

The Sponsor submitted a rationale for why the dosing should be changed to 3 U and 6 U. These data were reviewed by Dr. Chung and are summarized here:

The applicant states that the new dosing regimen (as currently proposed) is supported by the two clinical pharmacology studies (i.e., studies MKC-T1-176 and MKC-T1-177) conducted with the Gen2 device and the Phase 3 trial in type 1 diabetes subjects (i.e., study 171). From clinical pharmacology studies, the applicant relies on only PK data (i.e., relative bioavailability estimates) to justify the proposed dosing conversion. However, Dr. Chung considers the corresponding PD effect to be equally or more important in evaluating the adequacy of the proposed dosing regimen because it is the PD effect that ultimately drives efficacy (i.e., HbA1c reduction). Considering this, Dr. Chung concluded that the clinical pharmacology data in this submission does not adequately support the new proposed dosing regimen and the respective dosing conversion factors in the dosage chart.

The applicant also compared the overall mean daily prandial doses from the Phase 3 trial 171 in Type 1 diabetes mellitus to justify the proposed dosing. However, the approximation derived based on Phase 3 data makes several assumptions such as no differences in basal insulin dose between treatment groups, comparable titration between two arms, and a similar dose-response relationship for prandial insulin between treatment groups, and therefore, is not considered acceptable from a Clinical Pharmacology standpoint.

Reviewer's comment: What effect this change, i.e. from 4 units to 3 units, in the estimated conversion between Afrezza and injected rapid acting insulin has on dose initiation and titration of Afrezza is unknown. Therefore, in agreement with the Clinical Pharmacology reviewer, I recommend that labeling define the cartridges as 4 units and 8 units rather than 3 units and 6 units. This is a more conservative approach that may mitigate hypoglycemia risk related to switching from injected to inhaled mealtime insulin. Because insulins are titratable the only downside of this approach is perhaps a slightly longer time to reach the adequate mealtime inhaled dose. Please see the Clinical Pharmacology review for further details.

Lack of data assessing within-subject variability in Afrezza response.

The within-subject variability of Afrezza was not studied. Clinical implications of a high within-subject variability could be a less consistent therapeutic effect on a dose-to-dose and day-to-day basis. While this is not approvability issue, the Clinical Pharmacology reviewer believes that the within-subject variability should be assessed in a post-marketing study.

Reviewer's comment: I agree with this recommendation because a less consistent therapeutic effect could be a safety concern, e.g. hypoglycemia.

4.4. 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

Maximal glucose lowering activity is observed by approximately 40-60 minutes after administration of TI Inhalation Powder. Glucose-lowering activity returns toward baseline level by approximately 160 minutes after administration of TI Inhalation Powder

4.4.3 Pharmacokinetics

Pulmonary administration of TI Inhalation Powder resulted in appearance of insulin in the systemic circulation within 3 to 5 minutes after inhalation. The PK profile of TI Inhalation Powder has a Tmax of approximately 10–15 minutes (across all studies using TI Inhalation Powder, tmax consistently occurred around 14 minutes after inhalation, independent of dose, formulation, inhaler, or subject population). The duration of exposure shows a return to near-baseline concentration within about 180 minutes.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A total of 63 clinical studies have been conducted over the course of the TI Inhalation Powder clinical development program.

Please see the cycle 1 and cycle 2 clinical reviews for tables of studies included in those submissions. Newly completed and ongoing studies submitted for the current cycle are shown in Table 3 and Table 4. The pivotal safety and efficacy studies are in bold text in Table 3.

Table 3 – Pharmacokinetic and Biopharmaceutic Studies

Study Identifier/ Study Phase	Design and Objective	Study population	Test Product(s): Dosage Regimen and Route of Administration	Number of subjects exposed and duration of treatment	Study status
MKC-TI-147 Phase 1	Single-center, open-label, 2-part, randomized, crossover clinical trial to evaluate the bioavailability and dose proportionality of different TI Inhalation Powder formulations (3 U, 4 U, and 6 U of insulin/mg)	Healthy volunteers 18–45 years T2DM 18–65 years	TI Inhalation Powder: 20 U and 40 U of a 3 U insulin/mg, 4 U of insulin/mg, and 6 U of insulin/mg formulation and 60 U of a 6 U of insulin/mg formulation Inhaler: Gen2C	27 subjects 3 single doses of each treatment in a prescribed, crossover sequence over 3 days	Completed
MKC-TI-167 Phase 1	Open-label, randomized, single center crossover design to evaluate insulin exposure and dose proportionality following inhalation of two formulations of TI Inhalation Powder (3 U and 4 U insulin/mg) and cartridge fill weights ranging from approximately (b) (4) mg to (b) (4) mg	Healthy volunteers 18–45 years	TI Inhalation Powder: 10 U, 20 U, and 30 U of a 3 U insulin /mg formulation, 30 U and 40 U of a 4 U insulin/mg formulation Inhaler: Gen2C	48 subjects 3 or 4 single doses on treatment days based on the assigned dosing sequence.	Completed
MKC-TI-176 Phase 1	Open-label, randomized, 4-way crossover design to evaluate insulin exposure and	Healthy volunteers 18–55 years	10 U, 30 U, 60 U, or 80 U of TI Inhalation Powder, 15 IU of subcutaneous (sc) regular human insulin	35 subjects Single doses of the study treatment in a 4-	Completed

	effect of TI Inhalation Powder at multiple doses		Inhaler: Gen2C	way crossover with a fifth sc RHI dose	
MKC-TI-177 Phase 1	Open-label, randomized, 2-way crossover design to compare insulin exposure and response of TI Inhalation Powder versus sc RAA	T1DM 18–60 years	20 U of TI Inhalation Powder, 8 IU of sc insulin lispro Inhaler: Gen2C	17 subjects Single doses of the study treatment	Completed

Table 4 - Clinical Efficacy and Safety Studies

Study Identifier/ Study Phase	Design and Objective	Study population	Test Product(s): Dosage Regimen and Route of Administration	Number of subjects exposed and duration of treatment	Study status
Type 2 Diabetes Trials					
MKC-TI-158 Phase 2	Single-center open-label, crossover-pilot extension of clinical trial MKC-TI-119 to evaluate the effect of frequent self-monitoring of blood glucose versus as-needed SMBG on the efficacy and safety of TI Inhalation Powder	T2DM ≥18 and ≤70 years	TI Inhalation Powder: frequent SMBG vs PRN in a cross-over design Inhaler: Gen2C	5 subjects 8 months with 1 month FU period	Completed
MKC-TI-162 Phase 3	Open-label, randomized, forced-titration efficacy and safety study of TI Inhalation Powder	T2DM ≥18 and ≤80 years	TI Inhalation Powder vs insulin aspart in combination with insulin glargine Inhaler Gen2C	37 subjects 16 weeks	Terminated early in favor of Trial MKC-TI-175
MKC-TI-175 Phase 3	Multicenter, double-blind, placebo-controlled, randomized, clinical trial evaluating the efficacy and safety of prandial TI Inhalation Powder	Insulin-naïve T2DM poorly controlled with 1 OADs ≥18 years	TI Inhalation Powder vs T Inhalation Powder (placebo) Inhaler: Gen2	353 subjects 24 weeks with a 4-week follow up	Completed
Type 1 Diabetes Trials					
MKC-TI-171 Phase 3	Multicenter, open-label, randomized, forced-titration clinical trial evaluating the	T1DM ≥18 years	TI Inhalation Powder vs insulin aspart, both in combination with a basal insulin	518 subjects 24 weeks with a 4-week follow up	Completed

efficacy and safety of TI Inhalation Powder.		Inhalers: Gen2C and MedTone C (allowed head-to-head comparison of the two inhalers as requested in the Complete Response letter.			
Comparison of pulmonary safety of inhalers.					
Combined Type 2 and Type 1 Diabetes Trials					
MKC-TI-119 Phase 2	Single-center, open-label, PD clinical trial to evaluate the effect of TI Inhalation Powder on postprandial glucose levels in subjects with T1DM and T2DM ingesting meals with varied carbohydrate content	≥18 and ≤70 years T1DM or T2DM	TI with MedTone inhaler in original protocol Gen2 inhaler in amendment 1	18 subjects up to 16 weeks	Completed
MKC-TI-134 Phase 3	Multicenter, open-label, randomized safety and efficacy trial of TI Inhalation Powder in subjects with T1DM or T2DM and diagnosed with asthma or COPD	≥18 years with asthma ≥40 years with COPD T1DM and T2DM	TI Inhalation Powder vs. usual antidiabetic medications Inhaler: Gen2C	3 subjects 12 months	Ongoing
MKC-TI-164 Phase 3	Multicenter clinical substudy evaluating pulmonary function in a subset of subjects enrolled in one of the 3 parent studies	T1DM and T2DM ≥18 and ≤80 years	TI Inhalation Powder vs. insulin aspart both in combination with insulin glargine Inhaler: Gen2C	3 subjects 16 weeks	Terminated early to move resources to trials MKC-TI-171 and MKC-TI-175).
MKC-TI-139 Phase 3	Phase 3 open-label, multicenter, safety trial to convert subjects that had been using Exubera to treatment with TI Inhalation Powder	T1DM and T2DM Patients who had been using Exubera	TI Inhalation Powder Inhalers: MedTone C and D and Gen2C	16 subjects 72 months	Ongoing

Note that two Phase 3 clinical studies and a Named Patient/Compassionate Use (NPP/CU) Program are currently ongoing:

- Study MKC-TI-134 is a special population study evaluating safety and efficacy in subjects with obstructive lung disease (chronic obstructive pulmonary disease [COPD] or asthma).
- Study MKC-TI-139 is a US study in subjects who were unable to use sc insulin and were transferred from treatment with Exubera® (insulin human [rDNA origin]) Inhalation Powder (Pfizer, New York, NY, USA) to TI Inhalation Powder.

- In the EU, the NPP/CU allows individual patients to receive TI Inhalation Powder according to local/regional requirements. (Both MKC-TI-139 and the NPP/CU were initiated to transfer patients who previously received Exubera to TI Inhalation Powder after Exubera was discontinued by Pfizer in 2008).

Studies conducted with the Gen2 inhaler:

Note that the original TI Inhalation Powder development program used the MedTone inhaler. The Sponsor switched to the Gen2 inhaler in 2010 because it is a smaller device and requires only one inhalation per cartridge. Clinical data with the Gen2 inhaler come from the following ten studies (Studies MKC-TI-119, MKC-TI-147, MKC-TI-158, MKC-TI-162, MKC-TI-164, MKC-TI-167, MKC-TI-171, MKC-TI-175, MKC-TI-176, and MKC-TI-177), including 2 new pivotal Phase 3 trials (Studies MKC-TI-171 and MKC-TI-175). Refer to Tables 5.1 and 5.2 for the descriptions of these studies.

5.2 Review Strategy

For the efficacy and safety review of Afrezza, I reviewed the data separately for T1 and T2DM, as the underlying pathogenesis of each disease is distinct. 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). This strategy also allows for a separate risk/benefit analysis of the two diabetes types. When appropriate, data are pooled for the two types of diabetes, e.g. analysis of deaths and non-fatal serious adverse events.

Efficacy review:

The two new clinical trials are reviewed for efficacy independently of each other. No integrated summary of efficacy is presented because the two new trials are in distinct types of diabetes mellitus, i.e. type 1 and type 2. Because the new trials used the MedTone device efficacy is not integrated with the original trials.

Safety review:

In the Sponsor's submission, the following were included:

- "Previous results" or "previous submissions" include the 2009 Original NDA ISS and the 2010 Amendment Safety Update
- "New results" or "new studies" include the new studies initiated since the previous submission
- Comparisons of the previous and the new results.

The review strategy was to examine the data for any significant changes or findings in the safety profile of Afrezza since the previous submissions. Therefore, in this review I generally present the 'new results' and comment on the comparisons of the previous and new results.

For most safety analyses I used the pooled phase 2/3 safety database (discussed below) which allows for comparisons of incidence rates between Afrezza and comparator. I also reviewed major safety findings such as subject deaths, serious adverse events (SAEs), and discontinuations

due to treatment-emergent adverse events (TEAEs) from studies that were not part of the pooled database.

For this document I reviewed non-pulmonary safety. The review of pulmonary safety is being conducted by Dr. Paterniti from the Division of Pulmonary Allergy and Rheumatology Products. Comparative pulmonary safety between the two TI Inhalation System devices is a primary safety concern for this resubmission because the new trials used the Gen2 device whereas the original trials used the MedTone device.

Additionally, hypoglycemia is reviewed individually for each trial because of differing trial designs, study populations, and comparators.

In addition, the following disciplines contributed to the clinical safety and efficacy review by providing consultative reports:

Biostatistics – Cynthia Liu, M.A., Division of Biometrics II
Human Factors, Label, Labeling and Packaging – Dr. Sarah Vee, DMEPA
Device – Mr. Sugato De, CDRH
Lung cancer – Dr. Lee Pai-Scherf, DOP2/OHOP
Pulmonary safety – Dr. Miya Paterniti, DPARP/OND

5.3 Discussion of Individual Studies/Clinical Trials

In this section, the two new phase 3 clinical trials submitted for evidence of efficacy are described. These two studies are Study 171 (Type 1 Diabetes) and Study 175 (Type 2 Diabetes). Information pertinent to both studies is presented first, followed by discussion of the individual studies in further detail.

In brief, U.S. study sites were managed by MannKind, and non-U.S. sites were managed by Contract Research Organizations (CROs), specifically (b) (4) in Brazil and (b) (4) in Russia and Ukraine. The independent insulin titration monitoring was managed by (b) (4). The central laboratory was (b) (4) (in the U.S.) and (b) (4) for Russia, Ukraine, and all insulin antibody samples.

Afrezza Dosing:

For both trials Afrezza dosing was as follows:

Timing of Administration

Afrezza TI was to be administered immediately before or within approximately the first 20 minutes after the first mouthful of food. The later dosing time was considered if patients experienced hypoglycemia within the first 90 minutes after a normal meal.

Conversion of “Afrezza units” to “subcutaneous units”

Afrezza TI Inhalation Powder for the Gen2C inhaler is packaged in 2 different cartridge dosage strengths, 10 U and 20 U:

- 10 U approximates 4 IU of Rapid Acting Insulin Analog (RAA)
- 20 U approximates 8 IU of RAA

Afrezza TI Inhalation Powder for the MedTone C inhaler is packaged in 2 different cartridge dosage strengths, 15 U and 30 U:

- 15 U approximates 4 IU of RAA
- 30 U approximates 8 IU of RAA

Afrezza Starting Dose

In trial 171 subjects who were randomized to Afrezza TI-Gen2C treatment group transferred to Afrezza TI Inhalation Powder as shown in Table 5.

Table 5 - Afrezza TI Dose Conversion for the Gen2 Inhaler

RAA Bolus Dose (IU)	Afrezza TI Dose (U)
0 – 4	10
>4 – 8	20
>8 – 12	30
>12 – 16	40
>16 – 20	50
>20 – 24	60

Dose conversion for the MedTone inhaler was similar except that 0-4 IU RAA=15 U Afrezza TI Dose, and so on.

In trial 175, all subjects were started at a dose of 10 U Afrezza TI or placebo per meal.

Prandial Insulin Titration

Note that prandial titration for subjects in the Afrezza TI treatment groups (Gen2 and MedTone) was based on 90-minute postprandial BG values (PPG), whereas prandial titration for subjects in the aspart insulin group in Study 171 was based on BG values prior to the next meal. The Sponsor claimed that the distinctly different time-action profiles of Afrezza TI and RAA insulin require different time points for monitoring glucose as a component of the titration approaches for dose adjustments.

Afrezza prandial dose titration

Subjects were required to adhere to the subject-driven forced-titration algorithms for their inhaled prandial insulin treatment. During the first 12 weeks of the 24-week treatment phase of

each study subjects titrated their study drug doses based on 7-point SMBG level determinations, according to the dosing guidelines shown in Table 6.

Table 6 – Recommended Afrezza TI Dose Adjustments for Gen2

Median 90 min PPG	Afrezza TI Dose Adjustment
<110 mg/dL	Decrease by 10 U
≥110 mg/dL to <160 mg/dL	Maintain current dose
≥160 mg/dL	Increase by 10 U at the same meal

Seven-point glucose profiles were to include an FPG test, 90 minutes after breakfast, before lunch, 90 minutes after lunch, before dinner, 90 minutes after dinner, and at bedtime. Subjects were to measure 7-point BG levels on at least 3 separate days within each week. Doses were to be titrated weekly based on the median of the 3 most recent measurements for each meal. The principal investigator (PI) or a designee contacted subjects by telephone weekly (or more often as needed) to discuss dosing and titration.

Dose titration for the MedTone inhaler was similar except that <110 mg/dL=decrease dose by 15 U Afrezza TI, and so on.

Subjects in the Afrezza TI Gen2 and Afrezza TI MedTone groups in both studies could also take supplemental insulin doses as instructed in the prandial insulin dosing algorithms.

- Subjects with a 90-minute PPG level ≥ 180 mg/dL (10.0mmol/L) were to take a supplemental (after-meal) 10 U Gen2 or 15 U MedTone dose of Afrezza TI. Subjects who developed more than 2 episodes of hypoglycemia after taking supplemental doses of Afrezza TI were to be instructed not to take additional supplemental doses of Afrezza TI and consult with the PI.
- Subjects who achieve 90-minute PPG levels of ≥ 110 mg/dL (6.1 mmol/L) to < 160 mg/dL (8.9 mmol/L) for a given meal (breakfast, lunch, or dinner), but have 2 out of 3 pre-prandial BG levels ≥ 160 mg/dL (8.9 mmol/L) for the subsequent SMBG 7-point measurement (before lunch, dinner, or bed time), were to take a supplemental dose of Afrezza TI on a regular basis 90 minutes after the start of the meal. If a regular supplemental dose was added, the mealtime insulin dose could be reduced at the PI's discretion.

Since dose correction with Afrezza TI does not rely on an estimate of meal type or size, and can take place after the meal with real-time BG feedback, additional dose adjustment based on factors such as carbohydrate counting was not allowed in the Afrezza TI arms of the studies. Instead, subjects were instructed on how to use 90-minute postprandial glucose values to determine the need for dose supplementation following the meal.

During the second 12 weeks of the treatment phase, the study drug doses were kept stable unless a change was required for the safety of the subject. Subjects who had 90-minute PPG levels ≥ 180

mg/dL (10.0 mmol/L) were instructed to take a 10 U supplemental after-meal dose of study treatment at the time of the PPG reading (i.e., same day and time).

As an independent third party, the Titration Monitoring Committee (TMC) monitored the adherence of investigator dosing decisions to protocol-specified guidelines. The TMC also reviewed subject data to identify subjects for whom a significant amount of eDiary data were missing or deviated from the protocol-specified algorithm. TMC actions included phone calls and/or emails to sites and, when necessary, site counseling by the TMC Medical Director. The site submitted reasons for non-adherence to the algorithm.

In addition, the PIs were provided access to their subjects' e-diary data using secure password-protected PI login to the vendor's server. Thus, the data collected in the e-diaries could be reviewed at each clinical visit and as needed to ensure compliance with the protocol dosing and titration regimens. Subjects who were unable to comply with the use of the e-diary were discontinued from the study at the discretion of the PI.

Study treatment could be used during intercurrent illnesses, including upper respiratory tract infection. At such times, more frequent monitoring of blood glucose concentrations and dose titration could have been required. In some subjects, at the discretion of the PI, substitution with injectable insulin was permitted.

Afrezza maximal dose

The maximal recommended total daily dose of Afrezza TI was to be 6 U/kg bodyweight of Afrezza TI as delivered by the MedTone inhaler, or 4 U/kg body weight as delivered by the Gen2 inhaler (e.g., for a 75 kg adult, the maximum daily dose was 450 U delivered by MedTone and 300 U delivered by Gen2). The total daily dose could be divided between different time points (different meal times and multiple dosing times for each meal). There was no maximum dose per meal.

Safety Assessments pertinent to both studies:

Safety assessments are discussed in more detail in section 4 of this document; this section lists the safety endpoints common to the two new phase 3 studies. The efficacy assessments are different between the two studies.

- Treatment-emergent adverse events (TEAEs) were captured and coded according to Medical Dictionary for Regulatory Activities (MedDRA) terminology including AEs of special interest: cough, respiratory events (non-infective), potentially immune-related events, diabetic ketoacidosis, ophthalmic events, and neoplasms. Potentially immune-related events were reported as events of special interest, identified from a pre-defined set of MedDRA codes, as described in the Sponsor's backgrounder.

Reviewer’s comment: This pre-defined set of MedDRA terms for potentially immune-related events was agreed upon by FDA during review of the study protocols, i.e. prior to initiation of studies.

- Selected clinical laboratory evaluation included routine hematology, chemistry including liver tests, lipids, and urinalysis) (shift tables and descriptive statistics).
- Vital signs and 12-lead ECGs that were locally read were obtained.
- In addition to TEAE capture, for both phase 3 studies, safety parameters of special interest included: pulmonary function tests (PFTs), hypoglycemic events, and anti-insulin antibodies ([IAB] anti-insulin immunoglobulin G concentration). PFTs are discussed separately in the pulmonary section of the backgrounder. Hypoglycemia and IABs are discussed here.

Hypoglycemia definitions

All episodes of hypoglycemia that met the following definitions of “mild or moderate” or “severe” hypoglycemia were recorded in the e-diary. These definitions were based on classifications for “documented symptomatic or asymptomatic” and “severe” hypoglycemia in the 2005 American Diabetes Association guidelines. Episodes of hypoglycemia reported in the e-diary were not reported as AEs unless they met the criteria for serious adverse events (SAEs).

Mild or moderate hypoglycemia was defined as a subject who experienced:

- SMBG levels <70 mg/dL AND/OR
- Symptoms of hypoglycemia relieved by self-administration of carbohydrates

Severe hypoglycemia was defined as follows: Any event of hypoglycemia requiring assistance of another person (not merely requested) to actively administer carbohydrate or glucagon. According to this definition, “required assistance” included situations in which the subject was rendered incapable of obtaining self-administered treatment (e.g., a glass of orange juice). The episode may have been associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements were not available during such an event, the neurological recovery attributable to the restoration of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Reviewer’s comment: These definitions are based on the ADA criteria and are acceptable. The mild or moderate definition is relatively nonspecific as it requires only confirmed low SMBG or symptoms rather than both. The definition of severe hypoglycemia in the protocol is consistent with the ADA definition.

Anti-insulin antibodies

IAB were measured using a validated radio-immune assay (RIA). The units are “Kronus units of insulin antibody/mL” and the validated range for Good Laboratory Practice compliance was from a lower limit of quantification of 1.6 Kronus units/mL to an upper limit of quantification following dilution of 1000 Kronus units/mL. The assay used in the two new studies was the same as that used in the original studies, allowing for comparison of results from old and new studies.

Statistical Considerations Pertinent to Both Studies:

The sponsor-defined populations included the “FAS” population (full analysis set or all randomized subjects). The “PP” set (Per Protocol set) was used for sensitivity analyses and included completers and those without major protocol violations. The Safety Population was comprised of all subjects treated with at least one dose of study treatment.

For both Study 171 (T1DM) and Study 175 (T2DM), the primary efficacy analysis was performed on the FAS population. All primary efficacy analyses were performed based on the randomized treatment assignment regardless of the actual treatment subject received during study. All data up to the initiation of rescue medication (for Study 175 only) or discontinuation/end of study treatment were used and analyzed using a Mixed Model Repeated Measures (MMRM) approach with terms for treatment, visit, region, basal insulin (for T1DM) or OAD (for T2DM) stratum, and treatment by visit interaction as fixed factors and baseline HbA1c as a covariate.

Reviewer’s comment: The National Academy of Sciences (NAS) recently released a report on missing data which was commissioned by FDA. The report states “Single imputation methods like [LOCF] should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified.”

In both studies, several secondary efficacy endpoints (e.g., responders of Week 24 HbA1c \leq 7.0% or 6.5%, fasting plasma glucose, body weight change) were planned without statistical testing procedure to control the Type 1 error rate.

Study 171 (TI + basal insulin vs. insulin aspart + basal insulin)

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

Sites:

91 principal investigators at 89 study sites in 4 countries (United States [US], Russia, Ukraine, and Brazil) screened 1 or more subjects in this study. The administrative structure of the study is presented in the study 171 clinical study report (CSR) in Table 1 for MannKind Corporation representatives and Table 2 for external resources.

Dates conducted: 19 Sep 2011 – 31 May 2013

Study Objective:

The primary study objective was to demonstrate that Technosphere Insulin (TI) Inhalation Powder administered using the Gen2 inhaler in combination with a basal insulin (TI Gen2 group) is noninferior (noninferiority margin 0.4%) to insulin aspart in combination with a basal insulin (insulin aspart group) in its effect on HbA1c in subjects with T1DM.

Design:

Open-label, randomized study with a 4-week basal insulin optimization phase and a 24-week treatment phase. Subjects were assigned to 1 of 3 treatment arms as follows:

- Subcutaneous (SC) insulin aspart in combination with SC basal insulin
- TI Inhalation Powder administered using the Gen2 inhaler in combination with SC basal insulin (TI Gen2)
- TI Inhalation Powder administered using the MedTone inhaler in combination with SC basal insulin (TI MedTone)

Note that the TI Gen2 group was compared with the insulin aspart group to evaluate the objectives. The TI Gen2 group was compared with the TI MedTone group to evaluate the primary pulmonary safety objective.

Reviewer's comment: Trial 171 was designed to address the deficiency listed in the cycle 2 Complete Response letter that one of the phase 3 studies with the Gen2 inhaler should include a MedTone arm so that pulmonary safety of the two inhalers could be directly compared. Note that the trial was not designed to directly compare the efficacy of TI using the two devices. This approach was agreed upon at the cycle 2 End of Review meeting held 4 May 2011.

Subjects:

Key Inclusion Criteria:

1. Men and women ≥ 18 years of age
2. Clinical diagnosis of type 1 DM for at least 12 months
3. Body mass index (BMI) ≤ 38 kg/m²
4. Stable dose of basal/bolus insulin therapy for at least 3 months with an FPG consistently < 220 mg/dL (12.2 mmol/L)
 - Basal insulin included NPH insulin, insulin glargine, or insulin detemir

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

- Bolus insulin was defined as 2 to 4 doses of regular human insulin or rapid-acting analog at meals
 - Subjects who were using PreMix insulin at least twice daily were allowed
5. HbA1c $\geq 7.5\%$ and $\leq 10.0\%$
 6. Fasting C-peptide ≤ 0.30 pmol/mL (≤ 0.90 ng/mL)
 7. Nonsmokers for the preceding 6 months
 8. Met prespecified pulmonary function test cutoffs based on the Third National Health and Nutrition Examination Survey (NHANES III) (see Dr. Paterniti's review)

Key Exclusion Criteria:

1. Total daily insulin dose ≥ 2 IU/kg/day.
2. History of insulin pump use within 3 months of Screening or use of CGM within 6 weeks of Screening.
3. History of use of pramlintide, oral antidiabetic drugs (OADs), or inhaled insulin in the previous 6 months.
4. Two or more unexplained severe hypoglycemic episodes within 3 months of Screening or an episode of severe hypoglycemia between Visit 1 and Visit 2. Unexplained refers to episodes of severe hypoglycemia that are not related to a dosing error, lack of or a change in meal size, or related to additional/unanticipated exercise.
5. 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 and Visit 2.
6. Severe complications of DM, in the opinion of the PI, including symptomatic autonomic neuropathy; disabling peripheral neuropathy; active proliferative retinopathy; nephropathy with renal failure, renal transplant, or dialysis; non-traumatic amputations due to gangrene; or vascular claudication.
7. Allergy or known hypersensitivity to insulin or to any of the drugs to be used in the study, or a history of hypersensitivity to TI Inhalation Powder or to drugs with a similar chemical structure.
8. History of recent blood transfusions (within previous 3 months), hemoglobinopathies, or any other conditions that affect HbA1c measurements.
9. History of COPD, asthma, or any other clinically important pulmonary disease (e.g., pulmonary fibrosis), or use of any medications for these conditions.
10. Any clinically significant radiological findings on screening chest x-ray.
11. Active respiratory infection within 30 days before Screening. If respiratory tract infection manifests after screening (Visit 1), but before the screening PFTs, Visit 2 may be out-of-window, so the subject will be considered a screen failure. However, the subject may return 30 days after resolution of the respiratory infection for rescreening.
12. Major organ system diseases
13. Current or previous chemotherapy or radiation therapy that could have resulted in pulmonary toxicity; use of medications for weight loss (e.g., sibutramine, orlistat) within 12 weeks of Screening; treatment with amiodarone within 12 weeks of Screening.
14. Clinically significant abnormalities on Screening laboratory evaluation or chest x-ray.

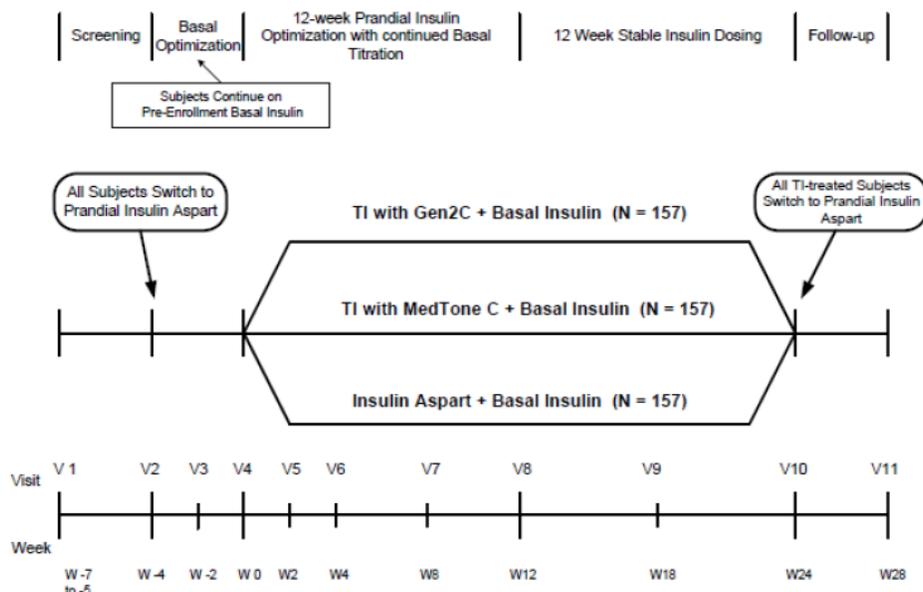
15. Women who were pregnant, lactating, or planning to become pregnant during the clinical study period; women of childbearing potential (defined as premenopausal and not surgically sterilized or postmenopausal for fewer than 2 years) not practicing adequate birth control.

Study Procedures and Visits:

The study consisted of 11 clinical visits (Figure 1):

- Screening visit
- 4-week basal insulin optimization phase (subjects not already using insulin aspart converted their mealtime insulin to insulin aspart and titrated their pre-enrollment basal insulin). All subjects remained on their pre-enrollment basal insulin (neutral protamine Hagedorn [NPH], glargine, or detemir) throughout the study. Subjects were required to achieve an FPG value of ≤ 180 mg/dL measured at the central laboratory at the end of the 4-week basal optimization phase.
- 24-week randomized treatment phase consisting of:
 - 12-week prandial insulin optimization phase with continued basal titration: Subjects assigned to receive TI Inhalation Powder using either the Gen2 or the MedTone inhaler converted their insulin aspart to TI Inhalation Powder and continued to titrate their basal insulin dose as needed.
 - 12-Week stable insulin dose phase (with prandial and basal insulin doses remaining stable). During these 12 weeks, insulin doses could be adjusted only for safety reasons or because a subject's clinical condition (for example, the occurrence of an infection or other stress) changes.
- Follow-up visit

Figure 1 - Study 171 Schematic



Source: Figure 5, Study 171 CSR

Reviewer's comment: the following is an excerpt from the cycle 2, 18 Jan 2011 CR letter:

These trials [the two required new phase 3 studies with the Gen2 device] should be of sufficient duration to permit an adequate titration of study medication and there should be at least twelve weeks of relatively stable insulin doses at the end of the treatment period so that the endpoint HbA1c adequately reflects preceding glycemic control.

Inadequate titration of insulin doses has been an important limitation of all phase 3 clinical trials conducted with the MedTone inhaler to date. Therefore, your phase 3 trials with the Gen2 inhaler 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.

Insulin Dosing and Titration:

Insulin dosing and titration was described previously in this document as it pertains to general Afrezza TI dosing procedures. The following section describes aspects specific to study 171, primarily the basal insulin dosing.

As noted above, at Visit 2, subjects not already using insulin aspart converted their mealtime insulin to insulin aspart. Details of the conversion guidelines were provided in the study protocol; essentially, a one-to-one unit conversion of prandial insulin was performed.

Also at Visit 2, subjects began to titrate/optimize their pre-enrollment basal insulin. During the 4 weeks of the basal insulin optimization phase, subjects followed a subject-driven forced-titration algorithm for their basal insulin doses. Basal insulin was to be adjusted (increased or decreased) by 1 IU to 4 IU at each dose every 3 days based on the median fasting blood glucose (FBG) from the 3 most recent SMBG values obtained within the previous 7 days and obtained after the last titration, with the goal of achieving FBG values <120 mg/dL and ≥100 mg/dL.

To be eligible to continue in the study and enter one of the Randomized Treatment groups at Visit 4, subjects had to complete 4 weeks of basal insulin optimization and achieve a central laboratory FPG ≤180 mg/dL.

Randomized Treatment Period Insulin Dosing

During the 12-week prandial insulin optimization phase with continued basal insulin titration, subjects could adjust their basal insulin doses once per week using the algorithm shown in Table 7. Titration was based on the median of the 3 most recent measurements within 7 days.

Table 7– Basal Insulin Titration Algorithm

Median FPG or Pre-dinner BG (at least 3 recent measurements within 7 days and obtained after the last titration)	Basal Insulin Dose Adjustment (IU)
< 100 mg/dL (5.6 mmol/L)	Decrease by 2 IU
100 mg/dL (5.6 mmol/L) to ≤ 120 mg/dL (6.7 mmol/L)	No change
> 120 mg/dL (6.7 mmol/L) and ≤ 130 mg/dL (7.2 mmol/L)	Increase by 1 IU
> 130 mg/dL (7.2 mmol/L) and ≤ 140 mg/dL (7.8 mmol/L)	Increase by 2 IU
> 140 mg/dL (7.8 mmol/L)	Increase by 4 IU, or more at the discretion of the PI

Prandial Insulin Dosing

Afrezza TI dosing:

Afrezza TI dosing was described previously. Recall that subjects in the Afrezza TI Gen2 and Afrezza TI MedTone groups also took supplemental insulin doses as instructed in the prandial insulin dosing algorithms, but subjects in the insulin aspart group did not.

Aspart dosing:

Insulin aspart was administered subcutaneously 5 to 10 minutes before a meal.

Adjustment of prandial doses of insulin aspart were to be based on subsequent premeal blood glucose values, (breakfast, lunch and dinner doses will be based on pre-lunch, pre-dinner and bedtime blood glucose, respectively), as outlined below in Table 8. In addition to the recommended guidelines provided for dose initiation and subsequent dose adjustments described

above, the PI may allow subjects to make additional dose adjustments/modifications (e.g., based on carbohydrate counting, meal size, SMBG results, snacks, PPG).

