

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022472Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA</b>	22-472
<b>Submission Date(s)</b>	October 13, 2013
<b>Brand Name</b>	AFREZZA <sup>®</sup> Inhaler
<b>Generic Name</b>	Insulin human [rDNA origin] inhalation powder
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<b>OND Division</b>	Metabolism and Endocrinology Products
<b>Sponsor</b>	MannKind Corporation
<b>Submission Type</b>	Resubmission: Response to the Complete Response Letter dated January 18, 2011
<b>Formulation Strength(s)</b>	AFREZZA <sup>®</sup> is available as single-use cartridges of: 10 and 20 U strength**
<b>Indication</b>	To improve glycemic control in adults with type 1 or type 2 diabetes mellitus
<b>Dosage &amp; Administration</b>	AFREZZA is administered via oral inhalation using the AFREZZA Inhaler.

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\* Dr. Sang Chung is the primary reviewer for this application and Dr. Manoj Khurana performed the PK/PD analyses and simulations

\*\* Afrezza dosing units as reported in the clinical pharmacology studies. Cartridge units that will be reported in the label have not been finalized.

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## 1 Executive Summary

Afrezza is a drug-device combination product consisting of a dry powder formulation of recombinant human insulin (i.e., technosphere insulin) and a breath-powered inhaler device (i.e., Gen2 inhaler). 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). An earlier (and the only) approved inhalation insulin product, Exubera, was withdrawn from market in October 2007, for reasons not related to lack of efficacy or safety concerns.

The applicant, MannKind Corp., has submitted 34 clinical pharmacology and 63 clinical studies in their entire program to support the characterization of product profile and efficacy and safety of Afrezza. Although some concerns remain about the magnitude of efficacy with Afrezza compared to subcutaneous (SC) insulins (refer to clinical review by Dr. Lisa Yanoff), the submitted data suggests that systemic absorption of technosphere insulin lowers blood glucose.

### 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed this resubmission along with previous submissions, and recommend approval of this application with the following recommendations:

- OCP does not agree with the new dosing regimen proposed by the applicant in the prescribing information for switching from SC insulin to Afrezza insulin, in absence of adequate supporting data. OCP proposes to include the dosing regimen tested in Phase 3 trials in the prescribing information.
- 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. This is an important aspect given (1) it is known that at higher dosage less-than dose proportional increment in benefit is seen for other insulin products, and (2) insulin products are titrated to effect in clinical practice. Therefore, if the dose at which diminishing benefits are seen for Afrezza is lower than the dose for SC insulin, it may have implications in dosing titration, specifically for patients who require higher dosage. Exploratory modeling and simulation exercise was performed to predict the dose-response profiles for Afrezza vs. SC regulator human insulin (RHI) (see Figure 9 on Page 23), 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). OCP recommends that further information on dose-response relationship for Afrezza relative to SC insulin be collected in post-marketing studies.

## 1.2 Phase IV Commitments

- 1) Assessment of dose/exposure-response relationship for Afrezza relative to SC insulin in a dose ranging PK-PD clamp study in subjects with type 1 diabetes
- 2) Assessment of within-subject variability in Afrezza response

## 2 Summary of Clinical Pharmacology Findings and Review Issues

### 2.1 Background

Through the clinical development program for TI inhaler there were modifications in the device and the dosing regimen. The devices used to support the original submission (dated 3/16/2009) and the responses to Complete Response Letter (CRL) 1 (dated 6/29/2010, see Attachment), and CRL2 (dated 10/13/2013, see Attachment) are listed in Table 1 below. Table 1 also describes the bridging data used by the applicant and the related outcome.

The applicant submitted 36 clinical pharmacology studies throughout the development of TI inhaler (see Attachment), among which two studies MKC-TI-176 and MKC-TI-177 were submitted in this resubmission. These studies provided information on the relative bioavailability of Afrezza against SC insulin, dosing regimen for switch from SC to inhalation route of administration, and effect of intrinsic and extrinsic factors on relative bioavailability. These aspects are summarized further in the following sections and reviewers' comments are inserted to remark on the findings in context of changes in devices.

**Table 1: Summary of Key Background**

Submission	Device	Tested in Phase 3 trials	Bridging	Outcome
Original	MedTone Model C	yes	-	-
	MedTone Model D (proposed for commercialization)	no	Model D was bridged to Model C in a clinical pharmacology bioequivalence (BE) study; however, results were considered not reliable because of the deficiencies found in Office of Scientific Investigations (OSI) inspection	This deficiency was noted in CRL1
CRL1 response	Gen2	no	BE study bridging MedTone Model C with Gen2 was submitted. However, dosing regimen for Gen2 was different than that for Model C (30 U delivered by Model C provided similar systemic exposures as 20 U delivered by Gen2) Therefore, bridging based on BE study alone was not considered sufficient. As a result OSI inspection for this study was not requested.	CRL2 letter stated that because of changes in the device and dosing regimen, a single BE study is not sufficient to bridge the efficacy and safety data from Model C to Gen2
CRL2	Gen2	yes	Although Gen2 was tested in Phase 3	

response			trials, the dosing regimen proposed in the label is different than what was tested in Phase 3 trials	
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## 2.2 Dosing Regimen

The dosing regimen recommended by the applicant in the proposed prescribing information is as follows. The dosing conversion chart based on the recommended dosing is shown in Figure 1.

### Section 2.1 of the proposed label

*“A single inhalation from one 3 unit cartridge of AFREZZA approximates the exposure to 3 units subcutaneously injected insulin. A single inhalation from one 6 unit cartridge of AFREZZA approximates the exposure to 6 units subcutaneously injected insulin.”*

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		

Figure 1: Afrezza dosage chart from the proposed label

However, note that the proposed dosing regimen (Figure 1) and the dosing conversion factors (Table 2) are different than that tested in Phase 3 trials evaluating the Gen2 device (i.e., Study MKC-TI-171 and MKC-TI-175), 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.”*

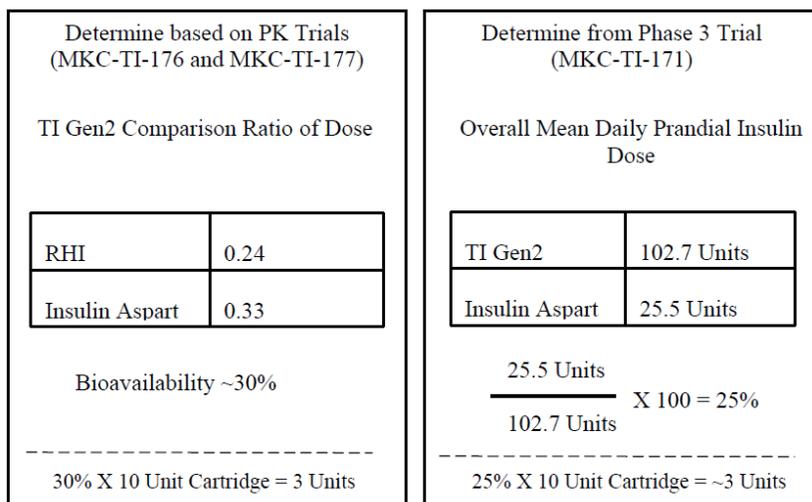
Table 2: AFREZZA Dosage Chart (Study MKC-TI-171)

RAA (Prandial) Bolus dose	TI Inhalation Powder Dose
0-4 IU	10 U
>4-8 IU	20 U
>8-12 IU	30 U
>12-16 IU	40 U
>16-20 IU	50 U
>20-24 IU	60 U

In the CRL2 resubmission, the applicant states that the new dosing regimen (as currently proposed) is supported by the two clinical pharmacology studies (i.e., studies MKC-TI-176 and MKC-TI-177) conducted with the Gen2 device and the Phase 3 trial in type 1

diabetes subjects (i.e., study MKC-TI-171). From clinical pharmacology studies, the applicant relies on only pharmacokinetics (PK) data (i.e., relative bioavailability estimates) to justify the proposed dosing conversion (see Figure 2). However, Agency considers the corresponding pharmacodynamics (PD) effect to be equally or more important in evaluating the adequacy of proposed dosing regimen because it is the PD effect that ultimately drives the efficacy (i.e., HbA1c reduction). Considering this, we found 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 (discussed in section 2.3).

The applicant also compares the overall mean daily prandial doses from Phase 3 trial in T1DM to justify the proposed dosing (see Figure 2). However, the approximation derived based on Phase 3 data makes several assumptions such as no differences in basal insulin dose and effect between treatment groups, comparable titration between two arms, and a similar dose-response relationship for both treatment groups. These assumptions are not supported - there were differences in basal insulin dose and dosing titrations between treatment arms, and information on similarity of dose-response between treatment groups is lacking.

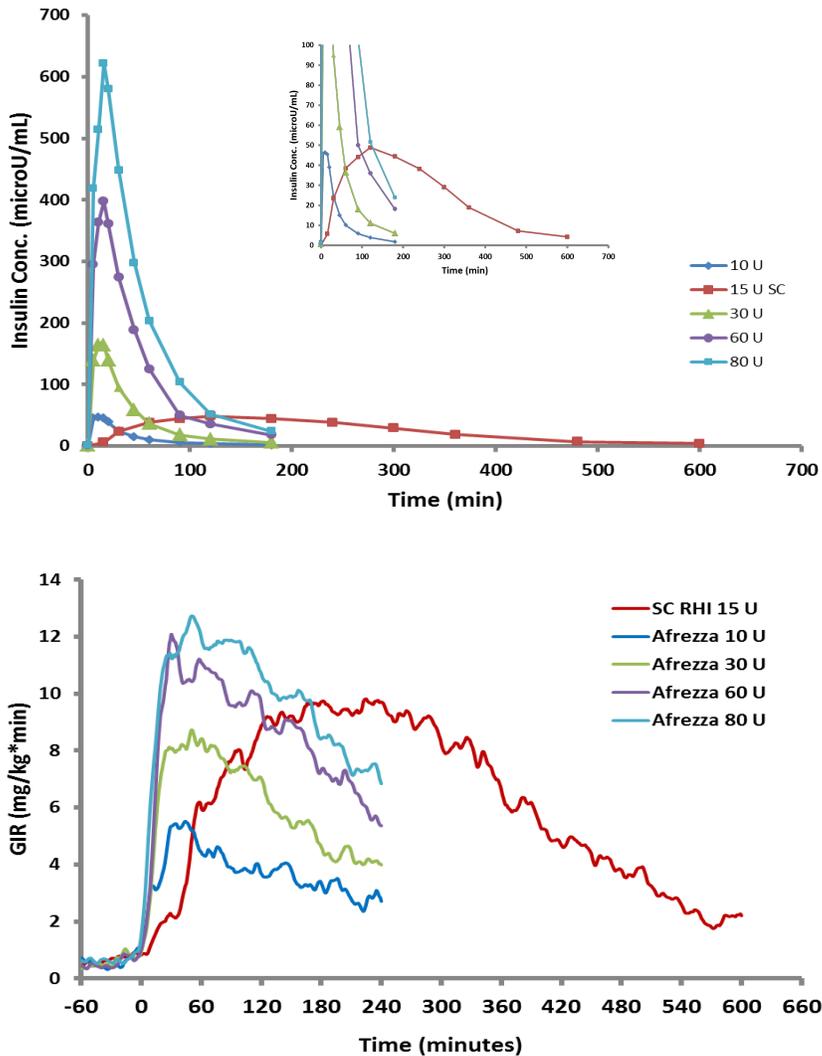


**Figure 2: Summary of application's justification for the proposed dosing conversion**

### 2.3 Assessment of Dosing Regimen Based on Clinical Pharmacology Data

The applicant conducted one dose-ranging study (i.e., study MKC-TI-176) 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 (RHI) (15 IU). In this study both PK and PD were assessed (see Figure 3); however, in this section we only focus on PD data and PK data are summarized in section 2.5. In this clamp study, glucose infusion rate was

measured up to 240 minutes for Afrezza arms and up to 600 minutes for SC arm. Area under the curve for GIR-time profile (i.e., AUCGIR) was the primary PD endpoint. The dosing conversion factors based on the comparison of  $GIRAUC_{0-240}$  between treatment groups and assuming a linear dose-response for SC insulin is shown in Table 3 below. Since a less-than dose proportional dose-response relationship for SC insulin is known, the dosing conversion in real life setting could be different than that reported in Table 3. However, for the approximate SC equivalent dose range (based on Afrezza dose range of 10-80 U) of approximately 3-25 units, the assumption of linearity is not unreasonable.



**Figure 3:** Insulin concentration (upper) and GIR (lower) – time profiles in healthy subjects from study MKC-T1-176 (data source: \\CDSESUB1\evsprod\NDA022472\0074\m5\datasets\mkc-ti-176\analysis\adam\datasets)

**Table 3: Comparison of dosing conversion factors - estimation based on AUCGIR comparison vs. the proposed labeling**

Dosing	Dose (U)	AUCGIR <sub>0-240</sub> (mg/kg/min)	Equivalent SC doses based on AUCGIR comparison (U)	Assumed equal SC doses in the proposed labeling (U)
SC	15	1596	-	-
AFREZZA	10	760	7.14	3
AFREZZA	30	1342	12.61	7-9
AFREZZA	60	1929	18.13	16-18
AFREZZA	80	2188	20.56	-

The above table clearly indicates that the recommended dosing conversion proposed to go from SC insulin to Gen-2 delivered Afrezza insulin (refer to data in 5<sup>th</sup> column) is not consistent with the data from PK/PD study (refer to data in 4<sup>th</sup> column). Further, these data also does not adequately support the dosing regimen tested in Phase 3 trials MKC-TI-171 and MKC-TI-175 for conversion from SC insulin to Gen-2 delivered Afrezza insulin (See above, AFREZZA Dosage Chart for Study MKC-TI-171).

A parallel characterization of dose-response covering a range of dosage for Afrezza and SC insulin in the same study is needed for more reliable determination of the dosing regimen for patients switching from SC insulin to Afrezza. In absence of such information it will be an unguided experiment at each patient level to adjust the dosing titration till they find the dosage suitable for him/her (unguided because it will not be known - how much additional benefit to expect by increasing the dose of Afrezza, whether the same dosing titration paradigm that is followed for SC insulin be followed with Afrezza, and how much dose of Afrezza need to be increased/decreased to achieve the desired glucose control). This lack of information is not in interest of patients for a therapy that could potentially be used by millions.

#### **2.4 Assessment of Dose-Proportionality in PD Response in Healthy Subjects and its Potential Impact on Titration**

Data from Study MKC-TI-176 were also analyzed to assess the dose-proportionality for PK and PD. Although, in the dose range tested, increase in PK (e.g., insulin AUC) was dose proportional (discussed in section 2.5), increase in PD (i.e., GIRAUC<sub>0-240</sub>) was less than dose proportional (see Table 4). 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 (see Figure 4 and Figure 5). Figure 4 shows the PD response for each exposure quartile (representing 12.5% interval) and demonstrates that with an increase in median insulin AUC<sub>0-180</sub> exposure from 7466 to 35261  $\mu\text{IU}/\text{mL} \cdot \text{min}$  (i.e., about 6.6 fold increase), median AUCGIR<sub>0-240</sub> only increased from 1542 to 2188 (i.e., 1.4 fold). Figure 5 is a scatter plot of insulin AUC<sub>0-180</sub> vs. AUCGIR<sub>0-240</sub>, which shows that (a) the variability in insulin exposure (AUC<sub>0-180</sub>) becomes larger with increasing dose (see Table 5), (b) the PD response (AUCGIR<sub>0-240</sub>) for 60 and 80 U dose are largely overlapping, and (c) a trend of less incremental dose-related benefit is evident from the best-fit line. Further, since only one dose of subcutaneously delivered insulin was evaluated in this study, it is not possible to directly

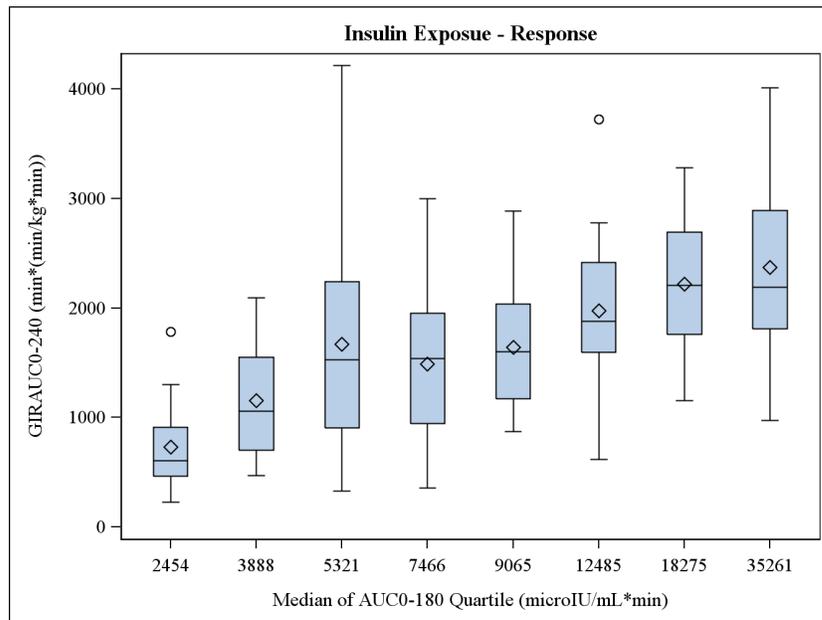
evaluate whether the non-proportional increase in AUCGIR observed for Afrezza would have also been observed for SC insulin.

**Table 4: Summary of Dose- GIRAUC<sub>0-240</sub> (Geometric mean) (data source: Study MKC-TI-176)**

Dose	10 U TI	30 U TI	60 U TI	80 U TI	Slope (90% CI)
N	32	32	32	32	
GIRAUC <sub>0-240</sub> (min*(mg/kg*min))	760.22	1342.52	1929.16	2188.60	0.512 (0.457, 0.567)
GIR <sub>max</sub> (mg/kg*min)	7.52	11.20	14.41	15.48	0.352 (0.304, 0.401)

**Table 5: Summary of between-subject variability (BSV, %CV) following Afrezza in healthy subjects (data source: Study MKC-TI-176)**

Dose	Afrezza (U)				SC RHI (IU)
	10	30	60	80	15
PK AUC <sub>0-180</sub>	42.3	61.1	72.7	89.6	35.4
PD AUCGIR <sub>0-240</sub>	56.7	40.9	34	33.5	36.9



**Figure 4: Relationship between insulin AUC<sub>0-180</sub> and GIRAUC<sub>0-240</sub>: Each quartile of AUC<sub>0-180</sub> represents 12.5% interval (data source: Study MKC-TI-176)**

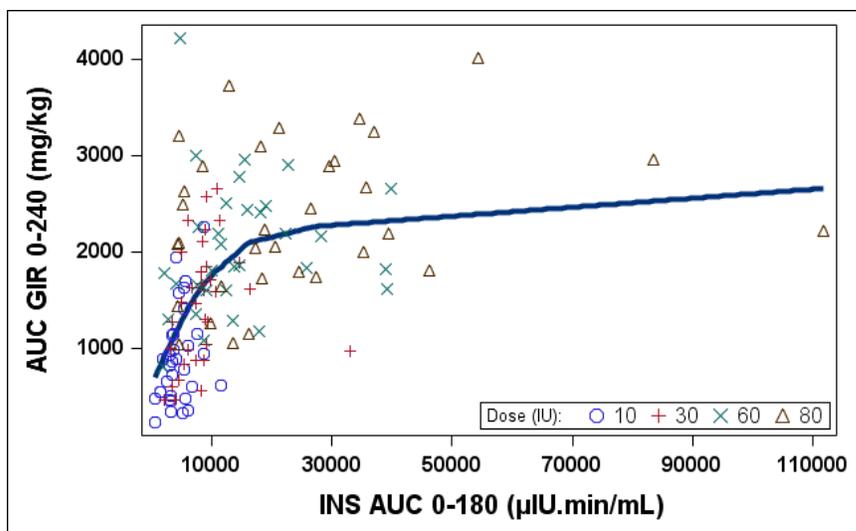


Figure 5: Scatter plot for insulin  $AUC_{0-180}$  vs.  $GIR AUC_{0-240}$ . (line: Loess fit, data source: Study MKC-TI-176)

## 2.5 Assessment of PK Dose-Proportionality and Relative Bioavailability for Gen2 Delivered Afrezza Insulin in Healthy Subjects

PK data from Study MKC-TI-176 in healthy subjects were analyzed to assess dose-proportionality for PK parameters – systemic exposure ( $AUC_{0-inf}$ ) and peak plasma concentration ( $C_{max}$ ). The increase in PK parameters was found to be dose-proportional, as slopes between PK parameters and doses were 0.949 (90% CI=0.880 to 1.019) and 1.067 (90% CI=1.013 to 1.120) for  $AUC_{0-inf}$  and  $C_{max}$ , respectively, based on a power model<sup>1</sup>. PK profiles following Afrezza doses of 10, 30, 60 and 80 U are shown in Figure 3 of section 2.3.

Systemic exposures for insulins (i.e., insulin AUC) from Afrezza doses were compared with the systemic exposure for insulin from SC administration to determine the relative bioavailability. Values of relative bioavailability of AFREZZA referencing that of 15 IU SC were approximately 24% and 62% based on  $AUC_{inf}$  and  $AUC_{180}$ , respectively.

As stated above the increase in PD measure (i.e.,  $AUC_{GIR}$ ) was less than dose proportional. Assuming that the PD response for SC will increase in a dose proportional manner (because of availability of data from only one dose), relative to SC, PD effect for AFREZZA were 36%, 23%, 17%, and 14% respectively for 10, 30, 60, and 80 U doses based on  $AUC_{GIR_{0-inf}}$  metric, and 71%, 42%, 30%, and 26% respectively based on  $AUC_{GIR_{240}}$  metric.

<sup>1</sup> Power model to test dose-proportionality: PK parameter (AUC or  $C_{max}$ ) =  $a \cdot \text{Dose}^{\text{slope}}$

## 2.6 PK and PD for Gen2 Delivered Afrezza Insulin in Type 1 Diabetes

Insulin PK and PD were also assessed in a crossover euglycemic clamp study (Study MKC-TI-177) in T1DM subjects (n=12) comparing Gen2 delivered AFREZZA insulin (20 U) with insulin lispro (8 IU, rapid acting analog (RAA)). Time profiles for insulin concentrations (upper panel) and glucose infusion rate (lower panel) are shown in the Figure 6 and PK data are presented in Table 6.

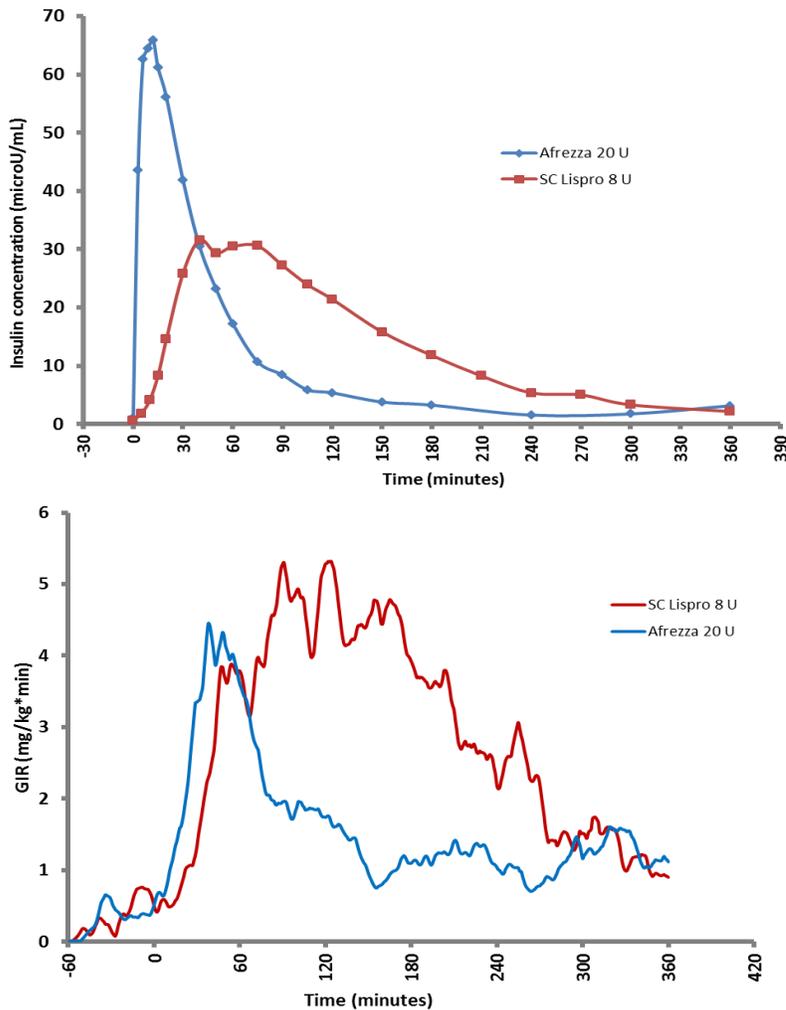


Figure 6: Insulin concentration (upper) and GIR (lower) – time profiles (TI – Gen2 delivered Afrezza, RAA –rapid acting analog insulin lispro; data source - \\CDSESUB1\evsprod\NDA022472\0074\m5\datasets\mkc-ti-177)

**Table 6: Summary of PK and PD parameters in T1DM**

<b>PK</b>	<b>Treatment</b>	<b>AUC<sub>0-360</sub></b>	<b>C<sub>max</sub></b>
	AFREZZA	3684.9	60.8
	RAA	4341.9	36.0
<b>PD</b>	<b>Treatment</b>	<b>AUCGIR<sub>0-360</sub></b>	<b>GIR<sub>max</sub></b>
	AFREZZA	522.8	6.1
	RAA	1007.2	9.4

As shown in Table 6, the relative bioavailability for Gen2 delivered insulin vs. insulin lispro (based on comparison of AUC<sub>360</sub>) is about 33%. Relative PD effect for Gen2 delivered AFREZZA is about 52% based on AUCGIR<sub>240</sub>.

*Reviewer's comment:*

- 1. It is not clear why in this study PD effect (GIR-time profile) for Afrezza does not mirror the PK (time-concentration) profile.*
- 2. PK comparison in this study may not provide meaningful information because the comparison is based on two different insulin molecules (i.e., RHI for AFREZZA and lispro). However, PD comparison is still meaningful, which shows no significant difference in GIR PD response between RIA and Afrezza up to about 50 minutes, after that PD response for Afrezza declines while it is maintained for RAA for up to 5 to 6 hours. This suggests that ratio of bolus to basal insulin required for adequate glycemic control in patients using Afrezza vs. SC insulin products might be different.*

## **2.7 Clinical Pharmacology Findings from Previous Submissions**

### **2.7.1 Comparability (1) between Gen2 and MedTone Model C, and (2) between two cartridges of 10 U and one cartridge of 20 U for Gen2 (from the amendment dated 6/29/2010)**

Insulin exposure comparability was evaluated in a 3-way crossover trial in healthy volunteers (Study MKC-TI-142) and results are summarized in the following tables. It was concluded that insulin PK was comparable between two inhalers (i.e., Gen2 and MedTone Model C) based on baseline adjusted and unadjusted PK profiles. Point estimates and confidence intervals for AUC and C<sub>max</sub> comparisons were within 0.80-1.25 (see Table 7). In addition, insulin PK was comparable between two cartridges of 10 U and one cartridge of 20 U for the Gen2 delivered insulin. Again, point estimates and confidence intervals for AUC and C<sub>max</sub> comparisons were within 0.80-1.25 (see Table 8).

**Table 7: Least square geometric mean ratios (90% confidence interval) of AUC and Cmax comparing Gen2 (20U) versus Model C (30 U) inhaler (n=46)**

	AUC	C <sub>max</sub>
Baseline unadjusted	1.006 (0.954, 1.060)	1.020 (0.948, 1.099)
Baseline adjusted (predose measurement)	0.997 (0.940, 1.059)	1.017 (0.941, 1.099)
Baseline adjusted (C-peptide)	1.060 (0.981, 1.145)	1.082 (0.992, 1.180)

**Table 8: Least square geometric mean ratios (90% confidence interval) of AUC and Cmax comparing 2 x 10 U versus 1 x 20 U dose of Gen2 delivered insulin (n=46)**

	AUC	C <sub>max</sub>
Baseline unadjusted	0.973 (0.923, 1.023)	0.954 (0.886, 1.028)
Baseline adjusted (predose measurement)	0.970 (0.914, 1.030)	0.951 (0.880, 1.028)
Baseline adjusted (C-peptide)	0.957 (0.886, 1.039)	0.930 (0.852, 1.014)

*Reviewer's comment: The above study results are considered exploratory because 1) the bioanalytical method used in this study was not inspected by OSI and 2) only PK was evaluated without PD. The verification of bioanalytical studies by OSI is considered important because the applicant had failed the pivotal BE study in the original submission because of deficiencies in conduct of analytical methods.*

### 2.7.2 Insulin Exposure Following Multiple Doses (from the original submission)

The applicant evaluated insulin PK after multiple doses (7 days) in T2DM subjects in a study designed to evaluate the effect of asthma on insulin PK/PD for Model C delivered Afrezza insulin (MKC-TI-027). Insulin PK was estimated under the euglycemic clamp procedure. Only the results for non-asthmatic patients are summarized in the Table 9. After multiple dose administration for 7 days, insulin AUC was increased by about 20%.