Table 8 – Insulin Aspart Dosing Algorithm

Median Pre-next Meal BG Level (at least 3 measurements on 3 separate days)	Insulin Aspart Dose Adjustment
< 100 mg/dL (5.6 mmol/L)	Decrease dose by 10% of current dose
≥ 100 mg/dL (5.6 mmol/L) to < 120 mg/dL (6.7 mmol/L)	Maintain current dose
≥ 120mg/dL (6.7 mmol/L) to < 140 mg/dL (7.8 mmol/L)	Increase by 1 IU
≥ 140 mg/dL (7.8 mmol/L) to < 180 mg/dL (10.0 mmol/L)	Increase dose by 2 IU
> 180 mg/dL (10.0 mmol/L)	Increase dose by = 3 IU (or 10% of dose)

Endpoints:

Efficacy

The primary efficacy endpoint of the study was the mean change in HbA1c (%) from Baseline (end of the basal insulin optimization phase at Visit 4 [Week 0, Randomization]) to Visit 10 (Week 24) in the TI Gen2 group vs. the insulin aspart group.

Secondary efficacy endpoints

- At Week 24 – the proportion of subjects achieving an HbA1c level of ≤7.0%, the proportion achieving ≤6.5%, the proportion achieving ≤7% with no episodes of severe hypoglycemia during the randomized treatment phase, and the proportion achieving ≤7% with no episodes of severe hypoglycemia during the phase of stable insulin dosing (the last 12 weeks of treatment).
- Mean change in FPG levels from randomization (Visit 4) to the end of treatment (Week 24).
- Mean change in 7-point glucose profiles from the week before randomization to the week before end of treatment (Week 24).
- The mean change in body weight from randomization (Visit 4) to end of treatment (Week 24).

Safety

- The primary safety endpoint was the change from Baseline (i.e., last measurements made before randomization) to the final treatment visit in FEV1 in the TI Gen2 and TI MedTone treatment groups.

Safety assessments also included the following for all treatment groups:

- PFT parameters (FEV1, FVC, and the FEV1/FVC ratio)
- Adverse events (AEs), including diabetic ketoacidosis, ophthalmic events, potentially immune-related events, cough, and hypoglycemia
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory test results
- Anti-insulin immunoglobulin G titers

Statistical Methods:

The randomization was stratified by region (North America, Latin America, and Eastern Europe) and basal insulin (insulin glargine, insulin detemir, and NPH insulin) to balance the effects of the region and different basal insulin groups across the treatment groups. No minimum number of subjects was required in any stratum, and the study was not designed to analyze each stratum separately.

Reviewer's comment: At the End of Review meeting FDA recommended (but did not require) that the Sponsor consider stratifying by baseline HbA1c as follows:

Stratification by baseline HbA1c is not required for interpretation of a valid study but can be used to increase the precision of estimates particularly if baseline HbA1c is expected to be strongly correlated with the change from baseline.

Sample size calculation

Assuming the upper noninferiority margin is 0.4% with a standard deviation of 1.0 and a 1-sided alpha of 0.025, the required sample size was estimated to be 471 subjects, randomized in a 1:1:1 ratio (TI Gen2:TI MedTone:insulin aspart) to achieve approximately 399 subjects (133 in each of the 3 treatment groups) completing the study, assuming a 15% drop-out rate. This sample size provided 90% power for a noninferiority design to test the primary efficacy endpoint between the TI Gen2 and insulin aspart treatment groups.

Study 175 (TI + OADs vs. placebo + OADs)

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

Study Sites:

Multicenter (86 sites) in Brazil, Russia, Ukraine, and United States. The majority of sites were in the U.S.

Dates conducted: 30 Nov 2011 to 17 Jun 2013

Study Objective:

The primary study objective was to demonstrate that prandial Technosphere Insulin Inhalation Powder (TI Gen2) is superior to Technosphere Inhalation Powder (placebo) in reducing HbA1c levels when added to antidiabetic regimen of insulin-naïve subjects with type 2 diabetes (T2DM) who are suboptimally controlled on optimal/maximally tolerated doses of metformin only or 2 or more oral antidiabetic (OAD) agents.

Design:

Randomized, double-blind, placebo-controlled study. Subjects were randomized in a 1:1 ratio to receive either TI or placebo. The design consisted of a 6-week run-in phase, a 24-week treatment phase (12-week prandial titration phase and 12-week phase of stable dosing), and a 4-week safety follow-up.

Reviewer's comment: This study design was recommended by FDA. This design was thought to be the most appropriate method for providing an unbiased evaluation of the administration of TI Inhalation Powder via the Gen2 inhaler in subjects with T2DM. In addition, per recommendation of FDA, to characterize the population of subjects with T2DM who would be likely to use TI Inhalation Powder, only subjects on stable doses of either metformin monotherapy or 2 or more OADs were allowed to enroll in Study MKC-TI-175. The Sponsor also chose to not allow thiazolidinedione (TZD) therapy due to the recent uncertainty regarding the long-term safety of this drug class. This plan was found acceptable by FDA.

Subjects:

Key Inclusion Criteria:

1. Men and women ≥ 18 years of age
2. Clinical diagnosis of T2DM for more than 12 months
3. HbA1c value $\geq 7.5\%$ and $\leq 10.0\%$
4. Body mass index (BMI) ≤ 45 kg/m²
5. Currently receiving as diabetes treatment only metformin or 2 or more OADs and on stable doses for at least 3 months before enrollment. Subjects had to be treated with optimal/maximally tolerated dose of each OAD:
 - Subjects receiving metformin had to be on at least 1.5 g daily, or up to the maximum tolerated dose
 - Subjects treated with a sulfonylurea had to be on at least 50% of the total maximum approved dose for a given agent
 - Subjects receiving a DPP-4 inhibitor had to receive the maximum approved dose specific for that agent
 - Meglitinides and alpha-glucosidase inhibitors had to be taken at the highest tolerated dose within the approved dose range.
6. No previous or current treatment with insulin, except during an acute illness, gestational diabetes, or at time of initial diagnosis of diabetes
7. Nonsmokers for the preceding 6 months
8. Met prespecified pulmonary function test cutoffs based on the Third National Health and Nutrition Examination Survey (NHANES III) (see Dr. Paterniti's review)

Key Exclusion Criteria:

1. Treatment with glucagon like peptide-1 (GLP-1) analogs, thiazolidinediones (TZD), or weight loss drugs (e.g., sibutramine, orlistat) within 3 months of Screening
2. Two or more unexplained severe hypoglycemic episodes within 3 months of Screening. Unexplained refers to episodes of severe hypoglycemia that are not related to a dosing error, lack of or a change in meal size, or related to additional/unanticipated exercise
3. Any hospitalization or emergency room visit due to poor diabetic control within 6 months before Screening
4. Evidence of serious complications of diabetes in the opinion of the PI (proliferative retinopathy; autonomic neuropathy with symptoms of gastroparesis or cardiac arrhythmia; nontraumatic amputations due to gangrene; vascular claudication; sensory neuropathy) that made manipulation of the Gen2 inhaler difficult
5. History of chronic obstructive pulmonary disease (COPD), clinically proven asthma, or any other clinically important pulmonary disease (e.g., pulmonary fibrosis)
6. Any clinically significant radiological findings on screening chest x-ray
7. Use of medications for asthma, COPD, or any other chronic respiratory conditions
8. Renal disease or renal dysfunction
 - For subjects who took metformin, serum creatinine levels ≥ 1.5 mg/dL (132.6 $\mu\text{mol/L}$) in men, ≥ 1.4 mg/dL (123.8 $\mu\text{mol/L}$) in women
 - For subjects who were not taking metformin, serum creatinine > 2.0 mg/dL (176.8 $\mu\text{mol/L}$) in men, > 1.8 mg/dL (159.1 $\mu\text{mol/L}$) in women; or blood urea nitrogen (BUN) > 50 mg/dL (17.9 mmol/L)
9. Significant cardiovascular dysfunction or history within 12 months of Screening
10. Allergy or known hypersensitivity to insulin or to any of the drugs to be used in the study, or a history of hypersensitivity to TI Inhalation Powder or to drugs with a similar chemical structure
11. Active respiratory infection within 30 days before Screening (subject may return after 30 days from resolution for rescreening)
12. Major organ system diseases, including cancer (other than excised cutaneous basal cell carcinoma) within the past 5 years or any history of lung neoplasms
13. Women who were pregnant, lactating, or planning to become pregnant during the clinical study period
14. Women of childbearing potential

Study Procedures and Visits:

The study consisted of 11 clinical visits (Figure 2)

- Visit 1: Screening (Week -8)

Eligibility was determined. See inclusion and exclusion criteria above.

- Visit 2: Start of run-in phase (Week -6)

After Screening, eligible subjects entered a 6-week run-in phase for baseline HbA1c stabilization, during which they continued their pre-enrollment OADs. Subjects received

counseling regarding nutritional management and physical activity, and training in use of glucose meters, self-monitoring of blood glucose (SMBG), and e-diaries.

- Visit 3a: Pre-randomization laboratory test visit (Week -1)

Subjects who had HbA1c values <7.5% or FPG values (measured by the central laboratory) >270 mg/dL (15.0 mmol/L) at the time of randomization were discontinued from further participation.

- Visit 3b: Randomization visit (Week 0)

Subjects who successfully completed the run-in phase and that achieved protocol-defined criteria for HbA1c and FPG levels (HbA1c \geq 7.5%; FPG \leq 270 mg/dL) were randomized in a 1:1 ratio to receive either TI Gen2 or placebo, which was added to their OAD regimen, for a 24-week randomized treatment phase. Doses of pre-enrollment OADs were kept unchanged during trial participation and could not be adjusted or altered during the study without discussion between the PI and the Sponsor. Subjects were trained to use the Gen2 inhaler at Visit 3b (Week 0).

- Visits 4, 5, 6, 7, and 8: Treatment phase (Weeks 2, 6, 12, 18, and 24, respectively).

The randomized treatment phase was divided into two 12-week phases. In the first 12 weeks, subjects received study drugs with upward dose titration to achieve target blood glucose levels of 110-160 mg/dL. In the second 12 weeks, subjects were maintained on relatively stable dosing as established in the first 12 weeks.

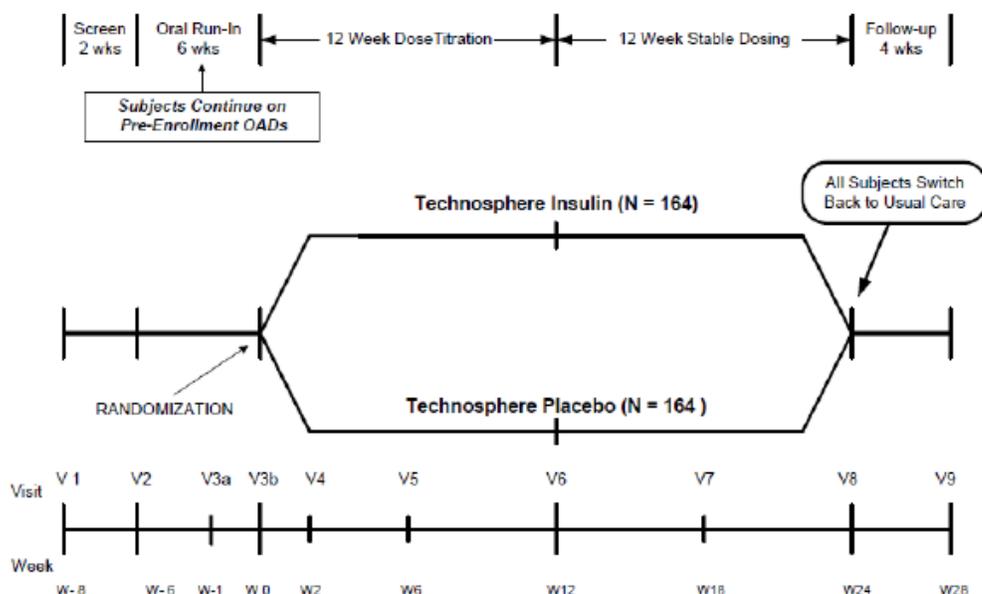
Also see description of Afrezza dosing above.

Subjects performed SMBG testing with glucose meters as instructed and recorded glucose values, hypoglycemic events, and all doses in their e-diaries. During the run-in and randomized treatment phases, the PI or clinical staff telephoned subjects weekly to discuss, as applicable, dosing, titration, and optimization of study treatment, based on e-diary data.

- Visit 9: Follow up visit (Week 28)

After completion of the 24-week randomized treatment phase, subjects were returned to an antidiabetic drug regimen deemed appropriate by the PI and were followed for safety for 4 weeks.

Figure 2– Study 175 Schematic



Source: Figure 5, Study 175 CSR

DSMB:

An independent Data Safety Monitoring Board (DSMB) was convened for this study. The DSMB consisted of no fewer than 7 members representing the fields of diabetology, pulmonology, and biostatistics. The DSMB reviewed safety data on an ongoing basis. The DSMB could recommend pertinent changes to the protocol and/or stopping of the study at any time if significant concerns regarding safety of the agent or study procedures arose.

Rescue Therapy:

Subjects whose hyperglycemia persisted or worsened beyond pre-specified thresholds received open-label rescue therapy (insulin glargine or glimepiride) in addition to their study treatment.

Subjects entering the study on only metformin were provided glimepiride (1 or 2 mg tablets) as rescue therapy if needed. Subjects entering on 2 or more OADs were provided insulin glargine provided as pens as rescue therapy if needed.

The algorithm for subjects to begin rescue therapy was:

- Between Randomization (Day 0) and through Week 6, if fasting SMBG levels measured on 3 different days within a week for at least 2 weeks were >270 mg/dL (15.0 mmol/L), the subject was instructed to notify the PI and have a central laboratory fasting plasma glucose (FPG) test performed. If the FPG value from the central laboratory was >270 mg/dL (15.0 mmol/L), the subject began the appropriate rescue therapy.

- After Week 6 and through Week 12, the same procedure was used but cutoff level was FPG value from the central laboratory >240 mg/dL (13.3 mmol/L).
- After Week 12 and up to Week 24 (but not including the visit at Week 24), the same procedure was used but cutoff level was FPG value from the central laboratory >200 mg/dL (11.1 mmol/L).

If, 6 weeks after the initiation of rescue therapy, the subject had consistently elevated FPG levels of >200 mg/dL they were withdrawn from the study.

Insulin dosing and titration:

The insulin dosing and titration for study 175 is similar to study 171 and described previously. All subjects started TI or placebo at a dose of 10 U.

One other difference noted by this reviewer is that for study 175, after 4 weeks of titration of the study treatment, in subjects with persistently elevated pre-meal BG levels >130 mg/dL, regular supplemental after-meal study drug administration was permitted.

In contrast to study 171, study 175 included a procedure to stop dose titration which consisted of 3 steps. Subjects who reached a dose of at least 30 U per meal and who no longer saw a decrease of at least 10 mg/dL (0.5 mmol/L) in the corresponding median 90-minute postprandial glucose (PPG) level, despite 3 subsequent 10 U dose increases (above 30 U), were required to stop mealtime dose increases and to consult the investigator.

Endpoints:

Efficacy:

The primary efficacy endpoint of the study was the mean change in HbA1c (%) from Randomization (Week 0) to Week 24 between the TI Gen2 and placebo groups.

Secondary efficacy endpoints:

- The proportion of subjects with an HbA1c value of $\leq 7.0\%$ and $\leq 6.5\%$ at Week 24 Mean change from the randomization visit to the Week 24 visit in fasting plasma glucose (FPG) levels (central laboratory results)
- Change in mean body weight from Randomization to the Week 24 visit
- 7-point BG profiles (before and after each meal and at bedtime) from the week before the randomization visit (Visit 3b) to those measured before the Week 12 and Week 24 visits.
- The proportion of subjects who received glycemic rescue therapy
- Time to glycemic rescue.

Statistical Methods:

Randomization was stratified by region (North America, Latin America, and Eastern Europe) and OAD therapy at time of entry. OAD therapy was stratified into: Metformin only/Metformin plus sulfonylurea/Metformin plus DPP-4 inhibitor/Metformin plus 1 or more OADs, not specified above/2 or more OADs not including metformin

The intent of the randomization was to balance treatment within each respective stratum; however, the study was not powered for testing treatment differences within each stratum independently. There was no minimum number of subjects required within each stratum.

Sample size:

Planned: Approximately 328 subjects (164 subjects per group) to achieve approximately 246 completers, assuming a 25% dropout rate. This sample size would enable a superiority test of the difference in the change of HbA1c levels between treatment groups at 24 weeks, assuming an upper superiority margin (Δ) of 0.5% with a standard deviation of 1.2, 90% power and a 1-sided alpha of 0.025.

6 Review of Efficacy

Efficacy Summary

Two pivotal trials with the Gen2 device were submitted to support the efficacy of Afrezza.

Study 171 – Type 1 Diabetes

The primary efficacy endpoint was the change from the end of the basal insulin optimization phase at Randomization to Week 24 in HbA1c between the TI Gen2 and insulin aspart groups. The baseline HbA1c for both groups was around 8%. The mean reduction in HbA1c from baseline to Week 24 in the TI Gen group was 0.20%, which was less than the 0.42% reduction observed in the aspart group. The treatment difference was 0.22% and the 95% confidence interval was 0.08% to 0.37%. The non-inferiority of TI Gen2 to aspart was demonstrated since the upper bound of the 95% confidence interval was less than 0.4%, the pre-defined non-inferiority margin. However, because the confidence interval was entirely greater than zero, TI Gen2 was statistically worse than aspart on HbA1c change. Also, responder rates were better with aspart vs. TI Gen2.

The caveats to interpretation of the trial results include the high and differential dropout rates which prompt concern regarding missing data. Non-inferiority was not demonstrated in FDA's sensitivity analysis. Further, non-inferiority studies rely on the assumption that the comparator worked as expected. In this trial, aspart was minimally titrated and the average daily basal and prandial insulin doses used in the TI Gen2 group were consistently higher than those used in the aspart group, in the face of a lesser improvement in HbA1c.

Study 175 – Type 2 Diabetes

The primary study objective was to demonstrate that mealtime TI Gen2 was superior to placebo, both on a background of metformin alone or at least two oral diabetes drugs, in reducing HbA1c

after 24 weeks. The baseline HbA1c in both groups was 8.3%. The 0.84% mean reduction in HbA1c from baseline to Week 24 in the TI Gen2 group was statistically significantly greater than the 0.41% mean reduction observed in the placebo group. The treatment difference was 0.42%. The superiority of TI Gen2 over placebo in reducing HbA1c was demonstrated since the upper bound of the 95% confidence interval was less than 0%, the pre-defined superiority margin. The FDA statistical reviewer has no concerns regarding the impact of missing data or data after rescue therapy on the primary efficacy analysis results for this trial. Responder analyses were consistent with the primary efficacy analysis. The efficacy of TI Gen2 for T2 diabetes may be considered modest compared to some of the other available antidiabetes therapies, including non-insulin oral antidiabetes drugs.

Overall efficacy conclusions

Overall, the additional efficacy data reviewed herein, i.e. the two new phase 3 studies, support the conclusions drawn during my original NDA review, in that while TI Gen2 ‘works’ as an insulin evidenced by the observed placebo-adjusted reduction in HbA1c in the newly submitted type 2 diabetes trial, and by the maintenance of glycemia in the type 1 diabetes trials (from both the current and previous review cycles), its efficacy may be modest, and it is clearly not as effective as subcutaneously administered prandial insulin.

6.1 Indication

The sponsor is seeking approval for TI for the following indication: to improve glycemic control in adults with type 1 or type 2 diabetes mellitus.

6.1.1 Methods

The review of clinical efficacy is based primarily on Trials 171 and 175 because these are the two trials that used the Gen2 device, although some consideration was given to pivotal studies with the MedTone device to put the new trial results into context. No integrated summary of efficacy is presented because the two new trials are in distinct types of diabetes mellitus, i.e. type 1 and type 2.

6.1.2 Demographics

Study 171 – Type 1 Diabetes

Across the three randomized treatment groups, subjects had a mean age of 37-40 years, there were slightly more female than male subjects, the majority of subjects were White, and approximately 40% were from the U.S (Table 9). The duration of diabetes was 16 – 17 years on average, and subjects were, on average, mildly overweight (mean BMI approximately 26 kg/m²).

Reviewer’s comment: The three randomized treatment groups appear balanced with respect to demographic and baseline characteristics. The population is reasonably

representative of the general population of patients with type 1 diabetes, although non-White subjects may be underrepresented.

Table 9 – Subject Demographics and Baseline Characteristics – Study 171

Appears this way on original

Demographic and Baseline Characteristics	TI Gen2 (N=174) n (%)	TI MedTone (N=173) n (%)	Insulin Aspart (N=171) n (%)
Age (years)			
N	174	173	171
Mean (SD)	37.0 (12.42)	40.0 (13.32)	39.0 (12.67)
Median	36.0	39.0	36.0
Range	[18, 71]	[18, 76]	[18, 76]
Age Group (years)			
18 - 30	56 (32.2)	47 (27.2)	47 (27.5)
31 - 49	93 (53.4)	84 (48.6)	88 (51.5)
50 - 64	18 (10.3)	33 (19.1)	28 (16.4)
65+	7 (4.0)	9 (5.2)	8 (4.7)

Demographic and Baseline Characteristics	TI Gen2 (N=174) n (%)	TI MedTone (N=173) n (%)	Insulin Aspart (N=171) n (%)
Sex			
Male	77 (44.3)	80 (46.2)	74 (43.3)
Female	97 (55.7)	93 (53.8)	97 (56.7)
Race			
White	164 (94.3)	166 (96.0)	167 (97.7)
Black Or African American	8 (4.6)	5 (2.9)	3 (1.8)
Asian	1 (0.6)	1 (0.6)	0
Native Hawaiian Or Other Pacific Islander	1 (0.6)	0	0
Other	0	1 (0.6)	1 (0.6)
Country			
USA	71 (40.8)	68 (39.3)	68 (39.8)
Russia	45 (25.9)	52 (30.1)	52 (30.4)
Ukraine	44 (25.3)	38 (22.0)	38 (22.2)
Brazil	14 (8.0)	15 (8.7)	13 (7.6)
Duration of DM (years)			
N	174	173	171
Mean (SD)	16.0 (10.27)	17.7 (10.69)	16.7 (10.01)
Median	13.8	15.2	16.0
Range	[1.1, 57.3]	[1.1, 49.5]	[1.0, 42.2]
Weight (kg)			
N	174	173	170
Mean (SD)	75.7 (15.75)	76.8 (14.87)	72.6 (15.24)
Median	74.4	76.3	69.7
Range	[41.7, 129.4]	[47.6, 124.0]	[46.6, 120.2]
BMI (kg/m²)			
N	174	173	169
Mean (SD)	26.0 (4.48)	26.2 (3.74)	25.4 (4.10)
Median	25.7	26.0	24.5
Range	[16.6, 38.6]	[18.1, 36.4]	[17.4, 37.2]
HbA1c (%)			
N	172	171	168
Mean (SD)	7.98 (0.767)	7.99 (0.732)	7.88 (0.751)
Median	7.90	8.00	7.90
Range	[6.20, 10.60]	[6.10, 10.20]	[5.80, 10.10]
Fasting Plasma Glucose (mg/dL)			
N	174	173	171
Mean (SD)	155.0 (67.62)	143.9 (60.79)	151.6 (67.44)
Median	144.5	137.0	149.0
Range	[21.0, 403.0]	[43.0, 358.0]	[23.0, 375.0]

Source: Table 22, Study 171 CSR

At screening, prior to the 4 week basal insulin optimization phase (i.e., Week -4), the mean

HbA1c values were 8.50%, 8.65%, and 8.56%, respectively for subjects who were subsequently randomly assigned to the TI Gen2, TI MedTone, and insulin aspart groups. At Baseline (i.e., Week 0), the mean HbA1c values were 7.98%, 7.99%, and 7.88%, respectively for the TI Gen2, TI MedTone, and insulin aspart groups.

Reviewer’s comment: *At the May 2011 End of Review Meeting, FDA commented that the Sponsor should increase the baseline HbA1c for inclusion and/or actively enroll patients in the upper range of the HbA1c inclusion criterion to help ensure that the mean baseline HbA1c will not be too low to be able to show a meaningful improvement in HbA1c over the duration of the study. FDA also stated that a mean baseline HbA1c of roughly 8.5% or above would likely be adequate. It appears that the enrollment HbA1c was closer to the FDA recommended target than was the baseline HbA1c.*

Examination of the data showed that subjects included in the Per Protocol (PP) population were similar across all treatment groups suggesting no specific subject demographic or baseline characteristics leading to exclusion from the PP population.

Other relevant baseline characteristics – Study 171

The study design allowed patients to continue their pre-enrollment basal insulin to improve generalizability of study results. Table 10 shows that randomization was successful in creating three treatment groups, roughly equivalent in the percentages of patients on each type of basal insulin.

Table 10 – Summary of Basal Insulin Stratification (Randomized Population)

	TI Gen2	TI MedTone	Insulin Aspart
	n (%)		
Insulin detemir	26 (14.9)	26 (14.9)	26 (15.3)
Insulin glargine	121 (69.5)	122 (70.1)	121 (71.2)
NPH insulin	27 (15.5)	26 (14.9)	23 (13.5)

Source: Table 24 Study CSR

Study 175 – Type 2 Diabetes

As shown in Table 11, in the FAS population, the 2 treatment groups were generally balanced for the demographic characteristics of race, age, age category, country, and duration of diabetes as well as clinical characteristics of baseline HbA1c, FPG, BMI, and OAD therapy. The mean HbA1c at baseline was 8.26% in the TI group and 8.35% in the placebo group.

Reviewer’s comment: *On average the population of T2DM patients being studied in this trial take at least 2 OADs and have a mean duration of diabetes of almost 10 years.*

Table 11 – Subject Demographics and Baseline Characteristics – Study 175

Demographic and Baseline Characteristic	Subjects, n(%)	
	TI Gen2 (N=177)	Placebo (N=176)
Age (yrs)		
N	177	176
Mean	56.7	56.7
SD	9.10	8.51
Median	57.0	57.0
Range	[27.0, 75.0]	[36.0, 79.0]
Age Group (yrs)		
18 - 30	1 (0.6)	0
31 - 49	37 (20.9)	33 (18.8)
50 - 64	102 (57.6)	110 (62.5)
>=65	37 (20.9)	33 (18.8)
Gender		
Female	95 (53.7)	102 (58.0)
Male	82 (46.3)	74 (42.0)
Race		
White	151 (85.3)	155 (88.1)
Black or African American	21 (11.9)	17 (9.7)
American Indian or Alaska Native	1 (0.6)	1 (0.6)
Asian	1 (0.6)	2 (1.1)
Other	3 (1.7)	1 (0.6)
Ethnic Group		
Hispanic or Latino	43 (24.3)	41 (23.3)
Not Hispanic or Latino	134 (75.7)	135 (76.7)
Country		
USA	88 (49.7)	87 (49.4)
Russia	55 (31.1)	56 (31.8)
Ukraine	19 (10.7)	19 (10.8)
Brazil	15 (8.5)	14 (8.0)
Duration of Diabetes (yrs)		
N	177	175
Mean	9.7	9.2
SD	5.79	5.38
Median	9.0	8.3
Range	[1.1, 34.7]	[1.0, 28.8]

Demographic and Baseline Characteristic	Subjects, n(%)	
	TI Gen2 (N=177)	Placebo (N=176)
Weight (kg)		
N	177	176
Mean	90.2	90.8
SD	17.22	17.34
Median	88.4	88.6
Range	[54.0, 142.3]	[58.0, 136.6]
BMI (kg/m²)		
N	177	176
Mean	31.8	32.4
SD	4.92	5.00
Median	31.3	31.6
Range	[21.6, 44.6]	[21.1, 44.4]
HbA1c (%) [1]		
N	176	176
Mean	8.26	8.35
SD	0.680	0.775
Median	8.10	8.30
Range	[6.60, 10.10]	[5.10, 10.90]
Fasting Plasma Glucose (mg/dL)		
N	176	176
Mean	179.1	177.2
SD	43.72	46.40
Median	172.0	171.5
Range	[49.0, 306.0]	[54.0, 316.0]
OAD Type		
Metformin Only	42 (23.7)	40 (22.7)
Metformin Plus Sulfonylurea	114 (64.4)	115 (65.3)
Metformin Plus DPP-4 Inhibitor	9 (5.1)	9 (5.1)
Metformin Plus 1 or More OADs Not Specified Above	9 (5.1)	9 (5.1)
2 or More OADs Not Including Metformin	3 (1.7)	3 (1.7)

Source: Table 18, Study 175 CSR

6.1.3 Subject Disposition

Study 171 – Type 1 Diabetes

Five hundred eighteen (518) subjects were randomized to one of the three treatment groups (Afrezza TI Gen 2=174, Afrezza TI MedTone=174, and insulin aspart=170).

Table 12 shows subject disposition for the randomized subjects in study 171.

Table 12– Subject Disposition Study 171

	Subjects, n (%)		
	Afrezza TI Gen2	Afrezza TI MedTone	Insulin Aspart
Randomized	174	174	170
Safety Population	174	173	171
Full Analysis Set (FAS)	174 (100)	174 (100)	170 (100)
Per Protocol (PP) Set	130 (74.7)	136 (78.2)	147 (86.5)
Completed randomized treatment phase	130 (74.7)	138 (79.3)	151 (88.8)
Withdrew during randomized treatment phase	44 (25.3)	36 (20.7)	19 (11.2)
Reasons for Discontinuation			
Adverse Event	16 (9.2)	9 (5.2)	0
Protocol Violation	2 (1.1)	2 (1.1)	2 (1.1)
Non-compliance	1 (0.6)	2 (1.1)	0
Lost to follow up	1 (0.6)	2 (1.1)	4 (2.4)
Death	0	0	1 (0.6)
Pregnancy	0	1 (0.6)	4 (2.4)
Physician decision	3 (1.7)	1 (0.6)	0
Subject decision	21 (12.1)	16 (9.2)	8 (4.7)
Other	0	3 (1.7)	0

Source: Adapted from Table 19 Study 171 CSR

Discontinuations were more frequent in the Afrezza TI randomized groups (i.e. Gen2 and MedTone) compared with the insulin aspart group, more often for adverse events, withdrawal by subject, and physician decision.

The verbatim text explanations for subjects who prematurely discontinued due to “Withdrawal by Subject,” “Physician Decision,” or “Other” revealed that the most frequently provided explanations were related to subjects’ unwillingness to comply with study requirements (14 in the Afrezza TI Gen2 group, 17 in the Afrezza TI MedTone group and 8 in the insulin aspart group). However, the second most common explanation provided was perceived lack of efficacy (5 in the Afrezza TI Gen2 group, 2 in the Afrezza TI MedTone group and none in the insulin aspart group) and other adverse experiences such as cough (1 in the Afrezza TI Gen2 group, none in the Afrezza TI MedTone group and none in the insulin aspart group).

Adverse events leading to subject discontinuation are discussed in Section 4 (Safety assessments) of this briefing document.

Reviewer’s comment: There was an overall higher rate of subject discontinuation in the Afrezza TI groups. The reasons related to this imbalance appear to be clustered in the categories of adverse events, and subjects’ choice – sometimes in relation to an adverse experience or perceived lack of efficacy. This finding does not support a claim that patients prefer Afrezza TI over insulin aspart, at least in this particular study.

Study 175 – Type 2 Diabetes

The Full Analysis Set population consisted of 353 subjects who were randomized to study treatment, 177 to the Afrezza TI Gen2 group and 176 subjects to the placebo group (Table 13).

Of note, twelve (6.8%) subjects of the Afrezza TI Gen2 group and 17 (9.7%) subjects of the placebo group received rescue therapy during the study.

Reviewer’s comment: The proportion of patients requiring rescue therapy was higher in the placebo group, yet it is concerning that 6.8% of subjects in the Afrezza TI group required rescue therapy, given that they were using a titratable insulin product.

Table 13– Subject Disposition Study 175

	Subjects, n (%)	
	Afrezza TI Gen2	Placebo
Randomized	177	176
Safety Population	177 (100)	176 (100)
Subjects who received rescue therapy	12 (6.8)	17 (9.7)
Full Analysis Set (FAS)	177 (100)	176 (100)
Per Protocol (PP) Set	144 (81.4)	131 (74.4)
Completed randomized treatment phase	150 (84.7)	139 (79.0)
Withdrew during randomized treatment phase	27 (15.3)	37 (21.0)
Reasons for Discontinuation		
Adverse Event	7 (4.0)	9 (5.1)
Protocol Violation	1 (0.6)	2 (1.1)
Non-compliance	1 (0.6)	3 (1.7)
Lost to follow up	6 (3.4)	4 (2.3)
Physician decision	1 (0.6)	1 (0.6)
Subject decision	10 (5.6)	14 (8.0)
Other	1 (0.6)	4 (2.3)
Source: Adapted from Table 14 and Table 15 CSR Study 175		

Overall, 27 (15.3%) subjects in the Afrezza TI Gen2 group and 37 (21.0%) subjects in the placebo group discontinued from the study.

AEs accounted for 7 (4.0%) dropouts in the Afrezza TI Gen2 group and 9 (5.1%) dropouts in the placebo group. Discontinuations due to AEs are discussed in section 4 of this review. Subjects who discontinued the study with reasons in the “Withdrawal by Subject,” “Physician Decision,” or “Other” categories were reviewed by the Sponsor for verbatim explanation of discontinuation. The most common reason was work/family conflict and relocation (Afrezza TI Gen2: 6; placebo: 6). “Persistently high FPG/PPG” was given as the reason by 3 placebo-treated subjects who withdrew from the study, and “Not satisfied with efficacy” was given as the reason for withdrawal by 1 placebo-treated subject and 1 Afrezza TI Gen2 subject.

6.1.4 Analysis of Efficacy Endpoint(s)

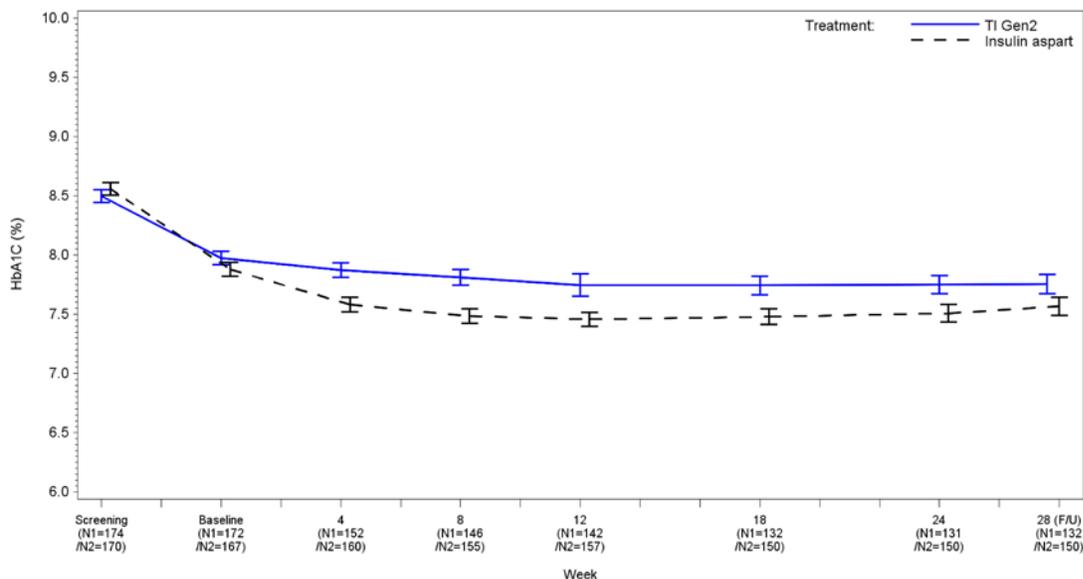
Please see Dr. Cynthia Liu’s statistical review for the Agency’s analysis of the primary endpoint for both studies 171 and 175. The analyses presented below are the Sponsor’s analyses sourced from the Complete Study Reports for the two studies.