**Table 9: Insulin PK parameters (geometric mean) in T2DM following multiple doses (Baseline-correction using previous concentrations)**

	Visit 3 (1 <sup>st</sup> dose) (n=15)	Visit 4 <sup>a</sup> (after 7 days) (n=14)
AUC <sub>0-6h</sub> (min*mU/L) <sup>a</sup> (% CV)	2583 (73.6)	3096 (83.1)
C <sub>max</sub> (mU/L) <sup>b</sup> (% CV)	31.8 (90.1)	38.5 (93.8)
T <sub>max</sub> (min)	15	9

a; geometric mean

*Reviewer's comment: Although this study was prematurely terminated because the applicant could not timely enroll subjects with asthma as planned, the results from non-asthmatic subjects can still be assessed. However, the applicant did not analyze the PD data from this study; therefore, only PK data are summarized.*

### 2.7.3 Intrinsic and Extrinsic Factors (from the original submission)

Impact of intrinsic and extrinsic factors on PK/PD of insulin was evaluated in the original submission for the Model C delivered AFREZZA insulin. In addition to insulin, these studies also evaluated the impact on fumaryl diketopiperazine (FDKP) exposures. FDKP is the main excipient used in the technosphere technology by the applicant. The following is a brief summary of major findings.

- Lung Disease

The applicant concluded that the effect of diseases such as COPD and asthma, and upper respiratory infection was not significant on insulin and/or FDKP exposure for Model C delivered AFREZZA insulin. Applicant noted that smoking increased insulin AUC and GIR by about 25% and 35%, respectively, compared to that of control.

*Reviewer's Comment*

*Agency found some limitations in the data provided to support conclusions for the effect of asthma and COPD. Only the assessment for the effect of smoking was reliable.*

*The clamp study conducted to assess the impact of asthma was terminated before completion. Applicant cited difficulties in timely enrollment of subjects with asthma. Overall only 5 subjects with asthma were enrolled compared to 15 in the control group. Further, applicant did not analyze PD data from this study. Based on the limited PK data, the comparison of PK at day 7 between asthmatics vs. non-asthmatics shows a decline in exposure by 57% (see Table 10). There was another study with the comparison between asthmatic and non-asthmatic as part of drug interaction with Albuterol (Study TI-113). However, the clamp procedures were not properly conducted in the study as C-peptide concentrations were significantly fluctuated during the study. Therefore, insulin PK parameters from the study may not be reliable for the pivotal comparability test.*

*For COPD, again a clamp study was conducted. However, clamp was not adequately controlled. Applicant provided following justification for not analyzing the PD data from this study: "The GIR analysis specified in the SAP was performed; however, the results of the analysis are not presented because the derived GIR parameters could not be interpreted. The individual BG values indicated that BG concentrations were not satisfactorily maintained during the clamp procedure, as BG concentrations were rarely at target concentration or within the upper and lower concentration limits. The large contributions of the lispro infusion to the overall insulin PK profiles and the significant amount of endogenous insulin secreted by some subjects (as indicated by the C-peptide concentrations) also made the data difficult to interpret as the glucose-lowering effect of TI Inhalation Powder was indistinguishable from that of infused insulin lispro. A review of the analysis confirmed that the GIR data could not be interpreted as intended for the study." Comparison of PK data between COPD vs. control subjects from this study demonstrated comparable insulin and FDKP exposures between two groups (see Table 10).*

*The effect of smoking was also analyzed in a clamp study. As noted by the applicant increase in insulin exposure (by 25%) and a corresponding increase in PD (i.e., AUCGIR by 35%) were observed. The systemic exposures for FDKP decreased by 29% (see Table 10).*

**Table 10: Summary of insulin and FDKP AUC in control and with disease or smoking**

	Parameter		Control	Disease or smoking	Ratio <sup>#</sup>
<b>COPD*</b> (n=17 COPD; 19 non-COPD)	Insulin	AUC <sub>0-240</sub> (mU*min/L)	2117	1933	1.1 (0.888, 1.352)
	FDKP	AUC <sub>0-240</sub> (ng*min/mL)	16676	18821	0.89 (0.735, 1.067)
<b>Asthma**</b> (n=15 nonasthmatics, 5 asthmatic T2DM)	Insulin	AUC <sub>0-360</sub> (mU*min/L)	2583 <sup>&amp;</sup> 3096 <sup>%</sup>	1823 <sup>&amp;</sup> 1319 <sup>%</sup>	0.71 0.43
	FDKP	AUC <sub>0-480</sub> (ng*min/mL)	15903	6833	0.43
<b>Smoking***</b> (n=12 smokers, n=12 non-smokers T2DM)	Insulin	AUC <sub>0-480</sub> (mU*min/L)	1677	2092	1.25
	GIR	AUC <sub>0-480</sub> (mg*min/kg)	362	490	1.35
	FDKP	AUC <sub>0-480</sub> (ng*min/mL)	17463	12376	0.71

\*: C-peptide baseline correction; clamp procedure

\*\* : baseline adjusted using t=0; clamp procedure

\*\*\*: baseline adjusted using later time points; clamp procedure

#: arithmetic mean ratio (disease/control) except COPD as geometric mean ratio of control/disease with 90% confidence interval

&: after 1<sup>st</sup> dose

%: after 7 days

*In conclusion, the available data from clinical pharmacology studies for AFREZZ does not conclusively support the recommendation for use in patients with underlying lung diseases. The data from clinical studies will be considered along with the available limited PK results to develop the final labeling recommendations.*

- Renal or hepatic impairment

Insulin exposure changes in the renal or hepatic impairment subjects have not been evaluated for insulin delivered by AFREZZA. Exposure change for FDKP was found to be not significant to warrant any dose adjustment, also suggesting no accumulation of carrier after single dose in these patients compared to patients with normal organ function.

Review of literature information for impact of renal or hepatic impairment on insulin exposures indicates a non-significant change in exposures for RHI (Abstract by Jaros et al., 2004 ADA), insulin degludec (Clin Pharmacokin 53:175-183, 2014), or insulin aspart (Br J Clin Pharmacol 60:469-476, 2005) based on organ function.

*Reviewer's comment: Studies evaluating the impact of hepatic and renal impairment only assessed the impact on FDKP exposures. Literature information for impact of organ function impairment on insulin exposures is also limited. Therefore, we recommend the following for labeling: the dose requirements for AFREZZA may be reduced in patients with renal or hepatic impairment. Careful monitoring and dose adjustment be considered as necessary.*

- The applicant reported that bronchodilators and inhaled steroids did not significantly affect insulin exposure (see Table 11).

**Table 11: Geometric mean ratio of insulin pharmacokinetic parameters in healthy volunteers (Study TI-114)**

Parameter	Treatment Regimen Comparison	Geometric Mean <sup>a</sup>		Geometric Mean Ratio (%) (90% CI)	p Value
		Test	Reference		
AUC <sub>0-360</sub> (mU·min/L)	TI after albuterol : TI alone	4490.7	4819.8	93.17 (79.14 – 109.69)	0.4647
C <sub>max</sub> (mU/L)	TI after albuterol : TI alone	78.562	77.746	101.05 (86.05 – 118.66)	0.9122
t <sub>1/2</sub> (min)	TI after albuterol : TI alone	31.4	33.3 <sup>b</sup>	94.11 (78.45 – 112.90)	0.5721
AUC <sub>0-360</sub> (mU·min/L)	TI after fluticasone : TI alone	4414.7	4819.8	91.59 (77.80 – 107.83)	0.3656
C <sub>max</sub> (mU/L)	TI after fluticasone : TI alone	75.405	77.746	96.99 (82.60 – 113.89)	0.7469
t <sub>1/2</sub> (min)	TI after fluticasone : TI alone	30.8	33.3 <sup>b</sup>	92.48 (77.09 – 110.94)	0.4677

<sup>a</sup>N = 12 unless stated

<sup>b</sup>N = 10

Data Source: Section 14.3, Table 14.3.1

*Reviewer's comment: Afrezza will be contraindicated for patients with lung diseases because of lack of long-term clinical efficacy and safety data. The magnitude of change observed in single dose DDI study under clamp procedures (Table 11) indicates that Afrezza dose adjustment may not be needed. However, caution should be exercised if Afrezza is co-administered with bronchodilators and inhaled steroids because of lack of long-term clinical data.*

## 2.8 Exploratory Simulations for Dose-Response Relationship of Afrezza vs. Subcutaneously Administered RHI

The objective of this exploratory analysis was to gain insight on the nature of dose-response (similarities or differences) for Afrezza and SC RHI. The PKPD study (#176) offered limited dose-response comparison of Afrezza (4 dose levels) versus one dose for SC-RHI. Therefore, modeling and simulations were used to simulate the PKPD behavior of these two formulations to construct a dose-response using systemic insulin concentration and PD (GIR) relationship. PK (insulin concentration-time) and PD (GIR-time) profiles for 4 single rising doses of Afrezza (from study 176) and 3 single doses of SC RHI (digitally extracted from Becker et al, Diab. Care, 30(10), 2007) from

euglycemic clamp studies were used. An effect compartment model similar to that described elsewhere was used to link the insulin concentrations to the GIR response data (see Woodworth et al. Establishment of Time-Action Profiles for Regular and NPH Insulin Using Pharmacodynamic Modeling *Diabetes Care* 1994, Vol 17(1) 64-69 and Tornøe CW et al. Grey-box modeling of pharmacokinetic/pharmacodynamics systems. *J Pharmacokinetic Pharmacodyn* 2004 Oct; 31(5): 401-17). Briefly, this model described the GIR over time kinetics using a hypothetical effect compartment, which accounts for observed temporal delay in the PD response (GIR) in relation to the systemic insulin concentrations. The relationship between effect compartment insulin concentrations and GIR response was explained using a sigmoidal Emax model ( $E_{max} * C_{e,ins}^{\gamma} / (EC_{50}^{\gamma} + C_{e,ins}^{\gamma})$ ) where,  $C_{e,ins}$  is insulin effect compartment concentrations (driven by transfer rate constant),  $EC_{50}$  is the insulin concentration producing 50% of the maximum effect ( $E_{max}$ ) and  $\gamma$  is the hill coefficient.).

The scheme for the modeling and simulation exercise is shown in Figure 7. Afrezza PK for 10, 30, 60, and 80 U dosages was adequately described with a two-compartmental model, while a one-compartmental model was sufficient for describing the PK profile for SC insulin at approximate dosage of 5.25, 10.5, and 21 IU (see Figures 8). Same PD model was used for both Afrezza and SC insulins; however, there were some differences in PD model parameters between two products (see Table 12). Mean PD profiles were also reasonably well characterized by the model (see Figures 9). The PD parameters reported by Woodworth et al explained the mean SC-RHI data in the Afrezza study 176 (for 15 IU dose) as well as mean PD data from Becker et al (~5 to 20 IU) assuring that underlying concentration-effect relationship was consistent for RHI and could be used to predict response at higher dose levels (beyond 20 IU) assuming PK is linear at those dose levels.

Once the respective PK/PD models were deemed reasonable in their ability to explain the observed data at mean level (based on graphical comparison of observed vs. predicted data), they were used to simulate PK and PD profiles at higher dosage (for SC RHI dose up to 400 IU, and for Afrezza dosage equivalent to 400 IU SC RHI based on the conversion factor of 2.5 to 1 – that is 10 U of Afrezza is presented as 4 IU of SC equivalent dose). The simulated dose-response curves for Afrezza insulin vs. SC RHI are shown in Figure 10.

The more reliable comparisons are red profile (AUC GIR 0-600 for RHI) vs. green profile (AUC GIR 0-240 for Afrezza). Purple profile, which shows the AUC GIR 0-600 for Afrezza, has limitations: Afrezza GIR data were only collected up to 240 minutes; therefore, there is no way to validate predictions beyond 240 minutes. Afrezza GIR 0-600 predictions are based on GIR data collected up to 240 minutes.

Comparison of red vs. green profiles shows that Afrezza may reach the point of diminishing return at a relatively lower dose compared to RHI. The clinically relevant dose range, i.e., dosage up to 80 IU, is magnified in the bottom panel of that figure. The non-linear relationship between insulin concentrations and its receptor mediated glucose disposition in the body may attribute to the non-proportionality in dose-PD response.

The strengths and limitations of this modeling and simulation exercise are summarized below:

- Strengths
  - PKPD model validated (graphical comparison) for four dosage of Afrezza
  - PKPD model validated (graphical comparison) for three dosage of subcutaneously administered RHI
- Limitations
  - Afrezza and SC RHI data comes from two separate studies (cross-study comparison)
  - Assumed that PK is linear at higher dosage; no data to substantiate that
  - Exploratory in nature (parameter values are based on publications; only attempts to explain mean observations)

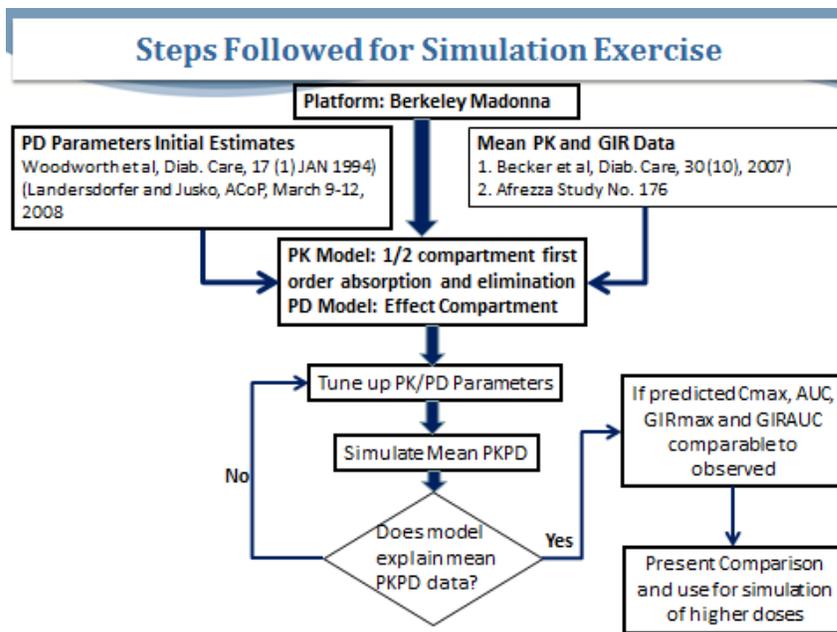
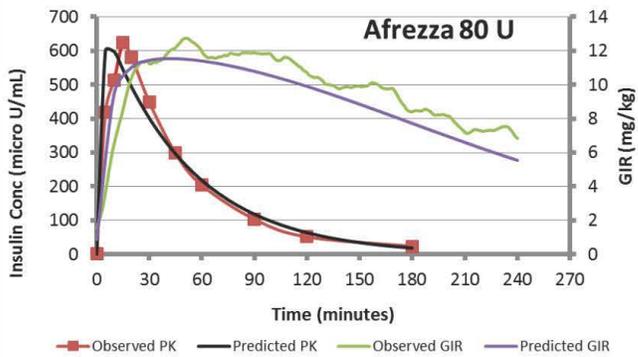
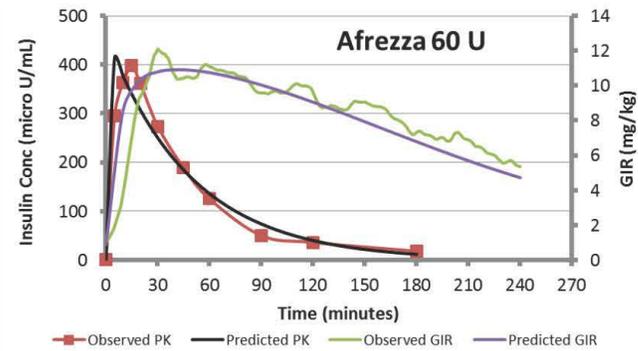
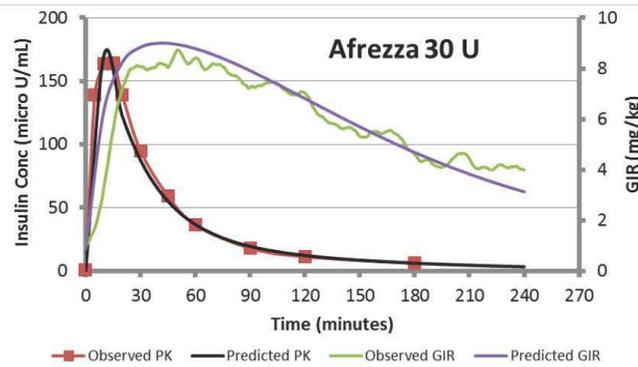
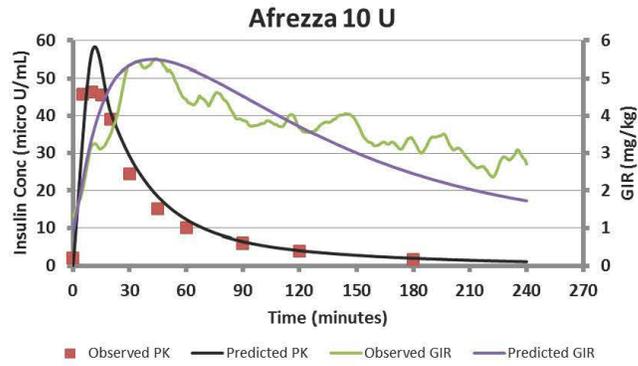


Figure 7: Schematic summary for the modeling and simulation

Table 12: PD model parameters for Afrezza vs. SC insulin

	Afrezza	SC
$E_{max}$ (mg/kg/min)	14*	14*
$EC_{50}$ (micro U/mL)	37	63**
$E_0$ (mg/kg/min)	0.9	0.2
$\gamma$	1	2
$T_{eq}$ (min)*	35	30

\*Similar to parameters ( $E_{max}$  of 5.6 mmol/min,  $EC_{50}$  of 440 pmol/L) from Woodworth et al. Diabetes Care 1994, Vol 17(1):64-69.



**Figure 8: Observed vs. Model Predicted insulin concentration vs. time and GIR vs. time profiles for Afrezza insulin**

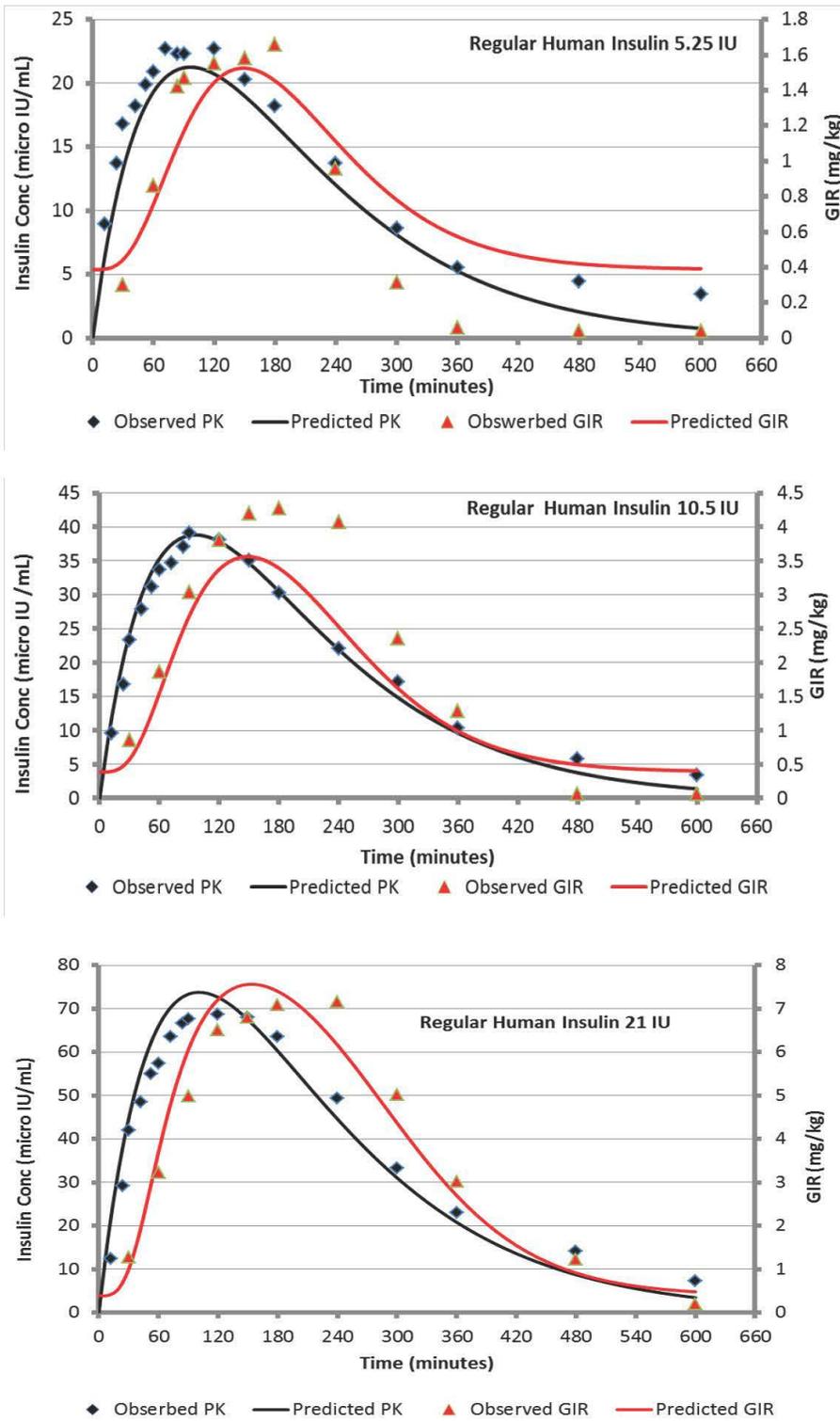


Figure 9: Observed vs. Model Predicted insulin concentration vs. time and GIR vs. time profiles for SC insulin

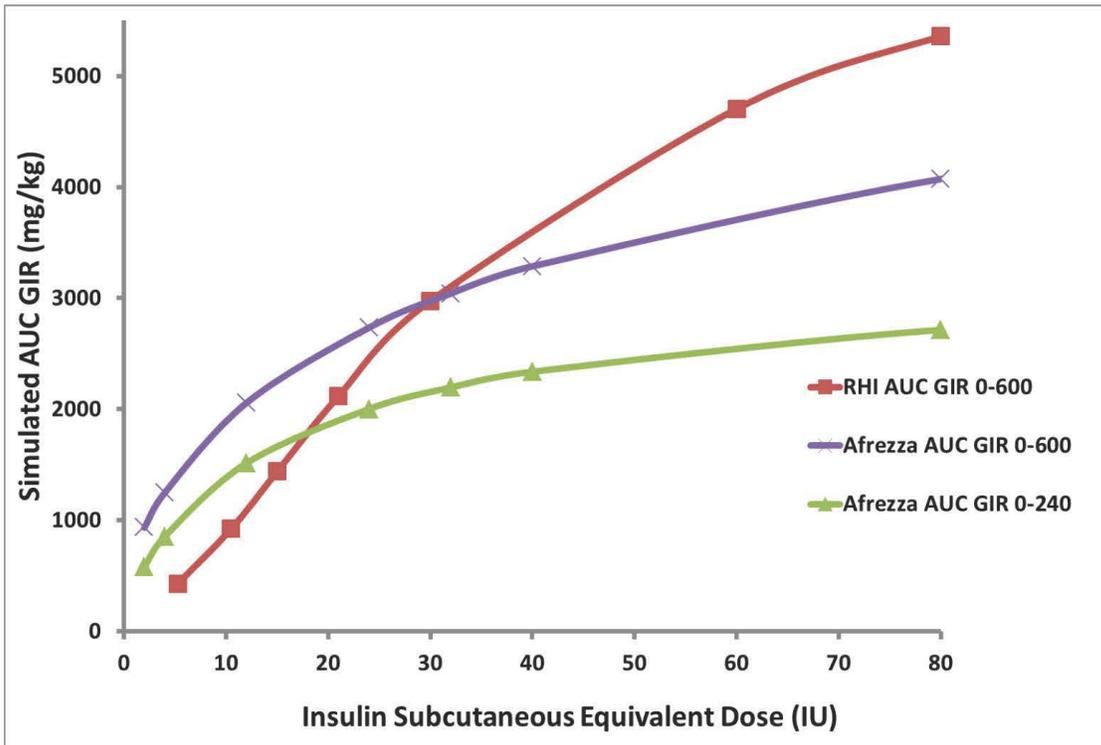
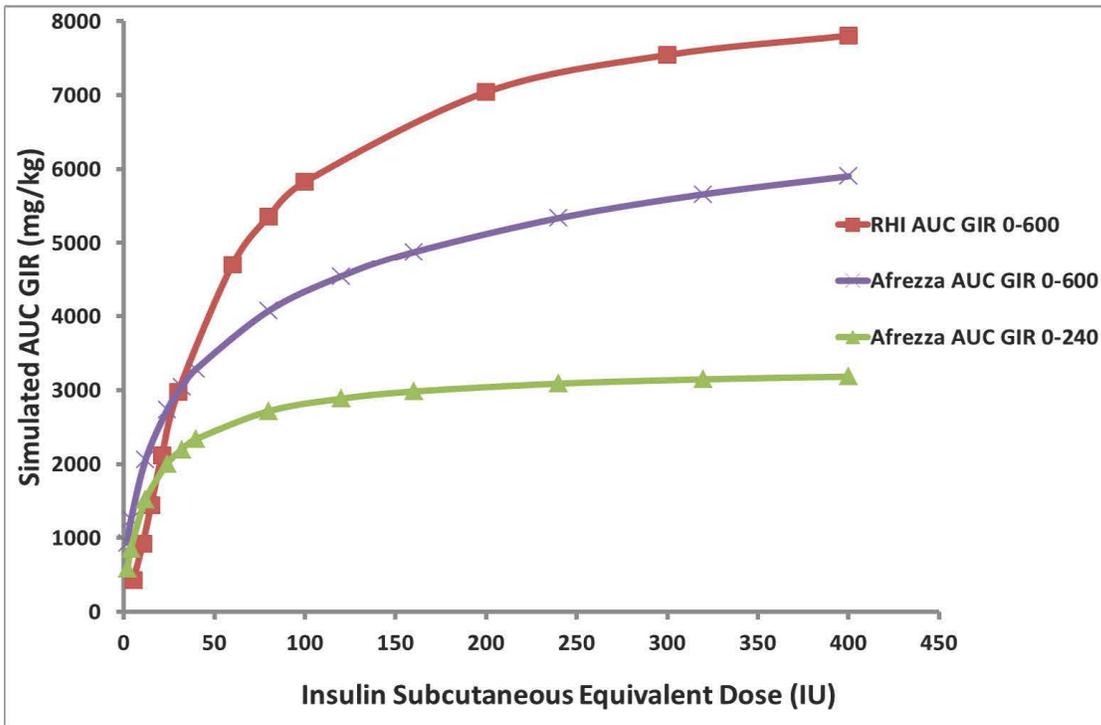


Figure 10: Simulated dose-response curve for Afrezza insulin vs. SC RHI. Top panel covers the extended range; the bottom panel focuses on the clinically relevant dose range

### 3 Individual Study Review

#### 3.1 Dose-Response in healthy subjects following AFREZZA using Gen2 inhaler (MKC-TI-176)

Study MKC-TI-176: A Phase 1, Open-label, Randomized, Crossover Design Clinical Trial in Healthy Normal Volunteers to Evaluate Insulin Exposure and Effect Following Inhalation of Technosphere® Insulin Inhalation Powder at Multiple Doses Using the Gen2C Inhaler (EDR: [\Cdsub1\evsprod\NDA022472\0074\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\mkc-ti-176](#))

The insulin dose-response was evaluated in a randomized, crossover trial with healthy volunteers (n=32) for the following 5 treatments under the clamp procedures:

- Crossover treatments
  - 10 U (one 10 U cartridge)
  - 30 U (one 10 U + one 20 U cartridge)
  - 60 U (three 20 U cartridge)
  - 80 U (four 20 U cartridge)
- RHI as a 15 IU SC injection (final treatment)

The information on formulations was as follows:

<b>Study drug:</b>	Technosphere Insulin Inhalation Powder
<b>Active ingredient:</b>	Human insulin, recombinant DNA origin
<b>Formulation:</b>	Each milligram of formulation contains 3.0 U of human insulin
<b>Dosage form:</b>	Inhalation powder
<b>Frequency:</b>	As per dosing sequence
<b>Packaged as for Gen2C Inhaler:</b>	Premetered single-dose cartridges filled with 3.3 mg or 6.7 mg of Technosphere Insulin Inhalation Powder containing 10 U or 20 U of insulin, respectively
<b>Manufactured by:</b>	MannKind Corporation
<b>Storage conditions at clinical site:</b>	Refrigerated at 2°C to 8°C (or 36°F to 46°F)
<b>Storage conditions by subject:</b>	Not applicable
<b>Packaging description:</b>	Blister card comprised of 5 blister strips, each containing 3 cartridges (15 cartridges per blister card). Each blister card is overwrapped in a foil pouch. Three blister cards per box (45 cartridges per box)
<b>Lot numbers:</b>	10 IU, Lot D110006 20 IU, Lot D110007
<b>Study drug:</b>	Regular human insulin
<b>Active ingredient:</b>	Regular insulin human injection, USP (rDNA origin)
<b>Formulation:</b>	100 U/mL (U-100)
<b>Dosage form:</b>	SC injection, 15 IU per dose
<b>Frequency:</b>	Single dose
<b>Manufactured by:</b>	Eli Lilly and Company
<b>Storage conditions at clinical site:</b>	Not in-use stored under refrigeration (36°F to 46°F [2°C to 8°C]); in-use can be kept unrefrigerated for 31 days (below 86°F [30°C])
<b>Storage conditions by subject:</b>	Not applicable
<b>Packaging description:</b>	10 mL vials
<b>Lot and batch numbers:</b>	Purchased commercially. Lot A869941J

Blood sampling scheme was as follows:

Sample No.	Sample Time (min)	Variable
1	Approximately 30 minutes before dosing	For all samples: <ul style="list-style-type: none"> <li>5 mL SST tube for C-peptide, insulin, and blood glucose monitored by the Biostator</li> </ul>
2	Approximately 15 minutes before dosing	
3	0 (within 3 min before dosing)	
4	15	
5	30	
6	60	
7	90	
8	120	
9	180	
10	240	
11	300	
12	360	
13	480	
14	600	

At Visit 2, eligible subjects arrived at the clinic in the fasted state (no caloric intake after 10 PM the previous evening except water). They were trained and practiced inhalations with an empty cartridge placed in the Gen2C inhaler. Once trained, the subjects inhaled using an empty cartridge with the Gen 2 inhaler, then immediately consumed a 360 calorie meal.

Blood samples for insulin and C-peptide were taken over a 3-hour period relative to the empty cartridge inhalation to determine each subject's mealtime C-peptide-to-insulin relationship. A drop of blood from these samples was analyzed in the clinic for blood glucose (BG) using a glucose meter.

#### Major Steps for the Glucose Clamp Procedure (Visits 3 through 7)

Hyperinsulinemic, euglycemic clamp procedures were conducted at Visits 3 through 7. Practice inhalations with an empty cartridge placed in the Gen2C inhaler were performed before any dosing. Subjects arrived at the site in the fasting state (no caloric intake except water after 10 PM the evening before dosing) and were connected to the Biostator equipment to start the hyperinsulinemic infusion. The target blood glucose was 90 ( $\pm$ 10) mg/dL, and the insulin infusion rate was "locked" at 0.15 mU/kg•hr at least 90 minutes before dosing. The glucose clamp procedure visits, final visit, and the interim safety visit required a total of approximately 400 mL of blood.

Insulin PK and PD parameters for Afrezza are summarized in Tables 13 and 15 and their comparison against SC RHI is shown in Tables 14 and 16. It was concluded that insulin PK was proportional to inhaled doses as slopes between PK and dose were 0.949 (90% CI=0.880 to 1.019) and 1.067 (90% CI=1.013 to 1.120) for  $AUC_{0-inf}$  and  $C_{max}$ , respectively, in a power model. Mean values of relative bioavailability (RA) of AFREZZA referencing that of 15 IU SC RHI were approximately 24% and 62% based on  $AUC_{0-inf}$  and  $AUC_{0-180}$ , respectively.

Glucose infusion rate (GIR) of the clamp procedures was the pharmacodynamic (PD) measure and GIRAUC was the primary PD endpoints. The increase in GIRAUC was

less-than dose proportional. Assuming the proportionality in PD following SC, values of relative effect (PD) of AFREZZA were 36, 23, 17, and 14% for GIRAUC<sub>0-inf</sub> referencing that of SC.

**Table 13: Summary of insulin PK parameters in healthy subjects (C-peptide corrected)**

Parameter	10U TI (N = 32)	30U TI (N = 32)	60U TI (N = 32)	80U TI (N = 32)	Slope (90% CI) <sup>a,b</sup>
<b>AUC<sub>(0-120)</sub> (min*µIU/mL)</b>					
n	32	32	32	32	
Mean	3863.2	9325.4	22424.3	34893.6	
Geometric Mean	3416.52	8161.34	19015.68	27608.14	1.000 (0.939, 1.061)
SD	1634.31	5693.38	16294.82	31258.28	
Median	3869.4	8333.4	16433.5	29353.3	
%CV	42.3	61.1	72.7	89.6	
Min	600.4	3236.4	7044.9	9022.6	
Max	9139.8	33135.2	93548.5	175579.1	
<b>AUC<sub>(0-inf)</sub> (min*µIU/mL)</b>					
n	29	32	31	32	
Mean	4760.5	10231.1	24242.0	36661.3	
Geometric Mean	4151.07	9087.54	20951.49	29608.04	0.949 (0.880, 1.019)
SD	1903.21	5679.94	16423.00	31438.66	
Median	5111.8	9361.0	18758.7	31091.6	
%CV	40.0	55.5	67.7	85.8	
Min	658.4	3424.6	8293.5	10076.2	
Max	9677.4	33722.5	95079.2	178408.0	
<b>C<sub>max</sub> (µIU/mL)</b>					
n	32	32	32	32	
Mean	63.3	187.8	444.3	681.5	
Geometric Mean	53.82	149.80	350.23	494.38	1.067 (1.013, 1.120)
SD	44.24	156.40	361.79	704.66	
Median	50.0	129.9	308.5	481.1	
%CV	69.9	83.3	81.4	103.4	
Min	15.6	56.1	88.0	131.4	
Max	233.6	840.1	1827.1	3704.5	

<sup>a</sup> From power model:  $\log(\text{parameter}) = \text{period} + \log(\text{dose}) + \text{subject}$ , where subject is a random effect and dose is a continuous effect with compound symmetry variance/covariance matrix. Dose proportionality is achieved if the confidence limits are between 0.893 and 1.107.

<sup>b</sup> 15IU RHI treatment arm was not used in the analysis of dose response.

Source: Section 14.2, Table 14.2.1.2.1, Table 14.2.1.3.1

**Table 14: Insulin Relative BA following AFREZZA referencing SC in healthy subjects**

Parameter	15IU RHI (N=32) (Reference)	10U TI (N=32)	30U TI (N=32)	60U TI (N=32)	80U TI (N=32)
<b>AUC<sub>(0-120)</sub> (min*µIU/mL)</b>					
N	32	32	32	32	32
LS Mean	515.07	341.65	272.04	316.93	345.10
Ratio		0.66	0.53	0.62	0.67
(90% CI)		(0.57,0.77)	(0.46,0.61)	(0.53,0.71)	(0.58,0.77)
<b>AUC<sub>(0-∞)</sub> (min*µIU/mL)</b>					
N	29	27	29	28	29
LS Mean	1531.43	416.04	302.87	350.91	379.94
Ratio		0.27	0.20	0.23	0.25
(90% CI)		(0.23,0.32)	(0.17,0.23)	(0.19,0.27)	(0.21,0.29)
<b>C<sub>max</sub> (µIU/mL)</b>					
N	32	32	32	32	32
LS Mean	4.03	5.38	4.99	5.84	6.18
Ratio		1.34	1.24	1.45	1.53
(90% CI)		(1.16,1.54)	(1.08,1.43)	(1.26,1.67)	(1.33,1.76)

From ANOVA model: log(parameter) = sequence + treatment + subject, where subject is a random effect.  
Source: Section 14.2, Table 14.2.1.4.1

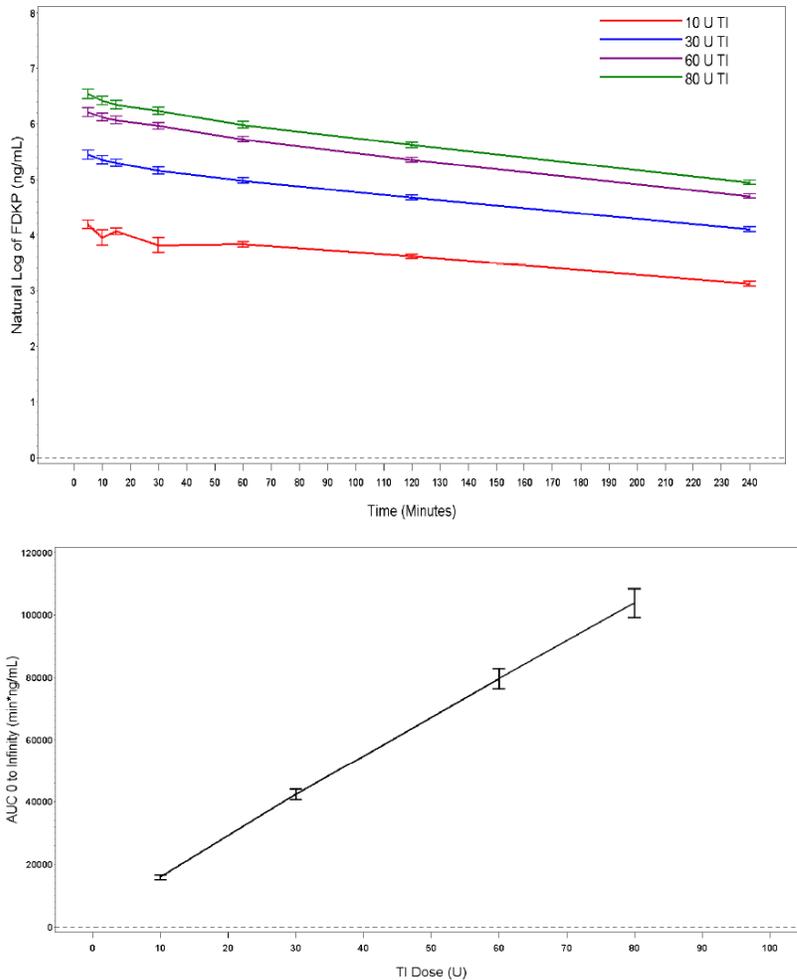
**Table 15: Summary of GIR data in healthy subjects**

		10U TI (N=32)	30U TI (N=32)	60U TI (N=32)	80U TI (N=32)	Slope (90% CI)*
GIR Moving Average Corrected						
AUC 0 TO 240 (min*(mg/kg*min))	N	32	32	32	32	
	Geometric Mean	760.22	1342.52	1929.16	2188.60	0.512 (0.487, 0.567)
AUC 0 TO INFINITY (min*(mg/kg*min))	N	31	31	32	32	
	Geometric Mean	935.42	1709.41	2552.86	2682.01	0.525 (0.482, 0.597)
Cmax ((mg/kg*min))	N	32	32	32	32	
	Geometric Mean	7.52	11.20	14.41	15.48	0.352 (0.304, 0.401)

**Table 16: Relative effect of AFREZZA to RHI in healthy subjects**

Statistic	Reference Arm:					
	15IU RHI (N=32)	10U TI (N=32)	30U TI (N=32)	60U TI (N=32)	80U TI (N=32)	
GIR Moving Average Corrected						
AUC 0 TO 240 (min*(mg/kg*min))	N	32	32	32	32	32
	LS Mean	106.42	76.02	44.75	32.15	27.36
	Ratio		0.71	0.42	0.30	0.26
	(90% CL)		(0.64,0.80)	(0.37,0.47)	(0.27,0.34)	(0.23,0.29)
AUC 0 TO INFINITY (min*(mg/kg*min))	N	32	31	31	32	32
	LS Mean	247.21	94.18	56.69	42.55	33.53
	Ratio		0.38	0.23	0.17	0.14
	(90% CL)		(0.33,0.44)	(0.20,0.27)	(0.15,0.20)	(0.12,0.16)
Cmax ((mg/kg*min))	N	32	32	32	32	32
	LS Mean	0.86	0.75	0.37	0.24	0.19
	Ratio		0.88	0.44	0.28	0.23
	(90% CL)		(0.79,0.97)	(0.39,0.48)	(0.25,0.31)	(0.20,0.25)

FDKP (the carrier in technosphere insulin) pharmacokinetics was also assessed in this study and increase in its systemic exposure was shown to be dose-proportional following inhalation administration of Afrezza (see Figure 11)



**Figure 11: Mean (SE) FDKP concentration-time profiles (upper panel) and its proportionality with doses (lower panel) following Afrezza in healthy subjects**

The sponsor's conclusions were as follows:

- The pharmacokinetic, pharmacodynamic, and safety data collected during this study in normal human volunteers was protocol-compliant, evaluable, of high quality, and appropriate for analysis.
- In healthy volunteers, there was increasing insulin exposure at each successive dose level of TI Inhalation Powder as reflected in  $C_{max}$  and in the total insulin concentration-time data ( $AUC_{0-inf}$ ) when using the Gen2C inhaler.
- Insulin exposure over 3 hours following administration of 10 U and up to 80 U of TI Inhalation Powder, reflected by the  $AUC_{0-180}$  of C-peptide corrected, RIA insulin concentration-time data, was shown to be dose proportional.

- In healthy volunteers, the median percent (%) bioavailability of TI Inhalation Powder based on analysis of the ratio of the log-transformed  $AUC_{0-inf}$  of C-peptide corrected, RIA insulin concentration data was approximately 24% relative to 15 IU SC RHI.
- FDKP demonstrates direct proportionality between the administered dose of TI Inhalation Powder and serum concentrations of FDKP as reflected by  $AUC_{0-inf}$ . This is seen as a demonstration of the ability of the Gen2 inhaler to deliver TI Inhalation Powder reliably to the deep lung, i.e., the only site of FDKP absorption. The elimination kinetics of FDKP from Technosphere particles remained constant over all dose levels.
- The direct dose proportionality demonstrates no saturation of absorption capacity up to 80 U of TI Inhalation Powder in HNVs.
- The elimination kinetics of FDKP from Technosphere particles remained constant, demonstrating no saturation of elimination.
- In HNVs, there was a non-linear increase in glucodynamic effect with increasing doses of TI Inhalation Powder administered using the Gen2C inhaler, in agreement with the  $E_{max}$  model for insulin concentration and insulin effect.
- TI Inhalation Powder was well tolerated by the subjects in this study. There were no serious or significant AEs. Most AEs that occurred during the study overall, and for either treatment group, were events of mild, asymptomatic, hypoglycemia assessed as related to the study procedure.
- All AEs were mild except for moderate dyspnea in 1 subject, assessed as unlikely related to TI Inhalation Powder.
- All except 2 AEs were assessed as unrelated or unlikely related to treatment with TI Inhalation Powder. Cough was an infrequent AE during the study, only occurring following administration of TI Inhalation Powder in 2 subjects. Both events of cough were mild and assessed as related to treatment in 1 of the subjects.
- Hypoglycemia was a frequent AE following administration of TI Inhalation Powder. Hypoglycemia increased with increasing dose level of TI Inhalation Powder. In all cases, the event was assessed as mild, subjects were clinically asymptomatic, and each instance was classified by the investigator as related to the inability of the Biostator infusion system to maintain euglycemia following administration of inhaled and SC insulin in these subjects.

**Reviewer’s Comment:**

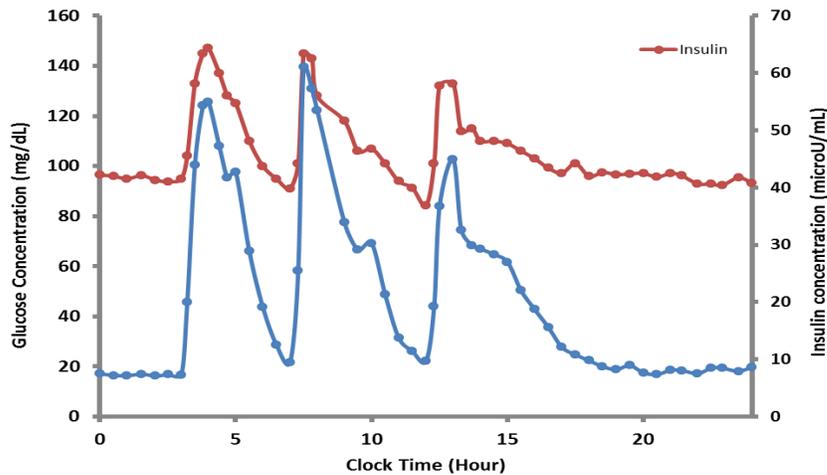
- *Insulin exposure time following Afrezza*

Although peak insulin concentrations were significantly higher than that of SC (see Figure 3) insulin, overall duration of insulin exposure following Afrezza administration was significantly shorter than that of SC insulin (see Table 17). In general, exogenously administered meal-time insulin products are designed to mimic the natural insulin secretion pattern following meals. A representative profile for glucose absorption and insulin release pattern after mixed meal administration in healthy subjects is shown in Figure 12. It shows that glucose absorption and insulin secretion lasts for about 4 hours after each meal. Therefore, the duration of insulin exposure for Afrezza (ranging between 60-180 minutes) may not be sufficient to provide an adequate postprandial glucose control. Or perhaps patients may need to take supplemental doses or adjust the dose of basal insulin to achieve adequate glycemic control.

**Table 17: Insulin PK parameters related to the exposure time following Afrezza**

	Afrezza				RHI
	10 U	30 U	60 U	80 U	15 U
T <sub>max</sub> (min)	11.3	13.1	14.5	16.7	156.6
Duration to baseline (min)	150-180	180*	180*	180*	>480

\*: limited by sampling scheme



**Figure 12: Mean glucose (blue symbols and line) and natural insulin (red symbols and line) concentrations following the breakfast, lunch and dinner in healthy subjects (n=14, redrawn from Figure 1, Polonsky *et al.*, J Clin Invest, 81:442-448, 1988)**

- *Non-proportionality in dose-PD relationship*

Although literature information as well as the simulated dose-response relationship (see Section 2.8) indicates that there is non-proportionality in dose-PD relationship for both

SC and Afrezza insulin administration. However, the degree of non-proportionality following Afrezza (see Table 4) seems to be more than that of SC in literature (see the following table, data from Reinhard et al., *Diabetes Care*, 30:2506-2507, 2007). Further, we simulated the PK/PD profiles for higher dosage to better understand the dose-response relationship, which was discussed above in section 2.8.

	<b>GIRAUIC (mg/kg)</b>	
<b>Dose (IU/kg)</b>	<b>SC glulisine</b>	<b>SC RHI</b>
0.075	499	416
0.15	1090	1076
0.3	1476	1555

### 3.2 Insulin PK and PD in T1DM following AFREZZA using Gen2 inhaler (MKC-TI-177)

Study MKC-TI-177: A Phase 1, Single-center, Open-label, Randomized, Crossover Design Clinical Study in Subjects with Type 1 Diabetes to Compare Insulin Exposure and Response Following Inhalation of Technosphere® Insulin Inhalation Powder Using the Gen2C Inhaler Versus SC Rapid-Acting Analog (EDR:

[\\Cdsesub1\evsprod\NDA022472\0074\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\mkc-ti-177](http://Cdsesub1\evsprod\NDA022472\0074\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\mkc-ti-177))

Insulin PK and PD was assessed in a crossover study with T1DM following AFREZZA using Gen2 and SC lispro with specific information on the formulations as follows:

<b>Sequence</b>	<b>Treatment Phase</b>	
	<b>Visit 2 (Period 1)</b>	<b>Visit 3 (Period 2)</b>
1	One 20 U cartridge TI	8 U RAA
2	8 U RAA	One 20 U cartridge TI

Study drug:	Technosphere Insulin Inhalation Powder
Active ingredient:	Human insulin (tDNA origin)
Formulation:	Each milligram of formulation contains 3.0 U of human insulin
Dosage form:	Inhalation powder
Frequency: Si	ngle dose
Packaged as for Gen2 Inhaler:	Premetered single-dose cartridges filled with 6.7 mg of Technosphere Insulin Inhalation Powder containing 20 U of insulin
Manufactured by:	MamKind Corporation
Storage conditions at clinical site:	Refrigerated at 2°C to 8°C (or 36°F to 46°F)
Storage conditions by subject:	Not applicable
Packaging description:	Blister card comprised of 5 blister strips, each containing 3 cartridges (15 cartridges per blister card). Each blister card is overwrapped in a foil pouch. Three blister cards per box (45 cartridges per box)
Batch number(s):	D12002

Study drug:	Insulin lispro
Active ingredient:	Insulin lispro injection, USP (tDNA origin)
Formulation: 10	0 U/mL (U-100)
Dosage form:	SC injection, 8 U per dose
Frequency: Si	ngle dose
Manufactured by:	Eli Lilly and Company
Storage conditions at clinical site:	Stored unopened in a refrigerator (2°C to 8°C [36° to 46°F]); DO NOT FREEZE. Unrefrigerated (below 30°C [86°F])
Storage conditions by subject:	Not applicable
Packaging description:	10 mL vials
Lot and batch numbers:	Purchased commercially; Lot and batch (A923934A)

The clamp procedures were the same as the Study 176, and blood sampling scheme was as follows:

Sample No.	Sample Time (min)	Variable
1	-20 (approximately 20 minutes before dosing)	For all samples: <ul style="list-style-type: none"> <li>• 5 mL serum separating tube (SST) for insulin assay</li> <li>• Blood glucose monitored by the Biostator</li> <li>• Early blood samples up to and including 30 minutes after dosing were to be drawn within <math>\pm 1</math> minute of the sample time. Later blood samples were to be drawn within <math>\pm 3</math> minutes of the sample time.</li> <li>• All sampling times were measured from Time 0, dosing, regardless of the previous sample's actual time of sample collection.</li> <li>• Actual time of collection of all samples were recorded</li> </ul>
2	-10 (approximately 10 minutes before dosing)	
3	0 (within 3 minutes before dosing)	
4	3	
5	6	
6	9	
7	12	
8	15	
9	20	
10	30	
11	40	
12	50	
13	60	
14	75	
15	90	
16	10	
17	12	
18	15	
19	18	
20	24	
21	30	
22	36	

The primary parameters were summarized in the following tables.

**Table 18: Summary of PK parameters following AFREZZA and RAA SC in T1DM**

Parameter	TI (RIA) (N = 12)	TI (ECLIA) (N = 12)	RAA (RIA) (N = 12)
<b>AUC<sub>(0-360)</sub> (min·µIU/mL)</b>			
n	12	12	11
Mean	3684.9	3011.9	4341.9
Geometric Mean	3046.68	2254.59	3795.17
SD	3068.95	3393.76	2193.72
Median	2832.1	2060.8	3850.5
%CV	83.3	112.7	50.5
Min	1561.6	1044.3	960.0
Max	12889.8	13488.7	9367.7
<b>AUC<sub>(0-inf)</sub> (min·µIU/mL)</b>			
n	5	12	11
Mean	2495.9	3073.0	4510.6
Geometric Mean	2299.04	2304.47	3971.12
SD	1186.49	3467.69	2231.56
Median	1924.6	2098.8	4013.2
%CV	47.5	112.8	49.5
Min	1581.4	1066.9	1051.9
Max	4335.5	13795.5	9637.0
<b>C<sub>max</sub> (µIU/mL)</b>			
n	12	12	11
Mean	60.8	56.2	36.0
Geometric Mean	50.91	43.80	34.04
SD	48.28	55.86	11.43
Median	48.2	42.9	41.9
%CV	79.4	99.5	31.7
Min	25.8	21.8	16.1
Max	203.5	226.2	50.4

Parameter	TI (RIA) (N = 12)	TI (ECLIA) (N = 12)	RAA (RIA) (N = 12)
<b>t<sub>max</sub> (min)</b>			
n	12	12	11
Mean	8.9	10.3	52.3
Geometric Mean	8.24	9.69	48.69
SD	4.19	3.49	18.76
Median	7.5	9.0	50.0
%CV	47.0	34.1	35.9
Min	6.0	6.0	20.0
Max	20.0	15.0	75.0
<b>t<sub>1/2</sub> (min)</b>			
n	5	12	11
Mean	47.4	51.6	39.2
Geometric Mean	45.23	43.95	36.84
SD	15.54	30.15	13.44
Median	47.1	47.0	38.6
%CV	32.8	58.4	34.3
Min	27.5	19.1	17.8
Max	63.9	102.8	61.3

Source: Section 14.2, Table 14.2.1.2.1

**Table 19: Summary of 5-minute average GIR PD parameters following AFREZZA and RAA SC in T1DM**

Parameter	TI (RIA) (N = 12)	RAA (RIA) (N = 12)
<b>AUC<sub>(0-240)</sub> (min•[mg/kg•min])</b>		
n	12	12
Mean	522.8	1007.2
Geometric Mean	454.06	676.43
SD	202.52	656.41
Median	554.5	1097.2
%CV	38.7	65.2
Min	55.8	40.6
Max	907.0	1853.9
<b>AUC<sub>(0-120)</sub> (min•[mg/kg•min])</b>		
n	7	7
Mean	814.5	814.0
Geometric Mean	786.15	510.14
SD	234.40	618.63
Median	828.1	929.0
%CV	28.8	76.0
Min	527.3	40.9
Max	1209.7	1786.6
<b>GIR<sub>max</sub> (mg/kg•min)</b>		
n	12	12
Mean	6.1	9.4
Geometric Mean	5.76	8.15
SD	2.04	4.26
Median	6.3	11.1
%CV	33.3	45.4
Min	2.5	2.3
Max	9.3	14.2
<b>t<sub>max</sub> (min)</b>		
n	12	12
Mean	77.3	127.0
Geometric Mean	60.79	108.80
SD	74.06	80.29
Median	52.5	107.5
%CV	95.9	63.2
Min	29.0	41.0
Max	296.0	338.0

Source: Section 14.2, Table 14.2.2

The sponsor's conclusions were as follows:

- PK analyses were performed on a complete and evaluable set of serum assay data for 12 subjects in the PK population.

- In subjects with type 1 diabetes, following inhalation of 20 U of TI Inhalation Powder using the Gen2 inhaler, the mean baseline corrected insulin concentration-time profiles demonstrate rapid absorption, with median time to maximum serum insulin concentration of 7.5 minutes, and a return towards the pre-dose (baseline) concentrations by approximately 180 to 240 minutes.
- The absorption and elimination phases of RAA were slower than for TI Inhalation Powder, consistent with the SC injection route of delivery.
- The between-treatment comparison of 20 U of TI Inhalation Powder and 8 U SC RAA demonstrated a ratio in the dose normalized  $AUC_{(0-360)}$  of  $\sim 0.33$  (RIA determination) and 0.25 (ECLIA determination).
- The pharmacological effect of the administered insulin, as measured by the GIR, demonstrated a more rapid onset of action following the administration of TI Inhalation Powder and a shorter duration of peak effect than seen following administration of RAA. Baseline corrected GIR for TI Inhalation Powder peaked at median time of 53 minutes compared to 108 minutes for RAA.

### 3.3 Interim analysis of Study MKC-TI-118

The applicant submitted interim analysis report for Study MKC-TI-118 (b) (4). The objectives of the study and information on amendments from sponsor's report are presented below:

“The objective of this study was to compare the effect of Technosphere® Insulin (TI) Inhalation Powder, insulin lispro (Humalog®, Eli Lilly & Co.), and Exubera® (Pfizer Inc.) on endogenous glucose production (EGP), determined by a meal challenge test and, in the fasting state, using a glucose-clamp procedure in subjects with type 2 diabetes mellitus. The study utilized radiolabeled isotopes to distinguish between EGP and exogenous glucose. The study design incorporated 2 procedures: a meal challenge followed by a fasted hyperinsulinemic-euglycemic clamp procedure.

For the meal challenge, subjects received all 3 treatments at separate visits, in a crossover fashion, after a meal. In the second part of the study, subjects received all 3 treatments in a crossover fashion at separate visits and under euglycemic clamp conditions, but in a fasted state. The results were examined after completion of the meal challenge. It was apparent that the relative insulin exposure after the 3 treatments was not well matched, making comparison between the treatments difficult, and that the doses would have to be adjusted.

The protocol was amended to adjust the doses for the second half of the study to ensure the most comparable assessment of EGP. The 2 most significant changes in Amendment 1, and the rationale for each change, are: (1) the lispro dose was changed to 10 IU and the TI doses being investigated were 60 U and 90 U. The TI Inhalation Powder doses were selected based on an expected more comparable insulin exposure (60 U) and in order to assess EGP for the highest TI dose (90 U). (2) The Exubera® arm was excluded as a comparator because this agent has been withdrawn from the market.

A summary of the study methods and preliminary results from the meal challenge portion of the study are presented here. Results are based on preliminary, non-QC data.”

*Reviewer’s Comment: Interim study results have been submitted without the complete study report, and the interim study report is based on preliminary, non-QC data. There were significant amendments for the study as stated above. Therefore, the results from the interim analyses are not acceptable for labeling.*

### 3.4 Bioanalytical Studies

A radioimmunoassay (RIA) method (b) (4) method 197-1001) was validated for the quantitation of human insulin in human serum from 8 – 160 µIU/mL, and it seems acceptable as indicated by the following evaluation data.