The analyses are presented for the type 1 diabetes trial in sections 6.1.4.1.1 (primary endpoint), 6.1.4.1.2 (secondary endpoints), 6.1.4.1.3 (other endpoints), and 6.1.4.1.4 (subpopulations), and then similarly sections 6.1.4.1.2 through 6.1.4.1.4 for the type 2 diabetes trial. In section 6.1.8 (Analysis of Clinical Information Relevant to Dosing Recommendations), the review again pertains to both trials.

6.1.4.1.1 Analysis of Primary Efficacy Endpoint: Study 171 – Type 1 Diabetes

Figure 3 shows the observed mean change in HbA1c from Screening to Week 28. Note that the randomized treatment period occurred during the Baseline to Week 24 visits, whereas the figure starts with the Screening visit.

Figure 3 – Study 171 - Primary Efficacy Endpoint: Observed Mean Change (SE) in HbA1c (%) from Screening to Week 28 by Randomized Treatment Group (FAS Population)



Source: Figure 4 Study CSR

The primary efficacy endpoint was the change from the end of the basal insulin optimization phase at Visit 4 (Week 0, Randomization) to Visit 10 (Week 24) in HbA1c (%) between the TI-Gen2 and insulin aspart groups. In the Sponsor’s analysis, the model-adjusted mean change (decrease) in HbA1c from the model-adjusted baseline values (7.94% in the TI Gen2 group and 7.92% in the insulin aspart group) over 24 weeks as assessed by the MMRM model for the FAS population was greater in the insulin aspart treatment group (-0.40%) than in the TI Gen2 group (-0.21%), for a treatment difference of 0.19% (95% CI 0.02 to 0.36) (Table 14). The mean change in the TI arm was statistically significantly less (or worse) than that in the aspart arm. Similar results were observed for the corresponding analyses of the PP population. Please see Dr. Liu’s statistics review for agency analyses including sensitivity analyses.

Table 14 – Trial 171 ANCOVA of Mean Change from Baseline in HbA1c (%) at Week 24, MMRM Model, FAS Population

Time Point	Statistic	TI + Basal	Aspart + Basal	TI + Basal vs. Aspart + Basal
Baseline	N	172	167	
	Mean	7.94	7.92	
	SE	0.046	0.047	
Week 24	N	131	150	
	Mean	7.73	7.52	
	SE	0.051	0.050	
Change from Baseline to Week 24	N			
	LS Mean	-0.21	-0.40	0.19
	SE	0.062	0.060	0.086
	95% CI	-0.35, -0.08	-0.52, -0.28	0.02, 0.36
Noninferiority margin = 0.4% upper bound of the 95% CI				
Source: Table 29, Study CSR				

Reviewer’s comment: The study results show that the primary objective of noninferiority of TI Gen2 to insulin aspart was met (noninferiority margin 0.4). However, TI Gen2 was statistically worse than insulin aspart.

To put these results in perspective I show here the primary efficacy analysis of Study 009, the pivotal phase 3 study in T1DM with the MedTone inhaler submitted with the first NDA cycle. For this study, 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 15). 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%).

Table 15 – Trial 009 ANCOVA of Mean Change from Baseline in HbA1c (%) at Week 52, ITT Population with LOCF

Time Point	Statistic	TI + Glargine	Aspart + Glargine	TI + Glargine vs. Aspart + Glargine
Baseline	N	277	262	
	Mean	8.41	8.48	
	SD	0.92	0.97	
Week 52	N	277	262	
	Mean	8.28	8.09	
	SD	1.18	1.13	
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)	0.08 – 0.40
Noninferiority margin = 0.4% upper bound of the 95% CI				
Source: Copied from original clinical review with original source Table 14, Trial 009 CSR				

In my view the results of studies 009 and 171 are very similar: note that the treatment difference in study 009 (0.24%) is very close to study 171 (0.22%) with both favoring the comparator, insulin aspart, the difference being that in Study 171 the non-inferiority margin was (barely) met, while in Study 009 it was narrowly missed. In a non-inferiority trial design the assessment of efficacy is based on ‘implied’ efficacy relative to a comparator that is assumed to also be effective, with a non-inferiority margin pre-specified based on historical data of how the comparator should perform. While a specific non-inferiority margin must be specified for the purposes of trial design and statistical analysis, in my view it is important to also consider the data beyond strictly whether or not the non-inferiority margin was met.

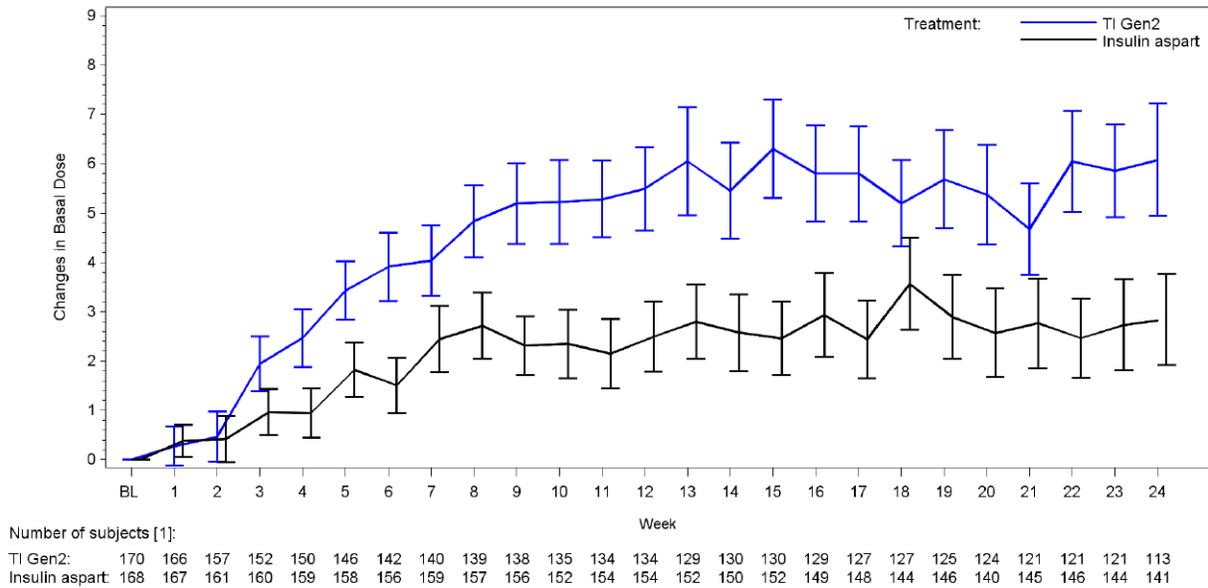
Analysis of Basal Insulin Doses Used– Study 171

The analysis of the primary efficacy endpoint cannot be fully interpreted without an examination of the relative insulin doses used by each study group, and a key component to an understanding of the primary efficacy analysis is a comparison of the use of basal insulin between the two treatment groups.

Doses of basal insulin used were higher in the TI groups than in the aspart group, whether examining the doses as means or medians, as shown in Figure 4 and Table 16. At Week 24 the median daily basal insulin dose for the TI Gen2 group was 32 U (increased from 28 U at Baseline) and the median daily basal insulin dose for the insulin aspart group was 26 IU (increased from 25 U at Baseline). When examining change over time, the increase in dose was also higher for the TI Gen 2 group. The change in median basal insulin dose from Week 1 to

Week 24 was approximately 4 U in the TI Gen 2 group and 1 IU in the insulin aspart group.
 Data for the MedTone group are also shown.

Figure 4 – Study 171 – Mean Daily “Basal” Insulin Dose Change from Baseline (SE) in IU/day) over time (Safety Population) in Aspart and Afrezza TI Gen 2 Arms



Source: Sponsor’s figure submitted to NDA 31 Jan 2014

Table 16 - Study 171 – Sponsor’s Table of Average Daily Dose of Basal Insulin (IU/Day) Since Randomization by Time Periods (Safety Population)

Weeks Post Randomization	Category/ Statistics	TI Gen2 (N=174) n (%)	TI MedTone (N=173) n (%)	Insulin Aspart (N=171) n (%)
Overall	N	171	173	170
	Mean	35.14	33.75	30.51
	SD	17.864	15.596	19.461
	Median	31.86	30.08	26.08
	Range	[9.2, 119.3]	[7.1, 78.5]	[6.0, 144.0]
Week 1	N	168	168	168
	Mean	31.84	31.52	29.00
	SD	15.756	15.729	17.991
	Median	28.61	29.29	25.00
	Range	[8.0, 94.3]	[5.4, 102.7]	[6.0, 132.3]
Week 4	N	154	157	160
	Mean	33.48	33.71	29.50
	SD	16.903	16.485	18.467
	Median	30.64	29.71	25.21
	Range	[9.0, 102.0]	[7.0, 90.0]	[6.0, 138.0]
Week 12	N	137	142	155
	Mean	36.79	34.86	30.75
	SD	20.404	16.958	20.258
	Median	33.86	30.00	26.00
	Range	[7.9, 126.4]	[7.0, 95.1]	[6.0, 142.1]
Week 24	N	116	122	143
	Mean	37.14	35.06	31.60
	SD	22.076	16.224	22.655
	Median	32.00	30.50	26.00
	Range	[8.0, 139.0]	[8.0, 92.0]	[6.0, 158.0]

Source: Table 27 Study CSR

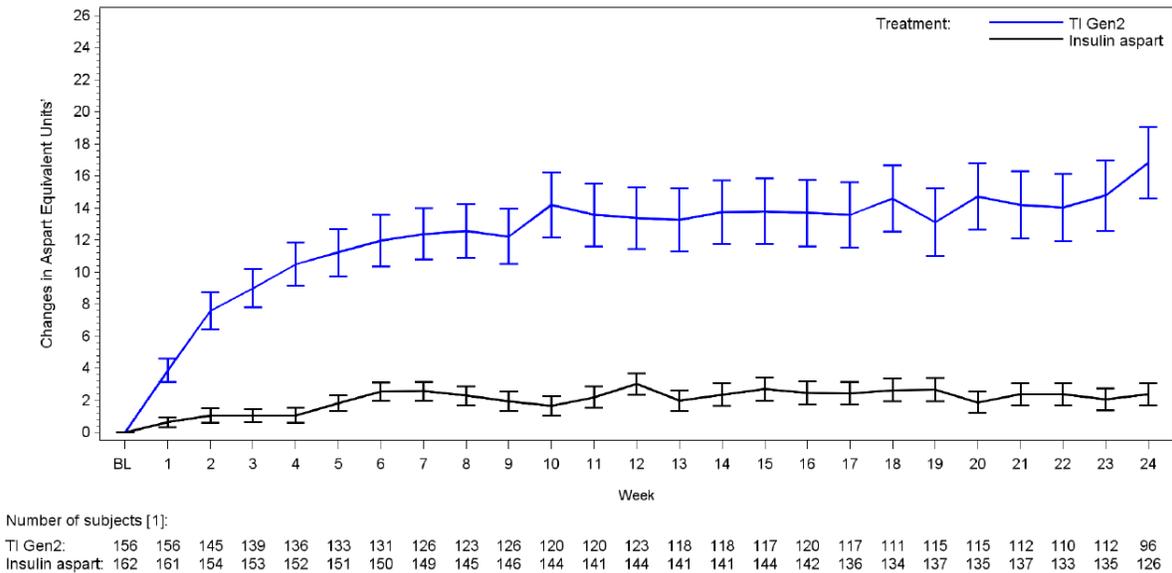
Reviewer’s comment: The TI Gen2 group’s requirement of more basal insulin compared with the insulin aspart group is further evidence that TI Gen2 is less effective than insulin aspart, because the TI Gen2 study group needed more basal insulin to achieve a higher HbA1c compared with the insulin aspart group. The higher basal insulin use the TI group is also substantiated by the finding of a lower FPG in the TI group at Week 24 (see **Secondary Endpoints**).

In an attempt to understand why there was a higher daily dose of basal insulin used in the Afrezza arm, FDA examined several possibilities, including whether perhaps the insulin aspart group was titrated less because more subjects were already at the fasting glucose target. From the data submitted by the Sponsor, FDA concluded that only a small percentage of subjects in each treatment group reached basal insulin titration targets by Week 12. This finding suggests that the differing basal insulin use between treatment arms was not due to subjects having reached titration goals.

Analysis of Prandial Insulin Doses Used – Study 171

The mean daily doses of inhaled prandial insulin increased throughout the randomized treatment phase (from 84.7 U at Week 1 to 115.4 U at Week 24 in the Afrezza TI Gen2 group and from 117.5 U at Week 1 to 137.7 U at Week 24 in the Afrezza TI MedTone group) (Figure 5 and Table 17). In contrast, in the insulin aspart group, the mean daily dose of insulin aspart showed only a slight increase (24.3 U at Week 1 and 25.9 U at Week 24).

Figure 5 – Study 171 – Mean (SE) Daily “Prandial” Insulin Dose Change from Baseline (IU/day) over time (Safety Population) in Aspart and Afrezza TI Gen 2 Arms



Note: Afrezza TI results shown in aspart equivalent units. Afrezza TI dose converted using conversion factor specified in the protocol (i.e., 10 units of Afrezza TI = 4 units of aspart).

Table 17 - Study 171 - Average Daily Dose of Prandial Insulin since Randomization by Time Periods (Safety Population)

	Category/Statistics	Afrezza TI Gen2	Afrezza TI MedTone	Insulin aspart
Overall	Mean (SD)	102.7 (51.8)	135.9 (64.4)	25.5 (12.6)
	Median	92.5	117.3	23.8
	Range	[30, 355]	[45, 354]	[5, 97]
Baseline	Mean (SD)	75.00 (38.6)	106.24 (52.2)	23.53 (13.0)
	Median	60	90	21
	Range	[30, 210]	[45, 390]	[6, 112]
Week 1	Mean (SD)	84.7 (41.6)	117.5 (51.6)	24.3 (12.5)
	Median	77.2	105.4	22
	Range	[30, 245]	[45, 302]	[6, 100]
Week 4	Mean (SD)	98.6 (52.6)	142.78 (69.9)	24.58 (12.4)
	Median	90	132.4	22.86
	Range	[30, 367]	[45, 533]	[5.0, 97.9]
Week 8	Mean (SD)	105.9 (55.1)	139.9 (72)	26 (13.3)
	Median	95.8	124.88	22.9
	Range	[30, 360]	[45, 406]	[3, 96]
Week 12	Mean (SD)	107.4 (59)	140 (75.8)	25.6 (12.6)
	Median	93.1	135	24
	Range	[30, 360]	[45, 395]	[3, 85]
Week 24	Mean (SD)	115.4 (63.2)	137.7 (76.8)	26 (14.1)
	Median	99.9	120	23.7
	Range	[30, 360]	[45, 420]	[8, 103]

Source: Table 28 Study CSR; Sponsor's table from information request dated 13 Feb 2013

Reviewer's comment: It appears that the Afrezza TI groups underwent substantial increases in dose over the study period (by design primarily in the first 12 weeks of the study) whereas the insulin aspart group had a similar dose from start to end of the randomized treatment phase. This finding makes it appear that virtually no titration occurred in the aspart arm.

Nonetheless, it appears both groups were inadequately titrated to reach glycemic goals; the Afrezza TI Gen2 titration algorithm allowed for an increase of 10 U per week, which theoretically would allow for an increase of 120 U over the 12 week prandial insulin titration period. Why the average daily dose only increased by 30 U over the 24 week randomized study period (i.e. mean of 85 U to 115 U) is unclear.

Other observations from these data include:

Assuming the stated conversion factor for Gen2 (4 IU aspart = 10 U Afrezza TI) the Gen2 group was using more prandial insulin than the insulin aspart group at Week 24 (115 U Afrezza TI Gen2 is roughly equivalent to 46 IU of rapid acting insulin analog) and overall (103 U Afrezza TI Gen2 is roughly equivalent to 41 IU of rapid acting insulin analog).

It is notable that the aspart group experienced an improvement in HbA1c from Baseline to Week 24 of -0.40% with virtually no increase in the average dose of prandial insulin.

Given that the basal insulin optimization phase was only 4 weeks in duration, the effect of basal insulin titration would not be expected to be fully reflected in the Baseline HbA1c. Therefore, the improvement in HbA1c from Baseline to Week 24 was likely driven, in part, by previous titration of basal insulin. Consequently, it is difficult to determine whether there was a reasonable contribution of prandial insulin to the improvement in HbA1c in either treatment arm.

Taking these observations together, it is not clear how to interpret the results of this non-inferiority study. It is concerning that if the insulin aspart group had been titrated more effectively, differences in efficacy between Afrezza TI and insulin aspart might have been greater and the non-inferiority margin may not have been excluded. It is worth reiterating that in a non-inferiority trial design we are basing the efficacy determination on the assumption that the comparator contributed to the effect, and that the within-trial comparator effect size was similar to the historical effect size for trials similarly designed. In T1DM insulin trials this is doubly challenging because two active insulins (basal + prandial) are each contributing to the overall effect.

It is worth reiterating that in a non-inferiority trial design we are basing the assessment of efficacy on ‘implied’ efficacy relative to a comparator that is assumed to also be effective. While TI does seem to ‘work’ as an insulin for T1DM evidenced by maintenance or improvement in HbA1c in a disease state for which the natural history is deterioration of glycemic control without exogenous insulin, TI has been consistently shown to be less effective than rapid acting insulin analogs for glycemic control. This finding was seen across trials and with both devices.

Again, FDA explored reasons for why the aspart arm appeared to undergo virtually no titration. From data submitted by the Sponsor it was clear that the lack of titration in aspart dose was not because subjects were already at target. There were fewer patients in the aspart group that reached titration targets than in the Afrezza group. This finding suggests that the differing prandial insulin titration between treatment arms was not due to subjects having reached titration goals. Whatever the reason for the difference, this finding is important because the inadequate titration of aspart raises doubts as to whether we are judging Afrezza against an optimally performing comparator, which is a crucial aspect of a non-inferiority trial.

Sensitivity Analyses of the Primary Endpoint

There were a substantial percentage of dropouts (25% and 11% dropouts in the Afrezza TI Gen2 and insulin aspart treatment arms, respectively) which could have potentially impacted the primary non-inferiority analysis. Among the sensitivity analyses conducted by the sponsor, all showed similar findings to the primary analysis except for the multiple imputation under the non-inferiority null method where 0.4% was added to every discontinued patient in the Afrezza TI-Gen2 group. That analysis showed a treatment difference of 0.3% (Afrezza TI-Gen2 minus insulin aspart) with 95% CI = (0.15%, 0.48%), failing to satisfy the non-inferiority criterion.

The FDA statistician’s stated concern that missing data add uncertainty to the results. Please see her review for details. This uncertainty is not addressed in standard analyses, which treat the missing data as ignorable or as ignorable after accounting for covariates. The concerns intensify the greater the amount of missing data. The FDA statistician’s analysis using the completers cohort had similar findings to the primary analysis based on the overall population. However, the dropouts in the Afrezza arm had mean increases in A1c during the 12-week titration period while mean decreases were observed in the aspart arm. Based on these data, the missing at random assumption, used in the applicant’s primary analysis, does not hold for the Afrezza arm. One may question whether the overall treatment difference would have been larger than the 0.22% difference shown in the primary analysis, if all the dropouts had stayed in the study. FDA requested that the sponsor perform a sensitivity analysis that would help further evaluate the impact of missing data.

Method	Afrezza LS Mean Change in HbA1c	Aspart LS Mean Change in HbA1c	Treatment Difference LS Mean (95% CI)
FDA’s requested analysis “Analysis 1”: 0.4% was added to every discontinued Afrezza subject assuming all subjects MNAR	-0.07%	-0.38%	0.31% (0.15, 0.48)
Applicant’s analysis “Analysis 2”: 0.4% was added to MNAR Afrezza subjects* as adjudicated by the applicant	-0.14%	-0.37%	0.23% (0.06, 0.39)
Source: Applicant’s analyses Key: MNAR=Missing Not at Random (for analysis 2, defined as due to apparent lack of efficacy as adjudicated by applicant) *N=5			

Analysis 1 in this table is the analysis requested by FDA. This method involves multiple imputation under the non-inferiority null which includes adding 0.4% to the imputed Week 24 A1c value for all discontinued subjects in the Afrezza arm. The treatment difference was 0.31% and the CI was 0.15% to 0.48%. For this sensitivity analysis, the non-inferiority criterion was not met. Analysis 2 which was additionally submitted by the applicant, adds 0.4% only for subjects that were adjudicated to be missing not at random. For this analysis missing not at random was defined as due to apparent lack of efficacy as adjudicated by the applicant. There were only 5 subjects who were clearly identified to have dropped out due to apparent lack of efficacy. Therefore, analysis 2 adds 0.4% for only these 5 subjects. The results are more similar to the primary efficacy analysis. This analysis is subjective in that it relies on adjudication of reasons for dropout.

In summary, the degree of missing data for A1c at Week 24 raises issues on the reliability and confidence in the results.

6.1.4.1.2 Analysis of Secondary Endpoints(s): Study 171 – Type 1 Diabetes

Responder Analysis – Study 171

In the Sponsor's analyses, the proportion of subjects who achieved the ADA recommended glycemic goal $\leq 7.0\%$ at Week 24 was greater for the insulin aspart group (46/150, 30.7%) than for the TI Gen2 group (24/131, 18.3%); $p = 0.0158$. The proportion of subjects achieving an HbA1c level of $\leq 6.5\%$ at Week 24 was greater for insulin aspart (19/150, 12.7%) than for TI Gen2 (10/131, 7.6%); $p = 0.2144$.

The proportion of subjects who achieved the ADA recommended glycemic goal of $\leq 7.0\%$ at end of trial in the subgroup of individuals who had a baseline HbA1c $> 7.0\%$, was 10.19% vs. 21.38% in the TI Gen2 vs. insulin aspart arm respectively ([Fisher's exact $p=0.0105$] FDA analysis). In the subgroup of subjects who started with a Baseline HbA1c $> 6.5\%$, 5.36% vs. 10.49% of individuals in the TI Gen2 vs. insulin aspart arm had an HbA1c decrease to $\leq 6.5\%$ respectively ([Fisher's exact $p=0.1025$] FDA analysis). Note, in the FDA analyses dropouts were considered non-responders.

Reviewer's comment: These responder analyses are consistent with the analysis of the primary endpoint, i.e., there were fewer patients who achieved recommended glycemic control goals (either 7% or 6.5%) in the TI Gen2 compared to aspart arm.

Fasting Plasma Glucose – Study 171

The reduction in the mean FPG from Baseline to Week 24 was greater for the TI Gen2 group compared to the insulin aspart group (-25.27 mg/dL for TI Gen2 vs +10.15 mg/dL for insulin aspart; the treatment difference was -35.42 mg/dL [95% CI: -56.25, -14.59]).

Reviewer's comment: The relative reductions in FPG from baseline to Week 24 may be due to the differences in the amount of basal insulin used between the treatment groups, rather than due to TI *per se*. Therefore, I do not give much weight to this analysis in supporting the primary efficacy endpoint, or in demonstrating effectiveness of TI.

Body Weight – Study 171

At Week 24, subjects in the TI Gen2 group had a weight loss (mean change from Baseline -0.39 kg), whereas subjects in the insulin aspart group had a weight gain (mean change from Baseline 0.93 kg; $p = 0.0079$). At Week 24, there was a significant difference between treatment groups in change from Baseline favoring the TI Gen2 group (-1.32 kg; 95% CI -2.33 to -0.31 kg; $p = 0.0102$).

Reviewer's comment: Analysis of body weight is difficult to interpret in light of the difference in efficacy between TI and insulin aspart seen in the trial. It would not be appropriate to conclude a body weight advantage for TI in light of the worse efficacy.

6.1.4.1.3 Other Endpoints: Study 171 – Type 1 Diabetes

Comparison of blood glucose values collected from 7-point glucose profiles was presented by the Sponsor to evaluate glucose excursions pre- and post-mealtime in each treatment group and then compare the relative magnitude of excursions between treatment groups. The analyses showed that the pre-lunch to post-lunch and pre-dinner to post-dinner blood glucose changes were generally less in the TI Gen2 group than in the insulin aspart group. The pre-breakfast to post-breakfast changes were generally less in the insulin aspart group. These data are not presented in further detail here.

Reviewer’s comment: Glucose data derived from glucometers, particularly from patients’ at-home use, are generally less reliable than centrally obtained and analyzed plasma glucose. Therefore, I consider data from the 7-point glucose profiles presented by the Sponsor to be exploratory, but not sufficient to inform risk/benefit assessment.

6.1.4.1.4 Subpopulations: Study 171 – Type 1 Diabetes

Please see Dr. Liu’s statistics review for comment on subgroup analyses.

Dr. Liu found that females in the insulin aspart group had the greatest reduction compared to insulin aspart treated males, TI treated females, and TI treated males (Table 18).

Table 18 – Study 171: Efficacy Results for HbA1c (%) by Sex

FAS Gender	Change from Baseline at Week 24 : LS Mean ± SE (N)		Treatment Difference	
	TI-Gen2	IAsp	LS Mean ± SE	95% CI
Male	-0.21 ± 0.14 (58)	-0.18 ± 0.14 (65)	-0.03 ± 0.14	(-0.31, 0.25)
Female	-0.17 ± 0.09 (73)	-0.58 ± 0.09 (82)	0.41 ± 0.10	(0.20, 0.61)

The results were obtained using ANCOVA on subjects who had a baseline and Week 24 HbA1c values. Similar findings were observed when MMRM approach was employed.

Source: reproduced from Dr. Liu’s review

Reviewer’s comment: Of note, in Study 009, males taking insulin aspart in combination with Lantus had more reduction in HbA1c when compared to the other subgroups.

6.1.4.2.1 Analysis of Primary Efficacy Endpoint: Study 175 – Type 2 Diabetes

The primary efficacy endpoint of the study was the mean change in HbA1c (%) from Randomization (Week 0) to Week 24 between the TI Gen2 and placebo groups using MMRM analysis (Table 19). In the FAS population, the adjusted mean change in HbA1c from baseline to Week 24 for subjects who received TI Gen2 in addition to background OADs was -0.82% versus subjects who received placebo and background OADs (-0.42); this difference was statistically

significant (95% confidence interval [CI]: -0.57, -0.23; $p < 0.0001$). The results in the PP population were consistent with those seen in the FAS population.

Table 19 – Study 175 - ANCOVA of Primary Endpoint – Change in HbA1c From Baseline to Week 24 -MMRM Analysis with FAS Population

Time Point	Statistic	TI+OADs	Placebo+OADs	TI+OADs- Placebo+OADs
Baseline	N	176	176	
	LS Mean (SE)	8.25 (0.057)	8.27 (0.058)	
Week 24	N	139	129	
	LS Mean (SE)	7.43 (0.061)	7.85 (0.062)	
Treatment Difference	LS Mean Change	-0.82 (0.061)	-0.42 (0.062)	-0.40
	95% CI			-0.57 – (-0.23)
	p value			<0.0001

Source: Table 23 Study CSR

Reviewer’s comment: To put these results into context, I examined FDA reviewed (labeled) studies of antidiabetes drugs representing various classes, studied in combination with metformin alone and at least two other OADs (Table 20). While cross-study comparison is difficult and generally not recommended, on its face, the magnitude of the effect size achieved with TI in comparison to these other antidiabetes agents is surprisingly modest, especially in light of the fact that TI can be titrated.

Table 20 – Efficacy of Non-titratable Antidiabetes Drugs on a Background of Metformin or at Least Two Other Oral Antidiabetes Drugs

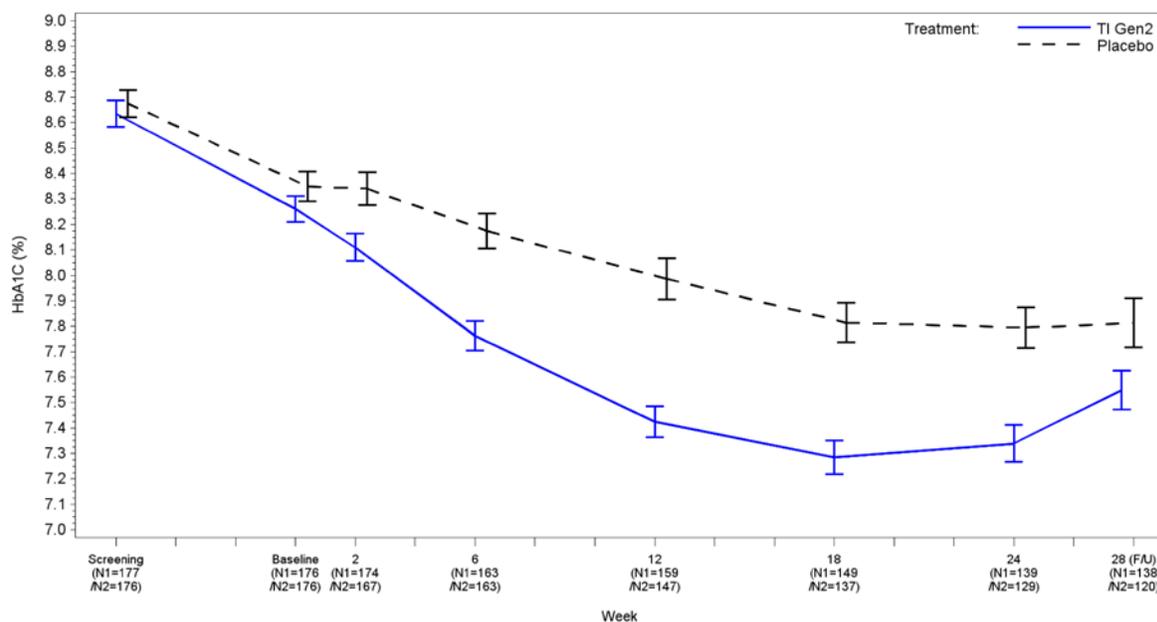
Drug (Proprietary name)	Class	Dose (mg)	Background therapy	Placebo-adjusted change in HbA1c (%)	Treatment duration (weeks)
Saxagliptin (Onglyza)	DPP4 inh	5	Met	-0.8	26
		5	Met + SU	-0.7	24
Canagliflozin (Invokana)	SGLT2 inh	300	Met	-0.8	26
		100	Met + Pio	-0.62	26
		300		-0.76	
		100	Met + SU	-0.71	26
		300		-0.92	
Liraglutide (Victoza)	GLP-1 agonist	1.8	Met	-1.1	26
		1.8	Met + SU	-1.1	26
		1.8	Met + Rosi	-0.9	26
Colesevelam (Welchol)	Bile acid sequestrant	3.8	Met	-0.5	26
		3.8	Met + Other OADs	-0.6	26

Key: Met=metformin; SU=sulfonylurea; Pio=pioglitazone; Rosi=rosiglitazone; inh=inhibitor
 Source: Drug labeling for each product

Observed Mean HbA1c over Time During the Randomized Treatment Phase

In both treatment groups, the mean HbA1c levels declined from the Screening visit to the Baseline visit (i.e., the run-in phase). In subjects on TI Gen2 and OADs, the mean HbA1c level decreased from 8.64% at Screening to 8.26% at Baseline. In subjects on placebo + OADs, the mean HbA1c level decreased from 8.68% at Screening to 8.35% at Baseline. In the TI Gen2 group, the observed mean HbA1c level decreased during the first 12 weeks of treatment (dose titration) and remained fairly constant during the latter 12 weeks (stable dosing). The HbA1c value began to rise from Week 24 to Week 28 after the end of study treatment. In the placebo group, the observed mean HbA1c level also decreased during the 24 weeks of study treatment, but to a lesser extent than the TI Gen2 group (Figure 6).

Figure 6 – Mean HbA1c Change over Time, Study 175



Note(s): N1 = TI Gen2, N2 = Placebo; Error bar denotes +/- standard errors
HbA1c collected after receiving rescue therapy are excluded.
Source: Figure 4, Study 175 CSR

Reviewer’s comment: It is unclear why mean HbA1c increased from week 18 to week 24; nevertheless, the increase was small and does not appear to drive the overall modest efficacy observed for TI vs. placebo.

Sensitivity Analyses of the Primary Endpoint

The Sponsor performed sensitivity analyses including the Pattern Mixture analysis and an analysis that included all HbA1c data collected after the initiation of rescue therapy, and concluded that these were consistent with the primary efficacy analysis.

Reviewer’s comment: Dr. Liu also performed extensive sensitivity analyses for study 175 and verified the Sponsor’s sensitivity analyses. Please see her review for details. In brief,

Dr. Liu concluded that all sensitivity analyses showed findings similar to the primary efficacy analysis and support the superiority finding.

6.1.4.2.2 Analysis of Secondary Endpoints(s): Study 175 – Type 2 Diabetes

Responder Analysis – Study 175

The Sponsor compared the proportions of HbA1c responders who achieved target HbA1c levels ($\leq 6.5\%$ and $\leq 7.0\%$) at Week 24 between the 2 treatment groups using logistic regression. Overall, 24 (15.9%) subjects in the Afrezza TI Gen2 group, and 6 (4.2%) subjects in the placebo group, reached the target of HbA1c $\leq 6.5\%$; (OR 4.4, 95% CI 1.7 – 11.2, $p = 0.0021$). For the target of HbA1c $\leq 7\%$, 57 (37.7%) in the Afrezza TI Gen2 group and 27 (19.0%) subjects in the placebo group reached this goal, (OR 2.7, 95% CI 1.55 – 4.8, $p = 0.0005$).

The FDA statistical reviewer also examined these data including non-rescued patients with missing data at Week 24 and rescued patients as non-responders. As shown in Table 21, results were similar.

Table 21– Study 175 (T2DM): Responder Rate for HbA1c at Week 24

(from the FDA reviewer’s statistical review)				
FAS Population	Afrezza TI-Gen2	Placebo	Difference in Proportion	Asymptotic 95% CI
HbA1c $\leq 6.5\%$ at Week 24	24/177 (13.6%)	6/176 (3.4%)	10.2%	(4.4%, 15.9%)
HbA1c $\leq 7.0\%$ at Week 24	57/177 (32.2%)	27/176 (15.3%)	16.9%	(8.2%, 25.6%)
Non-rescued patients with missing data at Week 24 and rescued patients were treated as non-responders.				

For the subset of patients with HbA1c $> 6.5\%$ at Baseline, 13.64% vs. 3.43% of the TI Gen2 treated vs. placebo treated subjects had HbA1c decreased to $\leq 6.5\%$ (Fisher’s Exact $p = 0.0009$). For the subset of patients with HbA1c $> 7.0\%$ at Baseline 32.18% vs. 15.12% of the TI Gen2 treated vs. placebo treated subjects had HbA1c decreased to $\leq 7.0\%$ (Fisher’s Exact $p = 0.0002$).

Reviewer’s comment: The responder analyses support the primary efficacy analysis; a significantly higher percentage of Afrezza TI-treated patients reached glycemic goals compared with placebo-treated patients.

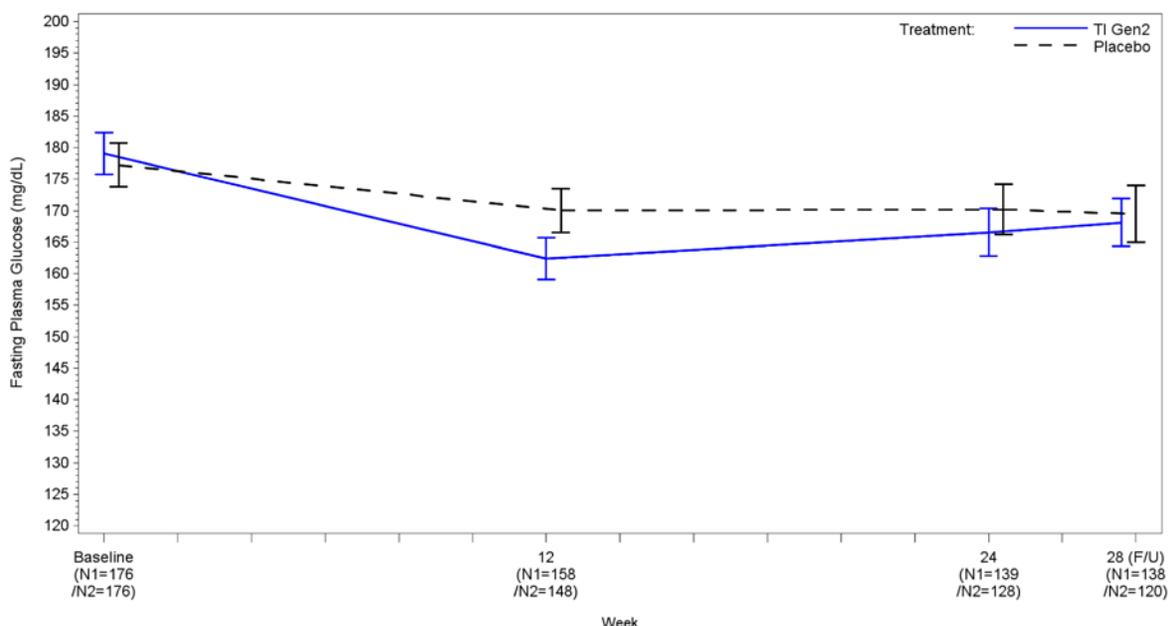
Fasting plasma glucose - Study 175

FPG appeared to decrease slightly in both groups, with the greatest difference between the groups at Week 12, and then increase in the TI group and remain stable in the placebo group, such that by Week 24, the mean FPG in the treatment groups was similar (Figure 7).

In the Sponsor’s analysis, at Week 24, the adjusted mean change of FPG was a decrease of 11.20 mg/dL from baseline in the TI Gen2 group and a decrease of 3.78 mg/dL from baseline in the placebo group. The treatment difference between the groups in FPG reduction was 7.42 mg/dL, (95% CI: -18.03, 3.18; p = 0.1698). The FDA statistical reviewer’s analysis used a different methodology but the results were similar, i.e. no significant difference between TI and placebo (Table 22).

The Sponsor’s results using the Per Protocol population were similar.

Figure 7 - Observed Mean (SE) of FPG Measurements over Time (FAS Population)



Source: Sponsor’s CSR for study 175

**Table 22 – Study 175 (T2DM): Statistical Results for FPG (mg/dL)
 (reproduced from Dr. Liu’s statistical review)**

FAS Population	LS Mean Change from baseline ± SE (N)		Treatment Difference	95% CI
	TI-Gen2	Placebo		
Reviewer’s analysis ¹	-10.6 ± 4.1 (138)	-5.6 ± 4.3 (128)	-4.9 ± 4.8	(-14.4, 4.5)
Sponsor’s analysis ²	-11.2 ± 3.8 (139)	-3.8 ± 3.9 (128)	-7.4 ± 5.4	(-18.0, 3.2)

¹ Reviewer’s analysis using change from baseline in FPG as the dependent variable.
² Sponsor’s analysis using FPG as the dependent variable.
 Data collected after initiation of rescue therapy were excluded from the analysis.

Reviewer’s comment: The explanation for this finding is likely that TI, used as prandial insulin, is not having a significant impact on FPG; the mean reduction in HbA1c compared

to placebo observed in the study is likely due to a decrease in average post-prandial glucose.

Body Weight

In the Sponsor’s analysis, from baseline to Week 24, subjects’ mean body weight increased 0.49 kg in the TI Gen2 group and decreased 1.13 kg in the placebo group, with a between-group difference of 1.62 kg favoring the placebo group, 95% CI: 0.90 - 2.34; p <0.0001). The FDA statistical reviewer’s analysis showed similar results (Table 23).

**Table 23 – Study 175 (T2DM): Statistical Results for Body Weight (kg)
 (reproduced from Dr. Liu’s statistical review)**

FAS Population	LS Mean Change from baseline ± SE (N)		Treatment Difference	95% CI
	TI-Gen2	Placebo		
Reviewer’s analysis ¹	0.51 ± 0.33 (152)	-1.17 ± 0.35 (142)	1.67 ± 0.36	(0.97, 2.38)
Sponsor’s analysis ²	0.49 ± 0.33 (152)	-1.13 ± 0.35 (142)	1.62 ± 0.37	(0.91, 2.34)

¹ Reviewer’s analysis using ANCOVA with terms for baseline weight, treatment, region, and OAD type.
² Sponsor’s analysis using ANCOVA with terms for baseline weight, treatment, region, OAD type, and change from baseline in HbA1c at Week 24.
 Data collected after initiation of rescue therapy were included in the analysis. Similar findings were observed when data collected after initiation of rescue therapy were excluded from the analysis.

Reviewer’s comment: This result is not remarkable given that insulin is known to cause body weight gain.

Rescue therapy and time to rescue

As stated previously, twelve (6.8%) subjects of the TI Gen2 group and 17 (9.7%) subjects of the placebo group received rescue therapy during the study. This difference was not statistically significantly different.

Both the Sponsor’s analyses and the FDA’s analyses showed no difference in time to rescue between the TI and placebo group. However, the numbers of rescued subjects were small in the two groups. Dr. Liu noted that when time to rescue was included as an additional covariate in the primary analysis model, similar findings to the primary efficacy analysis were observed.

6.1.4.2.3 Other Endpoints: Study 175 – Type 2 Diabetes

Supportive efficacy analyses:

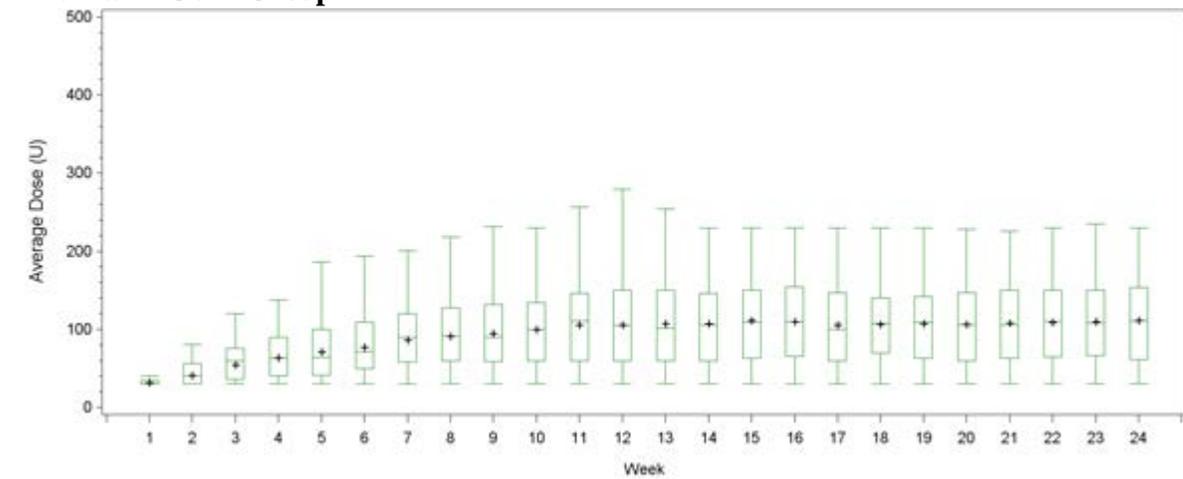
One (0.6%) subject in the TI Gen2 group and 9 (5.1%) subjects in the placebo group introduced at least 1 concomitant antidiabetic medication (excluding pre-enrollment OADs and rescue therapy, if any) during the randomized treatment phase. These cases are considered protocol deviations, since subjects were required to remain on stable regimens for the treatment of diabetes during the randomized treatment phase.

Reviewer’s comment: The higher use of disallowed concomitant anti-diabetes medication in the placebo group supports the finding of greater efficacy in the TI group vs. placebo.

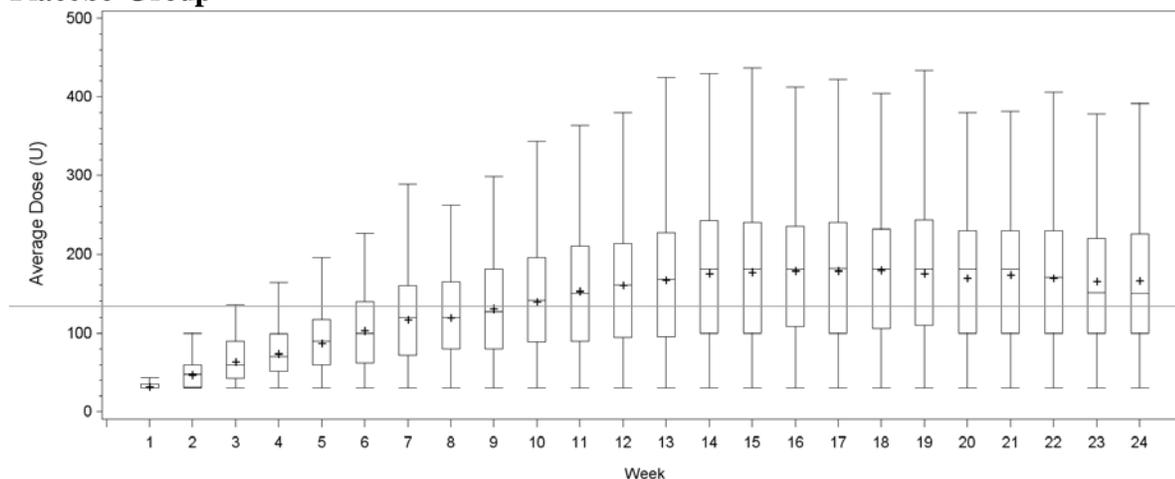
Doses of trial product achieved – Study 175

The average daily dose of study treatment was 92.3 U for the Afrezza TI Gen2 group and 128.0 U for the placebo group. As shown in Figure 8, the average daily dose of Afrezza TI Gen2 as well as placebo increased in the first 12 weeks (dose titration) and then stabilized in the last 12 weeks (stable dosing). The average daily dose during stable dosing was substantially higher in the placebo group than the Afrezza TI Gen2 group.

Figure 8 - Study 175 - Box Plots of Average Daily Dose of Prandial Insulin since Randomization by Time Periods (Safety Population)
Afrezza TI Gen2 Group



Placebo Group



Source: Figure 3 Study CSR

Reviewer's comment: The data in this figure suggest that the dose of Afrezza TI was titrated over the first 12 weeks and then kept stable over the last 12 weeks, and that the placebo group, presumably because of lack of effect, titrated study product to higher doses than those in the Afrezza TI arm.

In regards to the three step procedure in study 175 intended to stop futile dose titration (described in section 2), only four subjects in the placebo group met the criteria to stop dosing.

6.1.4.2.4 Subpopulations: Study 175 – Type 2 Diabetes

In the Sponsor's analyses, treatment effects on mean change from baseline in HbA1c at Week 24 between the TI-Gen2 and placebo groups were consistent across the subgroups defined by age (< 65 years or ≥ 65 years), gender, race, region, country, ethnic, OAD type, and baseline HbA1c ($\leq 8.0\%$ or $> 8.0\%$ as defined by the sponsor), as no significant treatment-by-subgroup interactions were observed (all $p > 0.10$).

Please see Dr. Liu's statistics review for comment on subgroup analyses. Dr. Liu confirmed the Sponsor's analyses.

6.1.5 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing issues are discussed throughout this review.

6.1.6 Discussion of Persistence of Efficacy and/or Tolerance Effects

None

6.1.7 Additional Efficacy Issues/Analyses

Sensitivity analyses based on financial disclosures and ‘high enrollers’

The FDA statistician ran additional analyses excluding data from sites that had the potential to prominently influence or ‘drive’ the overall primary efficacy analysis.

Site (b) (6) was associated with a sub-investigator who had reportable financial interests in MannKind Corporation. This site enrolled (b) (6) subjects in Study 171. Excluding those (b) (6) subjects the results of the primary efficacy analysis were: -0.20 for TI-Gen2, -0.42 for IAsp, +0.22 for treatment difference, with 95% CI = 0.08, 0.37) similar to the primary analysis results.

To ensure that no individual site was driving the results of primary efficacy analysis, the FDA statistician ran analyses for study 171 excluding Site 852 (32 subjects, the highest enrollment), Site 507 (27 subjects, 2nd highest enrollment), and Site 483 (23 subjects, 3rd highest enrollment); the results were all similar to the primary analysis results.

7 Review of Safety

Safety Summary

This review contains the primary non-pulmonary safety review for Afrezza. The primary pulmonary safety review was conducted by Dr. Paterniti from the Division of Pulmonary, Allergy, and Rheumatology products (DPARP). In this section, I briefly summarize Dr. Paterniti’s review findings and conclusions.

The conclusions in this section reflect exposure of 3017 patients to TI and includes 1026 patients with type 1 diabetes and 1991 patients with type 2 diabetes. The mean exposure duration was 8.17 months for the overall population and 8.16 months and 8.18 months for type 1 and 2 diabetes patients, respectively. In the overall population, 1874 were exposed to TI for 6 months and 724 for greater than one year. 620 and 1254 patients with type 1 and type 2 diabetes, respectively, were exposed to TI for up to 6 months. 238 and 486 patients with type 1 and type 2 diabetes, respectively, were exposed to TI for greater than one year (median 1.8 years combining the two types).

The mean age of the population was 50.2 years and 20 patients were older than 75 years of age. 50.8% of the population were men; 82.6% were White, 1.8% were Asian, and 4.9% were Black or African American. 9.7% were Hispanic. At baseline, the type 1 diabetes population had diabetes for an average of 16.6 years and had a mean HbA1c of 8.3%, and the type 2 diabetes population had diabetes for an average of 10.7 years and had a mean HbA1c of 8.8%. At baseline, 33.4% of the population reported peripheral neuropathy, 32.0% reported retinopathy and 19.6% had a history of cardiovascular disease.

The safety review suggests for the most part no change in the overall findings for non-pulmonary safety since the 2010 cycle 2 Resubmission. The majority of potential safety issues noted in the Complete Response letter were evaluated and no major additional concerns were noted. The one exception is the lung cancer concern (discussed in section 7.3.4).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

An overview of studies used to evaluate safety is shown in Table 24. Updates to the table below (which was included in the original Afrezza clinical review), using the 2013 data Cutoff July 31, 2013 are noted in *italic* font. **Bold** font is used to indicate studies included in the pooled Phase 2/3 safety database (discussed in section 7.1.3).

Table 24 – Overview of Clinical Safety Data for TI

Controlled safety/ efficacy trials	T1DM	009 and 101, 117a, 171
	T2DM	005, 0008, 102, 014, 026, and 103, 162b, 175
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	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, <i>118, 119, 142, 147, 158, 167, 176, 177</i>
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
Terminated (other)	T1DM	<i>117</i>
	T2DM	<i>162</i>
Ongoing Trials	T1DM	<i>134</i>
	T2DM	<i>139</i>
Source, ISS		
a- Study MKC-TI-117 was terminated early with 130 subjects.		
b- Study MKC-TI-162 was terminated early with 39 subjects.		

The Sponsor pooled data from both inhalation systems for the 2013 Resubmission, presenting general safety data for each device separately and for both devices combined. The Sponsor's analysis plans for the safety review including pooling of data from both devices were prespecified, agreed upon by FDA prior to the NDA resubmission and therefore, acceptable for review. I reviewed the Sponsor's data presentations, but did not reproduce all of those here; my

review presents general safety for both devices combined, with a brief discussion of the head-to-head comparison of safety of the two devices obtainable from trial 171 data.

The majority of the new controlled data was from the two new phase 3 studies (171 and 175) described previously.

Reviewer's comment: The pooling of safety information obtained from data with both devices provides the largest possible database to detect safety issues, and is appropriate, provided that there are no notable differences between the safety findings for the MedTone and Gen2 devices.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) in this 2013 Resubmission were coded according to MedDRA version 15.1. The AE data from the 2009 original NDA ISS and 2010 Resubmission were recoded to MedDRA version 15.1. One notable update changes the PTs of "hypoglycemia with loss of consciousness" and "hypoglycemic seizure" from the SOC Metabolism and Nutrition Disorders to the SOC Nervous System Disorders. The other changes are minor and would not be expected to change incidence assessments. Given that hypoglycemia events are analyzed separately by PT, the recoding does not impact these assessments.

I compared investigator verbatim terms to the Sponsor's preferred terms for selected 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. Table 7.1 shows in bold font the studies included in the pooled safety database. Ongoing studies were not included in the pooled safety database.

As in the original NDA submission, the pooling strategy applied for the Integrated Summary of Safety (ISS) in this resubmission 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 ≥ 14 days

Table 25 shows the number of subjects in pooled, controlled phase 2/3 clinical studies in the original 2009 NDA, the 2010 resubmission, and the current resubmission. As already noted, the new pooled safety data was generated primarily from the 2 new controlled clinical studies of TI with the Gen2 inhaler (Study 171 in subjects with T1DM and Study 175 in subjects with T2DM).

Since the 2009 Original NDA safety data cut-off date (15 Nov 2008) to the cutoff date of this 2013 Resubmission Safety Update (31 Jul 2013), 608 new subjects have been exposed to TI (238 subject-years exposure [SYE]) in Phase 3 clinical studies. Of these, 238 subjects (89 SYE) used the MedTone device and 370 subjects (149 SYE) used the Gen2 device.

Table 25 – Number of Subjects in Pooled, Controlled Phase 2/3 Clinical Studies

Submission	Number of Subjects in the Pooled, Controlled Phase 2/3 Studies								
	Type 1 DM			Type 2 DM			Total		
	TI	TP	Comparator	TI	TP	Comparator	TI	TP	Comparator
Subjects in 2009 Original NDA ISS	614	0	599	1795	114	1345	2409	114	1944
New subjects in 2010 Amendment Safety Update	65	0	65	0	0	0	65	0	65
New subjects in 2013 Resubmission Safety Update	347	0	171	196	176	18	543	176	189
Total subjects in 2013 Resubmission Safety Update	1026	0	835	1991	290	1363	3017	290	2198

Source: Sponsor's Table 3, ISS

Reviewer's comment: All of the FDA recommendations regarding safety assessments, pooling strategies and analysis methods appear to have been followed. The pooling strategy throughout all three review cycles is consistent with that commonly used in drug development programs and is acceptable.

Other data pools were used to examine safety in subgroups. For example, data were summarized for each inhaler type separately, as well as for both inhaler groups combined (TI Total). This strategy will allow for comparison of safety between old and new devices and if comparability is demonstrated, then this would be reassuring that the larger combined safety dataset could be reliably used to evaluate safety of Afrezza. Further, pooled analyses were performed for the T1DM population, the T2DM population, and the T1DM and T2DM combined population for reasons discussed in section 5.

7.2 Adequacy of Safety Assessments

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

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.

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.

Reviewer's comment: As noted in my two previous clinical safety reviews, the Sponsor had achieved adequate exposure at the time of original submission, based on the recommendations outlined in the Guidance, in part because of the >600 patients exposed for at least 2 years at that time.

Between the data cutoff dates of the 2010 Resubmission (15 May 2010) and this cycle 3/2013 Resubmission (31 July 2013), 1055 new subjects participated in Afrezza clinical studies. As of the database lock for the Resubmission, the total TI development program has exposed 2647 subjects to TI using the MedTone inhaler and 370 using the Gen2 inhaler (total 3017) in phase 2/3 clinical studies. Overall, 896 subjects were exposed to TI Inhalation Powder for 0 to 3 months, 978 for >3 to 6 months, 419 for >6 to 12 months, and 724 for >12 months.

Reviewer's comment: While the exposure numbers with the Gen2 inhaler are relatively low, the numbers are acceptable, provided that the new safety data from the Gen2 inhaler are generally consistent with the original safety data from the MedTone studies.

Demographics of safety population

To allow meaningful conclusions to be drawn regarding safety of Afrezza, the demographics and baseline disease characteristics of the safety population should be representative of intended users of Afrezza. Note that comments regarding 'balance' between treatment groups in terms of demographic and baseline characteristics, i.e. whether randomization was generally successful, are presented in Section 6 (Efficacy).

T1DM

Table 26 shows the demographic and baseline disease characteristics of the T1DM pooled controlled phase 2/3 trials safety population in the 2013 Resubmission. Table 7.10 in my original NDA clinical review shows the demographic and baseline disease characteristics of the T1DM safety population at the time of original 2009 NDA submission. There do not appear to be any important differences between the safety population in 2009 and the current 2013 T1DM safety population. Note that only new study (Study 171) that qualified for pooling was completed since the 2010 NDA resubmission.

Table 26 – Demographic and Baseline Disease Characteristics of the T1DM Pooled Controlled Phase 2/3 Trials Safety Population of 2013 Resubmission

	TI Gen2 (n=174)	TI MedTone (n=852)	Comparator (n=835)
Sex			
• % Male	44 %	52%	51 %
Race			
• Caucasian	84.5 %	89 %	90 %
• Black or African American	5 %	3.5%	3 %
• Hispanic	10 %	6 %	6 %
• Asian	0.5%	1%	0.5 %
• Other	0.5%	0.5%	1 %
Age (years)			
• Mean (SD)	37 (12)	39 (13)	39 (13)
• Median	36	38	37
• Range	18 - 71	18 - 76	18 - 76
Age Group			
• 18 – 64 years	96 %	98 %	98 %
• 64 – 74 years	4%	2 %	2 %
• > 74 years	0 %	0.1 %	0.2 %
BMI (kg/m ²)			
• Mean (SD)	26 (4)	26 (4)	26 (4)
• Median	26	26	25
• Range	16 - 40	16 - 40	17 - 41
Duration of Diabetes (years)			
• Mean (SD)	16 (10)	17 (11)	17 (11)
• Median	14	14	14.5
• Range	1 - 57	0.2 - 61	0.1 - 64
Source: ISS Tables 15 and 20			

Reviewer’s comment: The demographic and baseline disease characteristics of the T1DM safety population in the Afrezza development program appear reasonably representative of the overall T1DM population, although some race categories may be underrepresented in the studies.

T2DM

Table 27 shows the demographic and baseline disease characteristics of the T2DM pooled controlled phase 2/3 trials safety population in the 2013 Resubmission. Two new studies contributing subjects with T2DM, Studies 162 and 175, were initiated since the 2009 original NDA submission. Study 162 was terminated early with 39 subjects enrolled.

Table 27 – Demographic and Baseline Disease Characteristics of the T2DM Pooled Controlled Phase 2/3 Trials Safety Population of 2013 Resubmission

	TI Gen2 (n=196)	TI Med Tone (n=1795)	TP (n=290)	Comparator (n=1363)
Sex				
• % Male	47 %	51%	48%	51 %
Race				
• Caucasian	65 %	81 %	71 %	80 %
• Black or African American	12 %	5 %	6 %	5 %
• Hispanic	22 %	10 %	19 %	11 %
• Asian	0.5%	2 %	2 %	3 %
• Other	0.5%	1 %	1 %	2 %
Age (years)				
• Mean (SD)	57 (9)	56 (9)	56 (9)	56 (9)
• Median	57.5	57	57	56
• Range	27 - 75	19 - 82	26 - 79	18 - 78
Age Group				
• 18 – 64 years	78 %	83 %	80 %	84 %
• 64 – 74 years	22 %	16 %	18 %	15 %
• > 74 years	1 %	1 %	2 %	1 %
BMI (kg/m ²)				
• Mean (SD)	32 (5)	31 (5)	32 (5)	31 (5)
• Median	31.5	31	31	31
• Range	19 - 45	15 - 56	21 - 44	19 - 64
Duration of Diabetes (years)				
• Mean (SD)	10 (6)	11 (7)	9 (5)	11.5 (7)
• Median	9.5	9.5	8	10
• Range	1 - 36	0 - 45	1 - 29	0.3 - 52
Source: ISS Tables 16 and 22				
Comparator group includes both non-insulin and other insulin drugs				
Key: TP=Technosphere Powder Placebo using either inhaler				

As expected for a population of T2DM subjects, the mean age is older than the T1DM subjects and BMI is higher with the mean/median BMI being in the obese category.

The T2DM population had a mean/median duration of diabetes of roughly 10-11 years suggesting relatively advanced disease. This seems appropriate for clinical studies investigating an insulin product, i.e. insulin is not typically first line therapy for the treatment of T2DM.

For comparison, table 7.7 in my original NDA clinical review shows the demographic and baseline disease characteristics of the safety population at the time of original 2009 NDA submission. The major difference appears to be a greater proportion of Black or African American and Hispanic subjects included in the Gen2 studies.

Reviewer's comment: The demographic and baseline disease characteristics of the T2DM safety population in the Afrezza development program appear reasonably representative of the overall T2DM population.

A greater proportion of Black or African American and Hispanic subjects were included in the Gen2 studies, improving the generalizability of safety results compared to the original NDA submission.

In my clinical reviews for the 2009 original NDA submission and the 2010 resubmission, I also included smoking history in the Demographics tables. For the current review, smoking history is discussed by the pulmonary reviewer Dr. Paterniti because this risk factor is most relevant to pulmonary safety. Of note, there appear to be no important differences in the percentages of subjects who are ex-smokers between the previously submitted data and the current data (roughly one quarter of subjects).

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. For the new device, there is no additional data that suggests a safety risk or benefit related to hypoglycemia with Afrezza.

7.2.3 Special Animal and/or In Vitro Testing

See original NDA review.

7.2.4 Routine Clinical Testing

See original NDA review.

7.2.5 Metabolic, Clearance, and Interaction Workup

See original NDA review.

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

See 'Submission Specific Safety Concerns'

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.

Included in the submission for cycle 2 there was 1 death in the Named Patient Program/Compassionate Use Program in Europe.

Narratives for these deaths were included in the clinical reviews for the first two review cycles.

Since the previous submissions, 2 deaths occurred: 1 subject with T1DM who received comparator treatment in Study MKC-TI-171 and 1 subject with T2DM who received TI Inhalation Powder in the ongoing Study MKC-TI-139 (Table 28).

Consequently, using the 2013 Resubmission Safety Population 10 (0.33%) of 3017 Afrezza TI subjects and 7 (0.32%) of 2198 comparator subjects died. The Resubmission exposure-adjusted death rates were 0.44 per 100 subject-years and 0.33 per 100 subject-years for the Afrezza TI and comparator groups, respectively.

For a listing of all deaths in the complete Afrezza development program see Appendix 3, and for narratives of all deaths see Appendix 4 (Table 49).

Table 28– Deaths Listing for TI and Comparator, Cutoff date 31 Jul 2013

Trial/Patient Number	Age (years)	Sex	Diabetes Type	Total Daily Dose	Days to Death	Description
Comparator						
MKC-TI-171/1413	26	M	1	6,5, and 14 U insulin aspart and 24 U insulin detemir	45	Accidental drowning
TI						
MKC-TI-139/011*	64	F	2	TI 15-30 U at mealtimes	233	Acute leukemia
*This patient also experienced an SAE of abdominal pain requiring hospitalization						

The narrative for the patient who died while treated with TI is as follows:

Subject MKC-TI-139/011, a 64 year-old (yo) Caucasian female with T2DM and 7-year history of myeloproliferative disorder, initiated treatment with TI Inhalation Powder on 05 Nov 2009. On 01 Apr 2010 the subject was informed by her oncologist that the myelodysplastic syndrome had converted to an acute leukemia. The subject began chemotherapy treatment on 13 Apr 2010

with 78 mg intravenous (IV) azacitidine (Vidaza) in conjunction with Ativan 0.5 mg IV and Decadron 10 mg IV as pre-medications prior to chemotherapy. On an unspecified day in (b) (6), the subject experienced severe fever and severe shortness of breath and was subsequently admitted to the hospital. The subject had leukopenia and thrombocytopenia, likely related to the chemotherapy medication, Vidaza. The subject was treated with antibiotics and corticosteroids. The corticosteroids were used for a possible reaction to platelets given to treat thrombocytopenia. The subject also received high amounts of oxygen. The subject was not improving after receiving these treatments, and was subsequently placed on a morphine drip for comfort care. She died on (b) (6) from complications of leukemia. The investigator reported that per the hospital records, the subject died from acute respiratory failure possibly associated with a platelet transfusion reaction and acute leukemia. The death certificate, which was in the chart, listed cause of death as: 1) cardiopulmonary arrest, and 2) acute leukemia.

Reviewer's comment: In this case, alternatively causality is clear. The additional two deaths in the TI development program (one comparator-treated and one TI-treated) do not change the overall safety profile of TI from the 2009 original NDA submission and 2010 resubmission in terms of deaths. In summary, death rates were low and there is no apparent imbalance between TI and comparator based on controlled clinical data.

7.3.2 Nonfatal Serious Adverse Events

In the original NDA review, because serious adverse event rates were low, the controlled phase 2/3 trials for T1DM and T2DM were pooled to improve the likelihood of detecting potentially important imbalances between treatment groups. In the 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; 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 (Note that there were no additional cases of DKA in the current Resubmission) DKA is discussed in more detail in section 7.3.5 along with other adverse events of special interest.

As requested by the FDA, in the re-submission the Sponsor presented tabulations 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.

Results of the new analyses are similar to those of the original NDA. For T1DM patients, the incidence of SAEs in both the TI group and the comparator group was similar between the 2010 Resubmission (11.6% for both groups) and the 2013 Resubmission (9.1% for TI Inhalation Powder and 9.9% for comparator treatment). For T2DM, the incidence of SAEs in the TI group between the 2013 Resubmission and the original NDA (note the 2010 Resubmission did not add any T2DM patients to the pooled Phase 2/3 Safety Population) also remained similar (120/1991

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

[6.0%] and 114/1795 [6.4%], respectively). In the TI Placebo group, the incidence of SAEs was 11/290 (3.8%) in the 2013 Resubmission compared to 2/114 (1.8%) in the original NDA. The incidence of SAEs in the Comparator group between 2013 and 2009 was the same (106/1363 [7.8%] and 105/1345 [7.8%]).

Table 29 shows the incidence of SAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) for both diabetes types combined. Overall incidence of SAEs was similar between the original NDA and the current resubmission, and there is still no imbalance between TI and placebo or active comparator.

Table 29 – Incidence of Serious Adverse Events by System Organ Class and Preferred Term for T1DM and T2DM Combined, Pooled Phase 2/3 Safety Population, 2013 Resubmission

System Organ Class	TI			TP			Comparator [N=2198] [SYE=2152] n (%)
	Gen2 [N=370] [SYE=149] n (%)	MedTone [N=2647] [SYE=1903] n (%)	Total [N=3017] [SYE=2052] n (%)	Gen2 [N=176] [SYE=73] n (%)	MedTone [N=114] [SYE=25] n (%)	Total [N=290] [SYE=98] n (%)	
ANY TREATMENT-EMERGENT ADVERSE EVENT	11 (3.0)	202 (7.6)	213 (7.1)	9 (5.1)	2 (1.8)	11 (3.8)	189 (8.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	2 (0.1)	2 (0.1)	0	0	0	3 (0.1)
Lymphadenopathy	0	1 (0.0)	1 (0.0)	0	0	0	0
Thrombocytosis	0	1 (0.0)	1 (0.0)	0	0	0	0
Anemia	0	0	0	0	0	0	1 (0.0)
Pernicious anemia	0	0	0	0	0	0	1 (0.0)
Thrombocytopenia	0	0	0	0	0	0	1 (0.0)
CARDIAC DISORDERS	2 (0.5)	27 (1.0)	29 (1.0)	3 (1.7)	0	3 (1.0)	29 (1.3)
Coronary artery disease	0	6 (0.2)	6 (0.2)	1 (0.6)	0	1 (0.3)	3 (0.1)
Myocardial infarction	2 (0.5)	4 (0.2)	6 (0.2)	0	0	0	4 (0.2)
Atrial fibrillation	0	3 (0.1)	3 (0.1)	0	0	0	3 (0.1)
Angina unstable	0	2 (0.1)	2 (0.1)	0	0	0	3 (0.1)
Arteriosclerosis coronary artery	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Coronary artery occlusion	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Acute coronary syndrome	0	1 (0.0)	1 (0.0)	0	0	0	3 (0.1)
Bundle branch block right	0	1 (0.0)	1 (0.0)	0	0	0	0
Cardiac failure	0	1 (0.0)	1 (0.0)	0	0	0	0
Cardiac failure chronic	0	1 (0.0)	1 (0.0)	0	0	0	0
Cardiac failure congestive	0	1 (0.0)	1 (0.0)	0	0	0	0
Coronary artery stenosis	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Ischemic cardiomyopathy	0	1 (0.0)	1 (0.0)	0	0	0	0
Myocardial ischemia	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Pericarditis	0	1 (0.0)	1 (0.0)	0	0	0	0
Ventricular tachycardia	0	1 (0.0)	1 (0.0)	0	0	0	0
Acute myocardial infarction	0	0	0	0	0	0	1 (0.0)
Angina pectoris	0	0	0	1 (0.6)	0	1 (0.3)	3 (0.1)
Atrial flutter	0	0	0	0	0	0	1 (0.0)
Bundle branch block left	0	0	0	0	0	0	1 (0.0)
Coronary artery insufficiency	0	0	0	0	0	0	2 (0.1)
Cyanosis	0	0	0	1 (0.6)	0	1 (0.3)	0
Hypertensive heart disease	0	0	0	0	0	0	1 (0.0)
Sinus tachycardia	0	0	0	0	0	0	1 (0.0)
Supraventricular tachycardia	0	0	0	0	0	0	3 (0.1)
CONGENITAL, FAMILIAL AND GENETIC	0	0	0	1 (0.6)	0	1 (0.3)	0

Clinical Review
 Lisa B. Yanoff, M.D.
 NDA Class 2 Resubmission/22,472
 Technosphere Insulin Inhalation Powder/Afrezza

DISORDERS							
Skull malformation	0	0	0	1 (0.6)	0	1 (0.3)	0
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	1 (0.0)
Meniere's disease	0	0	0	0	0	0	1 (0.0)
ENDOCRINE DISORDERS	0	0	0	0	0	0	1 (0.0)
Myxedema	0	0	0	0	0	0	1 (0.0)
EYE DISORDERS	0	5 (0.2)	5 (0.2)	0	0	0	3 (0.1)
Retinal detachment	0	3 (0.1)	3 (0.1)	0	0	0	0
Retinal disorder	0	1 (0.0)	1 (0.0)	0	0	0	0
Vitreous hemorrhage	0	1 (0.0)	1 (0.0)	0	0	0	0
Diabetic retinopathy	0	0	0	0	0	0	1 (0.0)
Eye hemorrhage	0	0	0	0	0	0	2 (0.1)
Glaucoma	0	0	0	0	0	0	1 (0.0)
Optic atrophy	0	0	0	0	0	0	1 (0.0)
Optic neuropathy	0	0	0	0	0	0	1 (0.0)
GASTROINTESTINAL DISORDERS	0	15 (0.6)	15 (0.5)	0	1 (0.9)	1 (0.3)	14 (0.6)
Pancreatitis acute	0	4 (0.2)	4 (0.1)	0	0	0	0
Gastritis	0	2 (0.1)	2 (0.1)	0	0	0	2 (0.1)
Abdominal hernia	0	1 (0.0)	1 (0.0)	0	0	0	0
Anal fistula	0	1 (0.0)	1 (0.0)	0	0	0	0
Colitis ulcerative	0	1 (0.0)	1 (0.0)	0	0	0	0
Constipation	0	1 (0.0)	1 (0.0)	0	0	0	0
Duodenal ulcer	0	1 (0.0)	1 (0.0)	0	0	0	0
Erosive esophagitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Gastric ulcer	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Gastritis erosive	0	1 (0.0)	1 (0.0)	0	0	0	0
Gastrointestinal hemorrhage	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Intestinal obstruction	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Large intestine perforation	0	1 (0.0)	1 (0.0)	0	0	0	0
Esophageal ulcer	0	1 (0.0)	1 (0.0)	0	0	0	0
Pancreatic cyst	0	1 (0.0)	1 (0.0)	0	0	0	0
Pancreatitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Retroperitoneal hemorrhage	0	1 (0.0)	1 (0.0)	0	0	0	0
Vomiting	0	1 (0.0)	1 (0.0)	0	0	0	0
Abdominal discomfort	0	0	0	0	0	0	1 (0.0)
Abdominal pain	0	0	0	0	0	0	1 (0.0)
Abdominal pain upper	0	0	0	0	0	0	1 (0.0)
Colonic polyp	0	0	0	0	0	0	1 (0.0)
Gastroduodenitis	0	0	0	0	0	0	1 (0.0)
Gastroesophageal reflux disease	0	0	0	0	0	0	2 (0.1)
Hematemesis	0	0	0	0	0	0	1 (0.0)
Hiatus hernia	0	0	0	0	0	0	1 (0.0)
Inguinal hernia, obstructive	0	0	0	0	1 (0.9)	1 (0.3)	0
Esophagitis	0	0	0	0	0	0	1 (0.0)
Pancreatic necrosis	0	0	0	0	0	0	1 (0.0)
Pancreatitis chronic	0	0	0	0	0	0	1 (0.0)
Small intestinal obstruction	0	0	0	0	0	0	1 (0.0)
Umbilical hernia	0	0	0	0	0	0	1 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	6 (0.2)	6 (0.2)	0	0	0	3 (0.1)
Chest pain	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Generalized edema	0	2 (0.1)	2 (0.1)	0	0	0	0
Chest discomfort	0	1 (0.0)	1 (0.0)	0	0	0	0
Edema peripheral	0	1 (0.0)	1 (0.0)	0	0	0	0
Non-cardiac chest pain	0	0	0	0	0	0	1 (0.0)
Pyrexia	0	0	0	0	0	0	1 (0.0)
HEPATOBIILIARY DISORDERS	0	9 (0.3)	9 (0.3)	0	0	0	7 (0.3)
Cholecystitis	0	3 (0.1)	3 (0.1)	0	0	0	3 (0.1)