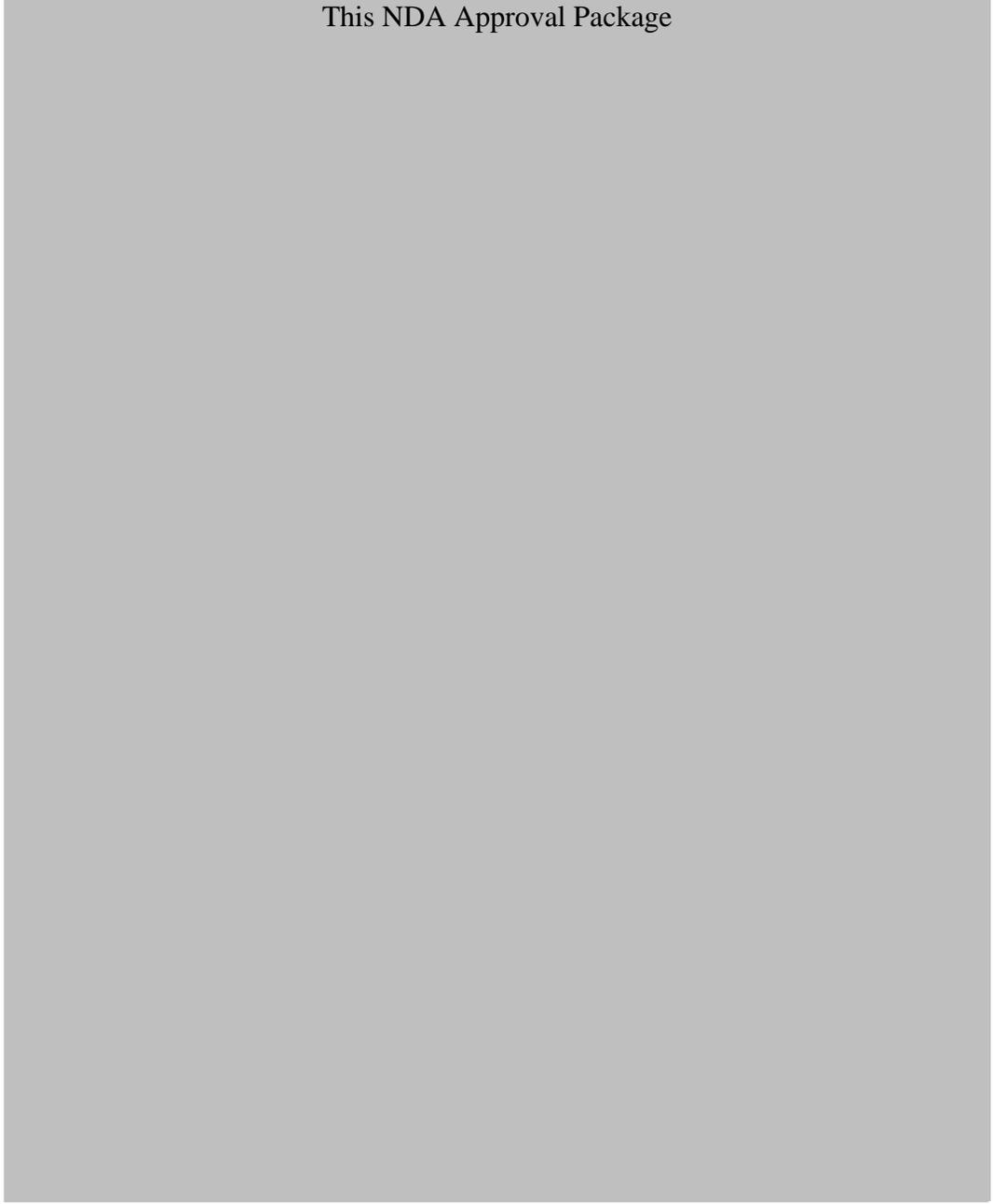
Report Title	Determination of Human Insulin in Human Serum by RIA
Report Number	(b) (4) 197-1001
Analyte Name and synonym	Insulin
Sample Volume:	100 µL / tube
Analytical Method Type	RIA
Sample Processing Method	None
Calibration Range:	5-160 µIU/mL
QC Concentrations in Stripped Serum	8 and 160 µIU/mL
Matrix QC Concentrations	Neat, Neat + 50, and Neat + 100 µIU/mL
QC Intra-batch Precision (%CV)	4.2% to 14.1%
QC Intra-batch Accuracy (%Diff)	-10.4% to 21.4%
QC Inter-batch Precision (%CV)	8.3% to 18.9%
QC Inter-batch Accuracy (%Diff)	-5.2% to 9.3%
Benchtop / 4°C Stability in Human Serum	6 Hours at Room Temperature 20 Hours at 4°C
Freeze/thaw Stability in Human Serum	5 Cycles at Room temperature/-70°C 5 Cycles at Room temperature / -20°C
Long-term Storage Stability in Human serum	51 days at -20°C and -70°C. Additional stability will be determined and the validation report will be amended
Dilution Linearity	415 µIU/mL diluted 4, 5 and 10 -fold
Selectivity (10 lots, spiked 15 µIU/mL)	100% lots tested within 100±25% Recovery
Selectivity (10 lots, spiked 100 µIU/mL)	100% lots tested within 100±25% Recovery

Blood samples for insulin assay by electrochemiluminescence assay (ECLIA) and hemolysis index determination were sent to an independent assay lab to evaluate the potential impact of cross-reactivity from lispro insulin, which was used in the clamp, in the RIA assay. It was concluded that the validated RIA method was reliable to estimate insulin PK in the presence of lispro insulin.

**4 Attachment**

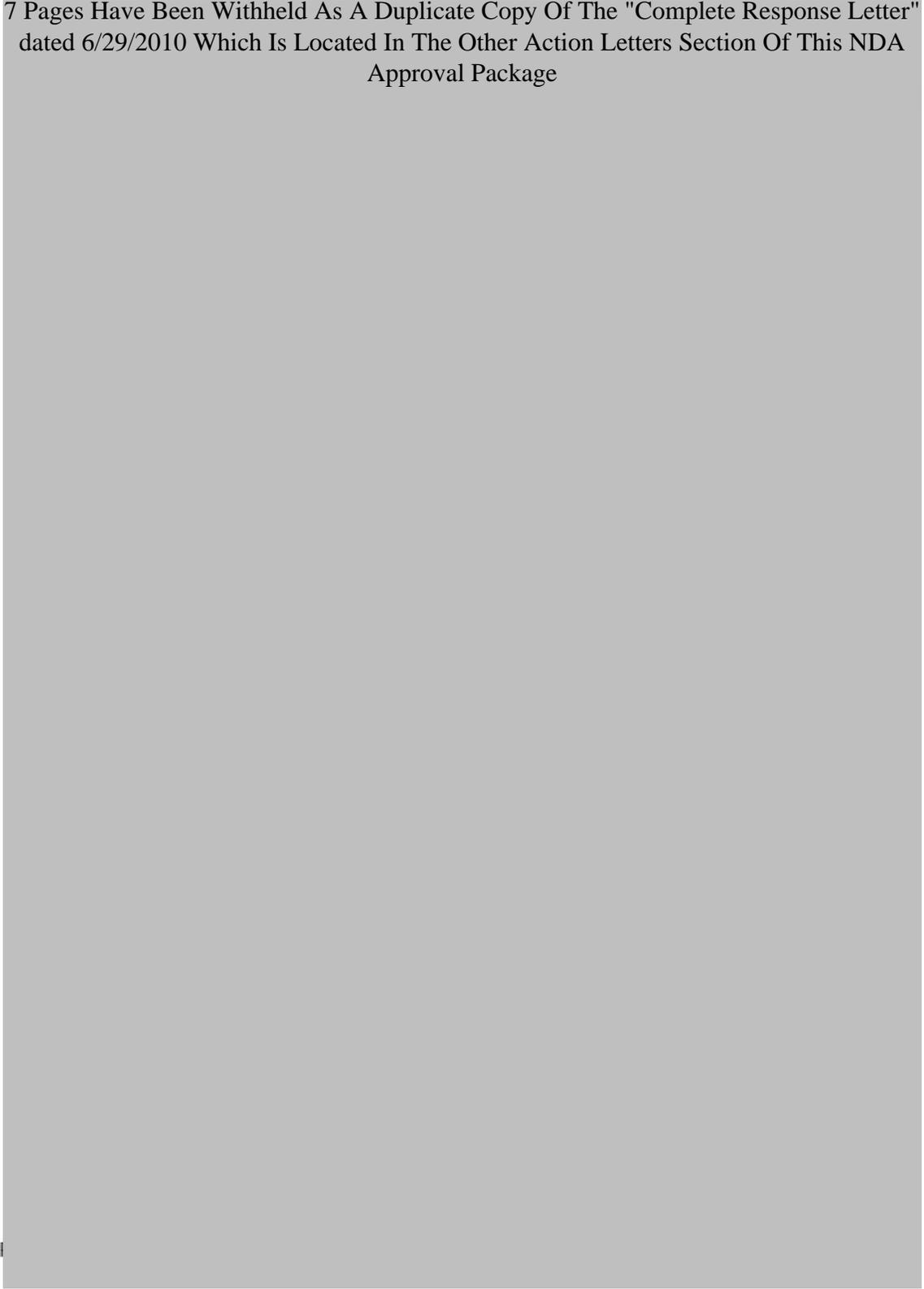
4.1 Complete Response Letter 1 Dated 3/12/2010

6 Pages Have Been Withheld As A Duplicate Copy Of The "Complete Response Letter" dated 3/12/2010 Which Is Located In The Other Action Letters Section Of This NDA Approval Package



4.2 Complete Response Letter 1 Dated 6/29/2010

7 Pages Have Been Withheld As A Duplicate Copy Of The "Complete Response Letter" dated 6/29/2010 Which Is Located In The Other Action Letters Section Of This NDA Approval Package



### 4.3 Tables of Studies/Clinical Trials

(Source: EMDAC ADVISORY COMMITTEE MEETING, APRIL 1, 2014)

A total of 63 clinical studies have been conducted over the course of the TI Inhalation Powder clinical development program. Tables 1-4 present an overview of these studies.

<b>Table 1 – Biopharmaceutics and Clinical Pharmacology Studies Submitted with the Original NDA</b>						
<b>Type of Study</b>	<b>Study Identifier/ Study Status</b>	<b>Study Objective</b>	<b>Study Design</b>	<b>Test Product(s): Dosage Regimen and Route of Administration</b>	<b>Subjects (number and diagnosis)</b>	<b>Duration of Treatment</b>
BA	PDC-INS-0001A Completed Full	evaluate relative bioeffect and bioavailability of 25 U of inhaled TI vs. 10 IU of sc RHI	OL, randomized 2-way crossover - euglycemic clamp	Test Product: TI Dosage: TI 25 U, 2 single doses on 2 separate treatment visits	9 HV	Short. 1 day each, TI and reference therapy
BA	PDC-INS-0001B Completed Abbreviated	characterize the PK and PD profiles of 25 U of insulin from 3 different TI formulations	OL, randomized, 4-way crossover study	Test Product: TI Dosage: TI 25 U with 3 formulations, single dose	11 T1DM	Short. 4 single doses administered over 2 to 14 days
BA	PDC-INS-0002 Completed Full	compare the bioeffect of inhalation of 3 doses of TI to 10 IU sc insulin in HV	Prospective, OL, randomized, 4-way crossover study	Test Product: TI Dosage: TI 25 U, 50 U, or 100 U per meal, 4 single doses on 4 separate treatment visits at least 3 days apart.	12 HV	Short (4 single doses on 4 treatment visits $\geq$ 3 days apart; 3 single doses of TI and 1 dose of RHI)
BA, BE	MKC-TI-110 Completed Full	compare the bioequivalence of TI formulations and the bioavailability of each TI formulation with that of sc insulin in T1DM	Prospective, single site, OL, 3-way crossover study	Test Product: TI Dosage: 30 U or 60 U	47 T1DM	Medium. 3 treatment visits scheduled 7-14 d apart
BA, BE	MKC-TI-116 Completed Full	determine the bioequivalence and safety parameters of two 15 U cartridges vs. one 30 U cartridge and the relative bioavailability of a 30 U cartridge compared to a single sc injection of 10 IU of RAA	Phase 2, OL, randomized, 2-way crossover hyper-insulinemic -euglycemic clamp clinical study	Test Product: TI Dosage: 30 units Cartridges contained either 15 U or 30 U	30 T1DM	Short. 1 dose at each of 2 visits
BA, BE	MKC-TI-138 Completed Full	evaluate the bioequivalence of TI when administered using MedTone Inhalers, Model C and Model D	Phase 1, OL, single dose, randomized, 2-way crossover study	Test Product: TI Dosage: 30 U via MedTone Inhaler	75 T1DM	Short (2 single doses over 2 treatment days)
PD & PK/PD	PDC-INS-0007 Completed Full	evaluate distribution of TI labeled with 99m technetium in	Prospective, OL, Non-	Test Product: 5 U 99m technetium-labeled TI	5 HV	Short (single dose)

		the lung directly after inhalation of TI using $\gamma$ scintigraphy, to assess the PK profile and safety of a single administration of TI	comparative study	Dosage: Variable, prandial dosing to a maximum of 10 U TI		
PK	MKC-TI-122 Completed Full	determine pulmonary concentrations of insulin and FDKP in the lungs utilizing BAL after administration of TI	Phase 1, OL, randomized, controlled clinical study	Test Product: TI Dosage: single 60 U dose before each bronchoscopy	13 HV	Short. Single dose at 1 treatment visit
PK,	MKC-TI-123 Completed Full	study controlled elimination and metabolism of $^{14}\text{C}$ -FDKP administered as an intravenous (iv) infusion and as an oral solution (Hepatic Metabolism study)	Single-dose, OL, 2-period crossover, nonrandomized, repeat administration controlled elimination and metabolism study	Test Product: $^{14}\text{C}$ FDKP solution Dosage: 1 iv infusion of 10 mg $^{14}\text{C}$ FDKP solution; 1 oral dose of 20 mg $^{14}\text{C}$ FDKP solution Route: iv; oral	7 male HV	Medium. Approx. 7 wk: 4 visits (2 treatment visits separated by 2 weeks) over 42 days
BA	PDC-INS-0001C Completed Abbreviated	compare the effect on postprandial bioavailability of 3 formulations of TI with sc insulin measured during study 0001B and to evaluate the time-action profiles of the TI formulations	OL, randomized, 3-way crossover study	Test Product: TI Dosage: Prandial TI 36 U of 3 formulations, single dose	7 T1DM	Short (3 single doses administered over 2- 14 days)
PD & PK/PD	MKC-TI-003B Completed Full	compare prandial inhalation of TI to sc regular insulin in T2DM on intensified insulin therapy	Prospective, OL, randomized, controlled, crossover study	Test Product: TI Dosage: TI 12 U, 24 U, 36 U, 48 U per meal, single dose	16 T2DM	Short (3 doses/day administered over two 1-week periods)
PD & PK/PD	MKC-TI-003B2 Completed Full	evaluate the safety and efficacy of prandial TI vs. sc RHI on BG after 1 wk of daily multiple doses; to compare serum insulin concentrations after a single dose of TI or sc RHI	Controlled, OL, randomized, replicated, crossover isoglycemic glucose clamp study	Test Product: TI Dosage: Prandial TI 48 U, single dose	13 T2DM	Medium (3 single doses of TI on 3 separate occasions over 6 - 13 wk)
PD & PK/PD	PDC-INS-0003 Completed Full	Evaluate intra-patient variability of the biologic action of inhaled TI vs. sc RHI during euglycemic clamp experiments	OL, randomized, 4-way crossover study	Test Product: TI Dosage: Prandial TI 100 U, single dose on 3 separate occasions	13 T2DM	Short (single dose administered on 4 separate occasions)
PD & PK/PD	PDC-INS-0003A Completed Full	evaluate the variability of the insulin absorption after pulmonary application of TI in	6-way crossover, randomized study	Test Product: TI & TIP Dosage: TI 48 U, 6 single doses; TIP,	15 T2DM	Short (6 single doses on 6 treatment visits separated by 2

		comparison to sc RHI in T2DM and to collect safety information about repeated applications of TI		practice inhalations		- 14 days)
PD & PK/PD	MKC-TI-025 Completed Full	compare 2 prototype TI cartridges for inhalation with sc RHI	Prospective, controlled, OL, randomized, replicated, crossover PK study	Test Product: TI Dosage: Prandial TI 30 U (using cartridge Prototype A and B) at each of 6 visits	20 T1DM	Short (3 phases separated by $\geq 14$ days, each with 3 treatment visits separated by 7 - 10 days)
PK	MKC-TI-113 Completed Full	compare PK parameters of TI alone and with albuterol and/or after MCT in subjects with asthma vs. matched healthy, subjects without asthma demonstrating normal lung function	Phase 1, OL, controlled clinical study	Test Product: TI Dosage: <i>All Subjects:</i> • 45 U TI • albuterol 200µg <i>Subjects with FEV1 &gt; 65% of predicted:</i> • Methacholine in increasing doses until FEV1 > by 20%	Asthma: 17  Normal lung function: 13	Medium. 4 treatment visits, 1 dose/visit
Intrinsic factor PK	MKC-TI-027 Completed Abbreviated	evaluate and compare, in a 2-part study, the PK and PD effects of TI over a 7-day treatment period in asthmatic and non-asthmatic subjects	Parallel OL, single dose of TI PFT; parallel prospective, controlled, 2-center, euglycemic clamp procedure	Test Product: TI Dosage: Three 30 U single doses, and individualized doses 3 or 4 times a day	21 asthmatic and non-asthmatic subjects with T2DM	Short (7 days)
PK	MKC-TI_105 Abbreviated (discontinued due to low enrollment)	compare prandial sc insulin with prandial TI in subjects with T2DM and asthma	12-month randomized, OL, parallel-group clinical study	Test Product: TI Dosage: Subject A: TI 15 U Subject B: TI 30 U	3 T2DM requiring insulin; concurrent asthma	Short. Subject A: 3 doses/day x 30 days; Subject B: 3 doses/day x 7days
PK in renal impairment	MKC-TI-017 Completed	compare FDKP administered as TP in subjects with mild or moderate DNP vs. matched subjects with normal renal function	Phase 1, single dose, OL, parallel design, controlled PK comparison study	Test Product: TP Dosage: Single dose, 20 mg TP	36 T1DM or T2DM with DNP or without DNP	Short: 1 dose administered at 1 treatment visit
PK in hepatic impairment	MKC-TI-111 Completed	compare FDKP administered as TP in subjects with mild or moderate CLD vs. matched subjects without CLD	Single-dose, OL, parallel design, controlled PK comparison study	Test Product: TP Dosage: Single dose, 20 mg TP	33 T2DM with CLD or without CLD	Short. 3 visits (1 treatment visit)
Other	PDC-INS-0011 Completed Full	evaluate effects of the timing of an individualized dose of TI on BG control in patients with T1DM before or after eating an isocaloric or	Prospective, randomized, 8-way crossover, open label study	Test Product: TI Dosage: Prandial TI 6 U, 12 U, 24 U; individualized dose of TI calculated at each visit according to a predetermined	13 T1DM	Short (4 - 10 wk consisting of 8 treatment visits, each separated by 1 - 14 days)

		hypercaloric meal		formula		
PK	MKC-TI-114 Completed Full	investigate the effect of albuterol and fluticasone on the PK of TI	Phase 1 OL study	Test Product: TI Dosage: 45 U	13 HV	Medium. single dose at 3 treatment visits
PK in smokers	MKC-TI-016 Completed Full	compare prandial inhalation of TI in smokers and nonsmokers	Parallel, controlled, multicenter, single-dose, 1-period euglycemic clamp study	Test Product: TI Dosage: Prandial 30 U TI, single dose	24 T2DM	Short (single dose at Visit 2)
PK	MKC-TI-112 Completed Full	evaluate PK and safety parameters of TI in subjects with T1DM or T2DM who develop a URI, comparing the subjects' status after resolution of the URI, and to assess the PK profile of FDKP after dosing with TI	Phase 2 multicenter, sequential enrollment, open-label study of TI after meal challenges in consenting subjects randomized in MKC-TI-030	Test Product: TI Dosage: TI 15 or 30 U administered before meal challenge	20 T1DM or T2DM with a URI also enrolled in MKC-TI-030	Short. 2 treatment visits (2nd visit scheduled 15-45 d after resolution of URI)
PD & PK/PD	PDC-INS-0001 Completed Full	compare inhalation of 100 U TI via dry powder inhaler to 10 IU of sc insulin or 5 IU of iv insulin	Unblinded, OL, randomized, 3-way crossover study	Test Product: TI Dosage: Prandial TI 100 U, 3 single doses on 3 separate treatment days $\geq$ 3 days apart.	5 HV	Short. 3 single doses of TI on 3 treatment visits at least 3 days apart
PD & PK/PD	PDC-INS-0002A Completed Full	compare inhalation of 4 different doses of TI to 2 different doses of sc insulin	Prospective, OL, randomized, 6-way crossover study	Test Product: TI & TIP Dosage: Variable, 6 U, 12 U, 24 U, or 48 U, and 1 to 3 TP practice doses	13 HV	Short. 6 single-dose visits separated by 1 - 14 days
PD & PK/PD	PDC-INS-0004 Completed Abbreviated	evaluate the effects of TI on postprandial BG excursions, compared with iv administration of RHI or sc insulin lispro	OL, randomized, 4-way, single dose crossover study	Test Product: TI Dosage: TI 12 U or 24 U, single dose	12 T2DM	Short (4 single crossover doses separated by 3- 28 days each)
PD & PK/PD	PDC-INS-0004A Completed Full	compare the effect of different doses of TI on daily BG control under isocaloric and hypocaloric dietary regimens	Prospective, OL study	Test Product: TI Dosage: 12 U, 24 U, or 48 U TI	26 T2DM	Short (4 treatment visits of 2 days duration separated by 2- 14 days)
PD & PK/PD	PDC-INS-0006 Completed Abbreviated	compare the effects of postprandial pulmonary delivery of a body-weight related dose of TI with preprandial sc injection of RHI on BG profiles	2-way crossover, randomized, double-blind study; pre-prandial sc insulin + postprandial placebo; preprandial placebo + postprandial	Test Product: TI & TP Dosage: TI 6 U, 12 U, 24 U per meal, based on body weight; TIP: 1 to 3 $\times$ 5 mg Technosphere particles practice inhale	30 T2DM	(Short. Single dose each on 2 treatment days, 1 - 6 days apart)

			TP as control			
Other	MKC-TI-104 Completed Full	compare the effects of prandial TI in multiple regimen formats vs. a prandial bolus fast-acting insulin analogue on postprandial BG in subjects using continuous sc insulin infusion	OL, single center	Test Product: TI Dosage: Variable; 15 to 90 U TI per meal	7 T1DM	4 seven day trial cycles
PK	MKC-TI-015 Completed Full	compare PK and safety of a single dose of TI in a cohort of nondiabetic subjects with COPD with a matched cohort of nondiabetic subjects without COPD	Phase 1b, single dose, OL, parallel-group, controlled hyperinsulinemic euglycemic clamp study	Test Product: TI Dosage: 1 dose of 30 U TI during a hyperinsulinemic euglycemic clamp procedure	38 nondiabetic subjects with and without COPD	Short: single dose of TI at 1 visit
Thorough QT study	MKC-TI-131 Completed Full	compare QTc-interval differences between healthy subjects exposed to therapeutic and suprathreshold doses of TP, placebo control, and active control	Phase 1, randomized, double-blind, crossover, placebo- and active-controlled cardiac safety study	Test Product: TP Dosage: • Supratherapeutic: 40 mg • Therapeutic: 20 mg	48 HV	Short. 4 treatment visits separated by $\geq 72$ h
Other	MKC-129 Completed Full	determine inspiratory flow rates using the Medtone Inhaler and an empty cartridge to evaluate pulmonary function and to study pressure profiles achieved by subjects	Single-visit pilot study of use of inhalation device with subjects from other MannKind TI studies	Test Product: Medtone Inhaler Dosage: N/A	56 T1DM or T2DM randomized to a TI group for $\geq 3$ mos. in Trials 009, 030, 102 or 103	Short. 1 visit with 2 inhalations
Other	MKC-TI-118 Ongoing at NDA submission	compare the effect of TI, insulin lispro, and Exubera on endogenous glucose production after a meal challenge and during a euglycemic glucose clamp procedure in T2DM	Randomized, OL, 2-way crossover arm with 7 visits for each completed subject.	Test Product: TI Dosage: 60 U to 90 U of TI depending on effect at initial visit	30 T2DM	Medium (2 treatment visits for the meal challenge, followed by 2-to 6-week blood-loss Recovery period, and 2 visits for glucose clamp procedure)

**Table 2 – Clinical Efficacy and Safety Studies Submitted with the Original NDA**

Study Identifier/ Study Phase	Study Objective	Study Design	Test Product(s): Dosage Regimen and Route of Administration	Subjects (number and diagnosis)	Duration of Treatment
<b>Type 2 Diabetes Trials</b>					
MKC-TI-005 Phase 2	To evaluate safety and glycemic	Multicenter, randomized, prospective,	•T Inhalation Powder (placebo) + glargine •TI 14 U + glargine	227 suboptimally treated T2DM	Short (11 weeks)

	response of TI dosed prandially, in addition to basal administration of Lantus	double-blind, placebo controlled, stepwise forced titration study	<ul style="list-style-type: none"> <li>•TI 28 U + glargine</li> <li>•TI 42 U + glargine</li> <li>•TI 56 U + glargine</li> </ul>		
PDC-INS-0008 Phase 2	To evaluate the efficacy and safety of inhaled TI compared to TP following diabetes education	Prospective, double-blind, randomized, placebo-controlled, parallel-group study, as an add-on to oral therapy, dose finding	<ul style="list-style-type: none"> <li>•TI + OAD</li> <li>•T Inhalation Powder (placebo) + OAD</li> </ul>	126 suboptimally treated T2DM	Short (12 weeks)
MKC-TI-010 Phase 3	To evaluate, using serial pulmonary function testing and imaging, the safety and tolerability of inhaled TI in subjects with type 2 diabetes	OL uncontrolled extension for pts who completed the two above trials	TI variable dosage 15 U to 90 U	229 T2DM	4 years
MKC-TI-026 Phase 2	To evaluate the safety and tolerability of 12 wks of treatment with TI	Prospective, controlled, OL, randomized, 12-week safety and efficacy study	<ul style="list-style-type: none"> <li>•TI + OAD</li> <li>•No TI (control) + OAD</li> </ul>	90 suboptimally treated T2DM	Short (12 weeks)
MKC-TI-014 Phase 3	To compare the efficacy of prandial TI + basal insulin vs. prandial rapid acting sc insulin + basal insulin	Randomized, OL, non-inferiority comparative study	<ul style="list-style-type: none"> <li>•TI + insulin glargine</li> <li>•Insulin aspart + insulin glargine</li> </ul>	309 T2DM receiving Lantus as basal insulin	Medium. 24 wk
MKC-TI-103 Phase 3	To evaluate the efficacy and safety of prandial inhalation of TI in combination with metformin or TI alone vs. 2 OADs (metformin and a secretagogue)	24-wk OL, randomized, controlled superiority study	<ul style="list-style-type: none"> <li>•TI</li> <li>•Metformin + secretagogue</li> <li>•TI + metformin</li> </ul>	528 suboptimally controlled T2DM	Medium. 6 months with primary endpoint at 3 months
MKC-TI-102 Phase 3	To evaluate the efficacy and safety of prandial inhalation of TI in combination with basal insulin vs. a prandial premix of intermediate- and rapid-acting	Prospective, OL, randomized, non-inferiority controlled study	<ul style="list-style-type: none"> <li>•TI + insulin glargine</li> <li>•Premix 70/30 Novolog insulin</li> </ul>	677 T2DM	Long (52 wk of treatment + 4 weeks of follow-up)

insulin in subjects treated with sc insulin ± OADs					
<b>Type 1 Diabetes Trials</b>					
<b>Study Identifier/ Study Phase</b>	<b>Study Objective</b>	<b>Study Design</b>	<b>Test Product(s): Dosage Regimen and Route of Administration</b>	<b>Subjects (number and diagnosis)</b>	<b>Duration of Treatment</b>
MKC-TI-101 Phase 2	To evaluate use of prandial inhaled TI in combination with basal sc Lantus® as basal insulin versus prandial sc NovoRapid® insulin in combination with basal sc Lantus® insulin	Randomized, open- label, multisite substitution study	•TI + insulin glargine •Insulin aspart + insulin glargine	120 subjects receiving basal prandial insulin therapy for T1DM	Medium. 12 wk
MKC-TI-009 Phase 3	To evaluate the efficacy and safety of TI in subjects with type 1 diabetes receiving sc basal insulin + prandial TI vs. prandial sc insulin + basal insulin	Prospective, OL, randomized, controlled, non-inferiority study	• TI + insulin glargine •Insulin aspart + insulin glargine	589 T1DM	Long (52 wk of treatment + 4 weeks of follow-up)
<b>Combined Type 2 and Type 1 Diabetes Trials</b>					
MKC-TI-030 Phase 3	Pulmonary safety trial - To study changes in pulmonary function outcomes over a 2-year period in subjects with type 1 or type 2 diabetes and diabetes-related abnormalities treated with TI vs. usual antidiabetic treatment and in subjects without abnormalities in glucose control	Prospective, multisite, multi-country, study incorporating 2 design strategies: 1) a randomized, OL clinical study comparing 2 groups of subjects with diabetes, and 2) an epi-demologic or observational clinical study comparing alternate study groups	•TI + usual antidiabetes treatment •Usual antidiabetes treatment	2053 T1DM or T2DM and nondiabetic control subjects at a ratio of approximately 10:1 (10 diabetics for every one nondiabetic)	Long (2 years)
MKC-TI-126	To evaluate pulmonary function in subjects who have completed trials 009, 102,	2-month safety follow-up study	Usual care without TI	Subjects with T1DM or T2DM who have completed previous efficacy and	2 months

103, or 030 for an additional 2-month safety follow-up period

safety trials

Newly completed and ongoing studies submitted for the current cycle are shown in Tables 3 and 4. The pivotal safety and efficacy studies are in bold text in Table 2.

<b>Table 3 – Pharmacokinetic and Biopharmaceutic Studies New in the 2013 Resubmission</b>					
<b>Study Identifier/ Study Phase</b>	<b>Design and Objective</b>	<b>Study population</b>	<b>Test Product(s): Dosage Regimen and Route of Administration</b>	<b>Number of subjects exposed and duration of treatment</b>	<b>Study status</b>
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)	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 effect of TI Inhalation Powder at multiple doses	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  Inhaler: Gen2C	35 subjects  Single doses of the study treatment in a 4-way crossover with a fifth sc RHI dose	Completed

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
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**Table 4 – Clinical Efficacy and Safety Studies New in the 2013 Resubmission**

<b>Study Identifier/ Study Phase</b>	<b>Design and Objective</b>	<b>Study population</b>	<b>Test Product(s): Dosage Regimen and Route of Administration</b>	<b>Number of subjects exposed and duration of treatment</b>	<b>Study status</b>
<b>Type 2 Diabetes Trials</b>					
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
<b>Type 1 Diabetes Trials</b>					
MKC-TI-171 Phase 3	Multicenter, open-label, randomized, forced-titration clinical trial evaluating the efficacy and safety of TI	T1DM ≥18 years	TI Inhalation Powder vs insulin aspart, both in combination with a basal insulin  Inhalers: Gen2C and MedTone C (allowed head-to-head	518 subjects  24 weeks with a 4-week follow up	Completed

	<b>Inhalation Powder.</b>		<b>comparison of the two inhalers as requested in the Complete Response letter.</b>		
<b>Comparison of pulmonary safety of inhalers.</b>					
<b>Combined Type 2 and Type 1 Diabetes Trials</b>					
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

## 4.4 Study synopsis

### 4.4.1 MKC-TI-176

Technosphere® Insulin Inhalation Powder  
MKC-TI-176

MannKind Corporation  
Final CSR 21 November 2012

## 2 SYNOPSIS

<b>Name of Sponsor:</b>	MannKind Corporation	
<b>Investigational Product:</b>	Technosphere Insulin Inhalation Powder	
<b>Name of Active Ingredient:</b>	Human insulin, recombinant DNA origin	
<b>Title of Study:</b>	A Phase 1, Open-label, Randomized, Crossover Design Clinical Trial in Healthy Normal Volunteers to Evaluate Insulin Exposure and Effect Following Inhalation of Technosphere Insulin Inhalation Powder at Multiple Doses Using the Gen2C Inhaler	
<b>Principal Investigators</b>	Elaine Watkins, DO, MSPH Profil Institute for Clinical Research, Inc. 855 3rd Avenue, Suite 4400 Chula Vista, CA 91911	
<b>Study Center(s):</b>	Profil Institute for Clinical Research, Inc, 855 3rd Avenue, Suite 4400, Chula Vista, CA 91911	
<b>Publication:</b>		
<b>Study Period:</b> First visit of the first patient: 12 December 2011 Last visit of the last patient: 30 May 2012	<b>Phase of development: 1</b>	
<b>OBJECTIVES:</b>		
<b>Primary Objective:</b>	To determine the insulin dose proportionality and linearity of Technosphere Insulin (TI) Inhalation Powder based on the area under the curve (AUC <sub>(0-180)</sub> ) after administration of the following doses using the Gen2C inhaler: <ul style="list-style-type: none"> <li>• 10 U (one 10 U cartridge)</li> <li>• 30 U (one 10 U and one 20 U cartridge)</li> <li>• 60 U (three 20 U cartridges)</li> <li>• 80 U (four 20 U cartridges)</li> </ul>	
<b>Secondary Objective:</b>	To: <ul style="list-style-type: none"> <li>• Determine the relative bioavailability of insulin administered using the Gen2C inhaler relative to 15 IU of subcutaneous (SC) RHI</li> <li>• Determine the insulin pharmacodynamics (PD): evaluation of the glucose infusion rate (GIR) necessary to maintain euglycemia in normal subjects maintained on a hyperinsulinemic-euglycemic clamp</li> <li>• Evaluate the safety of TI Inhalation Powder by analysis of the incidence, severity, and relationship to study treatments of adverse events (AEs)</li> </ul>	

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<b>Name of Sponsor:</b>	MannKind Corporation																																			
<b>Investigational Product:</b>	Technosphere Insulin Inhalation Powder																																			
<b>Name of Active Ingredient:</b>	Human insulin, recombinant DNA origin																																			
<b>METHODOLOGY</b>																																				
<b>Study Design:</b>	<p>This was a Phase 1, open-label, randomized, 4-way crossover with a fifth treatment of SC insulin in a hyperinsulinemic euglycemic clamp study in at least 32 fasted normal, healthy volunteers (HNVs). The objective of the study was to determine the dose proportionality and linearity, relative bioavailability, pharmacodynamic response, and safety of TI Inhalation Powder administered using the Gen 2C inhaler at the following dose levels:</p> <ul style="list-style-type: none"> <li>• 10 U (one 10 U cartridge)</li> <li>• 30 U (one 10 U and one 20 U cartridge)</li> <li>• 60 U (three 20 U cartridges)</li> <li>• 80 U (four 20 U cartridges)</li> </ul> <p>TI Inhalation Powder was compared to 15 IU SC RHI.</p> <p>TI Inhalation Powder treatments were administered in random order while SC RHI was administered as the last treatment for all subjects.</p> <p>A blood glucose (BG) target of <math>90 \pm 10</math> mg/dL was established and maintained by a variable rate glucose infusion.</p> <p>The study consisted of 7 clinic visits, and 1 or more telephone contacts before admission, at the discretion of the principal investigator (PI) or a designee, and an optional eighth visit, if necessary:</p> <ul style="list-style-type: none"> <li>• 1 screening (Visit 1)</li> <li>• 1 inhalation training and insulin/C-peptide evaluation (Visit 2)</li> <li>• 5 treatment visits (Visits 3, 4, 5, 6, and 7)</li> <li>• 1 follow-up visit (Visit 8) if required to follow ongoing AEs</li> </ul> <p>The glucose clamp procedure and dosing occurred at Visits 3 through 7.</p>																																			
<b>Treatments:</b>	<p>Subjects received treatment based on the following crossover design:</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th rowspan="2">Sequence</th> <th colspan="4">TI</th> <th>SC RHI</th> </tr> <tr> <th>Visit 3</th> <th>Visit 4</th> <th>Visit 5</th> <th>Visit 6</th> <th>Visit 7</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>10U</td> <td>10U + 20U</td> <td>3 × 20U</td> <td>4 × 20U</td> <td>15 IU</td> </tr> <tr> <td>2</td> <td>3 × 20U</td> <td>10U</td> <td>4 × 20U</td> <td>10U + 20U</td> <td>15 IU</td> </tr> <tr> <td>3</td> <td>4 × 20U</td> <td>3 × 20U</td> <td>10U + 20U</td> <td>10 U</td> <td>15 IU</td> </tr> <tr> <td>4</td> <td>10U + 20U</td> <td>4 × 20U</td> <td>10U</td> <td>3 × 20U</td> <td>15 IU</td> </tr> </tbody> </table>	Sequence	TI				SC RHI	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	1	10U	10U + 20U	3 × 20U	4 × 20U	15 IU	2	3 × 20U	10U	4 × 20U	10U + 20U	15 IU	3	4 × 20U	3 × 20U	10U + 20U	10 U	15 IU	4	10U + 20U	4 × 20U	10U	3 × 20U	15 IU
Sequence	TI				SC RHI																															
	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7																															
1	10U	10U + 20U	3 × 20U	4 × 20U	15 IU																															
2	3 × 20U	10U	4 × 20U	10U + 20U	15 IU																															
3	4 × 20U	3 × 20U	10U + 20U	10 U	15 IU																															
4	10U + 20U	4 × 20U	10U	3 × 20U	15 IU																															
<b>Treatment Duration:</b>	Each training and dosing visit lasted 1 day. There were at least 3 days between visits. A subject was in the study approximately 12 weeks, from screening to the last dosing visit.																																			
<b>Investigational Product:</b>	<p>TI Inhalation Powder</p> <p>Route of Administration: Oral Inhalation using the Gen 2 inhaler</p> <p>Dose and Lot Number: 10 IU, Lot D110006</p> <p>Dose and Lot Number: 20 IU, Lot D110007</p> <p>Lot Number: Gen2 Inhalers Lot D110026</p> <p>Lot Number: Empties Lot D110027</p>																																			

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<b>Name of Sponsor:</b>	MannKind Corporation
<b>Investigational Product:</b>	Technosphere Insulin Inhalation Powder
<b>Name of Active Ingredient:</b>	Human insulin, recombinant DNA origin
<b>Control Product/Reference:</b>	RHI Route of Administration: Subcutaneous Dose and Lot Number: 15 U, Lot A869941J
<b>PATIENT POPULATION</b>	
<b>Number of Patients:</b>	Approximately 72 HNVs were to be screened to achieve up to 32 randomized HNVs to complete all treatments. Subjects who dropped out were to be replaced.  Based on the within-subject coefficient of variation (CV) of 30% for AUC <sub>(0-180)</sub> , a sample size of 32 subjects in a 4-period crossover design had a 90% power to demonstrate dose proportionality for the power model.
<b>Inclusion Criteria:</b>	The key inclusion criteria were: <ul style="list-style-type: none"> <li>• Men and women aged 18 to 55 years who were considered healthy based on screening physical examination, medical history, clinical chemistry, and urinalysis</li> <li>• No previous smoking in the past 6 months (including cigarettes, cigars, pipes) and negative urine cotinine testing (&lt; 100 ng/mL)</li> <li>• Body mass index (BMI) &lt; 32 kg/m<sup>2</sup></li> <li>• FEV<sub>1</sub> ≥ 80% of the Third National Health and Nutrition Examination Survey (NHANES III) predicted</li> <li>• FVC ≥ 80% of the Third National Health and Nutrition Examination Survey (NHANES III) predicted</li> </ul>
<b>Exclusion Criteria:</b>	<ul style="list-style-type: none"> <li>• The key exclusion criterion was blood donation of 500 mL within the previous 56 days.</li> </ul>
<b>ASSESSMENT METHODS</b>	
<b>Pharmacokinetics/Pharmacodynamics:</b>	Insulin concentrations were measured pre-dose and serially following administration of study treatments. For each treatment, for each patient, 4 sets of insulin concentration values were produced: 1) uncorrected values, 2) C-peptide corrected values, 3) baseline corrected values, and 4) C-peptide, baseline corrected values, combined. The primary pharmacokinetic (PK) variables, based on C-peptide corrected insulin values, were: <ul style="list-style-type: none"> <li>• Area under the insulin concentration-time curve from time 0 to 180 minutes (AUC<sub>(0-180)</sub>) for each dose of TI Inhalation Powder</li> <li>• Area under the insulin concentration-time curve from time 0 to 600 minutes (AUC<sub>(0-600)</sub>) for SC RHI</li> <li>• C<sub>max</sub> for both study treatments</li> </ul> FDKP concentrations were also measured pre-dose and serially post-dose to assess delivery of TI Inhalation Powder. The pharmacodynamic variable was: <ul style="list-style-type: none"> <li>• Evaluation of the glucose infusion rate (GIR) necessary to maintain euglycemia in normal subjects maintained on a glucose clamp</li> </ul>

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<b>Name of Sponsor:</b>	MannKind Corporation
<b>Investigational Product:</b>	Technosphere Insulin Inhalation Powder
<b>Name of Active Ingredient:</b>	Human insulin, recombinant DNA origin
<b>Safety:</b>	Adverse events (AEs), vital signs, physical examination findings, and clinical laboratory tests.
<b>STATISTICAL METHODS AND ANALYSIS</b>	
<b>Pharmacokinetics:</b>	<p>The AUC<sub>(0-180)</sub> and C<sub>max</sub> of the C-peptide corrected insulin concentration data were analyzed to determine whether the average values for the PK parameters determined following administration of each dose level of TI Inhalation Powder were consistent. The analysis was based on a power model of the log-transformed AUC<sub>(0-180)</sub> and C<sub>max</sub> parameters with subject as a random effect, period, and dose as fixed effects. Dose proportionality was evaluated by comparing the proportionality slope and associated 90% CIs against predefined 90% CIs. Further, a sensitivity analysis, which applied a combination of a C-peptide correction and a baseline correction, was conducted to evaluate the potential impact of cross-reactivity from lispro insulin in the RIA assay.</p> <p>The relative bioavailability was evaluated as dose-normalized, pairwise comparisons between each TI Inhalation Powder dose level and 15 IU SC RHI. The ratios of TI Inhalation Powder to SC RHI and the 90% CIs for the ratios were derived from an ANOVA using subject as a random effect and treatment sequence and study treatment as fixed effects.</p> <p>Pharmacodynamic effect was measured by baseline corrected glucose infusion rates. These parameters were summarized and analyzed as described for the pharmacokinetic parameters. Dose effect response was analyzed using the power model and relative effect was analyzed using the model indicated for relative bioavailability.</p>
<b>Safety:</b>	<p>All subjects exposed to study medication were evaluated for safety. The number and percentage of subjects with AEs for each treatment were tabulated by system organ class and preferred term, by relationship to treatment, and by severity.</p> <p>Physical examination, vital signs findings, and safety laboratory parameters were not tabulated. Any significant changes from Baseline were to be documented on the AE page.</p> <p>Subject disposition, demographics, and baseline characteristics were summarized using descriptive statistics.</p>
<b>SUMMARY OF RESULTS</b>	
<b>Disposition of Patients:</b>	Thirty-five subjects were randomized into the study and 32 subjects completed all study treatments and visits.
<b>Treatment Discontinuation:</b>	Three subjects were discontinued prematurely: 1 subject was discontinued by the investigator for study non-compliance, 1 subject withdrew consent, and 1 subject was withdrawn following a treatment-related AE of mild chest discomfort.

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<b>Name of Sponsor:</b>	MannKind Corporation
<b>Investigational Product:</b>	Technosphere Insulin Inhalation Powder
<b>Name of Active Ingredient:</b>	Human insulin, recombinant DNA origin
<b>Subject Demographics:</b>	Most subjects were Caucasian (26/35; 74.6%) and there were 5 more males (20/35; 57.1%) than females (15/35; 42.9%) in the study. The mean age of subjects was 34.3 years (SD 9.67; range 18 to 53 years).
<b>Pharmacokinetics:</b>	<p>C-peptide concentrations, a marker of endogenous insulin secretion, were initially suppressed following administration of TI Inhalation Powder. This was followed by a gradual increase towards the end of the hyperinsulinemic-euglycemia clamp as insulin concentrations from exogenous administration declined. The suppression lasted longer for RHI, in agreement with the longer absorption period for subcutaneous administration.</p> <p>The primary dose response endpoint, the proportionality slope of <math>AUC_{(0-180)}</math> for the 4 TI Inhalation Powder dose levels was 1.000 (90% CI = 0.939 to 1.061), demonstrated proportionality between dose level and systemic insulin absorption through 3-hours post-dose. Results from the analysis of dose proportionality based on <math>AUC_{(0-inf)}</math> of C-peptide corrected insulin concentration data were consistent with these findings (slope = 0.949, 90% CI = 0.880 to 1.019).</p> <p>The slope of the maximal serum C-peptide corrected insulin concentrations (<math>C_{max}</math>) among all dose levels following administration of TI Inhalation Powder was 1.067, 90% CI = 1.013 to 1.120.</p> <p>C-peptide corrected insulin concentration-time profiles demonstrated that with every increase in dose level of TI Inhalation Powder administered, there is increasing systemic insulin exposure. Across the 4 dose levels, overall similar insulin kinetic profiles demonstrate rapid absorption, similar times of maximal insulin concentrations (at approximately 15 minutes post-dosing), and nearly complete return to pre-dose (baseline) concentrations by 180 minutes. Results were similar for insulin concentrations determined by ECLIA methodology.</p> <p>The median percent (%) bioavailability of TI Inhalation Powder using the Gen2C inhaler was approximately 24% relative to SC injection of 15 IU RHI based on analysis of <math>AUC_{(0-inf)}</math>.</p> <p>Mean serum concentration-time data of FDKP (the excipient which forms the matrix of Technosphere particles) following administration of TI Inhalation Powder demonstrated a mean <math>t_{max}</math> of approximately 8 to 9 minutes across all dose levels. The mean terminal half-life (<math>t_{1/2}</math>) ranged between 120 and 190 minutes and was dose independent. The total exposure (<math>AUC_{(0-inf)}</math>) of FDKP demonstrated direct proportionality to the administered dose of TI Inhalation Powder with no indication of saturation of absorption capacity. FDKP elimination kinetics remained constant over all doses tested.</p> <p>The sensitivity analysis, based on the observation of mean insulin levels prior to RHI or TI Inhalation Powder dosing of approximately 10 <math>\mu</math>U/mL and indicative of cross-reactivity between RHI and lispro insulin, produced corresponding results to the planned PK analyses of dose proportionality and relative bioavailability.</p>

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<b>Name of Sponsor:</b>	MannKind Corporation
<b>Investigational Product:</b>	Technosphere Insulin Inhalation Powder
<b>Name of Active Ingredient:</b>	Human insulin, recombinant DNA origin
	<p>The glucose infusion rate (GIR) during the euglycemic clamp following administration of each dose level of TI Inhalation Powder reached a maximum within approximately 30 to 50 minutes, whereas GIR peaked approximately 170 to 235 minutes after administration of SC RHI. Although increases in AUC<sub>(0-240)</sub> and GIR<sub>max</sub> were observed with each increasing dose of TI Inhalation Powder, these increases were non-linear.</p> <p>Evaluation of the total glucodynamic effect and assessment of the dose proportionality of TI Inhalation Powder was limited by the 4-hour (240 minutes) GIR monitoring period following treatment administration.</p>
<b>Safety:</b>	<p>Thirty-five subjects were included in the safety population.</p> <p>There were no deaths, other serious AEs, or significant AEs during the study.</p> <p>Thirty-one of thirty-five subjects (88.6%) experienced 1 or more AE(s) following a dose of TI Inhalation Powder (any dose level) compared to 9 of 32 subjects (28.1%) who had a AE(s) after receiving a dose of RHI. Almost all of this difference was attributable to the proportion of subjects who experienced study procedure related hypoglycemia following administration of TI Inhalation powder (30/35 subjects; 85.7%), compared to the proportion of those who experienced study procedure related hypoglycemia after receiving SC RHI (4/32; 12.5%). The remainder of the difference was due to other AEs. All events of hypoglycemia following either study treatment were mild in severity, subjects were clinically asymptomatic, and each instance was classified by the investigator as study procedure related, ie, the inability of the Biostator infusion system to maintain euglycemia following administration of inhaled and SC insulin in all subjects. The number of subjects experiencing hypoglycemia increased with increasing dose level of TI Inhalation Powder.</p> <p>There were 2 subjects who experienced 1 AE each which were classified by the investigator as study treatment related. Both AEs occurred following administration of TI Inhalation Powder. One subject experienced mild chest discomfort (80 U dose) and was subsequently withdrawn from the study, and the other subject experienced mild cough (30 U dose).</p> <p>All AEs that occurred during the study were mild in severity except for 1 subject who experienced 2 events of dyspnea, 1 of which was assessed as moderate in severity and unlikely related to treatment with administration of 10 U of TI Inhalation Powder. The other event of dyspnea in this subject was assessed as mild in severity of unrelated to treatment with 80 U of TI Inhalation Powder.</p>
<b>CONCLUSIONS</b>	
<b>Pharmacokinetics:</b>	<ul style="list-style-type: none"> <li>PK analyses were performed on a complete and evaluable set of serum assay data for 32 subjects in the PK population.</li> </ul>

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<b>Name of Sponsor:</b>	MannKind Corporation
<b>Investigational Product:</b>	Technosphere Insulin Inhalation Powder
<b>Name of Active Ingredient:</b>	Human insulin, recombinant DNA origin
	<ul style="list-style-type: none"> <li>• The observed rise in C-peptide concentrations following administration of TI Inhalation Powder indicated that the hyperinsulinemic clamp was unable to completely suppress all endogenous insulin secretion. This endogenous component, therefore, contributed to the total measured insulin concentration. These findings provided internal study validation for the selection and use of the C-peptide corrected, RIA-based determination of insulin concentration data on which the primary study analyses and conclusions were based.</li> <li>• In HNVs, there was increasing insulin exposure at each successive dose level (from 10 U to 80 U) of TI Inhalation Powder as reflected in <math>C_{max}</math> and in the total insulin concentration-time data (<math>AUC_{(0-inf)}</math>) when using the Gen2C inhaler. This increase in insulin exposure with each increasing dose level of TI Inhalation Powder occurred regardless of whether the resulting insulin concentration data were uncorrected, baseline corrected, or C-peptide corrected.</li> <li>• Insulin exposure over 3 hours following administration of TI Inhalation Powder, reflected by the <math>AUC_{(0-180)}</math> of C-peptide corrected, RIA insulin concentration-time data, was shown to be dose proportional.</li> <li>• In HNVs, the median percent (%) bioavailability of TI Inhalation Powder based on analysis of the ratio of the log-transformed, dose-normalized, <math>AUC_{(0-inf)}</math> of C-peptide corrected, RIA insulin concentration data was approximately 24% relative to 15 IU SC RHI.</li> <li>• FDKP demonstrates direct proportionality between the administered dose of TI Inhalation Powder and serum concentrations of FDKP as reflected by <math>AUC_{(0-inf)}</math>. This is seen as a demonstration of the ability of the Gen2 inhaler to deliver TI Inhalation Powder reliably to the deep lung, ie, the only site for FDKP absorption. The elimination kinetics of FDKP remained consistent across all dose levels studied. The direct dose proportionality of FDKP demonstrates no saturation of absorption capacity up to 80 U of TI Inhalation Powder in HNVs.</li> <li>• The results of the sensitivity analysis, which applied a combination of a C-peptide correction and a baseline correction, to the PK analyses of dose proportionality and relative bioavailability, produced corresponding results to the planned analyses.</li> <li>• In HNVs, there was an increasing but non-linear glucodynamic effect from increasing doses of TI Inhalation Powder administered using the Gen2C inhaler (ie, the incremental changes in glucodynamic effect decreased with increasing TI Inhalation Powder dose). The data also show that insulin effect from the inhaled dose of TI Inhalation Powder continues at 4</li> </ul>

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#### 4.4.2 MKC-TI-177

Technosphere Insulin Inhalation Powder  
MKC-TI-177

MannKind Corporation  
17 January 2013

## 2 SYNOPSIS

Name of the Sponsor: MannKind Corporation	Individual Study Table Referring to Part of the Dossier	For National Authority Use Only
Name of Finished Product: Technosphere Insulin Inhalation Powder		
Name of Active Ingredient: Human insulin, recombinant DNA origin		
<b>Title of Study:</b>	A Phase 1, Single-center, Open-label, Randomized, Crossover Design Clinical Study in Subjects with Type 1 Diabetes to Compare Insulin Exposure and Response Following Inhalation of Technosphere Insulin Inhalation Powder Using the Gen2C Inhaler Versus Subcutaneous Rapid-Acting Analog	
<b>Investigators:</b>	One investigator enrolled 17 subjects in this study. See Appendix 16.1.4 for details.	
<b>Study Center(s)</b>	One study center in 1 country enrolled subjects in this study. See Appendix 16.1.4 for details.	
<b>Publication (reference)</b>	Not applicable.	
<b>Study Period (date of first enrollment) (date of last completed)</b>	20 March 2012 – 28 September 2012	
<b>Objectives</b>	To characterize the pharmacokinetic (PK) profiles of one 20 U cartridge of TI Inhalation Powder and of 8 U of subcutaneous (SC) insulin lispro rapid acting insulin (RAA).	
<b>Primary Objective</b>	To characterize the glucose response profile by measuring the GIR following one 20 U cartridge of TI Inhalation Powder and following 8 U of SC insulin lispro RAA.	
<b>Secondary Objectives</b>	To evaluate the safety of one 20 U cartridge of TI Inhalation Powder.	
<b>Methodology</b>	Phase 1, open-label, randomized, crossover study of 20 U of TI Inhalation Powder in at least 12 subjects with type 1 diabetes mellitus in a hyperinsulinemic-euglycemic clamp procedure.  The study determined the safety, insulin exposure, and resultant glucose infusion rate (GIR) of the to-be-marketed formulation and cartridge fill weight administered using the to-be-marketed Gen2 inhaler in subjects with type 1 diabetes. Subcutaneous insulin lispro RAA was administered as the comparator.  The study consisted of 4 clinic visits and 1 or more telephone contacts before admission, at the discretion of the principal investigator (PI):	
	<ul style="list-style-type: none"> <li>• 1 screening visit (Visit 1)</li> <li>• 2 treatment visits (Visit 2 and Visit 3)</li> <li>• 1 follow-up visit (Visit 4)</li> </ul>	

Name of the Sponsor: MannKind Corporation	Individual Study Table Referring to Part of the Dossier	For National Authority Use Only											
Name of Finished Product: Technosphere Insulin Inhalation Powder	Volume:												
Name of Active Ingredient: Human insulin, recombinant DNA origin	Page:												
<p>Subjects were randomized to the order of administration of TI Inhalation Powder and SC RAA on the 2 different treatment days:</p> <table border="1" data-bbox="638 590 1261 762"> <thead> <tr> <th rowspan="2">Sequence</th> <th colspan="2">Treatment Phase</th> </tr> <tr> <th>Visit 2 (Period 1)</th> <th>Visit 3 (Period 2)</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>One 20 U cartridge TI</td> <td>8 U RAA</td> </tr> <tr> <td>2</td> <td>8 U RAA</td> <td>One 20 U cartridge TI</td> </tr> </tbody> </table> <p>Abbreviation: TI, TI Inhalation Powder; RAA, rapid acting analog</p> <p>A hyperinsulinemic-euglycemic clamp and administration of study treatment occurred on Visit 2 and Visit 3. A blood glucose (BG) target concentration of 90 mg/dL (<math>\pm</math> 10 mg/dL) was established and maintained by concomitant insulin infusion and variable rate glucose infusion. Venous blood samples were obtained pre-dose and serially following administration of each study treatment for determination of serum insulin concentrations by radio-immunoassay (RIA) and electrochemiluminescence immunoassay (ECLIA) methodology.</p>			Sequence	Treatment Phase		Visit 2 (Period 1)	Visit 3 (Period 2)	1	One 20 U cartridge TI	8 U RAA	2	8 U RAA	One 20 U cartridge TI
Sequence	Treatment Phase												
	Visit 2 (Period 1)	Visit 3 (Period 2)											
1	One 20 U cartridge TI	8 U RAA											
2	8 U RAA	One 20 U cartridge TI											
<b>Number of Subjects (Planned and Analyzed)</b>	Planned: 12 Actual: 17												
<b>Diagnosis and Main Criteria for Inclusion</b>	<p><b>Key Inclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Men and women aged 18 to 60 years</li> <li>• Diagnosis of type 1 diabetes for at least 12 months</li> <li>• No smoking in the previous 6 months (including cigarettes, cigars, pipes) and negative urine cotinine testing (&lt; 100 ng/mL)</li> <li>• C-peptide &lt; 0.3 ng/mL</li> <li>• One or more daily SC insulin injections of any insulin type or insulin pump use</li> <li>• Hemoglobin A1c (HbA1c) <math>\leq</math> 10.0%</li> <li>• Body mass index (BMI) &lt; 30 kg/m<sup>2</sup></li> <li>• Pulmonary function tests (PFTs) conducted at Visit 1: <ul style="list-style-type: none"> <li>- 1-second forced expiratory volume (FEV1) <math>\geq</math> 80% of the Third National Health and Nutrition Examination Survey (NHANES III) predicted</li> <li>- Forced vital capacity (FVC) <math>\geq</math> 80% of the Third National Health and Nutrition Examination Survey (NHANES III) predicted</li> </ul> </li> </ul>												