Clinical Review
 Lisa B. Yanoff, M.D.
 NDA Class 2 Resubmission/22,472
 Technosphere Insulin Inhalation Powder/Afrezza

Cholecystitis acute	0	2 (0.1)	2 (0.1)	0	0	0	0
Cholelithiasis	0	2 (0.1)	2 (0.1)	0	0	0	3 (0.1)
Drug-induced liver injury	0	1 (0.0)	1 (0.0)	0	0	0	0
Hepatitis toxic	0	1 (0.0)	1 (0.0)	0	0	0	0
Cholecystitis chronic	0	0	0	0	0	0	1 (0.0)
Gallbladder disorder	0	0	0	0	0	0	1 (0.0)
Hepatocellular injury	0	0	0	0	0	0	1 (0.0)
IMMUNE SYSTEM DISORDERS	0	1 (0.0)	1 (0.0)	0	0	0	0
Autoimmune disorder	0	1 (0.0)	1 (0.0)	0	0	0	0
INFECTIONS AND INFESTATIONS	2 (0.5)	27 (1.0)	29 (1.0)	0	0	0	29 (1.3)
Urinary tract infection	1 (0.3)	2 (0.1)	3 (0.1)	0	0	0	1 (0.0)
Diabetic gangrene	0	2 (0.1)	2 (0.1)	0	0	0	0
Furuncle	0	2 (0.1)	2 (0.1)	0	0	0	0
Pneumonia	0	2 (0.1)	2 (0.1)	0	0	0	5 (0.2)
Wound infection	0	2 (0.1)	2 (0.1)	0	0	0	0
Appendicitis	0	1 (0.0)	1 (0.0)	0	0	0	5 (0.2)
Carbuncle	0	1 (0.0)	1 (0.0)	0	0	0	0
Cellulitis	0	1 (0.0)	1 (0.0)	0	0	0	4 (0.2)
Cellulitis streptococcal	0	1 (0.0)	1 (0.0)	0	0	0	0
Cytomegalovirus infection	1 (0.3)	0	1 (0.0)	0	0	0	0
Diabetic foot infection	0	1 (0.0)	1 (0.0)	0	0	0	0
Diverticulitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Gastroenteritis viral	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Hepatitis viral	0	1 (0.0)	1 (0.0)	0	0	0	0
Injection site cellulitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Localized infection	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Osteomyelitis	0	1 (0.0)	1 (0.0)	0	0	0	2 (0.1)
Otitis media acute	0	1 (0.0)	1 (0.0)	0	0	0	0
Parotitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Perirectal abscess	0	1 (0.0)	1 (0.0)	0	0	0	0
Pulmonary tuberculosis	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Pyelonephritis chronic	0	1 (0.0)	1 (0.0)	0	0	0	0
Rectal abscess	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Staphylococcal infection	0	1 (0.0)	1 (0.0)	0	0	0	0
Upper respiratory tract infection	0	1 (0.0)	1 (0.0)	0	0	0	0
Arthritis bacterial	0	0	0	0	0	0	1 (0.0)
Bacterial sepsis	0	0	0	0	0	0	1 (0.0)
Bronchitis	0	0	0	0	0	0	1 (0.0)
Gangrene	0	0	0	0	0	0	1 (0.0)
Infection	0	0	0	0	0	0	1 (0.0)
Pelvic abscess	0	0	0	0	0	0	1 (0.0)
Peritonitis	0	0	0	0	0	0	1 (0.0)
Pilonidal cyst	0	0	0	0	0	0	1 (0.0)
Postoperative wound infection	0	0	0	0	0	0	1 (0.0)
Pyelonephritis	0	0	0	0	0	0	2 (0.1)
Sepsis	0	0	0	0	0	0	1 (0.0)
Staphylococcal scalded skin syndrome	0	0	0	0	0	0	1 (0.0)
Subcutaneous abscess	0	0	0	0	0	0	1 (0.0)
Tonsillitis	0	0	0	0	0	0	1 (0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.5)	16 (0.6)	18 (0.6)	1 (0.6)	0	1 (0.3)	19 (0.9)
Facial bones fracture	0	2 (0.1)	2 (0.1)	0	0	0	0
Rib fracture	1 (0.3)	1 (0.0)	2 (0.1)	0	0	0	1 (0.0)
Road traffic accident	0	2 (0.1)	2 (0.1)	0	0	0	4 (0.2)
Accidental overdose	0	1 (0.0)	1 (0.0)	0	0	0	0
Ankle fracture	0	1 (0.0)	1 (0.0)	0	0	0	4 (0.2)
Concussion	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Electric shock	0	1 (0.0)	1 (0.0)	0	0	0	0

Clinical Review
 Lisa B. Yanoff, M.D.
 NDA Class 2 Resubmission/22,472
 Technosphere Insulin Inhalation Powder/Afrezza

Fall	0	1 (0.0)	1 (0.0)	0	0	0	5 (0.2)
Hand fracture	0	1 (0.0)	1 (0.0)	0	0	0	0
Injury	0	1 (0.0)	1 (0.0)	0	0	0	0
Jaw fracture	0	1 (0.0)	1 (0.0)	0	0	0	0
Joint dislocation	1 (0.3)	0	1 (0.0)	0	0	0	1 (0.0)
Limb injury	0	1 (0.0)	1 (0.0)	0	0	0	0
Meniscus lesion	0	1 (0.0)	1 (0.0)	0	0	0	0
Overdose	0	1 (0.0)	1 (0.0)	0	0	0	0
Patella fracture	0	1 (0.0)	1 (0.0)	0	0	0	0
Upper limb fracture	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Brain contusion	0	0	0	0	0	0	1 (0.0)
Cerebral hemorrhage traumatic	0	0	0	0	0	0	1 (0.0)
Delayed recovery from anesthesia	0	0	0	0	0	0	1 (0.0)
Femur fracture	0	0	0	0	0	0	1 (0.0)
Fibula fracture	0	0	0	0	0	0	1 (0.0)
Foot fracture	0	0	0	0	0	0	1 (0.0)
Hip fracture	0	0	0	0	0	0	2 (0.1)
Humerus fracture	0	0	0	1 (0.6)	0	1 (0.3)	0
Intentional overdose	0	0	0	0	0	0	1 (0.0)
Lower limb fracture	0	0	0	0	0	0	1 (0.0)
Multiple fractures	0	0	0	0	0	0	1 (0.0)
Procedural complication	0	0	0	0	0	0	1 (0.0)
Spinal fracture	0	0	0	0	0	0	1 (0.0)
Tendon rupture	0	0	0	0	0	0	1 (0.0)
Thoracic vertebral fracture	0	0	0	0	0	0	1 (0.0)
INVESTIGATIONS	0	1 (0.0)	1 (0.0)	1 (0.6)	0	1 (0.3)	1 (0.0)
International normalized ratio increased	0	1 (0.0)	1 (0.0)	0	0	0	0
Blood potassium increased	0	0	0	0	0	0	1 (0.0)
Heart rate decreased	0	0	0	1 (0.6)	0	1 (0.3)	0
METABOLISM AND NUTRITION DISORDERS	2 (0.5)	66 (2.5)	68 (2.3)	0	0	0	65 (3.0)
Hypoglycemia	2 (0.5)	47 (1.8)	49 (1.6)	0	0	0	49 (2.2)
Diabetic ketoacidosis	0	10 (0.4)	10 (0.3)	0	0	0	4 (0.2)
Hyperglycemia	0	4 (0.2)	4 (0.1)	0	0	0	2 (0.1)
Ketoacidosis	0	4 (0.2)	4 (0.1)	0	0	0	1 (0.0)
Dehydration	0	2 (0.1)	2 (0.1)	0	0	0	0
Diabetes mellitus inadequate control	0	2 (0.1)	2 (0.1)	0	0	0	6 (0.3)
Ketosis	0	1 (0.0)	1 (0.0)	0	0	0	0
Diabetic complication	0	0	0	0	0	0	1 (0.0)
Metabolic syndrome	0	0	0	0	0	0	1 (0.0)
Obesity	0	0	0	0	0	0	1 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	14 (0.5)	14 (0.5)	1 (0.6)	1 (0.9)	2 (0.7)	12 (0.5)
Osteoarthritis	0	4 (0.2)	4 (0.1)	0	0	0	2 (0.1)
Intervertebral disc degeneration	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Intervertebral disc protrusion	0	2 (0.1)	2 (0.1)	0	0	0	3 (0.1)
Rotator cuff syndrome	0	2 (0.1)	2 (0.1)	0	0	0	0
Back pain	0	1 (0.0)	1 (0.0)	1 (0.6)	0	1 (0.3)	2 (0.1)
Intervertebral disc disorder	0	1 (0.0)	1 (0.0)	0	0	0	0
Musculoskeletal chest pain	0	1 (0.0)	1 (0.0)	0	0	0	0
Musculoskeletal pain	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Rheumatoid arthritis	0	1 (0.0)	1 (0.0)	0	0	0	0
Spinal osteoarthritis	0	1 (0.0)	1 (0.0)	0	0	0	2 (0.1)
Tenosynovitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Arthritis	0	0	0	0	0	0	1 (0.0)
Osteochondrosis	0	0	0	0	0	0	1 (0.0)
Polyarthritis	0	0	0	0	1 (0.9)	1 (0.3)	0
NEOPLASMS BENIGN,	1 (0.3)	13 (0.5)	14 (0.5)	1 (0.6)	0	1 (0.3)	10 (0.5)

Clinical Review
 Lisa B. Yanoff, M.D.
 NDA Class 2 Resubmission/22,472
 Technosphere Insulin Inhalation Powder/Afrezza

MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)							
Breast cancer	0	3 (0.1)	3 (0.1)	0	0	0	1 (0.0)
Prostate cancer	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Basal cell carcinoma	0	1 (0.0)	1 (0.0)	0	0	0	0
Benign salivary gland neoplasm	0	1 (0.0)	1 (0.0)	0	0	0	0
Breast cancer stage iii	0	1 (0.0)	1 (0.0)	0	0	0	0
Gastrointestinal cancer metastatic	0	1 (0.0)	1 (0.0)	0	0	0	0
Ovarian epithelial cancer	0	1 (0.0)	1 (0.0)	0	0	0	0
Pituitary tumor benign	0	1 (0.0)	1 (0.0)	0	0	0	0
Prostate cancer metastatic	0	1 (0.0)	1 (0.0)	0	0	0	0
Rectal cancer	1 (0.3)	0	1 (0.0)	0	0	0	1 (0.0)
Uterine leiomyoma	0	1 (0.0)	1 (0.0)	0	0	0	3 (0.1)
Adrenal adenoma	0	0	0	0	0	0	1 (0.0)
Benign pancreatic neoplasm	0	0	0	0	0	0	1 (0.0)
Cervix carcinoma	0	0	0	0	0	0	1 (0.0)
Colon cancer	0	0	0	0	0	0	1 (0.0)
Pancreatic carcinoma	0	0	0	0	0	0	1 (0.0)
Squamous cell carcinoma	0	0	0	1 (0.6)	0	1 (0.3)	0
NERVOUS SYSTEM DISORDERS	2 (0.5)	34 (1.3)	36 (1.2)	1 (0.6)	0	1 (0.3)	29 (1.3)
Loss of consciousness	0	13 (0.5)	13 (0.4)	0	0	0	9 (0.4)
Hypoglycemic unconsciousness	1 (0.3)	6 (0.2)	7 (0.2)	0	0	0	4 (0.2)
Hypoglycemic seizure	1 (0.3)	5 (0.2)	6 (0.2)	0	0	0	6 (0.3)
Transient ischemic attack	0	2 (0.1)	2 (0.1)	0	0	0	0
Ataxia	0	1 (0.0)	1 (0.0)	0	0	0	0
Carotid artery stenosis	0	1 (0.0)	1 (0.0)	0	0	0	0
Convulsion	0	1 (0.0)	1 (0.0)	0	0	0	0
Dizziness	0	1 (0.0)	1 (0.0)	0	0	0	0
Encephalopathy	0	1 (0.0)	1 (0.0)	0	0	0	0
Epilepsy	0	1 (0.0)	1 (0.0)	0	0	0	0
Third nerve paralysis	0	1 (0.0)	1 (0.0)	0	0	0	0
Multiple sclerosis	0	1 (0.0)	1 (0.0)	0	0	0	0
Pre-syncope	0	1 (0.0)	1 (0.0)	0	0	0	0
Cerebrovascular accident	0	0	0	0	0	0	5 (0.2)
Hypoglycemic coma	0	0	0	0	0	0	2 (0.1)
Ischemic stroke	0	0	0	1 (0.6)	0	1 (0.3)	1 (0.0)
Neuritis	0	0	0	0	0	0	1 (0.0)
Radiculitis lumbosacral	0	0	0	0	0	0	1 (0.0)
Sciatica	0	0	0	0	0	0	1 (0.0)
Syncope	0	0	0	0	0	0	1 (0.0)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	0	0	0	0	1 (0.0)
Pregnancy	0	0	0	0	0	0	1 (0.0)
PSYCHIATRIC DISORDERS	0	2 (0.1)	2 (0.1)	0	0	0	3 (0.1)
Depression	0	1 (0.0)	1 (0.0)	0	0	0	0
Psychotic disorder	0	1 (0.0)	1 (0.0)	0	0	0	0
Mental status changes	0	0	0	0	0	0	1 (0.0)
Suicide attempt	0	0	0	0	0	0	2 (0.1)
RENAL AND URINARY DISORDERS	0	4 (0.2)	4 (0.1)	0	0	0	6 (0.3)
Hydronephrosis	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Renal failure acute	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Calculus bladder	0	1 (0.0)	1 (0.0)	0	0	0	0
Nephrolithiasis	0	1 (0.0)	1 (0.0)	0	0	0	3 (0.1)
Calculus ureteric	0	0	0	0	0	0	1 (0.0)
Renal colic	0	0	0	0	0	0	1 (0.0)

Clinical Review
 Lisa B. Yanoff, M.D.
 NDA Class 2 Resubmission/22,472
 Technosphere Insulin Inhalation Powder/Afrezza

Renal failure	0	0	0	0	0	0	1 (0.0)
Urethral stenosis	0	0	0	0	0	0	1 (0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	4 (0.2)	4 (0.1)	0	0	0	2 (0.1)
Adenomyosis	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Benign prostatic hyperplasia	0	1 (0.0)	1 (0.0)	0	0	0	0
Cervical polyp	0	1 (0.0)	1 (0.0)	0	0	0	0
Prostatomegaly	0	1 (0.0)	1 (0.0)	0	0	0	0
Uterine prolapse	0	0	0	0	0	0	1 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.3)	7 (0.3)	8 (0.3)	0	0	0	2 (0.1)
Asthma	0	1 (0.0)	1 (0.0)	0	0	0	0
Atelectasis	0	1 (0.0)	1 (0.0)	0	0	0	0
Bronchial hyperreactivity	1 (0.3)	0	1 (0.0)	0	0	0	0
Bronchial obstruction	0	1 (0.0)	1 (0.0)	0	0	0	0
Cough	0	1 (0.0)	1 (0.0)	0	0	0	0
Dyspnea	0	1 (0.0)	1 (0.0)	0	0	0	0
Hemoptysis	0	1 (0.0)	1 (0.0)	0	0	0	0
Orthopnea	0	1 (0.0)	1 (0.0)	0	0	0	0
Vocal cord polyp	0	1 (0.0)	1 (0.0)	0	0	0	0
Hydrothorax	0	0	0	0	0	0	1 (0.0)
Pulmonary edema	0	0	0	0	0	0	1 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	2 (0.1)	2 (0.1)	2 (1.1)	0	2 (0.7)	2 (0.1)
Angioedema	0	1 (0.0)	1 (0.0)	1 (0.6)	0	1 (0.3)	0
Hyperhidrosis	0	1 (0.0)	1 (0.0)	1 (0.6)	0	1 (0.3)	0
Skin ulcer	0	0	0	0	0	0	1 (0.0)
Urticaria	0	0	0	0	0	0	1 (0.0)
VASCULAR DISORDERS	0	6 (0.2)	6 (0.2)	0	0	0	4 (0.2)
Aortic stenosis	0	2 (0.1)	2 (0.1)	0	0	0	0
Deep vein thrombosis	0	1 (0.0)	1 (0.0)	0	0	0	0
Hypertension	0	1 (0.0)	1 (0.0)	0	0	0	0
Hypertensive crisis	0	1 (0.0)	1 (0.0)	0	0	0	0
Hypotension	0	1 (0.0)	1 (0.0)	0	0	0	0
Essential hypertension	0	0	0	0	0	0	1 (0.0)
Extremity necrosis	0	0	0	0	0	0	1 (0.0)
Peripheral arterial occlusive disease	0	0	0	0	0	0	1 (0.0)
Thrombosis	0	0	0	0	0	0	1 (0.0)

Source: Table G.3.9.6.1.1, ISS

Reviewer's comment: Results of analysis of incidence rates of SAEs are consistent with the results from the original NDA review.

A listing of patients with serious adverse events (other than hypoglycemia-related SAEs which are discussed separately) occurring after randomization (n=9 for TI and n=13 for comparator) newly reported for the pooled Phase 2/3 Safety population (all from either study 171 or study 175) in the current Resubmission is shown in Table 30. Again, there is no apparent pattern of SAEs, as they cover a range of system organ classes/preferred terms. Many of the events in the T2DM trial were cardiovascular events which is not unexpected for this population.

Table 30 – Listing of Patients with Non-hypoglycemic Serious Adverse Events (SAEs) Occurring after Randomization in the Pooled Phase 2/3 Population since the 2010 Resubmission cutoff - T1DM and T2DM combined

Trial/inhaler type for trial 171 only	Sex/ Age	SAE PT	Duration of Randomized Treatment (Days) before event	Severity Characteristic of SAE	Outcome
TI					
171/MedTone	F/52	Rectal prolapse	98	Hospitalization (surgery)	Resolved
^171/Gen2	F/71	Cytomegalovirus with exertional dyspnea	23	Hospitalization	Discontinued study medication
^171/Gen2	M/58	Bronchial Hyperreactivity	20	Hospitalization	Discontinued study medication
171/MedTone	F/59	Cervical polyp	72	Hospitalization (surgery)	Resolved
^171/Med-Tone	F/62	Chest tightness	Post-treatment	Hospitalization	Resolved
175	M/66	Myocardial infarction	94	Hospitalization	Discontinued study medication
175	F/67	Rectal cancer	43	Hospitalization	Discontinued
175	M/64	Myocardial infarction	93	Hospitalization	Discontinued
175	M/74	Urinary tract infection	Post-treatment	Hospitalization	Resolved
Comparator					
171	F/52	Spinal osteoarthritis	48	Hospitalization (surgery)	Resolved
171	M/62	Mental status changes Appendicitis	30	Hospitalization	Resolved
175	M/46	Ischemic stroke	60	Hospitalization	Discontinued
175	F/65	Angioedema (secondary to ACE inhibitor)	157	Hospitalization	Resolved
175	M/56	Angina pectoris Stenosis of the right internal carotid artery	Post-treatment	Hospitalization	Resolved
175	M/52	Viral pericarditis	Post-treatment	Hospitalization	Resolved
175	F/68	Skull malformation *	65	Hospitalization	Resolved
175	F/64	Renal colic	23	Hospitalization	Resolved
^175	M/49	Squamous cell carcinoma	31	Hospitalization (surgery)	Discontinued
175	F/68	Back pain	126	Hospitalization	Resolved
175	F/53	Heart rate decreased Cyanosis Hyperhidrosis	30	Prolonged hospitalization	Resolved
175	M/80	Coronary artery disease	145	Hospitalization	Resolved
175	M/53	Humerus fracture	113	Hospitalization	Resolved
^Events for which narratives are provided below table					
*verbatim from investigator: Large dihcence of the tegmen mastoideum secondary to a congenital abnormality of the tegmen plate causing an acute CSF leak in left ear)					
Source: ISS					

Selected narratives for TI-treated patients experiencing SAEs since the 2010 Resubmission

Narratives are listed below by Study#/Site#/Patient#. For selected serious adverse event narratives from previous review cycles see Appendix 5.

171/141/2030 – Cytomegalovirus with exertional dyspnea 71 yo woman randomized to Gen2 arm; 23 days after randomization patient experienced an intermittent, mild, dry cough within 10 minutes of dosing. 20 days later, the subject experienced a separate intermittent, moderate dry cough that initially occurred mostly in the mornings. The cough became progressively worse and lasted all day with added dyspnea on exertion starting 23 days later. A chest x-ray showed “bronchial cuffing particularly in the mid zone of the left lung field but no defined infiltrate; no evidence of acute cardiopulmonary disease”. Liver enzymes were elevated. A chest x-ray done 12 days later was normal. PFTs were unchanged from baseline.

Reviewer’s comment: There is not enough evidence in this case narrative to allow for clear determination of causality.

171/210/1913 – Bronchial hyperreactivity 58 yo man randomized to Gen2 arm. The subject received TI, 10 – 20 U at mealtimes plus 10 U supplemental doses as needed, for approximately (b) (6) weeks when he experienced cough, chest pain and difficulty breathing and was hospitalized with the diagnosis of reactive airway disease. On hospital admission, the subject had a respiratory rate of 16 breaths per minute and oxygen saturation of 97%. The subject’s chest x-ray showed a tall hyperinflated lung with a slender heart, and a flattened hemidiaphragm consistent with the pattern of hyperinflation. The study medication was discontinued and the subject was treated with oral Albuterol 2.5 mg per 3 mL four times daily and oral Tussionex 8-10 mg per 5 mL every 12 hours for 10 days. The subject was discharged from the hospital in stable condition after 3 days. Levosalbutamol tartrate (Xopenex HFA) as needed for shortness of breath was started 10 days later. The subject was withdrawn from the study due to the reactive airway disease, which was considered resolved with sequelae. FEV1 was 3.39 L (85% predicted) at the screening visit and 3.45 L (87% predicted) at the baseline. FVC at these visits were 4.56 L (87% predicted) and 4.56 L (87% respectively. FEV1 and FVC testing was not conducted at the early termination visit.

Reviewer’s comment: It is unclear from the narrative whether the SAE experienced by this patient could have been foreseen by the investigator. The patient’s smoking history is not reported.

171/111/5353 – Chest tightness 64 yo woman experienced chest tightness described as “discomfort and pressure” while shoveling snow, in post-treatment phase of study 171. The patient had a history of dyslipidemia, hypertension, and a previous event of chest pain in 2004. The patient was admitted to a hospital for overnight observation and work-up. Work-up apparently focused primarily on a cardiac origin (rule out MI, stress test, etc.) which was all negative. A chest x-ray is not reported.

Reviewer’s comment: Chest tightness in a diabetic patient on exertion is suspicious for cardiac ischemia. A pulmonary focused workup was not described. A chest x-ray to rule

out mass was either not performed, or the results not reported. However, based on the narrative provided, a causal relationship between the event and TI is unlikely.

Placebo-treated patient

175/876/3953 – Squamous cell carcinoma 49 yo man in Ukraine randomized to Technosphere placebo in study 175 presented to the study site with discomfort in the oral cavity 31 days after randomization. Extensive workup revealed low-grade differentiated nonkeratinous squamous cell carcinoma of maxillary left alveolar bone. Papillary thyroid cancer was also found during the surgical treatment of the squamous cell carcinoma.

Reviewer’s comment: The short latency and the fact that the patient lives in an area under radiation surveillance following the Chernobyl disaster make a causal relationship to TI placebo powder unlikely.

Although the overall power to detect differences in TI vs. placebo in the incidence of SAEs in study 175 alone is limited by small numbers, examination of the data from this trial alone allows a comparison of TI vs. placebo. Table 31 shows that there were fewer SAEs among TI-treated patients than among placebo-treated patients.

Table 31 – SAEs During the Randomized Treatment Phase of Study 175

MedDRA Preferred Term	Subject, n(%)	
	TI Gen2	Placebo
All	5 (2.8)	9 (5.1)
Myocardial Infarction	2 (1.1)	0
Hypoglycemia	1 (0.6)	0
Rectal Cancer	1 (0.6)	0
Urinary Tract Infection	1 (0.6)	0
Ischemic Stroke	0	1 (0.6)
Angina Pectoris	0	1 (0.6)
Angioedema	0	1 (0.6)
Back Pain	0	1 (0.6)
Coronary Artery Disease	0	1 (0.6)
Cyanosis	0	1 (0.6)
Heart Rate Decreased	0	1 (0.6)
Humerus Fracture	0	1 (0.6)
Hyperhidrosis	0	1 (0.6)
Skull Malformation	0	1 (0.6)
Squamous cell Carcinoma	0	1 (0.6)

Source: Table 37, study 175 CSR

Reviewer’s comment: Overall, my conclusions from examination of these SAE data is that overall, for non-hypoglycemic serious adverse events, there does not appear to be a new safety signal for TI, either compared to placebo or active comparator.

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 population: the pooled phase 2/3 database for T1DM and T2DM combined showed that 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). Cough was the only adverse event leading to discontinuation that occurred in >1% of TI-treated patients in the controlled phase 2/3 database. Most of the other reported adverse events leading to discontinuation occurred in isolated TI- or comparator-treated patients. I concluded that the higher rate of withdrawals for non-pulmonary adverse events was possibly due, in part, 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.

T1DM

In the current Resubmission, dropouts due to AEs were more frequent among T1DM TI-treated patients (9.2% for Gen2, 6.1% for MedTone and 0.5% for comparator) (Table 32). Again, the dropouts appear to be driven predominantly by discontinuations due to adverse events in the Respiratory, Thoracic, and Mediastinal Disorders System-Organ Class, (4.4% with TI vs. 0% with comparator) primarily cough. The rate of dropout was higher among Gen2 treated patients than MedTone treated patients; this finding appears to be driven by a higher rate of withdrawal for cough and dyspnea. AEs leading to dropout that occurred in more than one subject in the TI Total group were cough (3.3%); dyspnea (0.6%); hyperglycemia diabetes mellitus inadequate control, hyperglycemia, bronchial obstruction, and headache (each in 0.3%).

Table 63 in the Sponsor's ISS tabulates the incidence of AEs leading to dropout among the T1DM population for the 2010 Resubmission, the current 2013 Resubmission, and the difference totals.

Reviewer's comment: I agree with the Sponsor's conclusion that comparison of AEs leading to discontinuation among subjects with T1DM in the 2010 Resubmission with those in the 2013 Resubmission showed no important differences. It is noteworthy that the rate of dropout was higher among Gen2 treated patients than MedTone treated patients. I discuss this finding in section 7.4.5 below in the context of a head-to-head comparison of safety between Gen2 and MedTone in trial 171.

Table 32 – Adverse Events Leading to Dropout –T1DM – 2013 Resubmission

Clinical Review
 Lisa B. Yanoff, M.D.
 NDA Class 2 Resubmission/22,472
 Technosphere Insulin Inhalation Powder/Afrezza

System Organ Class Preferred Term	TI			Comparator [N=835] [SYE=778] n (%)
	Gen2 [N=174] [SYE=67] n (%)	MedTone [N=852] [SYE=629] n (%)	Total [N=1026] [SYE=697] n (%)	
ANY TREATMENT-EMERGENT ADVERSE EVENT	16 (9.2)	52 (6.1)	68 (6.6)	4 (0.5)
CARDIAC DISORDERS	0	3 (0.4)	3 (0.3)	0
Angina pectoris	0	1 (0.1)	1 (0.1)	0
Cardiac failure congestive	0	1 (0.1)	1 (0.1)	0
Palpitations	0	1 (0.1)	1 (0.1)	0
EYE DISORDERS	1 (0.6)	1 (0.1)	2 (0.2)	0
Eye pruritus	1 (0.6)	0	1 (0.1)	0
Vision blurred	0	1 (0.1)	1 (0.1)	0
GASTROINTESTINAL DISORDERS	0	3 (0.4)	3 (0.3)	0
Abdominal discomfort	0	1 (0.1)	1 (0.1)	0
Breath odour	0	1 (0.1)	1 (0.1)	0
Dry mouth	0	1 (0.1)	1 (0.1)	0
Dyspepsia	0	1 (0.1)	1 (0.1)	0
Nausea	0	1 (0.1)	1 (0.1)	0
Vomiting	0	1 (0.1)	1 (0.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	4 (0.5)	4 (0.4)	0
Chest discomfort	0	1 (0.1)	1 (0.1)	0
Chest pain	0	1 (0.1)	1 (0.1)	0
Fatigue	0	1 (0.1)	1 (0.1)	0
Sensation of foreign body	0	1 (0.1)	1 (0.1)	0
IMMUNE SYSTEM DISORDERS	0	1 (0.1)	1 (0.1)	0
Drug hypersensitivity	0	1 (0.1)	1 (0.1)	0
INFECTIONS AND INFESTATIONS	0	3 (0.4)	3 (0.3)	1 (0.1)
Bronchitis	0	1 (0.1)	1 (0.1)	0
Sinusitis	0	1 (0.1)	1 (0.1)	0
Upper respiratory tract infection	0	1 (0.1)	1 (0.1)	0
Pulmonary tuberculosis	0	0	0	1 (0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	1 (0.1)
Head injury	0	0	0	1 (0.1)
Road traffic accident	0	0	0	1 (0.1)
INVESTIGATIONS	0	3 (0.4)	3 (0.3)	0
Pulmonary function test decreased	0	1 (0.1)	1 (0.1)	0
Weight decreased	0	1 (0.1)	1 (0.1)	0
Weight increased	0	1 (0.1)	1 (0.1)	0
METABOLISM AND NUTRITION DISORDERS	1 (0.6)	7 (0.8)	8 (0.8)	1 (0.1)
Hyperglycaemia	0	3 (0.4)	3 (0.3)	0
Hypoglycaemia	1 (0.6)	2 (0.2)	3 (0.3)	0
Diabetes mellitus inadequate control	0	2 (0.2)	2 (0.2)	0
Diabetic ketoacidosis	0	1 (0.1)	1 (0.1)	0
Ketosis	0	1 (0.1)	1 (0.1)	0
Metabolic syndrome	0	0	0	1 (0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (0.1)	1 (0.1)	0
Musculoskeletal chest pain	0	1 (0.1)	1 (0.1)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (0.1)	1 (0.1)	0
Breast cancer	0	1 (0.1)	1 (0.1)	0
NERVOUS SYSTEM DISORDERS	1 (0.6)	4 (0.5)	5 (0.5)	0

Headache	0	2 (0.2)	2 (0.2)	0
Dizziness	0	1 (0.1)	1 (0.1)	0
Hypoglycaemic seizure	0	1 (0.1)	1 (0.1)	0
Lethargy	1 (0.6)	0	1 (0.1)	0
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	0	1 (0.1)
Pregnancy	0	0	0	1 (0.1)
PSYCHIATRIC DISORDERS	0	1 (0.1)	1 (0.1)	0
Depression	0	1 (0.1)	1 (0.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	14 (8.0)	31 (3.6)	45 (4.4)	0
Cough	10 (5.7)	24 (2.8)	34 (3.3)	0
Dyspnoea	4 (2.3)	2 (0.2)	6 (0.6)	0
Bronchial obstruction	0	2 (0.2)	2 (0.2)	0
Asthma	0	1 (0.1)	1 (0.1)	0
Bronchial hyperreactivity	1 (0.6)	0	1 (0.1)	0
Dyspnoea exertional	1 (0.6)	0	1 (0.1)	0
Haemoptysis	0	1 (0.1)	1 (0.1)	0
Productive cough	0	1 (0.1)	1 (0.1)	0
Respiratory disorder	0	1 (0.1)	1 (0.1)	0
Respiratory tract congestion	0	1 (0.1)	1 (0.1)	0
Upper respiratory tract congestion	0	1 (0.1)	1 (0.1)	0
VASCULAR DISORDERS	0	2 (0.2)	2 (0.2)	0
Aortic calcification	0	1 (0.1)	1 (0.1)	0
Circulatory collapse	0	1 (0.1)	1 (0.1)	0

Source: Table 62, ISS

T2DM

Among the T2DM population, dropouts due to AEs were also more frequent among TI-treated patients (3.6% for Gen2, 7.9% for MedTone [7.5% Total TI] and 1.5 % for comparator) (Table 33). Total TP placebo had an incidence of dropout of 3.4%. The most common AEs that led to discontinuation in the TI were: cough in 2.5%, hyperglycemia in 0.5%, and dyspnea in 0.5%. This pattern appears similar to the T1DM population. One notable difference, however, is that the incidence of dropout is higher for MedTone-treated patients compared with Gen2-treated patients, in contrast to the T1DM population.

Table 63 in the Sponsor's ISS tabulates the incidence of AEs leading to dropout among the T2DM population for the 2010 Resubmission, the current 2013 Resubmission, and the difference totals.

Again, although the overall power to detect differences in TI vs. placebo in the incidence of dropout due to AEs in study 175 alone is limited by small numbers, examination of the data from this trial alone allows a comparison of TI vs. placebo and shows that the incidence of AEs leading to dropout was similar: 4.0% in the TI group, and 5.1% in the TP group.