Name of the Sponsor: MannKind Corporation	Individual Study Table Referring to Part of the Dossier	For National Authority Use Only
Name of Finished Product: Technosphere Insulin Inhalation Powder	Volume:	
Name of Active Ingredient: Human insulin, recombinant DNA origin	Page:	
	<b>Key Exclusion Criteria</b> <ul style="list-style-type: none"> <li>Total daily insulin requirement of <math>\geq 1.4</math> U/kg body weight</li> <li>Serum creatinine <math>\geq 2.0</math> mg/dL in men and <math>&gt; 1.8</math> mg/dL in women</li> <li>Current treatment with pramlintide acetate or exenatide</li> <li>Unstable diabetes control and evidence of severe complications of diabetes (ie, autonomic neuropathy)</li> <li>History of chronic obstructive pulmonary disease (COPD) or asthma, or any other clinically important pulmonary disease confirmed by pulmonary function testing or radiologic findings</li> </ul>	
<b>Test Product, Dose and Mode of Administration, Batch Numbers</b>	<b>Test Product</b> Technosphere Insulin Inhalation Powder <b>Mode of Administration</b> Oral inhalation using the Gen2 inhaler <b>Dose and Lot Numbers</b> 20 U, Batch D12002	
<b>Duration of Treatment</b>	Each training and dosing visit lasted 1 day. There were at least 3 days between visits. A subject was in the study approximately 4 to 7 weeks, from screening to the last dosing visit.	
<b>Reference Therapy, Dose and Mode of Administration, Batch Numbers</b>	<b>Reference Therapy</b> Insulin lispro RAA <b>Mode of Administration</b> SC injection <b>Dose and Lot Numbers</b> 8 U, Batch A923934A	
<b>Criteria for Evaluation</b>	<b>Pharmacokinetics</b> Final serum insulin concentrations were corrected for infused insulin from the euglycemia clamp (baseline corrected). The primary pharmacokinetic variables, based on baseline corrected insulin concentration values, were: <ul style="list-style-type: none"> <li>Area under the serum insulin concentration-time profile from time 0 to 360 minutes (<math>AUC_{(0-360)}</math>)</li> <li>Maximum serum insulin concentration (<math>C_{max}</math>)</li> <li><math>t_{max}</math>, time of <math>C_{max}</math></li> </ul>	

<p>Name of the Sponsor: MannKind Corporation</p>	<p>Individual Study Table Referring to Part of the Dossier</p>	<p>For National Authority Use Only</p>
<p>Name of Finished Product: Technosphere Insulin Inhalation Powder</p>	<p>Volume:</p>	
<p>Name of Active Ingredient: Human insulin, recombinant DNA origin</p>	<p>Page:</p>	
	<p><b>Pharmacodynamics</b> The pharmacodynamic (PD) variables were:</p> <ul style="list-style-type: none"> <li>AUC of the baseline corrected glucose infusion rate from 0 to 240 minutes – GIR-AUC<sub>(0-240)</sub> – necessary to maintain euglycemia in subjects with type 1 diabetes maintained on a glucose clamp</li> </ul> <p><b>Safety</b> Treatment-emergent adverse events (TEAEs), vital signs, physical examination findings, and clinical laboratory tests.</p>	
<p><b>Statistical Methods</b></p>	<p>The primary study analysis of insulin exposure consisted of constructing concentration-time profiles based on baseline corrected, RIA determined, serum insulin concentration data from the administration of TI Inhalation Powder and SC insulin lispro RAA for the PK population. Descriptive statistics (n, mean, standard deviation, median, minimum, maximum, and coefficient of variation) and PK parameters (AUC<sub>(0-160)</sub>, C<sub>max</sub>, t<sub>max</sub>, and half-life, t<sub>1/2</sub>) for baseline corrected insulin concentrations-time data were summarized.</p> <p>For the secondary study PK analyses, treatment difference ratios and their confidence intervals (CI) from analysis of variance (ANOVA), and associated descriptive statistics, were summarized for both uncorrected and baseline corrected PK parameters:</p> <ul style="list-style-type: none"> <li>AUC<sub>(0-inf)</sub></li> <li>Dose-normalized AUC<sub>(0-160)</sub></li> <li>Dose-normalized AUC<sub>(0-inf)</sub></li> <li>Dose-normalized C<sub>max</sub></li> </ul> <p>The ratio of TI Inhalation Powder to insulin lispro for dose-normalized AUC<sub>(0-160)</sub> and dose normalized C<sub>max</sub> were estimated from the treatment difference derived using analysis of variance (ANOVA) on the log-transformed parameters with sequence, subject nested within sequence, period, and treatment specified as factors in the model. The treatment difference was back-transformed to give the ratio of the treatment means. The 2-sided 90% CI of the ratio was computed.</p> <p>Analysis of PD data consisted of descriptively summarizing the baseline corrected GIR-AUC<sub>(0-240)</sub> following administration of each study treatment. In addition, PD data were also descriptively summarized by constructing baseline corrected GIR-time profiles for original GIR data and for GIR data transformed into 5-minute moving average windows. GIR-time data were presented graphically.</p> <p>All subjects exposed to study medication were evaluated for safety. The number and percentage of subjects with TEAEs for each treatment were tabulated by system organ class and preferred term, by relationship to</p>	

Name of the Sponsor: MannKind Corporation	Individual Study Table Referring to Part of the Dossier	For National Authority Use Only
Name of Finished Product: Technosphere Insulin Inhalation Powder	Volume:	
Name of Active Ingredient: Human insulin, recombinant DNA origin	Page:	
	<p>treatment, and by severity.</p> <p>Physical examination, vital signs findings, and safety laboratory parameters were not tabulated. Any significant changes from Screening were to be documented on the TEAE page.</p>	
<b>Summary – Conclusions</b>	<p>Most subjects were White (11/12; 91.7%) and there were 6 more males (9/12; 75.0%) than females (3/12; 25.0%) in the study. The mean age of subjects was 38.9 years (SD 9.01; range 25 to 55 years).</p> <p><b>Pharmacokinetics and Pharmacodynamics</b></p> <ul style="list-style-type: none"> <li>• In subjects with type 1 diabetes, following inhalation of 20 U of TI Inhalation Powder using the Gen2 inhaler, the mean baseline corrected insulin concentration-time profiles demonstrate rapid absorption, with median time to maximum serum insulin concentration of 7.5 minutes, and a return towards the pre-dose (baseline) concentrations by approximately 180 to 240 minutes.</li> <li>• The absorption and elimination phases of RAA were slower than for TI Inhalation Powder, consistent with the SC injection route of delivery.</li> <li>• The between-treatment comparison of 20 U of TI Inhalation Powder and 8 U SC RAA demonstrated a ratio in the dose normalized <math>AUC_{(0-360)}</math> of ~ 0.33 (RIA assay)</li> <li>• The pharmacological effect of the administered insulin as measured by the GIR demonstrated a more rapid onset of action following the administration of TI Inhalation Powder and a shorter duration of peak effect than seen following administration of RAA. Baseline corrected GIR for TI Inhalation Powder peaked at median time of 53 minutes compared to 108 minutes for RAA.</li> </ul> <p><b>Safety</b></p> <p>TI Inhalation Powder was well tolerated by subjects with type 1 diabetes in this study. There were no serious or significant TEAEs.</p> <p>Most TEAEs that occurred during the study overall, and for either treatment group, were events of mild hypoglycemia assessed as related to the study procedure. In all cases of hypoglycemia, subjects were clinically asymptomatic and the hypoglycemia resolved.</p> <p>Of the 12 subjects who participated under Amendment 1 of the protocol, hypoglycemia occurred as a treatment-emergent AE for 4 subjects (33.3%) following administration of TI Inhalation Powder, and for 1 subject (8.3%) following administration of SC RAA.</p> <p>Of the 5 subjects who participated under the original protocol, hypoglycemia occurred as a TEAE for 3 subjects (60.0%) following administration of TI Inhalation Powder. Hypoglycemia did not occur following dosing with SC RAA in these 5 subjects.</p>	

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<p>All events of hypoglycemia that were classified as related or possibly related to the study procedure (7 of 8 total episodes for both protocol versions) resulted from the failure of the Biostator infusion system to maintain euglycemia following the administration of inhaled or SC insulin.</p> <p>All except 2 TEAEs were assessed as unrelated or unlikely related to treatment with TI Inhalation Powder (mild cough and moderate throat irritation in one subject, which were also classified as possibly related to the study drug and the study procedure). There were no other TEAEs related to study treatment or to a study device.</p> <p>All TEAEs were mild except for 1 event of moderate hypoglycemia (assessed as unrelated to the study procedure, treatment, or study device) and 1 event of moderate throat irritation (assessed as possibly related to the study treatment), both experienced by 1 subject following administration of TI Inhalation Powder participating in Amendment 1 of the protocol. Both of these TEAEs resolved.</p> <p>There were no clinically significant or clinically relevant findings observed during the study for any laboratory parameter, vital signs measurement, or physical examination for any subject in the study.</p>		
<p><b>Conclusions</b></p> <p>Pharmacokinetics and Pharmacodynamics:</p> <ul style="list-style-type: none"> <li>• In subjects with type 1 diabetes, following inhalation of 20 U of TI Inhalation Powder using Gen2 inhaler, the mean baseline corrected insulin concentration-time profiles demonstrated rapid absorption with the time to maximum serum insulin concentration of 7.5 minutes, and a return towards the pre-dose (baseline) concentrations by approximately 180 to 240 minutes.</li> <li>• The absorption and elimination phases of RAA were slower than for TI Inhalation Powder, consistent with the SC injection delivery route.</li> <li>• Between-treatment comparison of 20 U of TI Inhalation Powder and 8 U SC RAA demonstrated a ratio in dose normalized AUC<sub>(0-160)</sub> of ~ 0.33 (RIA assay)</li> <li>• The pharmacological effect of the administered insulin, as measured by the GIR, demonstrated a more rapid onset of action following the administration of TI Inhalation Powder and a shorter duration of peak effect than seen with RAA. Baseline corrected GIR for TI Inhalation Powder peaks at median time of 53 minutes compared to 108 minutes for RAA.</li> </ul>		

Name of the Sponsor: MannKind Corporation	Individual Study Table Referring to Part of the Dossier	For National Authority Use Only
Name of Finished Product: Technosphere Insulin Inhalation Powder	Volume:	
Name of Active Ingredient: Human insulin, recombinant DNA origin	Page:	
	<p>Safety:</p> <ul style="list-style-type: none"> <li>• TI Inhalation Powder was well tolerated by subjects with type 1 diabetes in this study. There were no serious or significant TEAEs.</li> <li>• Most TEAEs that occurred during the study overall, and for either treatment group, were events of mild hypoglycemia assessed as related to the study procedure. In all cases of hypoglycemia, subjects were clinically asymptomatic and the hypoglycemia resolved.</li> <li>• All events of hypoglycemia classified as related or possibly related to the study procedure resulted from the failure of the Biostator infusion system to maintain euglycemia following the administration of inhaled or SC insulin.</li> </ul> <p>All except 2 TEAEs were assessed as unrelated or unlikely related to treatment with TI Inhalation Powder. There were no other TEAEs related to study treatment or to a study device.</p>	
<b>Final Report Date</b>	17 January 2013	

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SANG M CHUNG  
05/19/2014

MANOJ KHURANA  
05/19/2014

LOKESH JAIN  
05/19/2014

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA</b>	22472
<b>Submission Date(s)</b>	June 29, 2010
<b>Brand Name</b>	AFREZZA <sup>®</sup> and AFREZZA <sup>®</sup> Inhaler
<b>Generic Name</b>	Insulin monomer human [rDNA origin] inhalation powder
<b>Reviewers</b>	Sang M. Chung, Ph.D.
<b>Team Leader</b>	Sally Choe, Ph.D.
<b>OCP Division</b>	Clinical Pharmacology 2
<b>OND Division</b>	Metabolism and Endocrinology Products
<b>Sponsor</b>	MannKind Corporation
<b>Submission Type</b>	Re-Submission

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### 1 Executive Summary

#### 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the Re-submission to the Agency's Complete Response (CR) letter dated March 12, 2010. We conclude that the pharmacokinetics of 20 U insulin delivered by Gen2C Inhaler is comparable to that of 30 U insulin delivered by MedTone Inhaler Model C provided that there are no significant issues identified from the pending review of Division of Scientific Investigations on the Study MKC-TI-142. However, we defer to the clinical division to comment whether there was sufficient clinical information to support the Gen2C Inhaler as the new to-be-marketed device in this Re-submission.

#### 1.2 Phase IV Commitments

None

#### 1.3 Summary of Important Clinical Pharmacology Findings

##### Background

The sponsor submitted one new clinical pharmacology study to address the clinical pharmacology recommendation in the CR letter dated March 12, 2010 (see Attachment for the recommendation). In the original submission, the pivotal bioequivalence (BE)

study comparing the to-be-marketed inhaler (MedTone Inhaler Model D) to the inhaler used in the pivotal clinical efficacy trials (MedTone Inhaler Model C) was not acceptable because of inadequate bioanalytical study results based on the DSI review. The sponsor responded to the CR letter by conducting a new PK comparability study (MKC-142) comparing a new inhaler, Gen2C, to the inhaler that was used in the pivotal clinical efficacy trials from the original application. The sponsor is proposing this new inhaler, Gen2C to be the to-be-marketed inhaler.

In addition, the sponsor conducted a pediatric inhaler usage study (MKC-143) with empty cartridge to identify pediatric age limit to properly handle the inhalers. The inhalers require many steps to follow, and pediatric inhalation capability may change with aging because the inhalers are dependent on the passive inhalation. Therefore, the study was to identify appropriate pediatric age groups for the future pediatric efficacy and safety study of the inhalers.

### Summary

The sponsor assessed insulin pharmacokinetic comparability following the administration of 20 U of insulin from the new proposed to-be-marketed inhaler (Gen2C) and 30 U of insulin from the inhaler used in Phase 3 trials (MedTone Inhaler Model C) in healthy subjects (MKC-TI-142). The insulin pharmacokinetic parameters following Gen2C met the BE criteria to those of Model C (Table1).

**Table 1 Least square geometric mean ratios (90% confidence interval) of AUC and Cmax comparing Gen2C versus Model C inhaler (n=46)**

	<b>AUC</b>	<b>Cmax</b>
Baseline unadjusted	1.006 (0.954, 1.060)	1.020 (0.948, 1.099)
Baseline adjusted (predose measurement)	0.997 (0.940, 1.059)	1.017 (0.941, 1.099)
Baseline adjusted (C-peptide)	1.060 (0.981, 1.145)	1.082 (0.992, 1.180)

In the same study, the sponsor assessed comparability of two difference strengths of insulin package (10 U and 20 U) and it was concluded that insulin pharmacokinetics following two packages of 10 U was bioequivalent to that of one package of 20 U when Gen2 was used (Table 2).

**Table 2 Least square geometric mean ratios (90% confidence interval) of AUC and Cmax comparing 2 x 10 U versus 1 x 20 U dose (n=46)**

	<b>AUC</b>	<b>Cmax</b>
Baseline unadjusted	0.973 (0.923, 1.023)	0.954 (0.886, 1.028)
Baseline adjusted (predose measurement)	0.970 (0.914, 1.030)	0.951 (0.880, 1.028)
Baseline adjusted (C-peptide)	0.957 (0.886, 1.039)	0.930 (0.852, 1.014)

In addition, results of Study MKC-143 indicate pediatric subjects of ages as low as 4-5 can use Gen2C because Gen2C required fewer steps (8 steps) to use than those of Model D (b) (4) with acceptable performance assessed by inhalation variable.

## Individual Study Review

### Study MKC-TI-142

The sponsor conducted a Phase 1, open-label, randomized, crossover trial in healthy volunteers to evaluate the following two objectives:

- Primary Objective: The calculated confidence intervals (CI) for the ratios of the average log-transformed insulin Cmax and AUC<sub>0-120</sub> meeting the BE criteria following Gen2C (new proposed to-be-marketed inhaler) compared to those of MedTone Inhaler Model C (Phase 3 trial inhaler)
- Secondary Objective: The calculated CI for the ratios of the average log-transformed insulin Cmax and AUC<sub>0-120</sub> meeting the BE criteria following two packages of 10 U compared to that of one package of 20 U using Gen2C

While insulin dose of 30 U has been used with Model C inhaler, it was reduced to 20U with Gen2C inhaler because the exploratory study results indicated that the insulin exposure increased up to 63% with an initial model of Gen2C compared to that with Model C (Study MKC-TI-141, see Attachment for the supplemental data).

The information about the inhalers and formulations are summarized in Table 3.

**Table 3 Inhalers and formulations used in the study**

#### **Technosphere insulin inhalation powder**

<b>Study Drug:</b>	<b>Technosphere Insulin Inhalation Powder</b>
Active ingredient:	Human Insulin, recombinant DNA origin
Formulation:	Each milligram of formulation contains 3.0 Units of human insulin
Dosage form:	Inhalation Powder
Packaged as MedTone Inhaler Model C cartridge:	Premetered single-dose cartridges filled with Technosphere Insulin Inhalation Powder containing 30 U of insulin
Packaged as Gen2C cartridge:	Premetered single-dose cartridges filled with Technosphere Insulin Inhalation Powder containing 10 U or 20 U of insulin
Manufactured by:	MannKind Corporation
Packaging description of MedTone Inhaler Model C cartridges:	Blister packages containing 4 MedTone Inhaler Model C cartridges (30 U cartridges)
Packaging description of Gen2C cartridges:	Foil pouch containing a blister containing 8 Gen2C cartridges (10 U or 20 U cartridges)
Dose/Inhaler/Lot number/Expiration date:	30 U/MedTone Inhaler Model C/CLM09310A/May 2011 20 U/Gen2C/D090008A/June 2010 10 U/Gen2C/D090007A/June 2010

#### **Inhalers**

Investigational device:	MedTone Inhaler Model C and Gen2C inhaler
Product description:	Breath-powered inhaler
Manufactured by:	MannKind Corporation
Lot numbers:	MedTone Inhaler Model C/D070014 Gen2C/D090009 and CLM10056B

Clinical trial and bioanalytical study were conducted at the following sites:

Study conduct contract research organization	(b) (4)
Local laboratory (safety)	
Analytical laboratory for insulin and C-peptide	

Blood samples were obtained to evaluate for glucose, insulin, and C-peptide at time -30, -15, 0, 3, 6, 9, 12, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, 210, and 240 minutes post-dosing. C-peptide and insulin blood samples were sent to (b) (4) for their analyses. Blood glucose concentrations were measured using a glucose meter at the clinical site.

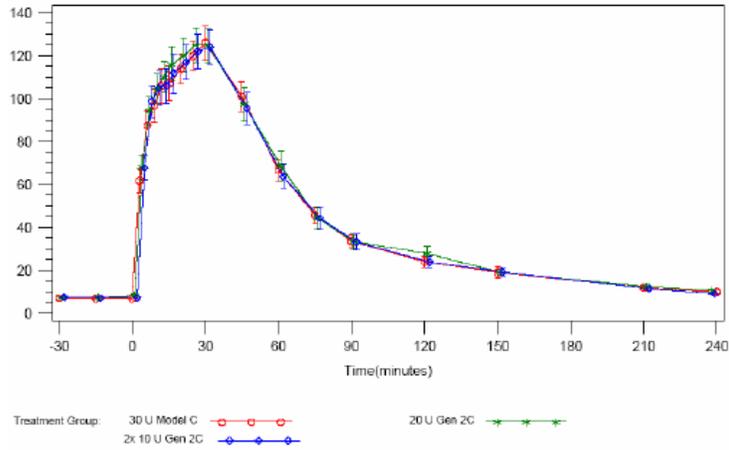
Insulin concentrations were determined using an electrochemiluminescence immunoassay method. The limits of quantification were 0.5  $\mu\text{IU/mL}$  to 400  $\mu\text{IU/mL}$ . C-peptide concentrations in serum were evaluated using a chemiluminescence immunoassay. The limits of quantification were 0.5  $\text{ng/mL}$  to 20  $\text{ng/mL}$ .

The insulin exposure was evaluated based on serum insulin  $\text{AUC}_{0-120}$  and  $C_{\text{max}}$  using the following 3 methods: uncorrected (raw) insulin concentrations, baseline-corrected insulin concentrations using average of 3 pre-dose insulin concentrations, and C-peptide-corrected insulin concentrations. C-peptide-corrected insulin concentrations were obtained following these three steps: 1) establish a linear correlation for each individuals between insulin and C-peptide concentrations following the placebo administration at Day 0 using linear mixed effect modeling, 2) calculate endogenous insulin concentrations using C-peptide concentrations after exogenous insulin was administered and the correlation that was established in step 1, and 3) subtract the endogenous insulin concentration from the total insulin concentration (see Attachment for the detailed statistical plan)

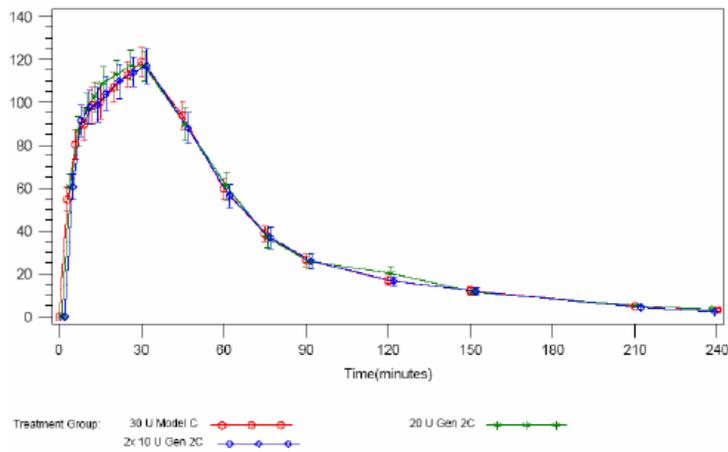
The insulin concentration-time profiles following the treatments are shown in Figure 1. Insulin pharmacokinetic parameters are summarized with results of BE assessment between Gen2C vs. Model C (Table 4) and between 2 x 10 U vs. 1 x 20 U dose (Table 5).

**Figure 1 Insulin concentration-time profiles**

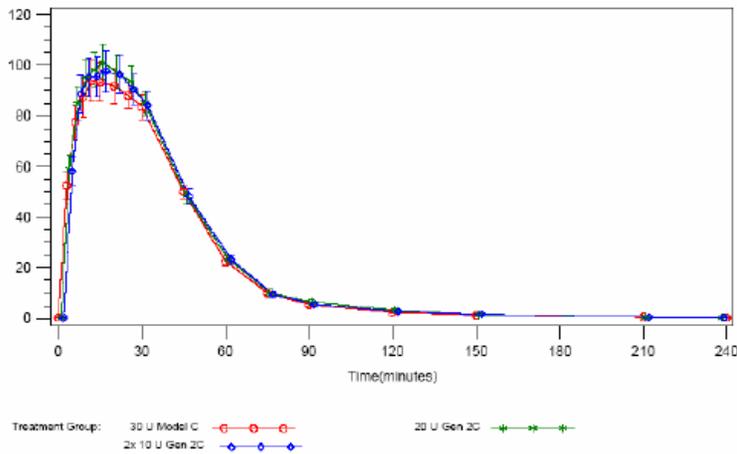
**Uncorrected mean (SD) insulin concentration-time profiles**



**Mean (SD) insulin concentration-time profiles following the baseline correction with the average of 3 pre-dose concentrations**



**Mean (SD) insulin concentration-time profiles following C-peptide-correction**



**Table 4 Mean insulin pharmacokinetic parameters and results of BE assessment between Gen2C and Model C**

**Baseline-uncorrected**

PK Parameter	Statistic	30 U ModC (n = 46)	20 U Gen2 (n = 46)	20 U Gen2 vs 30 U ModC
AUC <sub>0-120</sub> (min·μU/mL)	Geometric Mean	7760	7834	
	Ratio			1.006
	90% CI			[0.954, 1.060]
C <sub>max</sub> (μU/mL)	Geometric Mean	140	143	
	Ratio			1.020
	90% CI			[0.948, 1.099]

Abbreviations: AUC<sub>0-120</sub>, area under the serum concentration-time curve from time zero to 120 minute postdose; CI, confidence interval; C<sub>max</sub>, maximum observed serum concentration; PK, pharmacokinetic.

Geometric mean ratio and 90% confidence interval are model-adjusted values, derived from the mixed model with treatment, sequence, and period as fixed effect and subject as random effect.

**Baseline corrected using the average of 3 pre-dose concentrations**

PK Parameter	Statistic	30 U ModC (n = 46)	20 U Gen2 (n = 46)	20 U Gen2 vs 30 U ModC
AUC <sub>0-120</sub> (min·μU/mL)	Geometric Mean	6952	6964	
	Ratio			0.997
	90% CI			[0.940, 1.059]
C <sub>max</sub> (μU/mL)	Geometric Mean	133	135	
	Ratio			1.017
	90% CI			[0.941, 1.099]

Abbreviations: AUC<sub>0-120</sub>, area under the serum concentration-time curve from time zero to 120 minute postdose.; CI, confidence interval; C<sub>max</sub>, maximum observed serum concentration; PK, pharmacokinetic.

Geometric mean ratio and 90% confidence interval are model-adjusted values, derived from the mixed model with treatment, sequence, and period as fixed effect and subject as random effect.

**Baseline corrected with C-peptide**

PK Parameter	Statistic	30 U ModC (n = 46)	20 U Gen2 (n = 46)	20 U Gen2 vs 30 U ModC
AUC <sub>0-120</sub> (min·μU/mL)	Geometric Mean	4060	4294	
	Ratio			1.060
	90% CI			[0.981, 1.145]
C <sub>max</sub> (μU/mL)	Geometric Mean	97.4	105	
	Ratio			1.082
	90% CI			[0.992, 1.180]

Abbreviations: AUC<sub>0-120</sub>, area under the serum concentration-time curve from time zero to 120 minute postdose; CI, confidence interval; C<sub>max</sub>, maximum observed serum concentration; PK, pharmacokinetic.

Geometric mean ratio and 90% confidence interval are model-adjusted values, derived from the mixed model with treatment, sequence, and period as fixed effect and subject as random effect.

**Table 5 Mean insulin pharmacokinetic parameters and results of BE assessment between 2x10U and 1x20U using Gen2C**

**Baseline uncorrected**

PK Parameter	Statistic	2x 10 U Gen2 (n = 46)	20 U Gen2 (n = 46)	2x 10 U Gen2 vs 20 U Gen2
AUC <sub>0-120</sub> (min·μU/mL)	Geometric Mean	7577	7834	
	Ratio			0.973
	90% CI			[0.923, 1.025]
C <sub>max</sub> (μU/mL)	Geometric Mean	136	143	
	Ratio			0.954
	90% CI			[0.886, 1.028]

Abbreviations: AUC<sub>0-120</sub>, area under the serum concentration-time curve from time zero to 120 minutes postdose; CI, confidence interval; C<sub>max</sub>, maximum observed serum concentration; PK, pharmacokinetic.

Geometric mean ratio and 90% CI are model-adjusted values, derived from the mixed model with treatment, sequence, and period as fixed effect and subject as random effect.

**Baseline corrected with the average of 3 pre-dose concentrations**

PK Parameter	Statistic	2x 10 U Gen2 (n = 46)	20 U Gen2 (n = 46)	2x 10 U Gen2 vs 20 U Gen2
AUC <sub>0-120</sub> (min·μU/mL)	Geometric Mean	6712	6964	
	Ratio			0.970
	90% CI			[0.914, 1.030]
C <sub>max</sub> (μU/mL)	Geometric Mean	128	135	
	Ratio			0.951
	90% CI			[0.880, 1.028]

Abbreviations: AUC<sub>0-120</sub>, area under the serum concentration-time curve from time zero to 120 minutes postdose; CI, confidence interval; C<sub>max</sub>, maximum observed serum concentration; PK, pharmacokinetic.

Geometric mean ratio and 90% CI are model-adjusted values, derived from the mixed model with treatment, sequence, and period as fixed effect and subject as random effect.

**Baseline corrected with C-peptide**

PK Parameter	Statistic	2x 10 U Gen2 (n = 46)	20 U Gen2 (n = 46)	2x 10 U Gen2 vs 20 U Gen2
AUC <sub>0-120</sub> (min·μU/mL)	Geometric Mean	4136.5	4294.5	
	Ratio			0.957
	90% CI			[0.886, 1.035]
C <sub>max</sub> (μU/mL)	Geometric Mean	98.3	105.2	
	Ratio			0.930
	90% CI			[0.852, 1.014]

Abbreviations: AUC<sub>0-120</sub>, area under the serum concentration-time curve from time zero to 120 minutes postdose; CI, confidence interval; C<sub>max</sub>, maximum observed serum concentration; GM, geometric mean; PK, pharmacokinetic.

Geometric mean ratio and 90% CI are model-adjusted values, derived from the mixed model with treatment, sequence, and period as fixed effect and subject as random effect.

***Reviewer's comments***

Glucose parameters were not reported in this study. The glucose parameters were not used as the primary parameters in clinical pharmacology comparative studies when they have been conducted in healthy subjects without the clamp procedures because glucose parameters were often confounded by additional glucose administration based on glycemic rescue criteria. In the pivotal BE study of original application, this was demonstrated and there was additional glucose administration in majority of the subjects. With this consideration, clamp procedures should be considered if pharmacodynamic parameters are to be one of the primary endpoints in the future clinical pharmacology comparative trials.

**Study MKC-143**

The objectives of this study were to determine whether a pediatric population can handle, assemble, and operate the Gen2C and MedTone® Inhaler Model D delivery systems and to characterize the inspiratory profiles achieved by pediatric use of the Gen2C and MedTone Inhaler Model D delivery systems with an empty cartridge.

Healthy pediatric subjects sequentially enrolled into one of five age groups (4-5, 6-8, 9-10, 11-13, and 14-17 years); each group included up to 15 subjects who were randomly assigned to one of two sequences for inhaler use. A total of 74 subjects were analyzed.

- To determine whether pediatric subjects could successfully handle, assemble, and operate the inhalation delivery systems, the frequency of success or failure of each step and the number of subjects able to perform all steps correctly were summarized in Table 6.



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**Attachment:**

**1. Recommendation by the Office of Clinical Pharmacology in the CR letter**

The sponsor should consider one of the following options to resolve the deficiencies identified by the DSI:

Option 1. Re-analyze serum samples for the insulin and glucose exposure considering the following:

- 
- 
- 
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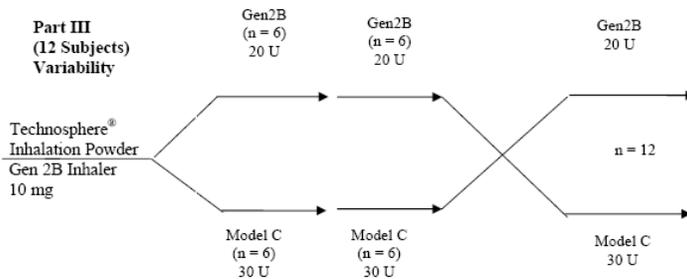
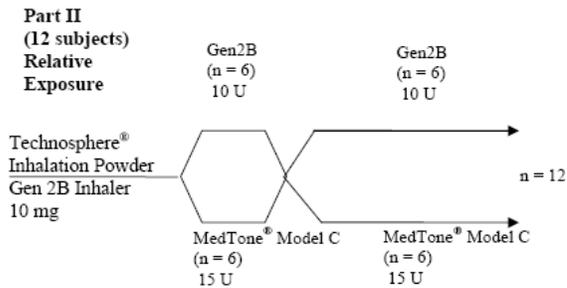
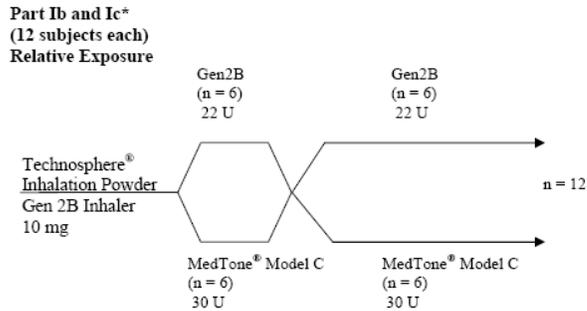
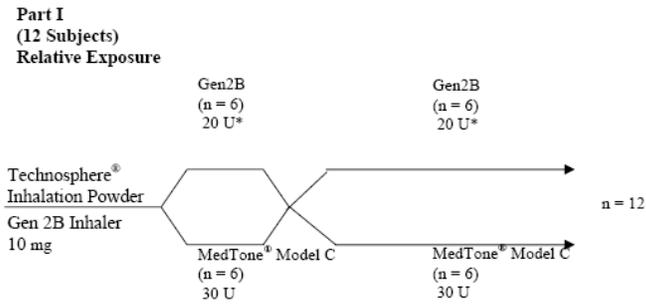
(b) (4)

Option 2. Re-conduct the pivotal bioequivalence study.

## 2. Pharmacokinetic data from MKC-TI-141

**Study Title:** a Phase 1, single-center, open-label, randomized, crossover design clinical trial in healthy normal volunteers to evaluate the bioavailability of Technosphere insulin inhalation powder in a Gen2B inhaler as compared to a MedTone inhaler Model C

Diagram summary of the treatments



C-peptide corrected insulin relative exposure (Part I and Ib)

PK Parameter	Statistic	Part I		Part Ib	
		Gen2B, 20 U (n = 11)	Model C, 30 U (n = 11)	Gen2B, 22 U (n = 10)	Model C, 30 U (n = 12)
AUC <sub>0-∞</sub> (min·μU/mL)	GM	3102.0	3796.6	4190.7	3640.6
	Ratio		0.824		1.114
	90% CI		[0.640, 1.061]		[0.847, 1.465]
	CV% (Inter-Subject)	51.39	49.73	52.44	47.48
C <sub>max</sub> (μU/mL)	GM	71.1	83.7	121.8	96.8
	Ratio		0.857		1.228
	90% CI		[0.702, 1.045]		[0.989, 1.524]
	CV% (Inter-Subject)	37.08	27.90	31.00	39.03

Abbreviations: AUC<sub>0-∞</sub>, area under the curve from time = 0 until the last quantifiable observation; CI, confidence interval; C<sub>max</sub>, maximum observed plasma concentration; CV%, intersubject coefficient of variability; GM, geometric mean; PK, pharmacokinetic.

Source: Section 14.2, Table 14.2.3.1.

### C-peptide corrected insulin relative exposure (Part II and III)

PK Parameter	Statistic	Part II		Part III	
		Gen2B 10 U (n = 10)	Model C 15 U (n = 10)	Gen2B 20 U (n = 12)	Model C 30 U (n = 12)
AUC <sub>0-∞</sub> (min·μU/mL)	GM	2121.4	1950.0	3941.1	3417.6
	Ratio		1.161		1.137
	90% CI		[0.871, 1.547]		[0.923, 1.400]
	CV% (intersubject)	38.34	51.45	28.45	48.71
C <sub>max</sub> (μU/mL)	GM	50.3	43.5	98.8	83.3
	Ratio		1.206		1.114
	90% CI		[0.985, 1.477]		[0.942, 1.317]
	CV% (intersubject)	38.77	56.01	30.42	40.25

Abbreviations: AUC<sub>0-∞</sub>, area under the curve from time = 0 until the last quantifiable observation; CI, confidence interval; C<sub>max</sub>, maximum observed plasma concentration; CV%, intersubject coefficient of variability; GM, geometric mean; PK, pharmacokinetic.

Source: Section 14.2, Table 14.2.3.2.

### C-peptide corrected insulin intra-subject variability (Part III)

PK Parameter	Statistic	Part III	
		Gen2B 20 U (n = 6)	Model C 30 U (n = 6)
AUC <sub>0-∞</sub> (min·μU/mL)	GM	4052.4	3410.4
	Ratio		1.188
	90% CI		[0.736, 1.918]
	CV% (intrasubject)	44.77	47.38
C <sub>max</sub> (μU/mL)	GM	100.6	75.5
	Ratio		1.334
	90% CI		[0.922, 1.929]
	CV% (intrasubject)	42.66	45.46

Abbreviations: AUC<sub>0-∞</sub>, area under the curve from time = 0 until the last quantifiable observation; CI, confidence interval; C<sub>max</sub>, maximum observed plasma concentration; CV%, intrasubject coefficient of variability; GM, geometric mean; PK, pharmacokinetic.

Source: Section 14.2, Table 14.2.3.3.

### Relative exposure of Technosphere Inhalation powder (diketopiperazine, FDKP)

PK Parameter	Statistic	Part I		Part Ib		Part II		Part III	
		Gen2B 20 U n = 11	Model C 30 U n = 11	Gen2B 22 U n = 10	Model C 30 U n = 12	Gen2B 10 U n = 10	Model C 15 U n = 10	Gen2B 20 U n = 12	Model C 30 U n = 12
AUC <sub>0-∞</sub> (min·ng/mL)	n	11	11	10	12	10	10	18	18
	Mean	23826	23472	29107	26732	11084	11308	22462	19806
	SD	6055	4019	4050	3932	2108	1332	4362	4524
C <sub>max</sub>	n	11	11	10	12	10	10	18	18
	Mean	175	161	219	194	93.4	95.8	204	179
	SD	69.0	28.6	48.8	48.9	22.8	25.0	45.8	56.7

Abbreviations: AUC<sub>0-∞</sub>, Area under the curve from time = 0 until the last quantifiable observation; C<sub>max</sub>, maximum observed plasma concentration; SD, standard deviation.

Source: Section 14.2, Table 14.2.2.2

### 3. Statistical Analysis Plan for the Primary Endpoint

Average Bioequivalence (BE) methods will be used to show the Bioequivalence (BE) of insulin from TI Inhalation Powder as delivered by the Gen2C Inhaler (20 U, test) and the MedTone® Inhaler Model C (30 U, reference).

Blood samples will be drawn at time -30 minutes, -15 minutes, 0 (immediately prior to dosing IMP), 3, 6, 9, 12, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, 210, 240 minutes post-dose. Blood samples will be assessed for levels of C-peptide, glucose and insulin.

The Bioequivalence assessment will use two PK parameters of AUC<sub>0-τ</sub> and C<sub>max</sub> and will be based on the two one-sided tests procedure to determine whether the average values for the PK parameters determined after administration of the test (T, 20 U Gen 2C) and reference (R, 30 U Model C) products were comparable. This approach involves the calculation of the 90% CI for the ratio of the geometric means of the PK parameters for the T and R products.

The following model is considered to assess the Average Bioequivalence,

$$y_{ijk} = \mu + F_i + P_j + Q_k + S_{ikl} + \varepsilon_{ijk} \quad (2)$$

where  $y_{ijk}$  is the natural log-transformation of the PK parameters from the  $i$ th subject in the  $k$ th sequence at the  $j$ th dosing period; the  $\mu$  is the overall mean;  $P_j$  is the fixed effect of the  $j$ th period

( $j=1,2,3$ );  $Q_k$  is the fixed effect of the  $k$ th sequence ( $k=1, 2, \dots, 6$ );  $F_l$  is the fixed effect of the  $l$ th treatment ( $l=2 \times 10\text{U Gen2C}, 20\text{U Gen2C}, 30\text{ U Model C}$ );  $S_{ikl}$  is the random effect of the  $i$ th subject in the  $k$ th sequence under treatment  $l$  and  $\varepsilon_{ijk}$ 's are the independent random errors.

A PROC MIXED analysis will be completed based on the above equation (2) with fixed effects for sequence, period, treatment and random effects for subjects within sequence. A compound symmetry variance covariance structure will be used. The primary endpoint analysis will be conducted on PK population 1. Subjects with missing data on PK parameters from treatment 20U Gen2C or 30 U Model C will not be included in the model analysis.

The 90% CI for the difference in log-transformed means of  $AUC_{0-\tau}$  or  $C_{\max}$  between two formulations will be calculated within the MIXED procedure. Exponentiation of each limit will give the 90% CI for the ratio of geometric means. To establish BE, the two 90% CIs for the ratios of the average log-transformed insulin  $AUC_{0-\tau}$  and  $C_{\max}$  for the 20 U cartridges using Gen2C Inhaler (Test) versus the 30 U cartridge using the MedTone<sup>®</sup> Inhaler Model C (Reference) should fall within a BE limit of 0.8 and 1.25.

The following is the SAS code to run the average BE analysis using PROC MIXED procedure, where all randomization sequence and period will be used to fit the model and PKPAR denoting the response PK parameters of  $AUC_{0-\tau}$  and  $C_{\max}$ . All three treatment groups will be kept in the model, and the log ratio of PKPAR between treatment groups will be given by the *estimate* statement. This *estimate* statement assumes that the treatment code for the 20 U Gen2C precedes the code for the 30 U Model C in sort order (this would be the case, for example, if 20 U Gen2C was coded as treatment 2, 30 U Model C was coded as treatment 3 and 2  $\times$  10U Gen2C was coded as treatment 1).

```

Proc mixed data=adpk method=reml;
    Classes sequence subject period trt;
    model log(pkpar)=sequence period trt/ddfm=kenwardroger;
    random subject (sequence);
    estimate 'GEN2C_20U vs ModelC_30U' trt 0 1 -1/cl alpha=0.1;
    ods output estimates=BEout;

run;

data BEout;
    set BEout;
    lowerb=exp(lower) *Lower bound on anti-log (original) scale ;
    upperb=exp(upper); *Upper bound on anti-log (original) scale;

run;

```

All PK parameters will be derived using the following methods.

- C-Peptide corrected insulin concentrations
- Baseline corrected insulin concentrations
- Uncorrected raw insulin concentrations

The BE analysis result based on C-Peptide corrected  $AUC_{0-\tau}$  and  $C_{max}$  will be the primary evaluation, and the BE analysis results based on the other insulin concentration correction methods will be secondary evaluations.

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/s/  
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SANG M CHUNG  
12/13/2010

SALLY Y CHOE  
12/13/2010

**ADDENDUM**  
**CLINICAL PHARMACOLOGY REVIEW**

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<b>NDA</b>	22-472
<b>Submission Date(s)</b>	March 16, 2009
<b>Brand Name</b>	AFREZZA <sup>®</sup> and AFREZZA <sup>®</sup> Inhaler
<b>Generic Name</b>	Insulin monomer human [rDNA origin] inhalation powder
<b>Reviewers</b>	Sang M. Chung, Ph.D.
<b>Team Leader</b>	Sally Choe, Ph.D.
<b>OCP Division</b>	Clinical Pharmacology II
<b>OND Division</b>	Metabolism and Endocrinology Products
<b>Sponsor</b>	MannKind Corporation
<b>Submission Type</b>	Standard 505(b)(1)
<b>Formulation Strength(s)</b>	AFREZZA <sup>®</sup> is available as single-use cartridges of: <ul style="list-style-type: none"><li>• 15-unit strength</li><li>• 30-unit strength</li></ul>
<b>Indication</b>	<ul style="list-style-type: none"><li>• AFREZZA<sup>®</sup>, a rapid acting insulin, is indicated for the treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia.</li></ul>
<b>Dosage &amp; Administration</b>	<ul style="list-style-type: none"><li>• AFREZZA<sup>®</sup> is administered via oral inhalation using the AFREZZA<sup>®</sup> Inhaler.</li><li>• AFREZZA<sup>®</sup> should be administered at the beginning of a meal.</li><li>• <span style="background-color: gray; color: gray;">(b) (4)</span></li><li>• AFREZZA<sup>®</sup> dosing must be individualized.</li></ul>

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This addendum is to finalize the pending recommendation in the original Clinical Pharmacology review upon the availability of the Division of Scientific Investigations (DSI) inspection review issued on January 4, 2010.

**Final Recommendation:**

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 22-472 for AFREZZA<sup>®</sup> and finds it not acceptable because the pivotal bioequivalence study results are not reliable based on the DSI inspection review.

**Pending Recommendation in the Original Review:**

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 22-472 for AFREZZA® and finds it acceptable provided that the DSI inspection review on the pivotal bioequivalence study is acceptable, and the Agency and the sponsor agree on the labeling.

**Reviewer’s Comment:**

The pivotal bioequivalence study is to assess the comparability of the to-be-marketed device to the device used in the pivotal clinical trials. The DSI inspection review by Dr. Sean Y. Kassim dated on January 4, 2010 indicated four significant failures in the bioanalytical aspects of the pivotal bioequivalence study (MKC-TI-138). These failures are related to the reliability of the insulin pharmacokinetic and glucose data. The DSI inspection review concluded that the accuracy of insulin study sample data could not be confirmed and therefore not acceptable for review. Refer to the detailed DSI inspection review in Attachment.

Based on the DSI inspection report, this reviewer concludes that the comparability of the to-be-marketed device to the clinical device is not known because the pivotal bioequivalence study results are not reliable.

The sponsor should consider one of the following options to resolve the deficiencies identified by the DSI:

Option 1. Re-analyze serum samples for the insulin and glucose exposure considering the following:

-  (b) (4)
- 
- 
- 

Option 2. Re-conduct the pivotal bioequivalence study.

**Attachment starts here.**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	Afrezza (insulin) inhalation powder

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/s/

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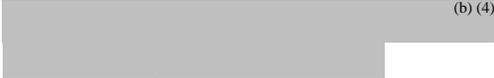
SANG M CHUNG  
01/11/2010

SALLY Y CHOE  
01/11/2010

CHANDRAHAS G G SAHAJWALLA  
01/12/2010

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA</b>	22-472
<b>Submission Date(s)</b>	March 16, 2009
<b>Brand Name</b>	AFREZZA <sup>®</sup> and AFREZZA <sup>®</sup> Inhaler
<b>Generic Name</b>	Insulin monomer human [rDNA origin] inhalation powder
<b>Reviewers</b>	Sang M. Chung, Ph.D.
<b>Team Leader</b>	Sally Choe, Ph.D.
<b>OCP Division</b>	Clinical Pharmacology II
<b>OND Division</b>	Metabolism and Endocrinology Products
<b>Sponsor</b>	MannKind Corporation
<b>Submission Type</b>	Standard 505(b)(1)
<b>Formulation Strength(s)</b>	AFREZZA <sup>®</sup> is available as single-use cartridges of: <ul style="list-style-type: none"><li>• 15-unit strength</li><li>• 30-unit strength</li></ul>
<b>Indication</b>	<ul style="list-style-type: none"><li>• AFREZZA<sup>®</sup>, a rapid acting insulin, is indicated for the treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia.</li></ul>
<b>Dosage &amp; Administration</b>	<ul style="list-style-type: none"><li>• AFREZZA<sup>®</sup> is administered via oral inhalation using the AFREZZA<sup>®</sup> Inhaler.</li><li>• AFREZZA<sup>®</sup> should be administered at the beginning of a meal.</li><li>•  (b) (4)</li><li>• AFREZZA<sup>®</sup> dosing must be individualized.</li></ul>

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## 1 Executive Summary

### 1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 22-472 for AFREZZA<sup>®</sup> and finds it acceptable provided that the DSI inspection review on the pivotal bioequivalence study is acceptable, and the Agency and the sponsor agree on the labeling.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Important Clinical Pharmacology Findings

#### REGULATORY BACKGROUND

The sponsor has submitted the NDA 22-472 for AFREZZA<sup>®</sup> (insulin monomer human [rDNA origin] inhalation powder) and its inhaler. The AFREZZA<sup>®</sup> is the second NDA from the insulin inhalation product class. The Agency approved the first formulation of inhalable insulin, EXUBERA<sup>®</sup>, on January 27, 2006. However, EXUBERA<sup>®</sup> (NDA 21-868) has been discontinued from marketing since October, 2007, (b) (4)

The sponsor requested a partial waiver of pediatric assessment for age birth to less than (b) (6) years of age mainly because the proposed inhaler is not an age appropriate device and a deferral of pediatric assessment for ages (b) (4) years because additional safety data from adults are needed. The sponsor has submitted a pediatric assessment plan (b) (4)

The Pediatric Review Committee (PeRC) meeting was held to discuss the appropriateness of the sponsor's proposed pediatric assessment plan on November 05, 2009. In general, the committee concluded that the plan was acceptable and recommended that the upper age limit in the partial waiver should be determined using results from the proposed device feasibility trials.

#### FORMULATION AND INHALER

The AFREZZA<sup>®</sup> is consisted of Technosphere<sup>®</sup> Insulin (TI, a dry powder inhalation formulation), a cartridge, and an inhaler. Main components of TI are insulin, fumaryl diketopiperazine (FDKP), and polysorbate 80. The FDKP is a novel excipient of the TI powder, which is the insulin carrier. The cartridge is a single dose package of TI inhalation powder, and the proposed dose strengths of cartridge are 15-U and 30-U. (b) (4)

The MedTone<sup>®</sup> Inhaler is a mechanical device for delivering the TI powder in the cartridge to the lung, and is re-

useable for up to one year. [REDACTED]

(b) (4)

The pivotal bioequivalence (BE) study was conducted for the comparability evaluation between to-be-marketed inhaler (Model D) and inhaler used in the Phase 3 trials (Model C), and the results of the study met the prespecified BE criteria. The DSI inspection on the pivotal BE study has been requested but the final review of the inspection is not available at this time of review.

## **CLINICAL PHARMACOLOGY TRIALS**

The sponsor has conducted about 26 clinical trials evaluating AFREZZA<sup>®</sup> clinical pharmacology in healthy, type 1 diabetes (T1D), and type 2 diabetes (T2D) subjects. The clinical pharmacology information for FDKP such as mass balance, the renal and hepatic impairment effects, and its effect on QT prolongation was submitted because FDKP is a novel excipient.

In assessing insulin pharmacokinetics (PK) and pharmacodynamics (PD), this reviewer noted that the critical study design elements were significantly different among the trials with different endpoints (e.g., AUC<sub>0-235min</sub> to AUC<sub>0-540min</sub>), different insulin baseline adjustments (e.g., average of predose, time zero, average of later phase, C-peptide, or no adjustment), different inhalers, different clamp procedure status, and different subject types. Furthermore, glucose parameters were often confounded by additional injection of regular human insulin or insulin analogue to rescue hyperglycemia, or additional glucose load to rescue hypoglycemia. These differences make the cross-study comparison of insulin PK and PD information difficult. Moreover, having the proper consistent study design elements is important for the following reasons:

- Insulin is an endogenous substrate with a short half-life (e.g., 32 minutes following TI in healthy subject under a clamp procedure). Therefore, a baseline adjustment is needed for the proper insulin PK and PD estimation, and the baseline correction methods can significantly affect the insulin data following an exogenous insulin administration. Furthermore, sampling scheme (up to 240 vs. 560 minutes after dosing) can significantly affect insulin PK and PD data because the relative contribution of endogenous insulin to exogenous insulin is changing with the sampling scheme.
- A clamp procedure is to experimentally control endogenous insulin and glucose fluctuation using infusion of exogenous insulin and glucose, and the clamp procedure elements can significantly affect insulin data from a trial.
- An inhaler can significantly affect insulin exposure following inhalation in addition to the formulation.
- Subject types (i.e., healthy, T1D, or T2D) may affect insulin data because insulin-glucose homeostatic feedback mechanism may differ among the types.

Therefore, insulin data should be interpreted within specific trial elements and the cross-study comparison for insulin pharmacokinetics and pharmacodynamics should be cautiously exercised.

The C-peptide seems to be a reasonable surrogate for the endogenous insulin because its changes reflect the fundamental insulin feedback responses to glucose changes and exogenous insulin. Therefore, C-peptide baseline adjustment should be considered for the future insulin clinical pharmacology trials.

Insulin dose was individually adjusted based on home blood glucose monitoring (HBGM) as needed to meet the target blood glucose (BG) goals, which were established to avoid hypoglycemia and hyperglycemia in Phase 3 trials. Therefore, conventional dose-response characterization was not available.

## **INSULIN PHARMACOKINETICS AND PHARMACODYNAMICS FOLLOWING INHALATION**

*GENERAL PHARMACOKINETIC AND PHARMACODYNAMICS:* The absolute bioavailability of insulin following 100-U TI was about 15% by the area under concentration-time curve ( $AUC_{0-360min}$ ) referencing that of 5-U intravenous (IV) insulin. The relative bioavailability was about 28% by the AUC as compared with that of 10-U subcutaneous (SC) insulin. The insulin pharmacodynamic (PD) effect on blood glucose was estimated using the area under glucose infusion rate ( $GIR_{0-360min}$ ). The PD effect was about 14% by the GIR referencing that of 5-U IV insulin and the PD effect was about 9% compared with that of 10-U SC regular insulin. The above baseline corrected insulin PK and PD data were obtained using a prototype inhaler from healthy subjects under clamp procedures.

The time to reach serum insulin maximum concentrations ( $t_{max}$ ) following TI (median of 10 minutes) was shorter than that of SC administration (median of 60 min) in T1D. The observed serum insulin  $C_{max}$  ranged from 55 to 219  $\mu U/mL$  following TI dosing ranged from 25 to 100-U and those included the physiologic  $C_{max}$  (known as about 76  $\mu U/mL$ ) in healthy subjects after a standardized meal. Dosing was individualized to achieve a blood glucose target in the pivotal clinical trials, and the mean dosing was about 36-66 U per dosing in the pivotal trials. The AUC ranged from 3502 to 12322  $\mu U \cdot min/mL$  following from 25 to 100-U TI dosing, and AUCs increased proportionally with dose. Variability in insulin pharmacokinetic following AFREZZA<sup>®</sup> was lower than that of EXUBERA<sup>®</sup> based on cross study comparison; 34% and 53% CV in C-peptide baseline adjusted AUCs for AFREZZA<sup>®</sup> and EXUBERA<sup>®</sup>, respectively.

The TI dosing resulted in a rapid onset of action on blood glucose with earlier time to peak effect on glucose infusion rate (median GIR  $t_{max}$ ; 35 minutes) than that of SC rapid-acting insulin analog (RAA, median GIR  $t_{max}$  of 110 minutes). The above baseline corrected insulin PD data were obtained from T1D under clamp procedures using the pivotal clinical trial inhaler (Model C).

*EFFECT OF LUNG RELATED DISEASE AND DRUGS:* Diseases such as asthma and chronic obstructive pulmonary disease (COPD) did not significantly affect insulin pharmacokinetics following TI. Drugs that can be potentially co-administered such as

albuterol and fluticasone did not significantly affect insulin pharmacokinetics following TI.

*INHALER*: The proposed inhaler is MedTone<sup>®</sup> Inhaler, Model D, and the sponsor demonstrated insulin exposure comparability between Model D and Model C, the inhaler used in the pivotal clinical trials.

## **FDKP, A NOVEL EXCIPIENT, PHARMACOKINETICS**

The major elimination route of FDKP was renal (97% following IV), and absorption from the gastrointestinal tract was negligible (<4% absolute bioavailability). Approximately, 20% of the FDKP dose was excreted in the urine following TI inhalation powder. The FDKP was not metabolized in the body. The t<sub>max</sub> of FDKP following TI inhalation powder ranged from 9 to 25 minutes. The terminal half-life (t<sub>1/2</sub>) ranged from 114 to 198 minutes, and it increased to 270 minutes in subjects with moderate renal impairment. The hepatic and mild renal impairment did not significantly affect FDKP pharmacokinetics. Disease such as COPD and asthma did not significantly affect FDKP pharmacokinetics. Thorough QT study was conducted following 20 mg (equivalent to FDKP amount in 67-U TI) and 40 mg (equivalent to FDKP amount in 133-U TI) Technosphere<sup>®</sup> inhalation powder without insulin, and it was concluded that FDKP did not prolong QT interval.

## **2 Question Based Review**

### **2.1 General attributes**

#### *2.1.1 What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?*

Technosphere<sup>®</sup> Insulin (TI) is a dry insulin powder formulation for AFREZZA<sup>®</sup>. Components and composition of TI are shown in Table 1. The FDKP (Figure 1), the sponsor's proprietary excipient in TI, is crystallized under acidic conditions, and the crystals assemble to form particles (Technosphere<sup>®</sup>). The particle is readily soluble at physiologic pH. Insulin is adsorbed onto pre-formed Technosphere<sup>®</sup> particles. The TI inhalation powder is targeted to contain 3-U insulin/mg. The proposed strengths of cartridge are 15-U and 30-U, and the nominal fill weights are 5 mg and 10 mg, respectively. Median particle diameters of Technosphere<sup>®</sup> and TI particles are 2-2.5 µm (Figure 2). The particle size is the important determining factor for extent and distribution of TI in the lung. The TI inhalation powder is filled into cartridges (Figure 2). User's aspiration produces air flow in the inhaler and the powder is delivered to the lung through the air flow.

While the to-be-marketed TI formulation has been used in Phase 3 trials, the sponsor bridged the new to-be-marketed inhaler (Model D) to the clinical trial device (Model C) via a pivotal insulin bioequivalence trial.

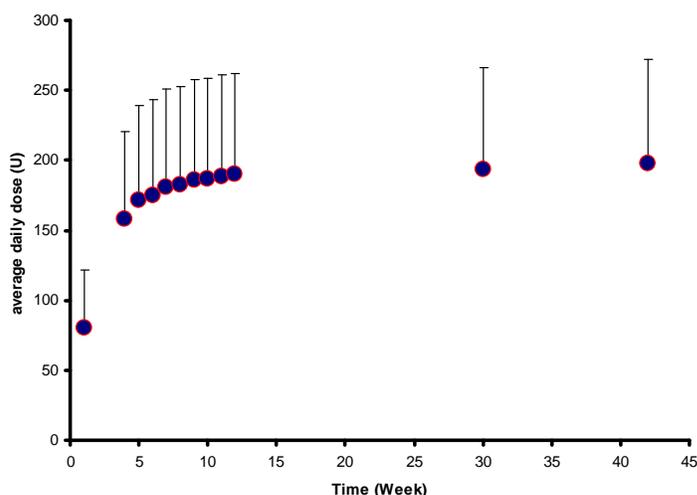


## 2.2 General clinical pharmacology

### 2.2.1 What are the characteristics of the exposure-response relationships (dose/concentration-response)?

Insulin dose was individually adjusted based on home blood glucose monitoring (HBGM) as needed to meet the target blood glucose (BG) goals, which were established to avoid hypoglycemia and hyperglycemia (definition in Appendix 4-1). Therefore, conventional dose-response characterization is not available. The detailed guideline for the dose adjustment is summarized in Appendix 4-1.

Total daily dose was stable after initial titration period in T1D and T2D (Figure 3). Mean (SD) mealtime doses of TI in T1D were 46.5 (23.3), 53.0 (23.5), 54.6-U (23.2) at breakfast, mid-day meal, and dinner, respectively (Study MKC-TI-009), and in T2D during the last 3 months of the trial were 63.1 (25.1), 65.9 (24.2), and 66.3-U (24.3) (30.6) at breakfast, mid-day meal, and dinner, respectively (Study MKC-TI-102).



**Figure 3** Mean (SD) total daily dose versus time since randomization in T2D (MKC-TI-102) (last two time points indicate midpoints of 3-6 months and 6-9 months, respectively.)

### 2.2.2 Does FDKP prolong the QT interval?

The effect of FDKP on QT interval was assessed in a single-blind, randomized, placebo-, and positive-controlled design following two parallel doses (20 mg or 40 mg; Study MKC-TI-131). Typical TI dose per treatment ranged from 15-U to 90-U and the FDKP

amount ranged from about 4 mg in 15-U TI to 27 mg in 90-U TI. Therefore, the FDKP doses of 20 mg (68-U TI equivalent) and 40 mg (133-U TI equivalent) are regarded as a therapeutic dose and a supra-therapeutic dose, respectively. It was concluded that there was no significant effect of FDKP on QT prolongation. Please see the review by Dr. Anshu Marathe for more details.