Table 33 - Adverse Events Leading to Dropout –T2DM – 2013 Resubmission

Clinical Review
 Lisa B. Yanoff, M.D.
 NDA Class 2 Resubmission/22,472
 Technosphere Insulin Inhalation Powder/Afrezza

Preferred Term	TI			TP			Comparator [N=1363] [SYE=1374] n (%)
	Gen2 [N=196] [SYE=82] n (%)	MedTone [N=1795] [SYE=1274] n (%)	Total [N=1991] [SYE=1356] n (%)	Gen2 [N=176] [SYE=73] n (%)	MedTone [N=114] [SYE=25] n (%)	Total [N=290] [SYE=98] n (%)	
ANY TREATMENT-EMERGENT ADVERSE EVENT	7 (3.6)	142 (7.9)	149 (7.5)	9 (5.1)	1 (0.9)	10 (3.4)	20 (1.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (0.1)	1 (0.1)	0	0	0	2 (0.1)
Lymphadenopathy	0	1 (0.1)	1 (0.1)	0	0	0	0
Anaemia	0	0	0	0	0	0	1 (0.1)
Thrombocytopenia	0	0	0	0	0	0	1 (0.1)
CARDIAC DISORDERS	2 (1.0)	13 (0.7)	15 (0.8)	0	0	0	4 (0.3)
Myocardial infarction	2 (1.0)	1 (0.1)	3 (0.2)	0	0	0	1 (0.1)
Myocardial ischaemia	0	3 (0.2)	3 (0.2)	0	0	0	0
Acute myocardial infarction	0	2 (0.1)	2 (0.1)	0	0	0	0
Acute coronary syndrome	0	1 (0.1)	1 (0.1)	0	0	0	0
Angina pectoris	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.1)
Arteriosclerosis coronary artery	0	1 (0.1)	1 (0.1)	0	0	0	0
Cardiac failure	0	1 (0.1)	1 (0.1)	0	0	0	0
Cardiac failure acute	0	1 (0.1)	1 (0.1)	0	0	0	0
Cardiac failure chronic	0	1 (0.1)	1 (0.1)	0	0	0	0
Coronary artery disease	0	1 (0.1)	1 (0.1)	0	0	0	0
Hypertensive cardiomyopathy	0	1 (0.1)	1 (0.1)	0	0	0	0
Palpitations	0	1 (0.1)	1 (0.1)	0	0	0	0
Tachycardia	0	1 (0.1)	1 (0.1)	0	0	0	0
Atrial fibrillation	0	0	0	0	0	0	1 (0.1)
Cardiac arrest	0	0	0	0	0	0	1 (0.1)
Coronary artery occlusion	0	0	0	0	0	0	1 (0.1)
EYE DISORDERS	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.1)
Retinal disorder	0	1 (0.1)	1 (0.1)	0	0	0	0
Retinopathy haemorrhagic	0	0	0	0	0	0	1 (0.1)
GASTROINTESTINAL DISORDERS	0	5 (0.3)	5 (0.3)	1 (0.6)	0	1 (0.3)	0
Constipation	0	1 (0.1)	1 (0.1)	0	0	0	0
Duodenal ulcer haemorrhage	0	1 (0.1)	1 (0.1)	0	0	0	0
Nausea	0	1 (0.1)	1 (0.1)	0	0	0	0

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

Pancreatitis	0	1 (0.1)	1 (0.1)	0	0	0	0
Toothache	0	1 (0.1)	1 (0.1)	0	0	0	0
Dry mouth	0	0	0	1 (0.6)	0	1 (0.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	11 (0.6)	11 (0.6)	1 (0.6)	0	1 (0.3)	0
Chest discomfort	0	4 (0.2)	4 (0.2)	1 (0.6)	0	1 (0.3)	0
Asthenia	0	2 (0.1)	2 (0.1)	0	0	0	0
Fatigue	0	2 (0.1)	2 (0.1)	0	0	0	0
Chest pain	0	1 (0.1)	1 (0.1)	0	0	0	0
Performance status decreased	0	1 (0.1)	1 (0.1)	0	0	0	0
Pyrexia	0	1 (0.1)	1 (0.1)	0	0	0	0
IMMUNE SYSTEM DISORDERS	0	3 (0.2)	3 (0.2)	0	1 (0.9)	1 (0.3)	0
Hypersensitivity	0	2 (0.1)	2 (0.1)	0	0	0	0
Drug hypersensitivity	0	1 (0.1)	1 (0.1)	0	1 (0.9)	1 (0.3)	0
INFECTIONS AND INFESTATIONS	0	14 (0.8)	14 (0.7)	0	0	0	1 (0.1)
Bronchitis	0	5 (0.3)	5 (0.3)	0	0	0	0
Upper respiratory tract infection	0	3 (0.2)	3 (0.2)	0	0	0	0
Gangrene	0	2 (0.1)	2 (0.1)	0	0	0	0
Pneumonia	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.1)
Diabetic foot infection	0	1 (0.1)	1 (0.1)	0	0	0	0
Diabetic gangrene	0	1 (0.1)	1 (0.1)	0	0	0	0
Endocarditis	0	1 (0.1)	1 (0.1)	0	0	0	0
Localised infection	0	1 (0.1)	1 (0.1)	0	0	0	0
Pharyngitis	0	1 (0.1)	1 (0.1)	0	0	0	0
Pulmonary tuberculosis	0	1 (0.1)	1 (0.1)	0	0	0	0
Staphylococcal sepsis	0	1 (0.1)	1 (0.1)	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (0.1)	1 (0.1)	0	0	0	3 (0.2)
Hand fracture	0	1 (0.1)	1 (0.1)	0	0	0	0
Fall	0	0	0	0	0	0	1 (0.1)
Hip fracture	0	0	0	0	0	0	1 (0.1)
Rib fracture	0	0	0	0	0	0	1 (0.1)
Road traffic accident	0	0	0	0	0	0	1 (0.1)
INVESTIGATIONS	0	5 (0.3)	5 (0.3)	0	0	0	0
Alanine aminotransferase increased	0	1 (0.1)	1 (0.1)	0	0	0	0
Blood creatine phosphokinase increased	0	1 (0.1)	1 (0.1)	0	0	0	0
Carcinoembryonic antigen increased	0	1 (0.1)	1 (0.1)	0	0	0	0
Gamma-glutamyltransferase increased	0	1 (0.1)	1 (0.1)	0	0	0	0
Pulmonary function test abnormal	0	1 (0.1)	1 (0.1)	0	0	0	0
Pulmonary function test decreased	0	1 (0.1)	1 (0.1)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	0	14 (0.8)	14 (0.7)	0	0	0	6 (0.4)
Hyperglycaemia	0	10 (0.6)	10 (0.5)	0	0	0	1 (0.1)
Diabetes mellitus inadequate control	0	2 (0.1)	2 (0.1)	0	0	0	0
Dehydration	0	1 (0.1)	1 (0.1)	0	0	0	0
Diabetes mellitus	0	1 (0.1)	1 (0.1)	0	0	0	0

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

Ketoacidosis	0	1 (0.1)	1 (0.1)	0	0	0	0
Hypoglycaemia	0	0	0	0	0	0	4 (0.3)
Obesity	0	0	0	0	0	0	1 (0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.1)
Intervertebral disc protrusion	0	1 (0.1)	1 (0.1)	0	0	0	0
Rheumatoid arthritis	0	1 (0.1)	1 (0.1)	0	0	0	0
Musculoskeletal pain	0	0	0	0	0	0	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.5)	4 (0.2)	5 (0.3)	1 (0.6)	0	1 (0.3)	1 (0.1)
Bile duct cancer	0	1 (0.1)	1 (0.1)	0	0	0	0
Breast cancer stage iii	0	1 (0.1)	1 (0.1)	0	0	0	0
Ovarian epithelial cancer	0	1 (0.1)	1 (0.1)	0	0	0	0
Pituitary tumour benign	0	1 (0.1)	1 (0.1)	0	0	0	0
Rectal cancer	1 (0.5)	0	1 (0.1)	0	0	0	0
Pancreatic carcinoma	0	0	0	0	0	0	1 (0.1)
Squamous cell carcinoma	0	0	0	1 (0.6)	0	1 (0.3)	0
NERVOUS SYSTEM DISORDERS	0	14 (0.8)	14 (0.7)	1 (0.6)	0	1 (0.3)	3 (0.2)
Headache	0	4 (0.2)	4 (0.2)	0	0	0	0
Cerebral arteriosclerosis	0	1 (0.1)	1 (0.1)	0	0	0	0
Encephalitis	0	1 (0.1)	1 (0.1)	0	0	0	0
Haemorrhagic stroke	0	1 (0.1)	1 (0.1)	0	0	0	0
Hypoaesthesia	0	1 (0.1)	1 (0.1)	0	0	0	0
Hypoglycaemic seizure	0	1 (0.1)	1 (0.1)	0	0	0	0
Liird nerve paralysis	0	1 (0.1)	1 (0.1)	0	0	0	0
Ischaemic stroke	0	1 (0.1)	1 (0.1)	1 (0.6)	0	1 (0.3)	0
Loss of consciousness	0	1 (0.1)	1 (0.1)	0	0	0	1 (0.1)
Multiple sclerosis	0	1 (0.1)	1 (0.1)	0	0	0	0
Psychomotor hyperactivity	0	1 (0.1)	1 (0.1)	0	0	0	0
Syncope	0	1 (0.1)	1 (0.1)	0	0	0	0
Diabetic neuropathy	0	0	0	0	0	0	1 (0.1)
VIIth nerve paralysis	0	0	0	0	0	0	1 (0.1)
PSYCHIATRIC DISORDERS	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.1)
Depression	0	1 (0.1)	1 (0.1)	0	0	0	0
Psychotic disorder	0	1 (0.1)	1 (0.1)	0	0	0	0
Alcohol abuse	0	0	0	0	0	0	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (2.0)	75 (4.2)	79 (4.0)	7 (4.0)	0	7 (2.4)	1 (0.1)
Cough	2 (1.0)	47 (2.6)	49 (2.5)	6 (3.4)	0	6 (2.1)	0
Dyspnoea	1 (0.5)	8 (0.4)	9 (0.5)	0	0	0	0
Throat irritation	0	4 (0.2)	4 (0.2)	0	0	0	0
Asthma	0	3 (0.2)	3 (0.2)	0	0	0	0
Bronchial hyperreactivity	0	2 (0.1)	2 (0.1)	0	0	0	0
Bronchospasm	0	2 (0.1)	2 (0.1)	0	0	0	0
Oropharyngeal pain	1 (0.5)	1 (0.1)	2 (0.1)	0	0	0	0
Wheezing	0	2 (0.1)	2 (0.1)	1 (0.6)	0	1 (0.3)	0
Allergic pharyngitis	0	1 (0.1)	1 (0.1)	0	0	0	0
Asphyxia	0	1 (0.1)	1 (0.1)	0	0	0	0
Bronchitis chronic	0	1 (0.1)	1 (0.1)	0	0	0	0
Increased upper airway secretion	0	1 (0.1)	1 (0.1)	0	0	0	0
Laryngospasm	0	1 (0.1)	1 (0.1)	0	0	0	0

Ketoacidosis	0	1 (0.1)	1 (0.1)	0	0	0	0
Hypoglycaemia	0	0	0	0	0	0	4 (0.3)
Obesity	0	0	0	0	0	0	1 (0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.1)
Intervertebral disc protrusion	0	1 (0.1)	1 (0.1)	0	0	0	0
Rheumatoid arthritis	0	1 (0.1)	1 (0.1)	0	0	0	0
Musculoskeletal pain	0	0	0	0	0	0	1 (0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.5)	4 (0.2)	5 (0.3)	1 (0.6)	0	1 (0.3)	1 (0.1)
Bile duct cancer	0	1 (0.1)	1 (0.1)	0	0	0	0
Breast cancer stage iii	0	1 (0.1)	1 (0.1)	0	0	0	0
Ovarian epithelial cancer	0	1 (0.1)	1 (0.1)	0	0	0	0
Pituitary tumour benign	0	1 (0.1)	1 (0.1)	0	0	0	0
Rectal cancer	1 (0.5)	0	1 (0.1)	0	0	0	0
Pancreatic carcinoma	0	0	0	0	0	0	1 (0.1)
Squamous cell carcinoma	0	0	0	1 (0.6)	0	1 (0.3)	0
NERVOUS SYSTEM DISORDERS	0	14 (0.8)	14 (0.7)	1 (0.6)	0	1 (0.3)	3 (0.2)
Headache	0	4 (0.2)	4 (0.2)	0	0	0	0

Source: Table 64, ISS

T1DM and T2DM populations combined

Overall, for the pooled phase 2/3 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 which is similar to the results for the pooled phase 2/3 data from the original NDA review.

When combining the T1DM and T2DM populations the incidence of dropout due to AEs is similar between MedTone-treated patients and Gen2-treated patients, 7.3% and 6.2% respectively.

Reviewer's comment: Observations regarding these dropout/discontinuation data include:

- **There appears to be no meaningful change in the incidence of discontinuations in the current Resubmission with respect to previous submissions**
- **The rate of dropout due to adverse events is notably higher in Afrezza TI treated study arms than in the comparator group.**
 - **The differential dropout rate appears to be largely due to a higher rate of dropouts due to adverse events related to cough and other pulmonary adverse events, among Afrezza TI-treated patients.**
 - **Preferred terms related to lack of efficacy were not uncommon reasons for dropout in Afrezza TI groups**
- **When comparing Gen2 and MedTone devices, there was a higher rate of discontinuation with the Gen2 device among T1DM patients, with the converse among T2DM treated patients.**

- **Greater weight should be placed on the larger, combined population which showed no important difference in the incidence of discontinuations due to AEs between the devices.**

Selected narratives for patients experiencing AEs leading to dropout since the 2010 Resubmission

Narratives are listed by Study#/Site#/Patient#

171/378/1653 – Bronchoobstruction – 53 yo man in study 171 randomized to the MedTone inhaler experienced ‘bronchoobstruction’ 34 days after randomization. This event was not described but was reportedly treated with salbutamol. PFTs appeared to show a decline in lung function. “There was a concomitant mild reduction in lung function as indicated by lung function tests: FEV1 at baseline was 2.88 L (80% predicted), at an unscheduled visit (after the investigator noted ‘abnormal breath sounds’ in the patient) was 2.61 L (73% predicted), and at the early termination visit was 2.76 L (77% predicted). FVC for these visits was 3.75 L (81% predicted), 3.53 L (76% predicted), and 3.59 L (77% predicted), respectively.

Reviewer’s comment: The narrative gives very limited information, but it appears that the patient had possibly bronchospasm which led to study discontinuation.

171/507/1390 – Drug hypersensitivity (Verbatim term- drug allergy [swollen lips]) -36 yo female randomized to the MedTone arm in study 171, 3 days after starting TI experienced an event of ‘drug hypersensitivity’. The details are not described. The patient was mistakenly treated for herpes zoster with acyclovir for one day and then treatment was changed to cetirizine (antihistamine). Pulmonary functions tests remained stable: FEV1 at baseline was 3.25 L (99% predicted) and at the early termination visit was 3.15 L (96% predicted). FVC for these two visits were 3.79 L (95% predicted) and 3.77 L (94% predicted), respectively.

Reviewer’s comment: The narrative gives very limited information, but the event is likely a drug allergy and was coded properly.

175/505/3376 – Dyspnea – 57 yo man experienced cough 27 days after starting TI. The cough was described as dry, intermittent, and occurring within 10 minutes of dosing. Three days later the subject experienced dyspnea which led to study discontinuation. The quality and character of the dyspnea was not described. FEV1 was 3.60 L (88% predicted) at the baseline visit, and 3.69 L (90% predicted) at the early termination visit. FVC values at these visits were 5.12 L (95% predicted), and 5.35 L (99% predicted), respectively.

175/680/3189 –wheezing and cough – 66 yo man experienced wheezing and productive, continuous cough within 10 minutes of dosing, 84 days after randomization to Technosphere Placebo. The patient stopped study drug the next day and subsequently withdrew from the study. The adverse events were reported as resolved. FEV1 was 2.68 L (86% predicted) at baseline and 2.44 L (79% predicted) at the early termination visit. FVC values at these visits were 3.44 L (82% predicted) and 3.35 L (80% predicted), respectively.

7.3.4 Significant Adverse Events

Lung cancer

DMEP consulted the Division of Oncology Products 2 (DOP2) for input on interpretation of the lung cancer data. The following section summarizes the consult report prepared by Dr. Lee Paischerf, DOP2.

Given the mode of administration of Afrezza TI, and the experience with Exubera, lung and bronchial malignancies are a concern. It is known that human insulin can induce growth in vitro in a variety of cell lines and hypothetical concern exists that human insulin may have potential mitogenic properties via insulin-like growth factor (IGF-1)-1 receptor binding.

Pre-clinical data to study the carcinogenicity of Afrezza TI were submitted by the Sponsor. The Afrezza TI 2-year carcinogenicity study in pre-clinical models showed no drug-induced neoplastic findings with administration either via nasal inhalation or subcutaneous routes. The relevance of these non-clinical models to inform human risk may be limited (i.e., route of administration differs). In the rat carcinogenicity study, cell proliferation activity (proliferating cell nuclear antigen; PCNA) confirmed the absence of neoplasia/pre-neoplastic signals as assessed in alveolar and bronchiolar cells across treatment and control groups. However, it is noted that the existing data does not address whether long-term treatment with Afrezza TI may promote or enhance pre-existing pre-malignant bronchial and/or lung lesions.

In the Afrezza TI development program, four cases of lung malignancy were reported: two in the clinical program reported in the 2009 Original NDA and two spontaneously reported after the subjects' completion of participation in clinical trials (Table 34). Narratives for these patients are located in Appendix 6.

Table 34 – Lung Cancer Cases in Afrezza TI-Treated Patients

ID	AGE/SEX/ COUNTRY	DM TYPE	SMOK- ING HIS- TORY	AFREZZA TI EXPOSURE	DIAGNOS IS TIME	HISTOLOGY STAGE
Diagnosis while Participating in Study						
102/2909	61 yo male Argentina	T2DM	40 pack years	137 days	137 days	Neuro- endocrine oat cell type (small cell) lung cancer
005/407/3316 (followed by participation in uncontrolled extension study 010	66 yo male Czech Republic	T2DM	54 pack- years	627 days	627 days	Bronchogenic cancer, non- differentiated NSCL T4 N2 M0
Spontaneous Reports Submitted after Subjects had Completed Trial Participation						
0008/358	59 yo male USA	T2DM	Non smoker	3.5 years	2.5 years	Squamous NSCLC
030/618	73 yo female Russia	T2DM	Non smoker	1 year, 11 months	3.5 years	Squamous NSCLC, Stage II

Source: Adapted from FDA DOP2 consult report

Of the two patients with the diagnosis of lung carcinoma reported during study participation (oat cell and bronchogenic histology), both patients have a prior history of heavy tobacco exposure, making a causality attribution to Afrezza TI difficult. The two additional events of squamous cell lung cancer, spontaneously reported by investigators in the post-study setting, are of concern particularly because the patients have no history of tobacco use. However, because of reporting/detection bias, any interpretation of these two events must be taken with great caution.

A summary of lung cancer cases in Afrezza TI exposed patients versus comparators is presented in Table 35. In the pooled phase 2/3 safety database the exposure-adjusted incidence rate of lung cancer was 0.05% in the Afrezza TI group. In a database that includes all Phase 2/3 controlled and uncontrolled studies of >14 days duration, the exposure-adjusted incidence rate of lung cancer was 0.07% in the Afrezza TI group because of the additional case of the patient in uncontrolled study 010.

Table 35 –Lung Cancer in the Afrezza TI Program

	AFREZZA TI	COMPARATOR
Pooled phase 2/3 safety database		
N (SYE)	3017 (2052)	2488 (2250)*
Events of lung cancer	1	0
Percent with event	0.03%	0%
Exposure-adjusted incidence (per 100 SYE)	0.05	0
Phase 2/3 controlled and uncontrolled studies of >14 days duration		
N (SYE)	3283 (2747)	2494 (2267)
Events of lung cancer	2	0
Percent with event	0.06%	0
Exposure-adjusted incidence (per 100 SYE)	0.07	0
All exposed patients[^]		
Events of lung cancer	4	N/A
*Includes 290 subjects and 98 SYE exposed to Technosphere Placebo		
[^] Incidence rates not calculated because two cases are spontaneous reports		
SYE=Subject year exposure		

Dr. Pai-Scherf stated “Lung cancer is the most common cancer in the world and the leading cause of cancer-related mortality. According to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) statistics, the overall age-adjusted lung and bronchogenic cancer incidence rate during 2006-2010 was 61.4 per 100,000 men and women per year in United States. This rate corresponds to an annual incidence rate of 0.06%. The median age at diagnosis was 73 years. The incidence of lung and bronchus cancer increases rapidly after the age of 55 and is highest between the ages of 65-74. The Afrezza pooled safety population is based on trials conducted internationally. Based on World Health Organization (WHO), the estimated age-standardized incidence rate of lung cancer is highest in Eastern Europe and Eastern Asia compared to North America.’

‘A close examination of the four cases of lung cancer reported in the Afrezza TI program indicates that demographics and the available characteristics are consistent with what would be expected in this population. However, the current available evidence does not allow a meaningful analysis regarding the risk of lung cancer in patients exposed to Afrezza TI because of small numbers and confounding factors.’

Reviewer’s comment: Because of its mode of action and because of the experience with Exubera (see section 2.4) and the small imbalance of lung cancer cases observed in the Afrezza development program there is a concern of a potential lung cancer risk with Afrezza. The available data discussed here do not demonstrate a clear risk association for lung cancer. However, concern remains because the data currently available may not be sufficient to clearly rule out an excess risk of lung cancer due to Afrezza use, in part, because of the long latency and relative rarity of malignancy events compared with other types of adverse events such as hypoglycemia, diabetic ketoacidosis, and pulmonary

function decline. Therefore, the potential risk of lung cancer is best assessed in the postmarketing setting. The study designed to assess this potential risk should be a randomized, controlled clinical trial that is sufficiently large and of sufficient duration to evaluate the primary objective of comparing the incidence of pulmonary malignancy observed with Afrezza to a standard of care control group.

Pulmonary Safety

The consultants from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) identified several issues (e.g. decline in FEV1, bronchospasm in patients with underlying lung disease, and cough). These are outlined below.

1. Decline in FEV1

Based on pulmonary function testing, a greater decline in FEV1 with Afrezza therapy versus comparator was noted during the first 3 months of therapy. The treatment differences were small (on average about 40-60 mL) and the results from 2-year studies show that the early difference persisted, but did not appear to progress over the 2-year period. Of note, the 2-year pulmonary function data were obtained with the MedTone inhaler and 6-month pulmonary function data are available with the Gen2 inhaler.

Pulmonary function tests were performed in study 171 to assess pulmonary safety between the two devices. The Sponsor concluded that” Head-to head comparison between TI Gen2 and TI MedTone showed that there were no significant differences in the change from baseline to Week 24 in FEV1 or FVC. The overall magnitude and pattern of changes in lung function (FEV1, FVC and FEV1/FVC ratio) over a 24 week treatment period were similar between TI Gen2 and TI MedTone groups.”

Dr. Paterniti, in her DPARP consult review concluded similarly that, “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”.

Controlled pulmonary safety data beyond 2 years of treatment are not available.

Reviewer’s comment: This decline in FEV1 is consistent with that observed for Exubera. According to the pulmonary reviewer the clinical significance of this small decline is unclear but this should not preclude approval. While the data appear to suggest that the decline in FEV1 does not progress over 2 years, the pulmonary reviewer is recommending a postmarketing required study to further assess the characteristics, including degree, of the pulmonary function decline over a longer term. I agree with this recommendation. See Appendix 2, PMR #2. Labeling should inform patients of this risk.

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 Afrezza. Asthma symptoms and SAEs of bronchospasm were also noted. In another study, patients with COPD had a smaller mean decline (200 mL) and a slower recovery over 8 hours towards baseline.

Reviewer's comment: According to Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, a boxed warning can be used to highlight for prescribers that there is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g. patient selection, etc.). Boxed warnings are most likely to be based on observed serious adverse reactions, but there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate. The labeling for Afrezza should include a boxed warning to inform patients of the serious risk of bronchospasm in patients with chronic lung disease, i.e. asthma or COPD, contraindicate Afrezza in patients with chronic lung disease, and recommend thorough evaluation for potential lung disease prior to prescribing Afrezza. In the case of Afrezza, thorough evaluation for potential lung disease prior to prescribing Afrezza could mitigate the serious risk of bronchospasm.

Furthermore, the recommended REMS will help ensure that patients will be carefully selected for Afrezza therapy, i.e. use will be avoided in those with chronic lung disease.

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%).

Reviewer's comment: Cough is a common adverse reaction noted in Afrezza clinical trials. It may be due to the irritant factor of the dry powder formulation. Cough appears to be more of a tolerability issue than a safety issue, per se. Cough should be listed in the table of common adverse reactions in Afrezza labeling.

The pulmonary reviewer noted that patients who smoke were excluded from the Afrezza clinical trials, therefore no efficacy or safety information is available in this population. In addition, patients who smoke may be at risk for concomitant underlying lung disease.

Reviewer's comment: According to Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication. Because concomitant underlying lung disease is a theoretical risk, and could be ruled out in a smoker with the proper screening tests, I recommend that Afrezza should not be contraindicated in smokers, but that the Limitations of Use section

should note that the safety and efficacy of Afrezza in patients who smoke has not been established, and therefore, the use of Afrezza is not recommended in patients who smoke or who have recently stopped smoking.

In summary, the safety concerns noted by the consultants from DPARP can be mitigated through proper labeling, required postmarketing studies, and REMS, and are not approvability issues.

7.3.5 Submission Specific Primary Safety Concerns

Based on FDA request, the following (non-pulmonary) adverse events of special interest were summarized individually by the Sponsor:

- Metabolic (diabetic ketoacidosis [DKA])
- Cardiovascular
- Neoplasms
- Immunogenic

- Eye events
- Hypoglycemia
- Anti-insulin antibodies
- Device-related performance issues

The Sponsor identified the majority of these submission specific primary safety concerns *a priori* based on what would be expected of an inhaled insulin drug, e.g. hypoglycemia, pulmonary safety. FDA also requested analysis of eye events a submission specific primary safety concern after FDA review of the first NDA submission for this drug which showed a small imbalance in adverse eye events not favoring Afrezza, and requested an update of DKA events because of the imbalance in DKA events not favoring Afrezza in the original NDA.

The following sections summarize the findings of the adverse events of special interest using the pooled phase 2/3 safety database for incidence comparisons.

Diabetic Ketoacidosis (DKA) in Patients with T1DM

There were no additional cases of DKA identified in the new Phase 3 studies.

Review of the narratives for the cases submitted in previous review cycles suggested that most identified episodes were triggered by infections. (Narratives are presented in Appendix 7). There was one event of DKA that was directly attributed to improper use of the inhaler, but the narrative contained insufficient details to tell whether the subject actually had DKA or just severe hyperglycemia. One case occurred in a patient stopping the subcutaneous basal insulin on her own accord without consulting with her physician. One case was associated with an overdose of paracetamol and ensuing illness. The cases of DKA occurred as early as 3 days after start of Afrezza TI treatment up to > 400 days after start of Afrezza TI treatment with no

temporal apparent pattern. Basal insulin alone in sufficient doses should be adequate to prevent DKA, and the narratives suggested that some DKA events were due to missed doses of all insulins as well as infections. In general, however, narratives are insufficiently detailed to determine whether Afrezza TI, through under-insulinization, contributed to these events.

Nevertheless, randomization would be expected to balance out these predisposing factors, e.g. infections, behavioral factors, that led to episodes of DKA so the imbalance in incidence of DKA between Afrezza TI and comparator is concerning.

Reviewer's comment: The Resubmission does not change the overall review findings for DKA, in that a higher incidence of DKA was observed among Afrezza treated patients. DKA and glycemic control are linked, and in light of the observed worse efficacy of Afrezza TI compared with insulin aspart as a prandial insulin for glycemic control in T1DM patients, the possibility exists that Afrezza TI contributed to this observed imbalance.

Cardiovascular Safety

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 T1DM and is the last-line treatment for patients with T2DM who have failed all other available therapies. As I discussed in the original NDA review, the Afrezza program was not designed to evaluate cardiovascular safety by the manner suggested in the Guidance, e.g. the study designs did not contain prespecified and prospectively adjudicated cardiovascular endpoints, and the studies did not selectively recruit high risk patients. 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

In the original NDA the incidence of any cardiovascular and/or cerebrovascular TEAEs in subjects with T1DM and T2DM 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.

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 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.

In the current Resubmission, the Sponsor updated their previous analyses and also performed a custom analysis of MACE “FDA custom MACE” which they based on the FDA review of other non-insulin therapies that were already under development at the time of issuance of the 2008 Guidance. Note that this “FDA Custom MACE” is not necessarily a preferred or standard approach to MACE analysis, but was rather a unique approach crafted for applications ‘caught in the middle’ of submission for marketing approval and the 2008 Guidance for which prospective adjudication was not performed.

Using the same broad set of MedDRA PTs and methods used in the original 2009 NDA, the Sponsor showed that the incidence of any cardiovascular and/or cerebrovascular TEAE in patients with T1DM and T2DM was, again, comparable between treatment groups with 216/3017 subjects (7.2%, exposure-adjusted incidence rate 10.5 per 100 SYE) in the TI Total group and 175/2198 subjects (8.0%, exposure-adjusted incidence 8.1 per 100 SYE) in the Comparator group reporting at least one cardiac event. The Custom analysis also did not show an imbalance in cardiovascular events but event rate were very small, limiting conclusions. A total of only 4 subjects reported at least one major cardiac event; 1/1026 (0.1% exposure-adjusted incidence rate 0.1 per 100 SYE) in the TI Inhalation Powder group (no reports in the TI Gen2 group, one in the TI MedTone group), and 3/835 (0.4%; exposure-adjusted incidence rate 0.4 per 100 SYE) in the comparator group. Results were also similar when examining T1DM and T2DM separately.

In sum, regardless of the method of examining the data, an excess cardiovascular risk for Afrezza is not observed. Caveats to this conclusion include the low number of events overall and the lack of pre-adjudicated outcomes.

Reviewer’s comment: While the development program and available data for Afrezza would not be adequate to satisfy the recommendations from the 2008 Guidance to rule out excess cardiovascular risk, this approach was agreed upon between the Sponsor and FDA because, as an insulin product, Afrezza is not necessarily expected to meet the requirements of the 2008 Guidance. Recent experience with other insulin applications, e.g. insulin degludec suggests that some insulin products may have the potential to increase cardiovascular risk. To date, however, the available data for Afrezza suggest no excess risk, and while absence of evidence is not evidence of absence, this should not preclude approval. My recommendation is consistent with the 2008 Guidance, and in my view the cardiovascular safety of Afrezza can potentially be further evaluated in the post-marketing outcomes trial designed to assess lung cancer risk.

Therefore, I recommend that the long term outcomes trial designed to assess lung cancer risk 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). CV risk needn't be the primary objective of the outcomes trial for the above reasoning.

Malignancy

In the 2013 Resubmission, events reported as neoplasms were identified using the same MedDRA (Version 15.1) search strategy as used in the 2009 Original NDA ISS and were summarized by System Organ Class, including the Preferred Term that referred to either a benign or malignant neoplastic disease. These terms were reviewed by the Sponsor to identify malignant and benign neoplasms.

In the original NDA 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 concluded there were very few events and that the available data did not support an association between TI and malignancies.

In the Resubmission, there are 7 new neoplasm cases (2 malignant and 5 benign) that have been reported in phase 2/3 controlled clinical studies. Neither of the two new malignant neoplasm cases had a latency of at least 90 days. The two new cases include a rectal carcinoma in a TI treated patient and a case of squamous cell carcinoma of the hard palate in a TP-treated patient. The narrative for this case is presented in the section discussing SAEs.

Twenty-one malignant neoplasms were included in the analysis of malignant neoplasm (excluding the 5 cases of basal cell carcinoma and 1 case of squamous cell carcinoma of the nose): 13 of 3017 subjects (0.43%) who received TI, 1 of 290 subjects (0.3%) who received TP (placebo), and 7 of 2198 subjects (0.32%) who received comparator treatment (Table 36).

Table 36 – Number of Reported Malignancies in Type 1 or Type 2 Subjects, Excluding Non-Melanoma Skin Malignancies (Pooled Safety Population)

	All Malignancies			Malignancies with Latency ≥ 90 days	
	TI (N=3017)	TP (N=290)	Comparator (N=2198)	TI (N=3017)	Comparator (N=2198)
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		1		
Metastatic gastric cancer	1			1	
Pancreatic carcinoma			1		
Neuroendocrine tumor (lung involvement)	1			1	
Squamous cell carcinoma of the hard palate		1			
Total	13	1	7	10	5

Source: Reviewer's table

Reviewer's comment: The updated 2013 analysis of malignant neoplasm in the pooled phase 2/3 safety database is consistent with the original NDA, with no clear association between TI and overall malignant neoplasm. In addition, the FDA Oncology consultant who reviewed the data stated that the data show "heterogeneous tumor types that are consistent with the age group and population."

Immunogenic

As noted by Dr. Joffe in his original NDA Cross-discipline team leader memo, 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.

Potentially immune-related events were identified and summarized from a predefined set of MedDRA codes (Appendix 5 in the study protocol, which is provided in Appendix 16.1.1 of the study CSR). This list of events was agreed upon with FDA prior to initiation of the two Gen2 phase 3 studies 171 and 175.

Table 37 summarizes adverse events potentially related to allergic reactions in the combined T1DM and T2DM population using the pre-specified MedDRA terms and using all available pooled phase 2/3 data as of the 2013 Resubmission. Similar to the original NDA event rates were low and generally comparable between Afrezza and comparator (which mostly included other insulin therapies): 2.4% (73/3017) in the TI group, 1.5% (33/2198) in the comparator group, and 2.4% (7/290) in the TP group. 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 37 – Incidence of Potentially Immunogenic Adverse Events – T1DM and T2DM Combined (2013 Resubmission Safety Population)

System Organ Class Preferred Term	TI			TP			Comparator [N=2198] [SYE=2152] n (%)
	Gen2 [N=370] [SYE=149] n (%)	MedTone [N=2647] [SYE=1903] n (%)	Total [N=3017] [SYE=2052] n (%)	Gen2 [N=176] [SYE=73] n (%)	MedTone [N=114] [SYE=25] n (%)	Total [N=290] [SYE=98] n (%)	
ANY TREATMENT-EMERGENT ADVERSE EVENT	3 (0.8)	70 (2.6)	73 (2.4)	3 (1.7)	4 (3.5)	7 (2.4)	33 (1.5)
EYE DISORDERS	0	2 (0.1)	2 (0.1)	0	0	0	0
Eye swelling	0	1 (0.0)	1 (0.0)	0	0	0	0
Eyelid oedema	0	1 (0.0)	1 (0.0)	0	0	0	0
GASTROINTESTINAL DISORDERS	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Lip swelling	0	1 (0.0)	1 (0.0)	0	0	0	0
Lip oedema	0	0	0	0	0	0	1 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	3 (0.1)	3 (0.1)	0	0	0	0
Injection site reaction	0	2 (0.1)	2 (0.1)	0	0	0	0
Face oedema	0	1 (0.0)	1 (0.0)	0	0	0	0
IMMUNE SYSTEM DISORDERS	0	6 (0.2)	6 (0.2)	0	1 (0.9)	1 (0.3)	1 (0.0)
Drug hypersensitivity	0	6 (0.2)	6 (0.2)	0	1 (0.9)	1 (0.3)	1 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.5)	26 (1.0)	28 (0.9)	0	0	0	22 (1.0)
Myalgia	2 (0.5)	26 (1.0)	28 (0.9)	0	0	0	22 (1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.3)	23 (0.9)	24 (0.8)	1 (0.6)	2 (1.8)	3 (1.0)	3 (0.1)
Wheezing	1 (0.3)	14 (0.5)	15 (0.5)	1 (0.6)	1 (0.9)	2 (0.7)	3 (0.1)
Bronchospasm	0	5 (0.2)	5 (0.2)	0	0	0	0
Throat tightness	0	4 (0.2)	4 (0.1)	0	0	0	0
Laryngospasm	0	3 (0.1)	3 (0.1)	0	1 (0.9)	1 (0.3)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	11 (0.4)	11 (0.4)	2 (1.1)	1 (0.9)	3 (1.0)	6 (0.3)
Urticaria	0	5 (0.2)	5 (0.2)	0	0	0	3 (0.1)
Angioedema	0	3 (0.1)	3 (0.1)	1 (0.6)	0	1 (0.3)	0
Pruritus generalised	0	3 (0.1)	3 (0.1)	1 (0.6)	0	1 (0.3)	0
Rash generalised	0	0	0	0	0	0	2 (0.1)

Rash pruritic	0	0	0	0	1 (0.9)	1 (0.3)	0
Rash vesicular	0	0	0	0	0	0	1 (0.0)
VASCULAR DISORDERS	0	4 (0.2)	4 (0.1)	0	0	0	1 (0.0)
Flushing	0	4 (0.2)	4 (0.1)	0	0	0	1 (0.0)

Source: Sponsor's Table 88, ISS

Reviewer's comment: Although incidence comparisons do not suggest a greater incidence of potentially immunogenic adverse events when compared to placebo or comparator, findings of hypersensitivity reactions with Afrezza are supported by some events in the NDA, such as a patient who developed facial edema and respiratory difficulties after the second dose of TI (see my original NDA clinical review for details). Labeling for Afrezza should include information about hypersensitivity reactions in Warnings and Precautions because of the life-threatening nature of some potential reactions and to align with other insulin products.

Eye events

In the original NDA, when including all adverse events (serious and non-serious) in the pooled phase 2/3 trials there were 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). Given the 5 to 0 imbalance in cases of retinal detachment with TI vs. comparator, the Sponsor was asked to provide an updated analysis of eye events in the 2013 Resubmission.

Methods: Ophthalmic examinations were part of the complete physical examinations at the screening and end of study visits. The eye examination was a nondilated, fundoscopic examination using a hand-held ophthalmoscope to evaluate gross evidence of hemorrhage, viewable exudates, retinal color abnormalities, disk abnormalities, abnormalities in the region of the macula densa, or other grossly evident abnormalities. Note that active proliferative retinopathy was an exclusion criterion. Adverse events of special interest included retinal detachment, vitreous hemorrhage, and eye hemorrhage.

Since the previous submissions, 2 AEs of the eye occurred in subjects with T1DM in pooled, controlled studies (Study 171). One subject treated with comparator (insulin aspart) had a vitreous hemorrhage and one subject treated with TI Gen2 had an eye hemorrhage. No new AEs of the eye occurred in subjects with T2DM in pooled, controlled studies.

Reviewer's comment: The new data in the 2013 Resubmission do not change the previous observation of a 5 to 0 imbalance of retinal detachment not favoring Afrezza. Eye events should be followed as an adverse event of interest in postmarketing clinical trials.

Hypoglycemia

Hypoglycemia was reviewed thoroughly in the original NDA; analysis of hypoglycemia was challenging because each of the studies included somewhat different definitions of hypoglycemia, and different trial designs (some with forced titration and some with treat-to-target designs). For example, FDA review noted a drastic difference in the overall incidence of severe hypoglycemia in the two type 1 diabetes trials submitted with the original NDA (0% in Study 101 vs. ~35% in Study 009), which is, at least in part, due to the different definitions of severe hypoglycemia. An FDA statistician analyzed the hypoglycemia data (with a focus on severe hypoglycemia) to determine whether there was sufficient evidence to support the Sponsor's assertion that fewer hypoglycemic events are seen with TI compared to insulin controls. The FDA statistician's approach to evaluate hypoglycemia in the individual trials and not to pool the data given that the trials had different comparators and used different definitions of hypoglycemia. General observations from these analyses were:

- The incidence of hypoglycemia was numerically higher with Afrezza than placebo in placebo-controlled studies, 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 active comparator studies where Afrezza was compared with another insulin, the incidence of hypoglycemia was generally lower for Afrezza than comparator, but in these studies the comparator groups had better glycemic efficacy than the Afrezza groups, confounding the hypoglycemia analyses.

The FDA statistician noted that that Study 102 (Afrezza + glargine vs. 70/30 insulin in T2DM) was the only study that statistically clearly showed 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 noninferior to NovoLog Mix 70/30; therefore, differences in glycemic control do not explain these findings. However, as Dr. Joffe noted in his memo, cases of hypoglycemia with a blood glucose < 37 mg/dL were classified as severe (regardless of symptoms), and 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 was 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.

For the new data since the 2010 Resubmission, definitions of hypoglycemia were applied consistently across both studies 171 and 175 and were more appropriately based on the ADA definitions (definitions are listed in section 5.3 above). Nevertheless, the two new studies are analyzed separately because of the difference in diabetes type and comparator between the two studies. My review focuses on study 171 which had an active insulin comparator, because in the placebo-controlled study 175, the risk of hypoglycemia is expected to be higher. I also remind the reader that “Two or more unexplained severe hypoglycemic episodes within 3 months of Screening or an episode of severe hypoglycemia between Visit 1 and Visit 2” was an exclusion

criterion for participation in the clinical studies, because this may decrease the incidence or event rates compared with clinical practice.

Analyses of hypoglycemia included both event rate analyses and incidence rate analyses for ‘all hypoglycemia’, ‘mild or moderate’ and ‘severe’. For event rates analyses even if a subject had multiple events each event is counted. The incidence of hypoglycemia provides a measure of the number of subjects who experienced hypoglycemia where a subject is counted only once whether there was a single or multiple hypoglycemia events.

Study 171 – T1DM

Event rate analyses

The event rates for hypoglycemia in study 171 since randomization performed by the Sponsor are presented in Table 38. The Sponsor also performed analyses of event rate by demographic variables, by week, and by final HbA1c at Week 24. I consider these analyses exploratory and I do not discuss them here.

Please see Dr. Liu’s review for the FDA analyses of hypoglycemia.

Table 38 – Event Rates for Hypoglycemia Events – Study 171

Category	TI Gen2 (N=174)	TI MedTone (N=173)	Insulin aspart (N=171)	TI Gen2 - Insulin aspart P-value [1]
All Hypoglycemia				
Number of Subjects at Risk	174	173	171	
Number of Subjects with Events (%) [2]	167 (96.0)	166 (96.0)	170 (99.4)	
Number of Events	7919	8764	12571	
Exposure Time in Subject-Month	807.7	850.7	899.6	
Event Rate (per Subject-Month)	9.80	10.30	13.97	<.0001
Mild or Moderate Hypoglycemia				
Number of Subjects at Risk	174	173	171	
Number of Subjects with Events (%) [2]	166 (95.4)	166 (96.0)	170 (99.4)	
Number of Events	7854	8679	12441	
Exposure Time in Subject-Month	807.7	850.7	899.6	
Event Rate (per Subject-Month)	9.72	10.20	13.83	<.0001

Severe Hypoglycemia				
Number of Subjects at Risk	174	173	171	
Number of Subjects with Events (%) [2]	32 (18.4)	37 (21.4)	50 (29.2)	
Number of Events	65	85	130	
Exposure Time in Subject-Month	807.7	850.7	899.6	
Event Rate (per 100-Subject-Month)	8.05	9.99	14.45	0.1022
Hypoglycemia with Glucose \leq 36 mg/dL				
Number of Subjects at Risk	174	173	171	
Number of Subjects with Events (%) [2]	41 (23.6)	45 (26.0)	63 (36.8)	
Number of Events	94	111	230	
Exposure Time in Subject-Month	807.7	850.7	899.6	
Event Rate (per 100-Subject-Month)	11.64	13.05	25.57	0.0009

Source: Table 54, Study 171 CSR

The event rate for all hypoglycemia, mild/moderate hypoglycemia, and hypoglycemia with glucose \leq 36 mg/dL was significantly lower for the TI Gen2 group than the insulin aspart group. The event rate for severe hypoglycemia trended lower for the TI Gen2 group (8.05 events per 100-subject months) vs the insulin aspart group (14.45 events per 100-subject months) but did not reach statistical significance. The numbers of events of severe hypoglycemia were low (8.05 per 100 subject-months vs 14.45 per 100 subject-months, $p = 0.1022$).

Incidence Rates Analyses

The incidence of any hypoglycemia during the randomized treatment period of the study was comparable in the TI Gen2 (167 subjects, 96.0%) and the TI MedTone (166 subjects, 96.0%) groups and in the insulin aspart group (170 subjects, 99.4%) (Table 39). The exposure-adjusted incidence per subject-month was similar across groups for any hypoglycemia and mild/moderate hypoglycemia.

The incidence of severe hypoglycemia during the randomized treatment period of the study was slightly lower in the TI Gen2 (32 subjects, 18.4%) and the TI MedTone (37 subjects, 21.4%) groups than in the insulin aspart group (50 subjects, 29.2%). The exposure-adjusted incidence per subject-month for severe hypoglycemia was also numerically lower among TI-treated patients vs. aspart-treated patients (exposure-adjusted incidence per subject-month was 0.48, 0.52, and 0.67, for Gen2, MedTone and insulin aspart, respectively).

The Sponsor's logistic regression analysis indicated that the incidence of severe hypoglycemia was statistically significantly lower in TI Gen2 (18.4%) subjects than in those treated with SC insulin aspart (29.2%) ($p = 0.0156$).

Table 39 – Incidence of Hypoglycemia – Trial 171

Category	TI Gen2 (N=174)	TI MedTone (N=173)	Insulin aspart (N=171)
Total Exposure (Subject-years)	67.23	70.80	74.87
Incidence of Any Hypoglycemia [1]	167 (96.0)	166 (96.0)	170 (99.4)
Exposure-adjusted Incidence of Any Hypoglycemia [2]	2.48	2.34	2.27
Incidence of Mild or Moderate Hypoglycemia	166 (95.4)	166 (96.0)	170 (99.4)
Exposure-adjusted Incidence of Mild or Moderate Hypoglycemia	2.47	2.34	2.27
Incidence of Severe Hypoglycemia	32 (18.4)	37 (21.4)	50 (29.2)
Exposure-adjusted Incidence of Severe Hypoglycemia	0.48	0.52	0.67
Incidence of Hypoglycemia with Glucose <= 36 mg/dL	41 (23.6)	45 (26.0)	63 (36.8)
Exposure-adjusted Incidence of Hypoglycemia with Glucose <= 36 mg/dL	0.61	0.64	0.84

Study 175 – T2DM

The risk of hypoglycemia is expected to be higher with Afrezza vs. placebo; therefore, a brief summary of the Sponsor’s analyses of hypoglycemia is presented here. Please see Dr. Liu’s review for FDA analyses.

Event Rate Analyses

The event rate for all hypoglycemic events was significantly higher in subjects on TI Gen2 and OADs compared with subjects on placebo and OADs (Event rate per subject-month 1.16 for TI vs. 0.50 for placebo, $p < 0.0001$). The event rate was also higher among TI-treated patients for severe hypoglycemia events (2.37 vs 0.60 per 100 Subject months, $p=0.2$) but due to low numbers of events did not reach statistical significance.

Incidence Rate Analyses

The exposure adjusted incidence of ‘any hypoglycemic’ event was 1.63 per subject year vs. 0.78 per subject year exposure, for TI and placebo, respectively. The odds ratio for any hypoglycemic event was 5.2 (95% CI 3.7 – 8.3, $p < 0.001$).

The exposure adjusted incidence of severe hypoglycemic events was 0.12 per subject year vs. 0.04 per subject year exposure, for TI and placebo, respectively. The odds ratio for any hypoglycemic event was 3.1 (95% CI 0.8 – 11.8, $p=0.09$).

Reviewer’s comment: For the T1DM trial, conclusions regarding hypoglycemia are confounded by the difference in efficacy observed between the two study arms. For the T2DM trial, the result of greater hypoglycemia risk vs. placebo is expected. Results of both trials seem consistent with the original NDA.

In summary, there appears to be no excess hypoglycemia risk with Afrezza compared with subcutaneously administered insulin. However, hypoglycemia is a known risk with all insulins. Of note, the within-subject variability of Afrezza was not studied in the clinical pharmacology program. Clinical implications of a high within-subject variability could be a less consistent therapeutic effect on a dose-to-dose and day-to-day basis which could lead to under- and/or over-dosing. While this is not an approvability issue, the within-subject variability should be assessed in a required post-marketing study. These data may impact labeling recommendations for glucose monitoring and thereby mitigate the risk of hypoglycemia.

Device

A consultation was completed by Mr. Sugato De, M.S. Biomedical Engineer (ODE/DAGID/ARDB), Lead Reviewer (date of completion 21 Mar 2014). His review covers (1) the design attributes of the proposed inhalational system, (2) the in vitro performance of the device in terms of particle size, delivered dose and respirable dose, (3) stability of the combination product in both storage and simulated use conditions and (4) the biocompatibility considerations associated with the device. He concluded that the sponsor has adequately validated the proposed drug-device combination product in terms of in vitro performance and stability. He noted no approvability issues.

The remainder of this section summarizes device-related treatment emergent adverse event information generated from the pooled phase 2/3 safety database for both diabetes types combined.

For incidence comparisons of adverse event reporting, the reporting of adverse events included options to check causality for “drug”, “device” and “study procedure”. The Sponsor’s review indicated that this data collection may have resulted in adverse events being reported as causally related to “device” in cases where the attribution was intended to be drug-related.

Since the 2009 original NDA six device-related AEs in TI MedTone have been reported: diabetes mellitus inadequate control, trigger finger, dysgeusia and cough reported each by 5 subjects. The total incidence from the 2013 data, then, is 71 events (4.1%) for the MedTone inhaler delivering TI and 6 events (5.3%) for the MedTone inhaler delivering TP. From the new data, there were 10/370 (2.7%) subjects who reported a total of 13 device-related AEs using the Gen2 inhaler with TI including sinusitis, throat irritation, exertional dyspnea, ‘upper airway cough syndrome’ and cough (9 reports of cough). There were 4/176 (2.3%) subjects who reported a total of 4 device-related AEs using the Gen2 inhaler with TP (placebo): all cough. No serious adverse events associated with a Gen2 device failure have been reported. In addition, there were no AEs resulting from a Gen2 device failure.

Reviewer’s comment: I agree with the Sponsor’s conclusion that the adverse events reported as causally related to the device are drug-related. These data suggest no device-related safety concern from the pooled phase 2/3 safety database.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

For analysis of common adverse events in the original NDA, the most common adverse events were analyzed separately for each of the main phase 3 trials in patients with T2DM. These data were not pooled because these trials used different comparators. The phase 2 and phase 3 T1DM trials were pooled because these trials used similar treatments. Table 40 and Table 41 show the findings for common adverse events in the T1DM and T2DM populations, respectively. Note that all of these trials used the MedTone inhaler.

Table 40 – Common Adverse Events (incidence >2% and occurring \geq 0.5% more frequently with TI than comparator) in the phase 2/3 trials in patients with T1DM, excluding cough and hypoglycemia

Preferred Term	TI + glargine N=614	Aspart + glargine N=599
	n (%)	n (%)
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)

Source: Adapted from Table 9 Dr. Joffe's memo, original NDA review

Table 41 – Common Adverse Events (incidence >2% and occurring ≥0.5% more frequently with TI than comparator) in the main phase 3 trials in patients with T2DM, excluding cough and hypoglycemia

Study 014	TI + glargine N=151	Aspart + glargine N=158
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)
Study 102	TI + glargine N=323	NovoLog Mix 70/30 N=331
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)
Study 103	TI alone or TI + met N=355	Insulin secretagogue + met N=166
Any	201 (57)	73 (44)
Headache	10 (2.8)	2 (1.2)
Hyperglycemia	9 (2.5)	1 (0.6)
Study 030	TI N=656	Comparator N=678
Any	512 (78)	451 (67)
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)

Source: Adapted from Table 10 Dr. Joffe's memo, original NDA review

For the 2013 Resubmission, there were only one new phase 3 study in each diabetes type; therefore, each trial is analyzed individually. While trial 171 also had a MedTone arm, I focused on the comparison between the to-be-marketed inhaler and the comparator, i.e. aspart in study 171 and placebo in study 175. A discussion of a head-to-head comparison of safety between the two inhalers in study 171 is discussed in section 7.4.5.

Table 42 shows the most common adverse events occurring in $\geq 2\%$ of Subjects in trial 171, and occurring more frequently with TI than comparator. TI-treated patients reported more cough, upper respiratory tract infection, headache, dyspnea, bronchitis, and throat irritation than did insulin aspart-treated patients. For comparison, headache was also commonly reported by T1DM patients treated with the MedTone device in previous studies, as was pharyngolaryngeal pain which may be similar to throat irritation. Dyspnea was not reported commonly with the MedTone device. Note that none of the events of dyspnea were serious, although 4 led to premature study discontinuation.

Table 42 - Common Adverse Events Occurring in $\geq 2\%$ of Subjects in Trial 171, and Occurring More Frequently with TI than Comparator

Preferred Term	Subject, n (%)	
	TI Gen 2 (N=174)	Insulin aspart (N=171)
Cough	55 (31.6)	4 (2.3)
Upper Respiratory Tract Infection	14 (8.0)	12 (7.0)
Headache	7 (4.0)	4 (2.3)
Dyspnea	7 (4.0)	0
Bronchitis	6 (3.4)	4 (2.3)
Throat Irritation	5 (2.9)	1 (0.6)

Source: Adapted from Table 37, Study 171 CSR

Table 43 shows the most common adverse events occurring in $\geq 2\%$ of Subjects in trial 175, and occurring more frequently with TI than comparator. Because the placebo in trial 175 was Technosphere Powder, many of the adverse events related to inhaling a dry powder appear to be common in the placebo group as well. Therefore, events from the Respiratory, Thoracic, and Mediastinal Disorders System-Organ Class are shown in the table as well, regardless of whether the event was more common in the TI or TP group. The only additional event to which this approach applies is Bronchitis.

In comparison to the T2DM studies submitted in the original NDA, the commonly reported adverse events are similar.

Table 43 - Common Adverse Events Occurring in $\geq 2\%$ of Subjects in Trial 175, and Occurring More Frequently with TI than Placebo, and all Events from the Respiratory, Thoracic, and Mediastinal Disorders System-Organ Class Occurring in $\geq 2\%$ of Subjects

Preferred Term	Subject, n (%)	
	TI Gen 2 (N=177)	Placebo (N=176)
Cough	42 (23.7)	35 (19.9)
Nasopharyngitis	15 (8.5)	8 (4.5)
Influenza	10 (5.6)	3 (1.7)
Upper Respiratory Tract Infection	9 (5.1)	5 (2.8)
Oropharyngeal Pain	8 (4.5)	4 (2.3)
Headache	7 (4.0)	5 (2.8)
Diarrhea	6 (3.4)	3 (1.7)
Urinary Tract Infection	6 (3.4)	2 (1.1)
Bronchitis	5 (2.8)	7 (4.0)
Nausea	4 (2.3)	0
Edema Peripheral	4 (2.3)	0

Source: Adapted from Table 30, Study 175 CSR

Reviewer's comment: Analysis of common adverse events in the new phase 3 studies suggests a similar safety profile compared to the original NDA.

Table 44 shows common adverse reactions for type 2 diabetes mellitus patients occurring in $\geq 2\%$ of subjects and occurring more frequently with TI than comparator, across the entire development program. These data are recommended for labeling.

Table 44 - Common Adverse Reactions Patients with Type 2 Diabetes Mellitus (excluding Hypoglycemia) Treated with TI

	Placebo* (n = 290)	TI (n = 1991)	Non-placebo comparators (n=1363)
Cough	19.7%	25.6%	5.4%
Throat pain or irritation	3.8%	4.4%	0.9%
Headache	2.8%	3.1%	1.8%
Diarrhea	1.4%	2.7%	2.2%
Productive cough	1.0%	2.2%	0.9%
Fatigue	0.7%	2.0%	0.6%
Nausea	0.3%	2.0%	1.0%

*Carrier particle without insulin was used as placebo

Table 45 shows common adverse reactions for type 1 diabetes mellitus patients occurring in $\geq 2\%$ of subjects and occurring more frequently with TI than comparator, across the entire development program. These data are recommended for labeling.

Table 45 - Common Adverse Reactions Patients with Type 1 Diabetes Mellitus (excluding Hypoglycemia) Treated with TI

	Subcutaneous Insulin (n = 835)	AFREZZA (n=1026)
Cough	4.9%	29.4%
Throat pain or irritation	1.9%	5.5%
Headache	2.8%	4.7%
Pulmonary function test decreased	1.0%	2.8%
Bronchitis	2.0%	2.5%
Urinary tract infection	1.9%	2.3%

7.4.2 Laboratory Findings

Laboratory services were provided by a central laboratory. Before starting the study, the central laboratory supplied the sponsor with a list of reference ranges, units of measurement, and laboratory certifications.

For the original NDA submission, I 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 T1DM and T2DM. 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.

In the 2013 Resubmission, the Sponsor reanalyzed the data with the updated phase 2/3 pooled safety population, and reported no safety concerns regarding laboratory findings. I reviewed these data (not shown) and concur that there are no clinically meaningful changes in laboratory parameters with Afrezza compared to control in the updated safety database. No cases of biochemical Hy's law in TI-treated patients were reported. There were also no notable differences between the TI MedTone and TI Gen2 groups.

7.4.3 Vital Signs

In the two new phase 3 studies, vital signs obtained at all in-clinic visits included temperature, blood pressure (in the supine position), pulse, respiratory rate, weight, which were measured at Screening, and Visit 2 through Visit 10 (or ET if required). Height was measured at screening only. A clinically relevant abnormal vital sign value was recorded as an AE. Similar to the original NDA 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 T1DM and T2DM.

7.4.4 Electrocardiograms (ECGs)

In the two new phase 3 studies, standard 12-lead ECGs were recorded with the subject in the supine position at Screening, the final treatment visit, and the ET Visit. The PI reviewed the tracing, signed, and dated the report and determined whether any abnormal values were to be documented as clinically significant or not clinically significant. This methodology is similar to that of the original NDA submission in which ECGs 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 varies from one investigator to the next). Therefore, the ECG analyses have limited utility. As noted by Dr. Joffe in the original NDA CDTL memo, 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.

7.4.5 Special Safety Studies/Clinical Trials

Study 171 was designed so that a head-to-head comparison of pulmonary safety could be obtained between the MedTone and Gen2 devices. Therefore, this study provides opportunity to examine non-pulmonary safety comparing the two devices. Note that any narratives for notable SAEs and adverse events leading to dropout are presented in section 7.3 above; the purpose of this section is to focus on incidence rate comparisons of important safety events between the two devices.

There were no deaths in TI-treated patients. The incidence of SAEs was low in both treatment groups but higher in the MedTone group: Gen2, 5 subjects (2.9%); MedTone, 9 subjects (5.2%). Table 46 displays the SAEs by MedDRA PT.

Table 46 – Serious Adverse Events in Trial 171

Preferred Term	Subject, n (%)		
	TI Gen 2 (N=174)	TI MedTone (N=173)	Insulin aspart (N=171)
Any AE	5 (2.9)	9 (5.2)	7 (4.1)
Hypoglycemic Unconsciousness	1 (0.6)	4 (2.3)	2 (1.2)
Hypoglycemia	1 (0.6)	2 (1.2)	1 (0.6)
Hypoglycemic Seizure	1 (0.6)	1 (0.6)	1 (0.6)
Bronchial Hyperreactivity	1 (0.6)	0	0
Cytomegalovirus Infection	1 (0.6)	0	0
Joint Dislocation	1 (0.6)	0	0
Cervical Polyp	0	1 (0.6)	0
Chest Discomfort	0	1 (0.6)	0
Appendicitis	0	0	1 (0.6)
Drowning	0	0	1 (0.6)
Mental Status Changes	0	0	1 (0.6)
Spinal Osteoarthritis	0	0	1 (0.6)

Source: Adapted from Table 45, Study 171 CSR

Reviewer’s comment: The small numbers limit conclusions, but there do not appear to be any patterns suggesting a difference in safety between the two devices in regards to serious adverse events.

In regards to withdrawals due to adverse events, the proportion of subjects who withdrew from the study due to an adverse event was higher in the Gen 2 group (16 subjects [9.2%] vs. 9 subjects [5.2%] in the MedTone group) (Table 47). It appears that discontinuations for cough were twice as frequent with Gen2 (10 vs. 5 patients). The second most common cause of discontinuation in the Gen2 group was dyspnea (including exertional) (5 patients vs. none). Note that no subject discontinued due to an AE in the insulin aspart group. The most frequent AE leading to subject discontinuations in the TI Inhalation Powder group was Respiratory Events with Cough, accounting for 10 of the 16 subjects in the TI Gen2 group, and 5 of the 9 subjects in the TI MedTone group. Other AEs that led to early discontinuation in the TI Gen2 group were dyspnea (4 subjects), and 1 subject each due to bronchial hyperreactivity, hypoglycemia, exertional dyspnea, and eye pruritis. AEs that led to early discontinuation in the TI MedTone group were bronchial obstruction, inadequate diabetes control, dizziness, drug hypersensitivity, nausea, and sensation of foreign body in throat.

Table 47 – Adverse Events Leading to Discontinuation in Trial 171

Preferred Term	Subject, n (%)		
	TI Gen 2 (N=174)	TI MedTone (N=173)	Insulin aspart (N=171)
Any AE	16 (9.2)	9 (5.2)	0
Cough	10 (5.7)	5 (2.9)	0
Dyspnea	4 (2.3)	0	0
Bronchial Hyperreactivity	1 (0.6)	0	0
Dyspnea Exertional	1 (0.6)	0	0
Eye Pruritus	1 (0.6)	0	0
Hypoglycemia	1 (0.6)	0	0
Lethargy	1 (0.6)	0	0
Bronchial Obstruction	0	1 (0.6)	0
Diabetes Mellitus Inadequate Control	0	1 (0.6)	0
Dizziness	0	1 (0.6)	0
Drug Hypersensitivity	0	1 (0.6)	0
Nausea	0	1 (0.6)	0
Sensation of Foreign Body	0	1 (0.6)	0

Source: Adapted from Table 48, Study 171 CSR

Reviewer’s comment: Again, the small numbers limit conclusions, but there is an imbalance of cough and dyspnea leading to discontinuation among Gen2-treated patients vs. MedTone-treated patients.

A similar proportion of subjects in each TI treatment group experienced any AEs during the randomized treatment period: (58.0%) in the TI Gen2 group and 104 (60.1%) in the TI MedTone group. Table 48 displays common adverse events occurring in $\geq 2\%$ of subjects during the randomized treatment period.

Table 48 – Common Adverse Events Occurring in $\geq 2\%$ of Subjects in Trial 171, Including MedTone arm

Preferred Term	Subject, n (%)		
	TI Gen 2 (N=174)	TI MedTone (N=173)	Insulin aspart (N=171)
Cough	55 (31.6)	39 (22.5)	4 (2.3)
Upper Respiratory Tract Infection	14 (8.0)	16 (9.2)	12 (7.0)
Headache	7 (4.0)	5 (2.9)	4 (2.3)
Dyspnea	7 (4.0)	0	0
Bronchitis	6 (3.4)	1 (0.6)	4 (2.3)
Nasopharyngitis	5 (2.9)	13 (7.5)	12 (7.0)
Throat Irritation	5 (2.9)	3 (1.7)	1 (0.6)
Diarrhea	4 (2.3)	2 (1.2)	5 (2.9)
Oropharyngeal Pain	3 (1.7)	6 (3.5)	3 (1.8)
Influenza	2 (1.1)	9 (5.2)	3 (1.8)
Vomiting	2 (1.1)	3 (1.7)	5 (2.9)
Urinary Tract Infection	1 (0.6)	6 (3.5)	3 (1.8)
Nausea	1 (0.6)	5 (2.9)	6 (3.5)
Hypoglycemic Unconsciousness	1 (0.6)	4 (2.3)	2 (1.2)
Blood Creatine Phosphokinase Increased	0	2 (1.2)	4 (2.3)

Source: Adapted from Table 37, Study 171 CSR

Reviewer’s comment: Again, there is an imbalance in the rate of cough and dyspnea (both higher in Gen2 than MedTone).

Possible immunogenic events based on prespecified MedDRA terms:

4 events were reported in the TI MedTone group (2 drug hypersensitivity, 1 myalgia, 1 wheezing) and none were reported in the TI Gen2 group.

I did not observe any notable differences between Gen2 and MedTone in terms of vital signs, routine laboratory assessments, ECGs, or anti-insulin antibodies. The risk of hypoglycemia also appears similar between the two inhalers whether analyzing by numbers of subjects with events, or event rate; the numbers of subjects with events and the event rates were all slightly numerically lower for Gen2 compared to MedTone, but a statistical comparison was not performed.

Reviewer’s comment: Overall, the results of these adverse event analyses suggest no important differences in safety between Gen2 and MedTone. One caveat is that there are small numbers of events limiting conclusions. Given the small numbers, and because objective data is more sensitive and specific for picking up differences in safety issues compared with adverse event reporting, more weight should be given to Dr. Paterniti’s review of the spirometry data in comparing pulmonary safety between the two devices.

7.4.6 Immunogenicity

The Agency requested that immunogenicity be assessed in the two requested Phase 3 clinical trials. In pre-submission regulatory meetings, the Sponsor noted that the clinical trials will have a 24-week treatment period and that insulin antibody (IAB) titers are not expected to plateau during this treatment period. Also, the follow-up after treatment discontinuation is likely to be too short to show the return of the titers to baseline values. Therefore, while these studies would provide limited data, the information obtained would enable bridging to the long term Phase 3 studies conducted with the MedTone inhaler. The validated Kronus radioimmunoassay used to measure IAB levels (IgG, exclusively) was to be the same as used in the original NDA. FDA agreed with this proposal.

Methods: The concentration of anti-insulin antibody in serum was measured using a validated radioimmunoassay (RIA). Samples were extracted with activated charcoal to remove endogenous insulin and incubated with ¹²⁵I-labeled insulin overnight. IgG antibody-bound insulin was complexed with antihuman IgG in a second incubation, and the complex was precipitated by centrifugation. After washing and re-centrifugation, the radioactivity in the precipitate was measured. The amount of radioactivity in the precipitate was proportional to the concentration of insulin antibodies in the serum sample. The concentration was read from a standard curve by plotting counts per minute as a function of concentration. Four-parameter loglogistic curve-fitting software was used for this purpose. The units are "Kronus units of insulin antibody/mL" and the validated range for Good Laboratory Practice (GLP) compliance is from a lower limit of quantification (LLOQ) of 1.6 Kronus units/mL to an upper limit of quantification (ULOQ) (following dilution) of 1000 Kronus units/mL.

Results: IABs developed to a greater extent in subjects treated with TI than in subjects treated with the comparator. Additionally, subjects with T1DM showed a greater response than subjects with T2DM. There was no association between IAB levels and clinical outcome measures such as HbA1c levels, incidence of hypoglycemia, fasting blood glucose (FBG) levels, insulin doses, or serious TEAEs (including allergic events).

In sum, I 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 T1DM and T2DM with greater increases seen in patients with type 1 diabetes. Similarly, the higher antibody concentrations with Exubera did not have a clinical correlate.

7.5 Other Safety Explorations

See original NDA review for section 7.5.

7.5.1 Dose Dependency for Adverse Events

7.5.2 Time Dependency for Adverse Events

7.5.3 Drug-Demographic Interactions

7.5.4 Drug-Disease Interactions

7.5.5 Drug-Drug Interactions

7.6 Additional Safety Evaluations

See original NDA review for section 7.6.

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

7.6.3 Pediatrics and Assessment of Effects on Growth

Available pediatric data

One study in pediatrics has been completed: MKC-143 - Inspiratory Capacity and Handling Trial Using the Gen2C and MedTone Inhaler Model D Delivery Systems in a Healthy Pediatric Population. This was a Phase 1, single-center, randomized trial in which pediatric subjects were evaluated for their ability to handle, assemble, and operate the Gen2C and MedTone Inhaler Model D inhalation systems and for their ability to adequately inhale through each inhaler (without actual insulin). For the Gen2C [REDACTED] ^{(b) (4)}, a subject's inhalation effort must lift, de-agglomerate, and disperse the powder dose. A threshold of inhalation effort should therefore be defined for pediatric subjects above which performance of the device is relatively consistent and acceptable for drug delivery.

Healthy, nonsmoking pediatric subjects from 4 to 17 years old, inclusive, were enrolled and randomly assigned to 1 of 5 age groups: 4 to 5 years, 6 to 8 years, 9 to 10 years, 11 to 13 years, and 14 to 17 years. Each group contained up to 15 subjects.

According to the Sponsor, the data indicate that pediatric subjects as young as 4 years of age can easily operate, assemble, and appropriately inhale from Gen2C inhalers. Data from this trial are used to inform the pharmacokinetic study that evaluates exposure after administration of Technosphere Insulin Inhalation Powder in pediatric populations.

Pediatric Plan

The following is a top-line summary of the Pediatric Plan included in the 13 Oct 2013 Resubmission relative to versions previously submitted to the NDA. The following proposal was agreed upon by the Pediatric Review Committee (PeRC) at a meeting held on 4 Nov 2009.

Pediatric Waiver

The 13 Oct 2013 Resubmission included a waiver request for children up to 3 years 11 months of age. There is no change in this waiver request from the 28 June 2010 NDA Amendment.

Pediatric Deferral Request and Pediatric Plan

The 13 Oct 2013 Resubmission included the following; 1) A deferral for the initiation of pediatric studies in children 4 to 16 years 11 months (inclusive) until additional data in adults are available and submitted to FDA for review and 2) A pediatric Plan (b) (4)

- [Redacted]
- [Redacted]
- [Redacted]

Reviewer's comment: [Redacted] (b) (4)

At the time of this review, it has been determined by the Division and the Office of Clinical Pharmacology that two Clinical Pharmacology studies are not needed and the PREA related postmarketing required studies will only include one Clinical Pharmacology study and a safety/efficacy study (see Appendix 2, PMR#1).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable to this NDA

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Afrezza is not marketed.

9 Appendices

Appendix 1: REMS for Afrezza

I. GOAL

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

II. REMS

ELEMENTS

A. Communication Plan

MannKind Corporation will implement the following communication plan to healthcare providers likely to prescribe AFREZZA. The communication plan will include:

1. REMS Letters

MannKind Corporation will send a *REMS Letter for Healthcare Providers* and *REMS Letter for Professional Societies* within 60 days of this REMS approval (June 2014) and again after one year from the date of the REMS approval. If the commercial launch of AFREZZA occurs later than 90 days following REMS approval, an additional issuance of REMS Letters will be sent within 30 days of product launch. The REMS Letters will address the risk of acute bronchospasm in patients with chronic lung disease, including the fact that acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA, that AFREZZA is contraindicated in patients with chronic lung disease, and that healthcare providers should evaluate all patients for lung disease (a detailed medical history, physical examination, and spirometry [FEV₁] to identify potential lung disease) before starting on AFREZZA.

REMS Letters will be distributed by electronic mail (email).

Email will be the primary method to disseminate the REMS Letters. If an email is marked as unopened, a second email will be sent within 14 calendar days. If the second email is marked as unopened, the REMS Letter will be mailed within 14 calendar days. If a healthcare provider's or professional society's email address is not available or if the email is undeliverable, the REMS Letter will be mailed within 14 calendar days.

MannKind will make the *REMS Letter for Healthcare Providers* available via a link from the AFREZZA REMS website and through MannKind's sales and medical representatives upon

request for one year after the approval of the REMS (June 2014). A copy of or a link to the Prescribing Information (PI) and REMS Factsheet will accompany each REMS Letter for Healthcare Providers.

a. REMS Letter for Healthcare Providers

The intended audience for the *REMS Letter for Healthcare Providers* will be healthcare providers likely to prescribe AFREZZA and healthcare providers targeted by AFREZZA marketing activities.

b. REMS Letter for Professional Societies

MannKind Corporation will send the *REMS Letter for Professional Societies* to the following professional societies and organizations requesting the risk information in the letter be provided to their membership:

- American Diabetes Association
- American Association of Clinical Endocrinologists
- American Medical Association
- American College of Physicians
- Society of General Internal Medicine
- American Academy of Family Physicians
- National Medical Association
- Endocrine Society
- American College of Osteopathic Family Physicians
- American Association of Diabetes Educators
- American Association of Nurse Practitioners
- American Society of Health System Pharmacists
- American Pharmacists Association
- National Community Pharmacists Association
- American College of Clinical Pharmacy
- Association of Managed Care Pharmacy
- National Association of Managed Care Physicians

2. REMS Factsheet

A *REMS Factsheet* will be distributed with the REMS Letter for Healthcare Providers and made available to healthcare providers through MannKind Corporation's sales and medical representatives during the initial discussion with healthcare providers during the first 12 months after approval of this AFREZZA REMS. If the commercial launch of Afrezza occurs later than 90 days after REMS approval, distribution of the *REMS Factsheet* will continue during the initial discussion with healthcare providers during the first 18 months after approval of the REMS.

3. REMS Website

The AFREZZA REMS website for healthcare professionals (www.AfrezzaREMS.com) will include a prominent REMS-specific link and will continue for the duration of the REMS.

The REMS website will include the option to print versions of the PI, *REMS Letter for Healthcare Providers*, and the *REMS Factsheet*.

4. Dissemination of REMS information at scientific meetings

The AFREZZA *REMS Factsheet* will be prominently displayed at relevant scientific meetings where MannKind Corporation has a presence (e.g., booth) for the duration of the REMS.

The following are part of the REMS and are appended:

- AFREZZA *REMS Letter for Healthcare Providers* (print version)
- AFREZZA *REMS Letter for Healthcare Providers* (email version)
- AFREZZA *REMS Letter for Professional Societies* (print version)
- AFREZZA *REMS Letter for Professional Societies* (email version)
- AFREZZA *REMS Factsheet*
- AFREZZA REMS Website (www.AfrezzaREMS.com)

B. Timetable for Submission of Assessments

MannKind Corporation will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years from the date of the approval of the initial REMS (June 2014). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. MannKind Corporation will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix 2: PMRs and PMCs for Afrezza

1. An open-label pharmacokinetic (PK), and multiple-dose safety and tolerability dose-titration trial of AFREZZA in pediatric patients ages 4 to 17 years (inclusive) with type 1 diabetes (Part 1), followed by a prospective, multicenter, open-label, randomized, controlled trial comparing the efficacy and safety of prandial AFREZZA to prandial, subcutaneous, insulin aspart used in combination with subcutaneous basal insulin in pediatric patients 4 to 17 years old (inclusive) with type 1 or type 2 diabetes (Part 2). Part 2 of the trial should include a 4-week run-in phase and a 52-week randomized intervention phase.

Final Protocol Submission: **January 2015**
Study Completion: **July 2020**
Final Report Submission: **January 2021**

2. Conduct 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 or 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**

3. Conduct a dose-ranging PK-PD euglycemic glucose-clamp trial to characterize the dose-response of AFREZZA relative to subcutaneous insulin in patients with type 1 diabetes. Select at least three to four doses for each route of insulin administration to ensure both the linear and curvilinear portions of the dose-response curves are adequately captured and characterized. Compare the dose-response curves for AFREZZA and subcutaneous insulin noting the dose at which the response becomes curvilinear for each. These data may impact labeling recommendations for dosing and thereby mitigate the risk of diabetic ketoacidosis, which has been observed with AFREZZA.

Final Protocol Submission: *January 2015*
Trial Completion: *June 2016*
Final Report Submission: *March 2017*

4. A PK-PD euglycemic glucose-clamp trial to characterize within-subject variability for AFREZZA pharmacokinetic (PK) and pharmacodynamic (PD) parameters. These data may impact labeling recommendations for glucose monitoring and thereby mitigate the risk of hypoglycemia, which has been observed with AFREZZA.

Final Protocol Submission: *April 2015*
Trial Completion: *April 2016*
Final Report Submission: *January 2017*

Postmarketing Commitments

5. Modify removable mouthpiece cover to address potential risk of aspiration
Completion date: *January 2016*

Appendix 3: Deaths listing for TI and comparator across entire development program

Table 49 - Deaths Listing¹ for Afrezza TI and Comparator

Trial/Patient Number	Age (years)	Sex	Diabetes Type	Total Daily Dose ²	Time ³	Description
Afrezza TI						
MKC-TI-030/857/3469	59	M	1	180 U MedTone	479	Acute cardiovascular collapse
MKC-TI-030/458/3254	67	F	2	210 U MedTone	167	Bile duct cancer
MKC-TI-030/526/0539	60	F	2	90 U MedTone	109	Ischemic stroke and acute MI
MKC-TI-102/483/2524	56	M	2	210 U MedTone	217	Hemorrhagic stroke
MKC-TI-030/031/0237	55	F	2	90 U MedTone	67	Cardiac arrest
MKC-TI-030/162/0611	58	M	2	180 U MedTone	178	Multifactorial CVA
MKC-TI-102/523/2158	72	M	2	180 U MedTone	34	Ischemic heart disease
MKC-TI-102/488/2219	64	M	2	270 U MedTone	163	Acute MI
MKC-TI-102/508/2891	50	M	2	270 U MedTone	306	Sepsis
MKC-TI-010/409/1854	75	M	2	120 U MedTone	756	Acute MI
MKC-TI-102/067/2909	62	M	2	210 U MedTone	199	Neuroendocrine tumor
MKC-TI-010/407/3316	67	M	2	90 U MedTone	693	Bronchogenic carcinoma
MKC-TI-010/009/0246	73	M	2	270 U MedTone	520	Metastatic prostate CA
MKC-TI-010/403/2782	60	M	2	270 U MedTone	372	Metastatic pancreatic adenocarcinoma
MKC-TI-139/011	64	F	2	45-90 U Gen2	233	Acute leukemia
Comparator						
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

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

MKC-TI-014/524/074	72	M	2	SC insulin	298	Acute cardiac failure
MKC-TI-171/1413	26	M	1	SC insulin	45	Accidental drowning
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						
2 - Last dose prior to discontinuation if on Afrezza TI or type of therapy if on comparator						
3 - Days on treatment before death						

Appendix 4 – Deaths Narratives

Controlled phase 2/3 trials

MKC-TI-030/857/3469: A 59-yo Caucasian male in the Ukraine with type 1 DM received Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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.

MKC-TI-102/067/2909: A 62-yo Caucasian male in Argentina with T2DM. Afrezza 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 (b) (6) due to the neuroendocrine tumor.

Uncontrolled, Long term safety study, on Afrezza TI

MKC-TI-010/409/1854: A 75-yo Caucasian male in the Czech Republic with type 2 DM. Afrezza TI 30 U was administered via inhalation QID. The duration of Afrezza 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.

MKC-TI-010/407/3316: A 67-yo Caucasian male in the Czech Republic with T2DM. He received Afrezza 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 Afrezza 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 Afrezza 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 Afrezza TI. The patient died on [REDACTED]^{(b) (6)} from metastatic adenocarcinoma of the pancreas.

MKC-TI-139/011: A 64-yo Caucasian female with T2DM and 7-year history of myeloproliferative disorder, initiated treatment with Afrezza TI Inhalation Powder on 05 Nov 2009. On 01 Apr 2010 the subject was informed by her oncologist that the myelodysplastic syndrome had converted to an acute leukemia. The subject began chemotherapy treatment on 13 Apr 2010 with 78 mg intravenous (IV) azacitidine (Vidaza) in conjunction with Ativan 0.5 mg IV and Decadron 10 mg IV as pre-medications prior to chemotherapy. On an unspecified day in [REDACTED]^{(b) (6)} the subject experienced severe fever and severe shortness of breath and was subsequently admitted to the hospital. The subject had leukopenia and thrombocytopenia, likely related to the chemotherapy medication, Vidaza. The subject was treated with antibiotics and corticosteroids. The corticosteroids were used for a possible reaction to platelets given to treat thrombocytopenia. The subject also received high amounts of oxygen. The subject was not improving after receiving these treatments, and was subsequently placed on a morphine drip for comfort care. She died on [REDACTED]^{(b) (6)} from complications of leukemia. The investigator reported that per the hospital records, the subject died from acute respiratory failure possibly associated with a platelet transfusion reaction and acute leukemia. The death certificate, which was in the chart, listed cause of death as: 1) cardiopulmonary arrest, and 2) acute leukemia.

Death in Named Compassionate Use Program

MK201000002 Compassionate Use Program Switzerland

A 54-year-old Caucasian male patient in Switzerland with type 1 diabetes participating in a Compassionate Use Program of Afrezza TI began treatment on 07 Dec 2009 and continued to an unknown date in 2010. Afrezza 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]^{(b) (6)}, 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

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

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 Afrezza 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 Afrezza 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.

Appendix 5: Serious adverse event narratives from previous review cycles

T1DM Narratives from the Original NDA

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 Afrezza 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 Afrezza TI Inhalation Powder treatment. Afrezza 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 Afrezza 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 Afrezza TI after hospital discharge.

Seizure MKC-TI-030 092/2391: A 49-yo Caucasian male in the United States received Afrezza 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 Afrezza 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.

T2DM Narratives from the Original NDA

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 Afrezza 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 Afrezza TI and glargine. He was hospitalized for pericarditis 90 days after initiation of Afrezza 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 Afrezza TI and oral diabetic agents for the treatment of type 2 diabetes mellitus. Afrezza TI 60 U TID was administered from 28 Jul 2006 to 05 Apr 2008. On [REDACTED]^{(b) (6)}, 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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] 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] 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 Afrezza TI 15 U at breakfast, 45 U at lunch, and 90 U at dinner and Insulin glargine 22 IU at bedtime from [REDACTED] onward. The duration of treatment at the onset of the event was 254 days. On [REDACTED], 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 Afrezza TI U TID from [REDACTED] 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], the subject was diagnosed with an unspecified autoimmune disorder during a planned hospitalization that began on [REDACTED] 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] 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 Afrezza TI 30 U TID since [REDACTED], and metformin 850 mg po TID since 01 Oct 2006. The duration of treatment for Afrezza TI Inhalation Powder at the onset of the event was 87 days. On [REDACTED] 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza TI treatment as the investigator did not think the event was related to Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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.

From the 2010 Resubmission

Hypoglycemia requiring assistance

Site Number/Subject ID Number: 028/0214

A 52-year-old Caucasian female in the U.S. received Afrezza TI and Lantus for T1DM in trial 117. The subject was treated with Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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.

Afrezza 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 Afrezza 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 Afrezza 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

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

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 Afrezza TI before the meal. The subject felt fully recovered after eating the meal at 11:30 on 06 Sep 2009. The subject stopped taking Afrezza 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 Afrezza 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]^{(b) (6)}, 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]^{(b) (6)} 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]^{(b) (6)}. 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 Afrezza TI for T2DM. The subject's first dose of Afrezza 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-Afrezza TI-119 was on 20 Apr 2010. The subject was initiated into the extension trial MKC-Afrezza TI-158, receiving the first dose of Afrezza TI in that protocol on 21 Apr 2010. The duration of treatment at the onset of the event was 94 days. Afrezza 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]^{(b) (6)}, 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]^{(b) (6)} included glomerular filtration rate estimated at 43 ml/min/1.73m² (reference range: > 60 ml/min/1.73m²). 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]^{(b) (6)}. 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 Afrezza 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 Afrezza 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 Afrezza TI beginning on [REDACTED]^{(b) (6)}. Current daily dosage was prandial Afrezza 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 Afrezza TI; the subject continued Afrezza 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 Afrezza TI on [REDACTED]^{(b) (6)} at 30 U TID and 15 to 30 U as needed for other meals or snacks. Afrezza TI dosing was increased to 45 to 60 U at each

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

meal, beginning 18 Jul 2009. Treatment with Afrezza 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 Afrezza 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 [REDACTED] (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 Afrezza TI for T2DM. Prandial Afrezza 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 [REDACTED] (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 [REDACTED] (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 Afrezza TI due to severe needle phobia. Afrezza 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 Afrezza 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

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

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 [REDACTED]^{(b) (6)} and was extubated on [REDACTED]^{(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 Afrezza TI.

Appendix 6: Lung cancer narratives

Subject ID 102/2909: a 62-year-old Caucasian male with T2DM was enrolled in study 102. The subject received Afrezza TI inhalation powder from an unknown date through December 21, 2007. The patients' past medical history included 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 Afrezza TI, 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 005/407/3316: a 66-year-old male with T2DM was enrolled in study 005 and received Afrezza 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 (father died from lung cancer). The patient received Afrezza TI 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 030/618: a 73-year-old female with T2DM was enrolled in studies 030 followed by a 2-month safety follow-up study 126. The patient received Afrezza TI inhalation powder from April 21, 2006 through March 2, 2008. Doses of Afrezza TI (MedTone inhaler) were 15 U TID (21 Apr 2006 to 09 Jul 2006); 30 U TID (10 Jul 2006 to 09 Oct 2006), 45 U TID (10 Oct 2006 to 25 Dec 2006); 60 U TID (26 Dec 2006 to 27 Mar 2007), 75 U TID (28 Mar 2007 to 26 Jul 2007), and 90 U TID (27 Jul 2007 to 02 Mar 2008) The duration of treatment was 1 year and 11 months. The patient had no history of smoking, no family history of cancer and no exposure to pulmonary toxins. Medical history included: cataracts of both eyes, hypermetropia, arterial hypertension, arthrosis of right shoulder joint, atherosclerosis, bradyacusia of both ears, coronary heart disease, diabetic polyneuropathy, encephalopathy, post infarct cardiosclerosis, sinus tachycardia, stable angina pectoris, tenderness of palpitation in the cervical part of the spine, vertebral osteochondrosis and chronic pyelonephritis. Concomitant medication included: acetylsalicylic acid, bisoprolol, taurin 4%, lisinopril, molsidoman, metphormia, glibomet.

During the study, the subject's clinical course was unremarkable. Chest X-rays on Screening (20 Apr 2006) showed normal lung fields and the heart diameter widened to the left; at Visit 5 (28 Mar 2007) did not show any visible local or infiltrative shadows in the lungs; and at Visit 7 (05 Mar 2008) findings were unremarkable with no change since Screening. All laboratory (hematology and serum chemistry) values were normal and pulmonary function tests (PFTs) remained unremarkable.

She completed the study; enrolled in the 2-month safety follow-up study, MKC-TI-126, on 03 Apr 2008 and received only oral metformin, 850 mg BID. Pulmonary function tests (PFTs) during the study showed no meaningful changes. The subject completed the study, with the last study visit on 29 May 2008. The subject initiated antidiabetic treatment with insulin glargine at the end of the study and did not participate in any other clinical study. From completion of the MKC-TI-030 study to the present the subject did not receive any treatment with Afrezza TI. No further interaction occurred with the subject until spontaneous reporting of the event from the clinical site on 05 Mar 2012.

In July or Aug 2011, during an annual examination, chest fluorography revealed a shadow in the lungs. On 24 Oct 2011, spiral CT of the chest revealed a 55 mm x 48 mm mass of uneven density with distinct tortuous borders in the left lower lobe partly deforming the left lower lobe bronchi. On the left, in S1+2, was a circular focal shadow 8 mm in diameter; on the right at S1, there was small shadow of 2 mm in diameter. In the left lung apex, there was a pleural overlay. The heart chambers and large blood vessels were moderately enlarged. Chest showed enlarged lymph nodes: paratracheal, up to 8 mm; paraaortic, up to 12 mm; at bifurcation, 10 mm; and at bronchopulmonary, up to 9 mm. The left pleural cavity showed a small amount of liquid of up to 8 mm width. Overall chest CT scan indicated a focal lesion in the lower lobe left lung with sites of dissemination in the upper lobe, left side pleuritis, and chest lymphadenopathy.

The subject did not seek medical follow up until developing severe dyspnea in December 2011. On (b) (6), the subject was examined for severe pleuritis and was hospitalized from 10 (b) (6) to (b) (6). On (b) (6), bronchoscopy revealed impaired left lung and left-sided hydrothorax. Analysis of pleural liquid showed 2000 mL yellow fluid with positive Rivalta test for exudate, specific gravity = 1016, protein 33 g/L, WBC count = 50 to 60 x 10³, RBC count = 50 to 60 x 10³, lymphocytes = 94%, Neutrophils = 6%, and negative for acid-resistant mycobacterium. On (b) (6), plating of pleural fluid showed no growth. On (b) (6), cytology of pleural fluid showed single mesothelial cells and lysis of both RBCs and lymphocytes. On (b) (6), an oncologist provided a diagnosis of central cancerous tumor of the left lung presumably of squamous histology (T3 NX M0, Stage II) and pleuritis

In the opinion of the investigator, a causal relationship between the event and the study medication the subject received during the clinical study could not be excluded.

Subject ID 0008/358: a 59 -year-old Caucasian male initially participated in trial 0008 from 1JUN2004 and received Technosphere Placebo. At the conclusion of the 0008 trial the subject enrolled into the open label uncontrolled extension trial 010 on 22OCT2004. The subject

received Technosphere Insulin 15 U QD (22Oct2004 - 21Nov2004), 30 U QD (22Nov2004 - 02Mar2005), 15 U QD (03Mar2005 - 20Aug2006), 90 U QD (21Aug2006 - 21Apr2008). The duration of treatment was 3 years, 5 months, and 30 days. The subject completed the study and the last study visit was on 22Apr2008. Since then (for a total duration of 2 years, 7 months, and 16 days) the subject did not receive any treatment with Afrezza TI.

On 20Dec2010, the study coordinator was informed by the subject of his appointment with an oncologist for possible lung cancer. Per the study coordinator, subject developed symptoms of cough, throat tickle, intermittent fever and hoarseness of voice on 16Nov2010. The subject was initially treated with antibiotics, first with doxycycline, then azithromycin (29Nov2010), and subsequently with benzonatate, levaquin and oral prednisone (initiation date: 3Dec2010; doses and duration unknown). As the hoarseness of voice persisted, the subject was referred to an otolaryngologist. Otolaryngologist upon examination on 03Dec2010, found paralysis of the left vocal cord; the rest of the physical examination was unremarkable. CT of neck and chest was ordered and was performed on 07Dec2010. CT of the chest revealed large mass in the middle mediastinum at the level of carina extending into AP window and azygous and subcarinal lymph nodes. There were areas of hypodensity in the mass which may indicate necrosis – finding concerning for neoplasm particularly lymphoma, primary mediastinal tumor or metastatic disease. The lungs appeared well aerated without evidence of focal consolidation, volume loss or pleural effusion. No evidence of mass or nodules identified. Small hiatal hernia was identified and a small renal cyst. Neck CT, performed on 07Dec2010, revealed soft tissue thickening of the left maxillary sinus. Remaining of the paranasal sinuses and mastoid air cells were well aerated. Visualized intracranial structures were unremarkable. Parotid, submandibular glands and epiglottis appear normal. The left vocal cord appear midline. The thyroid gland appeared unremarkable. The vascular structures at the base of neck appear unremarkable. The aortic arch and its vessel branches appear unremarkable.

Subsequently on 17Dec2010, the subject underwent flexible bronchoscopy, endobronchial ultrasound, and ultrasound guided aspiration needle biopsy of the paratracheal lymph nodes. Bronchoscopy showed extensive ulcerative process in distal trachea, carina and bilateral main stem bronchi. There was narrowing of both main stem bronchi. There was clear ulceration at the carina and left main stem bronchus with a question of fistulization at that site. Biopsy specimens from the edges of this process in the airway were taken and which suggested “suspicious malignancy but indeterminate”. Bilateral, needle aspiration biopsy from the paratracheal lymph nodes was performed and on site cytology report was positive for non-small cell lung cancer favoring squamous cell carcinoma. Final pathology report on 20Dec2010 showed poorly differentiated nonsmall cell lung cancer favoring squamous cell carcinoma. MRI of the brain performed on 21Dec2010 revealed bilateral sphenoid and ethmoid sinusitis, periventricular white matter disease, no evidence of mass lesion or enhancing lesion that would be suspicious of a metastatic disease.

Past medical history was significant for type 2 diabetes mellitus, obesity, hypertension, hyperlipidemia; history of colon polyp from 07 Feb 1992 to 28 June 2004; pharyngovuloplasty for sleep apnea (b) (6), cholecystectomy in 1990, depression, penicillin allergy, bronchitis,

Clinical Review

Lisa B. Yanoff, M.D.

NDA Class 2 Resubmission/22,472

Technosphere Insulin Inhalation Powder/Afrezza

non-smoker (experimented with smoking cigarettes first 2 years of college (> 40 year ago) and has never smoked over 5 packs total in lifetime), and seborrheic keratosis. Significant family history included father with a history of colon cancer died at age 51, brother with history of prostate cancer at age 76, mother with the diagnosis of tuberculosis, and sister with asthma. The investigator reported not having complete information about the subject at this time and assigned the causality for the event as possibly related to the Afrezza TI the subject received during the trial. Alternate causality was not reported. There were no apparent environmental or other causal factors.

Appendix 7: Diabetic ketoacidosis narratives

Diabetic ketoacidosis MKC-TI-009 189/1283: A 33-yo African American female using Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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”. Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza TI 30 U TID starting [REDACTED]^{(b) (6)}. 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]^{(b) (6)}, 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 an HbA1c of close to 18% three days after starting Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza 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 Afrezza TI due to the event.

9.1 Literature Review/References

See original NDA review

9.2 Labeling Recommendations

Labeling recommendations are contained throughout this review. At the time of finalization of this review, the labeling has been mutually agreed upon by the Agency and Sponsor.

9.3 Advisory Committee Meeting

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 1, 2014. The purpose of the meeting was to discuss the evidence for the efficacy and safety of Afrezza, and ultimately vote on whether the totality of the evidence suggested that Afrezza should be approved. Presentations were given by both FDA staff and Sponsor staff and representatives.

As the clinical reviewer, I presented the Agency's position on the efficacy and non-pulmonary safety findings in the Afrezza marketing application with particular focus on the areas for which FDA has a concern, i.e. the interpretability issues of the pivotal type 1 diabetes study (discussed throughout this review), the modest efficacy seen in the pivotal type 2 diabetes study, and the potential lung cancer signal. In other words, my EMDAC presentation was crafted to shed light on some of the difficulties FDA was encountering when considering whether to approve Afrezza. As evidenced by my recommendation of approval and as discussed in section 1 of this review, I

do believe that there is a role for Afrezza in the armamentarium of diabetes drugs. That said, FDA was faced with a challenging application to review, because many of the trial conduct issues that plagued the original Afrezza NDA, and that the Sponsor had been advised to address, were still present in the current resubmission including poor titration of insulins and inadequate performance of the comparator.

Note that because of the differing trial interpretability issues, the clinical presentations and questions for the committee considered type 1 diabetes and type 2 diabetes separately. Presentations were also given by Dr. Lokesh Jain (Clinical Pharmacology), Dr. Miya Paterniti (pulmonary safety), and Dr. Trish Bright (Postmarketing Safety Studies and Exubera experience). Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA and Sponsor.

Attendance:

EMDAC Members Present (Voting): Erica H. Brittain, PhD; David W. Cooke, MD; Diana Hallare, MPH (Consumer Representative); Ed J. Hendricks, MD; Robert J. Smith, MD (Acting Chairperson)

EMDAC Members Not Present (Voting): Vera A. Bittner, MD, MSPH; Edward W. Gregg, PhD; William R. Hiatt, MD, FACP; Ellen W. Seely, MD; Charles A. Stanley, MD

EMDAC Member Present (Non-Voting): Mads F. Rasmussen, MD, PhD (Industry Representative)

Temporary Members (Voting): William J. Calhoun, MD, FACP, FCCP, FAAAAI, FACAAI; Katherine Flegal, PhD; Rebecca W. Killion; Morris Schambelan, MD; James K. Stoller, MD, MS; Erik R. Swenson, MD; Eva Szabo, MD; Abraham Thomas, MD, MPH, FACP, Peter W.F. Wilson, MD; Antoinette J. Wozniak, MD, FACP.

Questions to the Committee and Summary of Discussion and Vote:

1. DISCUSSION: Trials in type 1 diabetes demonstrate that Afrezza provides numerically and statistically less HbA1c reduction than a comparator subcutaneous insulin. Discuss whether the applicant has demonstrated that Afrezza is an effective treatment for patients with type 1 diabetes mellitus. In your discussion, please address each of the following issues:

- a. The impact of inadequate treatment optimization in the control arm on efficacy determination
- b. The impact of missing data on efficacy determination
- c. The relationship between Afrezza's clinical pharmacology (e.g., extent and duration of action, dose-response, inhalation flow-rate dependence) to its effectiveness as a "prandial" insulin

- d. Your level of concern with regard to how differences in efficacy will impact disease specific risks (e.g., risk of diabetic ketoacidosis) beyond achievement of therapeutic goals (i.e., prevention of diabetes related complications)
- e. The importance of having an alternative route of insulin administration available
- f. Comment on whether Afrezza is an appropriate substitute for subcutaneously administered mealtime insulin for most patients with type 1 diabetes or for a specific subgroup of individuals with the disease. If you believe the latter, describe this subgroup.

Committee Discussion: In terms of whether the applicant has demonstrated that Afrezza is an effective treatment for patients with type 1 diabetes mellitus, the committee noted that Afrezza may not be useful and efficacious in all type 1 diabetics. Further the committee elaborated that there are grounds for uncertainty in terms of its broad application to all patients with type 1 diabetes. The committee identified subgroups that may derive a net benefit from Afrezza compared to available alternatives, including patients who may have needle phobias, patients who are noncompliant on their current insulin regimen, patients who might need insulin between meals (supplemental doses), and patients with visual impairment or manual dexterity issues. However, the committee noted that there is no definitive data to conclude that patients would be more compliant with Afrezza as compared to injectable insulin.

In terms of the criteria applied to evaluating comparatively Afrezza versus rapid insulin analog, the committee stated that there is uncertainty based on the data provided and that the data are on the border in terms of non-inferiority exclusion. Furthermore, it was noted that the sensitivity analysis data do not resolve the borderline status.

The committee noted that there might be a subset of patients that either respond less well or are on such a high dose that they may not be getting an advantage from increasing doses of Afrezza, and therefore may be at risk of developing ketoacidosis. In this context, some committee members stated that they would envision patients using Afrezza would also have an alternative injectable rapid acting insulin to be used as a protective agent if they had uncontrolled glucose levels and/or experience problems with the Afrezza device.

In terms of the kinetics, some committee members noted that the more rapid on/off characteristic of Afrezza as compared to other insulin analogs may be advantageous in some patients as well as disadvantageous in other patients.

Reviewer's comment: The FDA Clinical Pharmacology reviewer has concluded that while Afrezza's pharmacokinetic profile suggests a rapid "on/off" the pharmacodynamic profile is more similar to the injected prandial insulins.

Regarding dose response, the committee expressed that there are some grounds for concern regarding loss of response to higher doses of Afrezza and that there is no progressing dose

response as doses are increased. However, the committee also expressed that insulin dosage typically is adjusted in diabetes according to the blood sugar levels and so the lack of a strict linearity over a range of dose responsiveness is probably not critical to the use of inhaled insulin.

Reviewer's comment: The FDA Clinical Pharmacology has concluded that it is unknown if the loss of response at higher doses occurs in a more clinically relevant range compared to injected prandial insulins. Therefore, there is a safety concern of diabetic ketoacidosis due to a possible plateauing of effect in the clinically relevant dose range. This issue will be further assessed in postmarketing studies. See PMR #3.

2. DISCUSSION: Trials in type 2 diabetes demonstrate that Afrezza is superior to placebo but is less effective than a short acting subcutaneous insulin comparator. Discuss whether the applicant has demonstrated that Afrezza is an effective treatment for patients with type 2 diabetes mellitus.

- a. Comment on the specific clinical setting where this agent is likely to be most useful.
- b. Discuss your level of concern with regard to data suggesting a less than dose proportional glucose lowering response and its potential impact on achievement of glucose targets in this population.
- c. Comment on any other issues discussed in the context of type 1 diabetes that you view as relevant to type 2 diabetes.
- d. Comment on whether Afrezza is an appropriate substitute for subcutaneously administered mealtime insulin for most patients with type 2 diabetes or for a specific subgroup of individuals with the disease. If you believe the latter, describe this subgroup.

Committee Discussion: In terms of whether the applicant has demonstrated that Afrezza is an effective treatment for patients with type 2 diabetes mellitus, it was the consensus of the committee that there are likely circumstances where Afrezza would be an effective treatment for patients with type 2 diabetes. But as was stated for type 1 diabetes, the committee noted that this drug would not be used in all patients, and probably would not be used simply as a replacement for other forms of insulin. The committee discussed the subgroup of patients that may derive the most benefit from Afrezza, which include those discussed for type 1 diabetes but also to include elderly patients that are receiving some degree of caregiver assistance outside of a nursing care facility.

The committee expressed concern about the potential for the more aggressive use of mealtime insulin without adequate basal long acting insulin coverage, and the broader concern over who is instituting the treatment and their understanding of the strategy of how to manage type 2 diabetes in the context of needing long acting insulin coverage in conjunction with the use of Afrezza. The committee noted that the understanding of this strategy by the provider, caregiver and

patient is important because many patients who are transitioned to insulin require long acting basal insulin to provide mealtime coverage.

Some committee members also expressed concern over not having adequate treat-to-target trials, and recommends having these trials conducted as it is ultimately needed to confirm the efficacy in achieving targets with Afrezza. The committee mentioned that the study design needs to be carefully developed to determine whether it should look at the use of Afrezza as a background with basal insulin being initiated first, or another construct on how Afrezza should be used.

Reviewer's comment: The Sponsor was advised (after the first Complete Response) that adequate titration of insulins was a key factor in interpretability of their clinical trials. FDA worked closely with the Sponsor to develop trials that should have been more successful in having subjects reach glycemic targets. For example, the trials reviewed in the current submission incorporated Titration Monitoring Committees. The inadequacy of the treat-to-target observed in the trials, in my view, was not due to a flaw in study design, but rather study conduct.

Further, a trial in type 2 diabetes patients with Afrezza as add-on to basal insulin was conducted and submitted at the time of the original NDA (Study 014; see section 2.4).

Some committee members commented that Afrezza may be appropriate for treatment with basal insulin or it may be a treatment option without the initiation of basal insulin; however the committee commented that they do not have the data to distinguish between treatment options, but would be concerned about initiating Afrezza without the basal insulin coverage.

3. DISCUSSION: Discuss the pulmonary safety findings in the Afrezza clinical development program (acute bronchospasm and pulmonary function decline over time).

a. Comment as to whether the pulmonary safety data (6 months with Gen2 device and 2 years with MedTone device) are sufficient to address the pulmonary safety of Afrezza.

Committee Discussion: Based on the pulmonary safety findings in the Afrezza clinical development program, it was the consensus of the committee that there was no particular reason for concern over the impact of changing the device from a safety perspective.

b. Discuss your level of concern with the pulmonary risks.

Committee Discussion: In terms of pulmonary risks, the committee was concerned with the development of acute bronchospasm episodes with the use of Afrezza in patients with undiagnosed asthma or other lung issues that would cause the patient to respond acutely with potential serious consequences. It was suggested that the first dose be administered under supervision with adequate support to deal with an acute bronchospasm events in order to mitigate the pulmonary risks. The committee noted that deterioration of pulmonary function (possibly

irreversible) may extend over a long period of time, and that the longest study presented occurred only over a 2 year period of time. Thus, the committee commented that the data may not provide assurance that there would not be development of deteriorating pulmonary function over a longer period of time. The committee also noted the need to evaluate a patient's pulmonary function prior to use of Afrezza and to conduct follow-up pulmonary function tests over time, such as every 6 months.

4. **DISCUSSION:** Discuss your level of concern with regard to the possible lung cancer risk with Afrezza use.

Committee Discussion: The committee noted that there is not enough evidence to conclude whether or not there is a lung cancer risk with Afrezza use based on animal and background data; however, the data and the background science create concern about these risks. The committee members raised concerns on the occurrence of two rather unusual tumors in non-smokers with squamous cell carcinomas. The committee noted that long-term follow-up studies should be conducted if Afrezza is approved as there is a need for collection of long term registry data on the occurrence of cancers over a long period of time (typically 12 years as recommended by FDA) and that this collection should also include demographic data (especially data on smoking). If the drug is approved by FDA, the committee expressed the importance of having post marketing studies with defined endpoints that is informative to delineate if what is being observed is accelerated cancer growth (progression) or the actual emergence of cancers. A number of committee members expressed that they would have appreciated more extensive or better designed pre-clinical studies to better probe this question of cancer promotion with the use of Afrezza and/or its vehicle, and perhaps more pre-clinical studies should be conducted at this time.

5. **DISCUSSION:** Discuss any other risk(s) which were not covered above.

Committee Discussion: The committee discussed concerns about retinal detachment that occurred in patients on Afrezza while none was observed in the control group. Since it is uncertain whether this is a meaningful signal or not, the committee suggested that ocular events be monitored in post-marketing studies. Another concern expressed by the committee was the detachability of the mouthpiece on the device and the threat of possible aspiration. The committee suggested that the mouthpiece be "hingeable" rather than detachable to prevent the possibility of aspiration of the cover. The committee also discussed concern over dosing of Afrezza and the need for more information from clinical use, possibly in the form of a trial that gives the provider more information on the proper dosing regimen. In particular, the committee suggested more information on how to approach and manage dose conversion against meal time insulin and how to anticipate and make adjustments that may be needed with basal insulin.

6. **VOTE:** Based on data in both the briefing materials and presented at today's meeting, has the applicant demonstrated that Afrezza is safe and effective for the treatment of adult patients with type 1 diabetes mellitus to support approval?

- a. DISCUSSION: If yes, please explain your rationale. Provide any recommendations you might have for post-marketing studies to evaluate identified safety signals.
- b. DISCUSSION: If no, please explain your rationale. If appropriate, what further data should be obtained?

Vote Result: Yes – 13 / No – 1 / Abstain – 0 / No-Voting - 1

Committee Discussion: The majority of the committee agreed that, based on data in both the briefing materials and presented at the meeting, the applicant has demonstrated that Afrezza is safe and effective for the treatment of adult patients with type 1 diabetes mellitus to support approval. The committee members who voted “Yes” noted that Afrezza may be a good option to use in between meals to treat hyperglycemia at times when a short acting insulin is not preferred. It was also noted that the data shows that Afrezza is not as effective as other forms of insulin; however, it was proven better than placebo. The panel member who voted “No” indicated that the benefits of this drug product (convenience, ease of use, and the possible decrease risk of hypoglycemia) do not outweigh the risks and that the biggest concern is with the cancer risk. This committee member recommended more robust pre-clinical data on cancer risk with use of the drug and more definitive data on hypoglycemia.

One panel member was unable to stay for the entire meeting, accounting for one “No Vote”. Please see the transcript for details of the committee discussion.

7. VOTE: Based on data in both the briefing materials and presented at today’s meeting, has the applicant demonstrated that Afrezza is safe and effective for the treatment of adult patients with type 2 diabetes mellitus to support approval?
 - a. DISCUSSION: If yes, please explain your rationale. Provide any recommendations you might have for post-marketing studies to evaluate identified safety signals.
 - b. DISCUSSION: If no, please explain your rationale. If appropriate, what further data should be obtained?

Vote Result: Yes – 14 / No – 0 / Abstain – 0 / No-Voting 1

Committee Discussion: The committee unanimously agreed that based on data in both the briefing materials and presented at today’s meeting, the applicant has demonstrated that Afrezza is safe and effective for the treatment of adult patients with type 2 diabetes mellitus to support approval. The committee noted that there is a tremendous delay for getting type 2 diabetic patients from oral agents to insulin, so this treatment option will likely help initiate insulin in these patients quicker. The committee also commented that many patients with type 2 diabetes are older and have weight problems, so having an agent that does not promote weight gain and possibly even promotes weight loss would be a tremendous advantage for these patients.

Clinical Review
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NDA Class 2 Resubmission/22,472
Technosphere Insulin Inhalation Powder/Afrezza

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Please see the transcript for details of the committee discussion.

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/s/

LISA B YANOFF
06/27/2014

JEAN-MARC P GUETTIER
06/27/2014