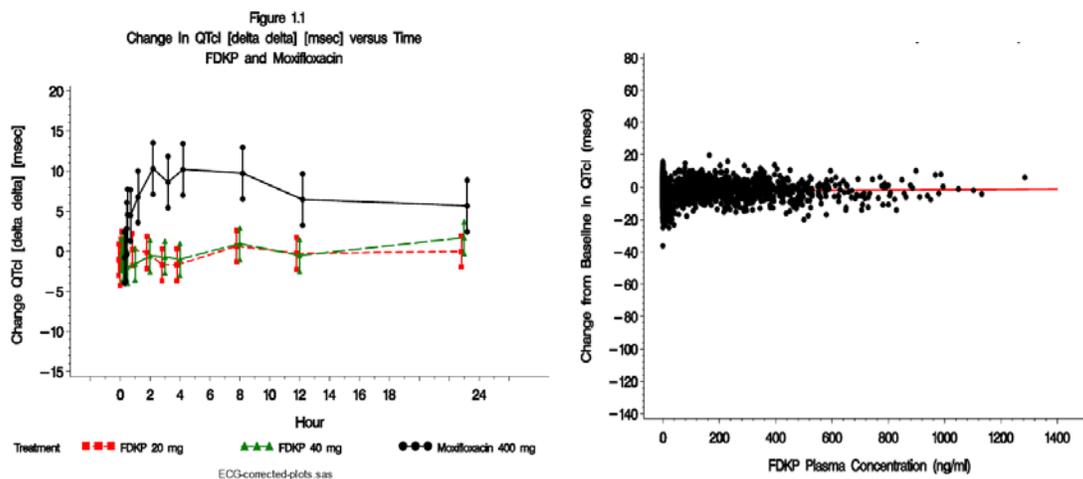


Figure 4 Change in individually corrected QTc (QTcI, double delta, msec) versus time (left) and QTcI placebo-corrected change from baseline versus FDKP plasma concentration (right)

### 2.2.3 What are the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics following AFREZZA?

#### 2.2.3.1 What is the insulin absolute and relative bioavailability following TI administration?

The insulin absolute bioavailability following 100-U TI in healthy subjects (n=5) was 14.9% by the baseline adjusted  $AUC_{0-360min}$  referencing that of 5-U IV regular insulin utilizing the prototype inhaler (Study PDC-INS-0001). The baseline was established using the average of 4 pre-dose insulin concentrations (i.e., 120, 90, 60, and 30 minutes predose) and a concentration at time 0. The study was conducted following euglycemic clamp procedures. The insulin relative bioavailability of 100-U TI was 28.3% by the  $AUC_{0-360min}$  referencing that of 10-U SC regular insulin in the same study. The insulin serum concentration-time profiles following TI, IV, and SC are shown in Figure 5, and pharmacokinetic parameters are summarized in Table 2. Mean (SD)  $t_{max}$  following TI was 13 (5) minutes and it was shorter than that of SC (126 (65) minutes).

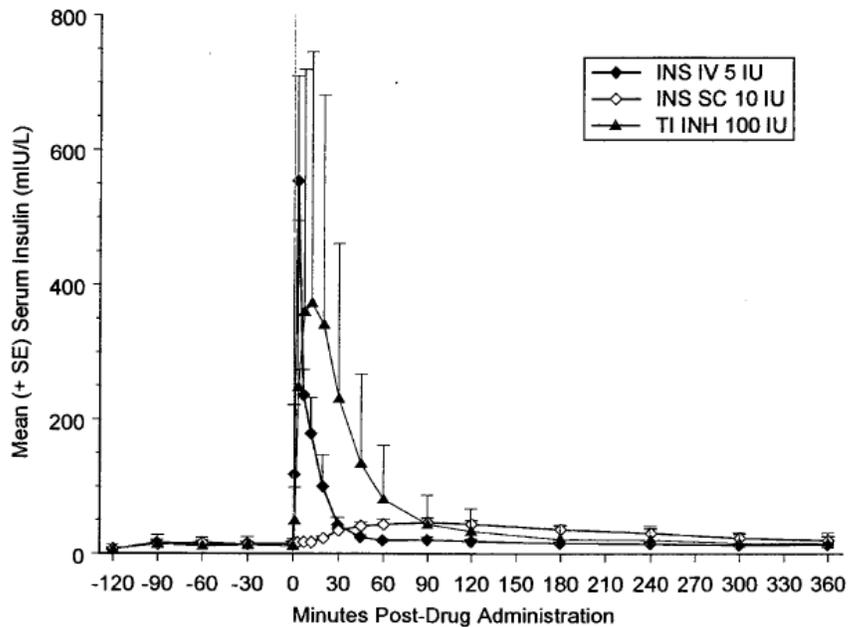


Figure 5 Mean (SE) serum insulin concentration-time profiles by treatments.

Table 2 Insulin pharmacokinetic parameters

Absolute Bioavailability		Geometric Mean			
Treatment Group	Parameter	Test	Reference <sup>1</sup>	Ratio <sup>2</sup>	90% CI <sup>3</sup>
TI INH 100 IU (N=5)	C <sub>max</sub> (mIU/L)	18.87	571.2	0.033	(0.021, 0.053)
	AUC <sub>180</sub> (min*mIU/L)	800.6	5444	0.147	(0.099, 0.219)
	AUC <sub>360</sub> (min*mIU/L)	846.9	5700	0.149	(0.104, 0.212)
Relative Bioavailability		Geometric Mean			
Treatment Group	Parameter	Test	Reference <sup>1</sup>	Ratio <sup>2</sup>	90% CI <sup>3</sup>
TI INH 100 IU (N=5)	C <sub>max</sub> (mIU/L)	18.87	15.40	1.225	(0.769, 1.951)
	AUC <sub>180</sub> (min*mIU/L)	800.6	1935	0.414	(0.278, 0.615)
	AUC <sub>360</sub> (min*mIU/L)	846.9	2993	0.283	(0.198, 0.403)
<sup>1</sup> INS SC 10 IU					
<sup>2</sup> Ratio = Test/Reference					
<sup>3</sup> CI = Confidence interval based on ANOVA model with sequence (of treatments), treatment, and period as factors.					

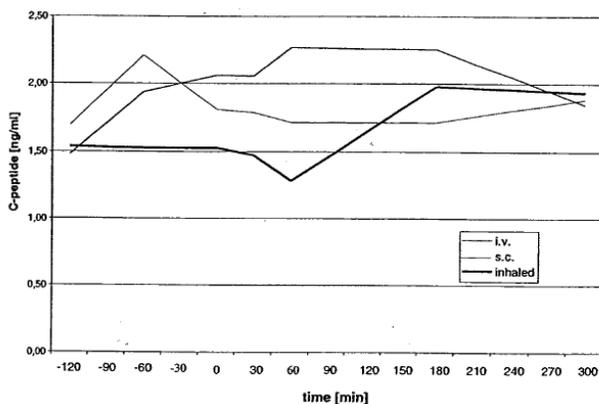
The relative bioavailability of EXUBERA<sup>®</sup> compared with SC regular insulin was about 10% (OCP review for EXUBERA<sup>®</sup>).

The sponsor stated that insulin half-life was not formally characterized in the trials because 1) insulin has been extensively used with more than 25 years as human insulin and 80 years as a therapeutic agent, and 2) half-life is often confounded by absorption process following extravascular administration and endogenous insulin. Meanwhile,

insulin half-life was reported as 32 minutes following 45-U TI with C-peptide adjustment in healthy subjects under a clamp procedure.

**Reviewer’s Comments:**

- Formulation and inhaler, and patient type in Study PDC-INS-0001 were different from those in the pivotal trials. Therefore, there should be caution in comparing the study results of PDC-INS-0001 with those in the pivotal trials. For example, relative bioavailability was 19% following 30-U TI using MedTone Model D in T1D (MKC-TI-116) and 24.6% following 25-U TI using a prototype inhaler (alpha) in healthy subjects (PDC-INS-0002) compared to that of 10-U SC RAA (rapid acting analogue). This difference is attributed from various factors including different inhalers, different subject types, and the different baseline correction. While PDC-INS-0002 by the baseline corrected  $AUC_{0-360min}$  under hyperinsulinemic euglycemic clamp procedure, the baseline was the concentration at time 0 in the study MKC-TI-116.
- Insulin was infused during the study at the rate of 0.15 mU/min/kg to achieve a target serum insulin range of 10-15  $\mu$ U/ml, and to suppress the endogenous insulin secretion. However, endogenous insulin appeared to fluctuate during the trial and the changes were not consistent among treatments as indicated in C-peptide level changes over the time (Figure 8). This demonstrates that the baseline correction by the average of predose insulin concentrations might not be the best way to adjust endogenous insulin in the study.



**Figure 6** Mean C-peptide concentrations during the clamp trial (Study PDC-INS-0001)

**2.2.3.2 How is pulmonary distribution following TI administration?**

Pulmonary distribution was estimated following 10-U TI labeled with  $^{99m}$ technetium using Model C inhaler in healthy subjects (n=5; study PDC-INS-0007). Mean of 67% of the labeled dose was delivered to the body. While mean of 39% of the dose was distributed to the lung, mean of 21% and 18% of the dose was distributed to the left and right lung, respectively. In addition, mean of 18% and 7% of the dose was found in the oropharynx and stomach, respectively.

Lung resident time of insulin and FDKP was evaluated following 60-U TI using Model C inhaler in healthy subjects (n=13; MKC-TI-122). Insulin and FDKP concentrations were measured in bronchoalveolar lavage fluid and blood samples. The amount in the lung was calculated from the measured concentration multiplied by the epithelial lining fluid volume, which was assumed to be 40 mL. It was concluded that the amount of insulin and FDKP remaining in the lung at 12 hours following the dose was 0.3% and 0.4% of the amount, respectively, at 30 minutes.

### 2.2.3.3 Is insulin PK proportional to dose?

Insulin pharmacokinetics was linear following TI up to 100-U dose (Figure 9). The baseline corrected insulin pharmacokinetics ( $C_{max}$  and  $AUC_{0-360min}$ ) was proportional to dose in healthy subjects (PDC-INS-0002) with slope=1 and its 95% confidence interval included 1 in a power model ( $PK=a*DOSE^{slope}$ ).

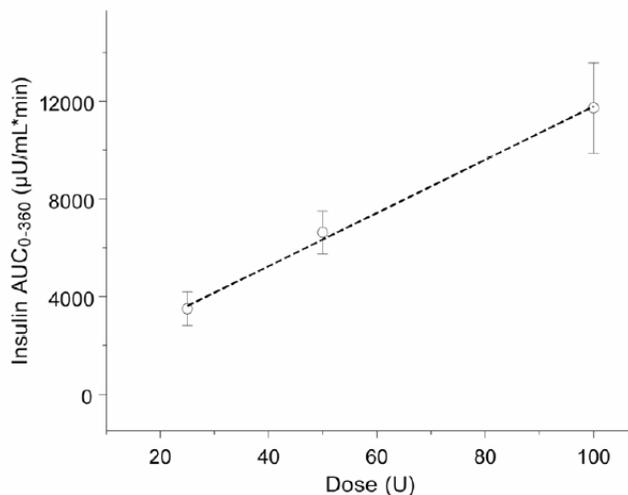


Figure 7 Insulin AUC versus dose in healthy subjects

### 2.2.3.4 Is insulin PK comparable among studies?

The sponsor attempted cross study comparison for  $t_{max}$ ,  $C_{max}$ , and AUC (Appendix 4-1) and concluded that insulin exposure ( $C_{max}$  and AUC) following TI dosing was not meaningfully changed with patient types and disease.

#### Reviewer's Comments:

- Study conditions were significantly heterogeneous with different endpoints (e.g.,  $AUC_{0-235min}$  to  $AUC_{0-540min}$ ), different baseline adjustments (e.g., average of predose, time zero, average of later phase, C-peptide, and no adjustment), different inhalers, and different clamp procedures as illustrated in Figure 10. Therefore, the cross study comparison for insulin pharmacokinetics may not be meaningful unless studies are carefully categorized with homogeneous study conditions.

- Variability on insulin AUC<sub>0-240min</sub> following TI dosing was comparable to that of SC in a few studies as follows:

Between subject variability in insulin AUC<sub>0-240min</sub>

Study	TI Inhalation Powder CV%	Subcutaneous Insulin
		CV%
PDC-INS-0002	40-60	42
MKC-TI-03B2	32	17
MKC-TI-110	62-64	51- 62
MKC-TI-116	40-46	40 <sup>a</sup>
MKC-TI-138	(b) (4)	NA

NA = not applicable

<sup>a</sup> Rapid-acting analog

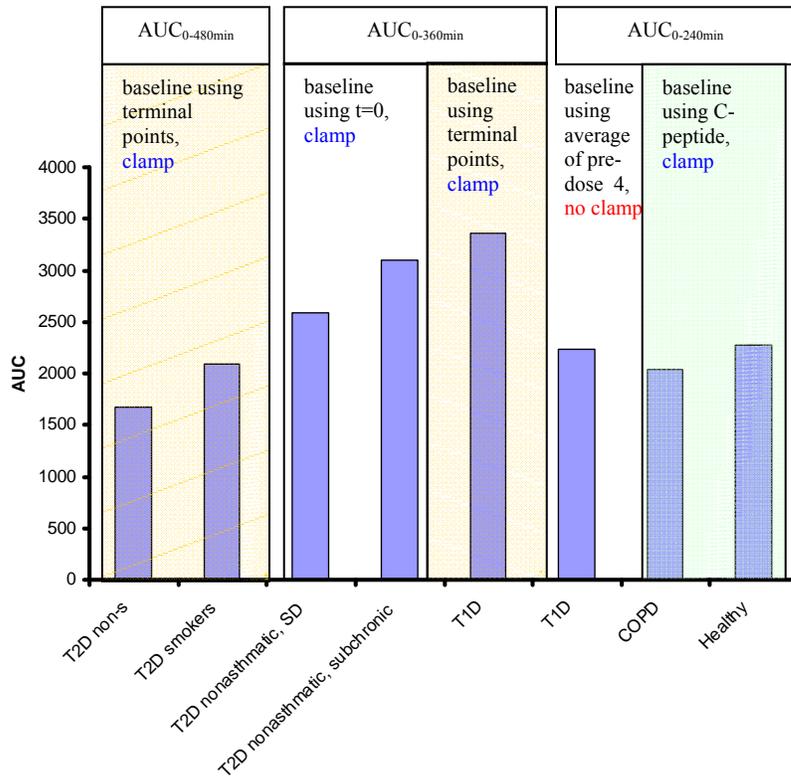


Figure 8 Insulin AUC ( $\mu\text{U}\cdot\text{min}/\text{mL}$ ) following 30-U TI using MedTone®, Model C

### 2.2.3.5 What is the insulin pharmacodynamics(PD) following TI compared to that of other route of administration?

The PD was measured as the area under glucose infusion rate ( $\text{GIR}_{0-360\text{min}}$ ). The glucose infusion rate was obtained as the response to insulin change with time in clamp procedures such as hyperinsulinemic euglycemic clamp. The  $\text{GIR}_{0-360\text{min}}$  ratio was defined as the bioeffect. The absolute bioeffect was about 14% following TI 100-U in healthy subjects referencing that of 5-U IV regular insulin, and the relative bioeffect was about 9% by the AUC as compared with that of 10-U SC regular insulin (Study PDC-INS-0001, Table 3). The mean (SD)  $t_{\text{max}}$  was 43(36.9) minutes following TI, and it was shorter than that of SC (133(62.6) minutes). The GIR profiles are shown in Figure 11.

Table 3 Glucose infusion rate (mg/kg/min) parameters

Absolute Bioeffect		Geometric Mean			
Treatment Group	Parameter	Test	Reference <sup>1</sup>	Ratio <sup>2</sup>	90% CI <sup>3</sup>
TI INH 100 IU (N=5)	$\text{GIR}_{\text{max}}$ (mg/kg/min)	0.41	6.96	0.058	(0.048, 0.070)
	AUC $\text{GIR}_{180}$ (mg/kg)	35.59	276.8	0.129	(0.097, 0.171)
	AUC $\text{GIR}_{360}$ (mg/kg)	44.39	329.9	0.135	(0.097, 0.187)
<sup>1</sup> INS IV 5 IU					
<sup>2</sup> Ratio = Test/Reference					
<sup>3</sup> CI = Confidence interval based on ANOVA model with sequence (of treatments), treatment, and period as factors.					

Relative Bioeffect		Geometric Mean			
Treatment Group	Parameter	Test	Reference <sup>1</sup>	Ratio <sup>2</sup>	90% CI <sup>3</sup>
TI INH 100 IU (N=5)	$\text{GIR}_{\text{max}}$ (mg/kg/min)	0.41	2.92	0.139	(0.116, 0.167)
	AUC $\text{GIR}_{180}$ (mg/kg)	35.59	275.8	0.129	(0.097, 0.171)
	AUC $\text{GIR}_{360}$ (mg/kg)	44.39	473.7	0.094	(0.068, 0.130)
<sup>1</sup> INS SC 10 IU					
<sup>2</sup> Ratio = Test/Reference					
<sup>3</sup> CI = Confidence interval based on ANOVA model with sequence (of treatments), treatment, and period as factors.					

**Reviewer’s Comments:**

- It is not clearly understood the reason why the 14% and 9% for absolute and relative bioeffects, respectively, were not parallel to insulin exposure (14.9% and 28.3% for absolute and relative bioavailability, respectively).
- The tmax was median of 35 and 110 minutes following 30-U TI and 10-U SC RAA, respectively, in T1D (Study MKC-TI-116), and tmax difference between TI administration and SC was not function of insulin or its analogue. Relative bioeffect following 30-U TI was about 20% compared with 10-U SC in T1D (Study MKC-TI-116). The GIR profiles are shown in Figure 12.
- The sponsor cited cross study comparison results about GIR following TI and others from publication by Heineman et al (Figure 13). Study conditions were not available in the publication. Therefore, there should be caution in the interpretation of the results.

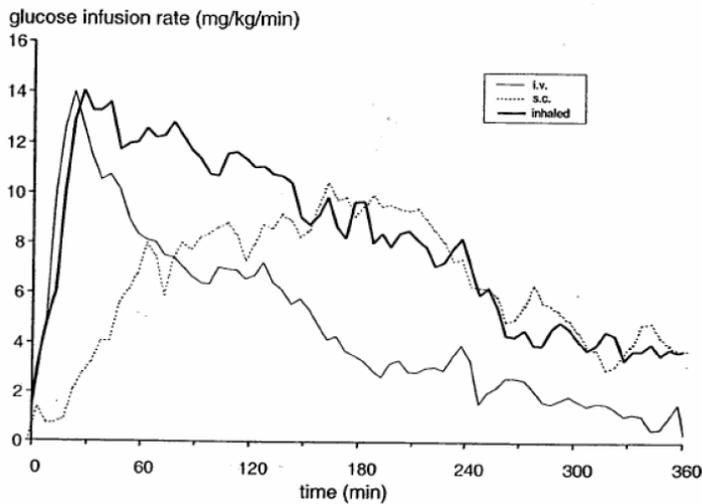


Figure 9 GIR profiles following TI, IV, and SC (Study PDC-INS-0001)

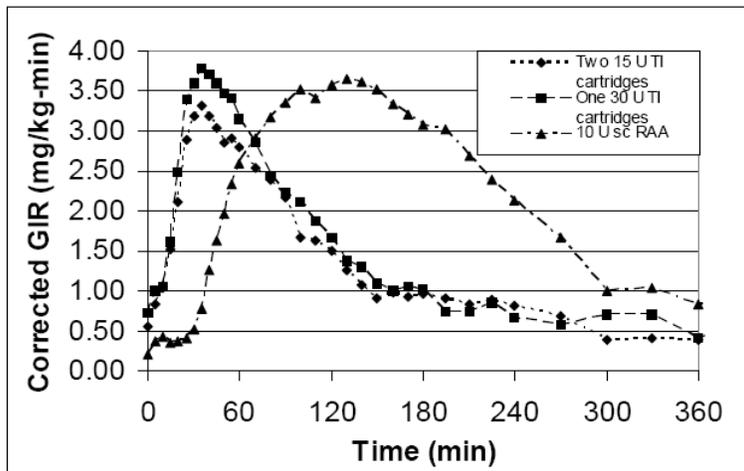
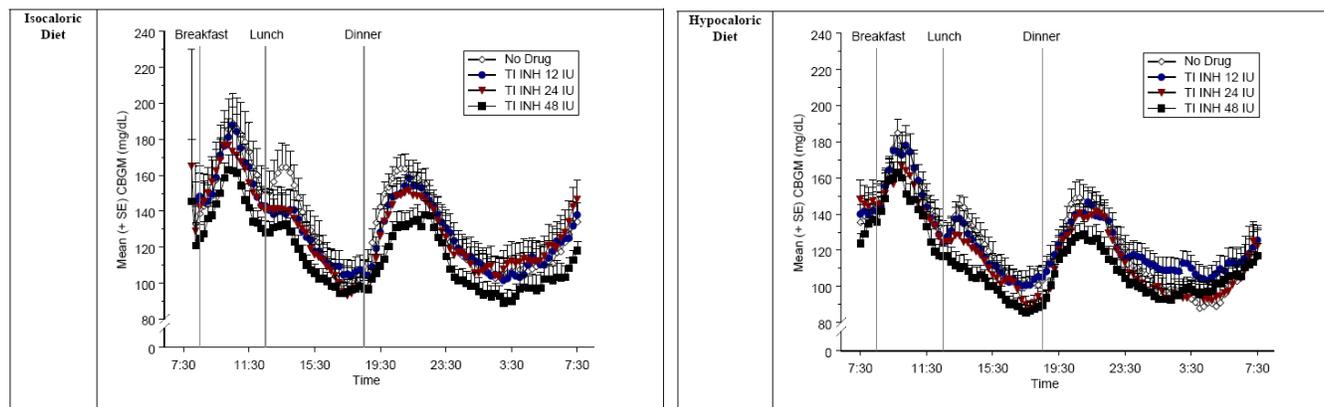


Figure 10 GIR profiles following TI and SC (Study MKC-TI-116)

**Figure 11** GIR profiles following various system (Heinemann L, Heise T, Br. J. Diab. Vasc. Dis. 2004; 4:295-301)

- Continuous blood glucose monitoring results following TI dosing a few times a day indicate that postprandial glucose changes varied with different size and composition of meals (n=25 T2D; PDC-INS-0004A; Figure 14). Mean glucose concentrations were lower in the late afternoon and during the night, and it is not clearly understood the reason why the glucose responses are different within a day.



**Figure 12** Serum Glucose (mg/dL) Based on Continuous Blood Glucose Monitoring (CBGM) – Mean Values Over 24 Hours

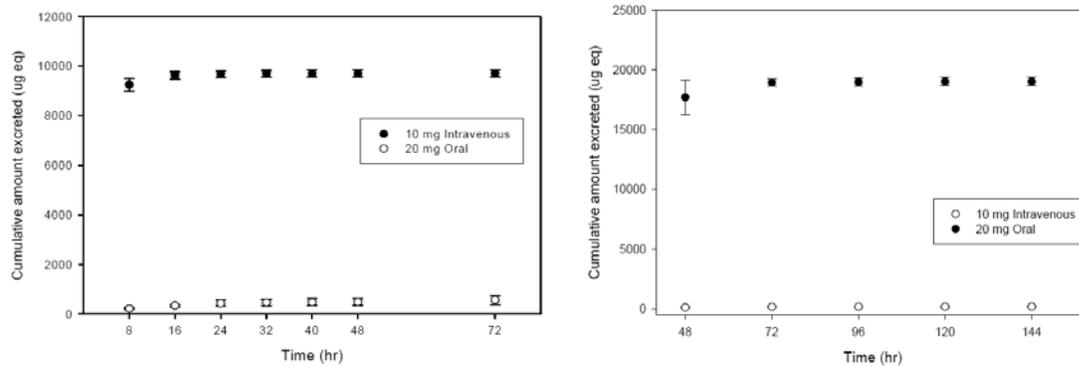
### 2.2.3.6 What is the FDKP pharmacokinetics following TI administration?

The FDKP is a novel excipient. The sponsor conducted several clinical pharmacology studies for FDKP including thorough QT study (Section 2.2.2), mass balance study, renal impairment study, and hepatic impairment study (Section 2.3.1).

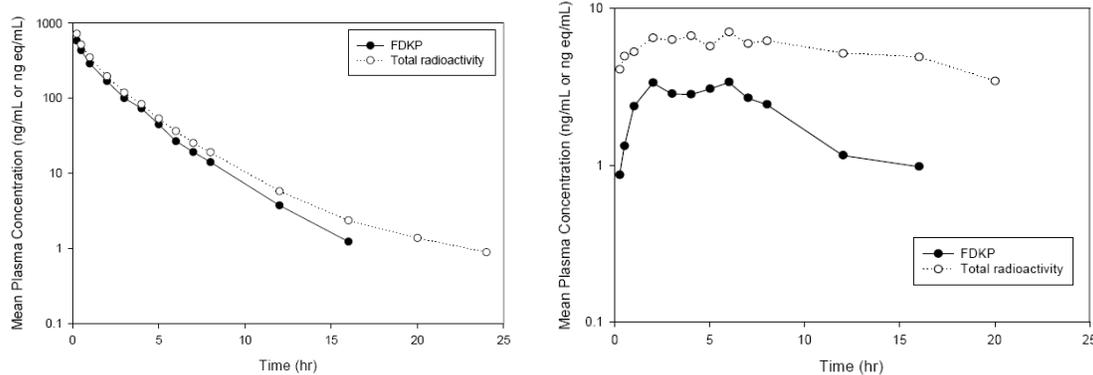
The mass balance of [<sup>14</sup>C]FDKP was studied following the IV and oral administration (MKC-TI-123). Following the IV administration, 97% and 1.7% of the dose was found in the urine and

feces, respectively (Figure 15). Following oral administration, approximately 2.5% and 97.1% of the dose was found in the urine and feces, respectively (Figure 15).

There was no evidence of hepatic metabolism of FDKP in human liver microsomes and human cryopreserved hepatocytes. There were no metabolites of FDKP detected in plasma or urine after IV administration in the mass balance study (Figure 16). Oral and TI bioavailability is low (<4% and about 20% for oral and TI, respectively). Therefore, it is expected no FDKP metabolites in plasma following oral and inhalation considering no metabolites in plasma following IV.



**Figure 13** Cumulative urinary (left) and fecal (right) excretion of total radioactivity following [<sup>14</sup>C]FDKP



**Figure 14** Plasma concentration-time profiles following [<sup>14</sup>C]FDKP: IV (left) and oral (right)

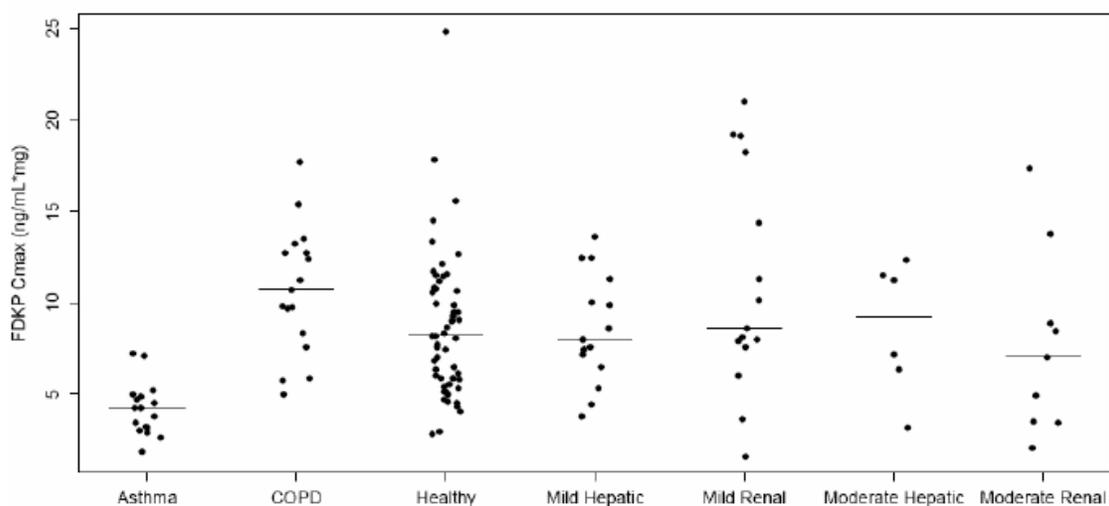
A median  $t_{max}$  of FDKP was about 10 minutes following TI dosing and  $t_{1/2}$  ranged from 114 to 198 minutes. The FDKP exposure was proportional to dose and comparable among clinical pharmacology trials (Appendix 4.1.6). There was no evidence of protein binding in equilibrium dialysis with human plasma. The FDKP concentration at 4 to 6 hours in the bronchoalveolar lavage samples following TI dosing was about 10% of samples at 30 minutes. Approximately 20% of the TI dose was excreted in the urine.

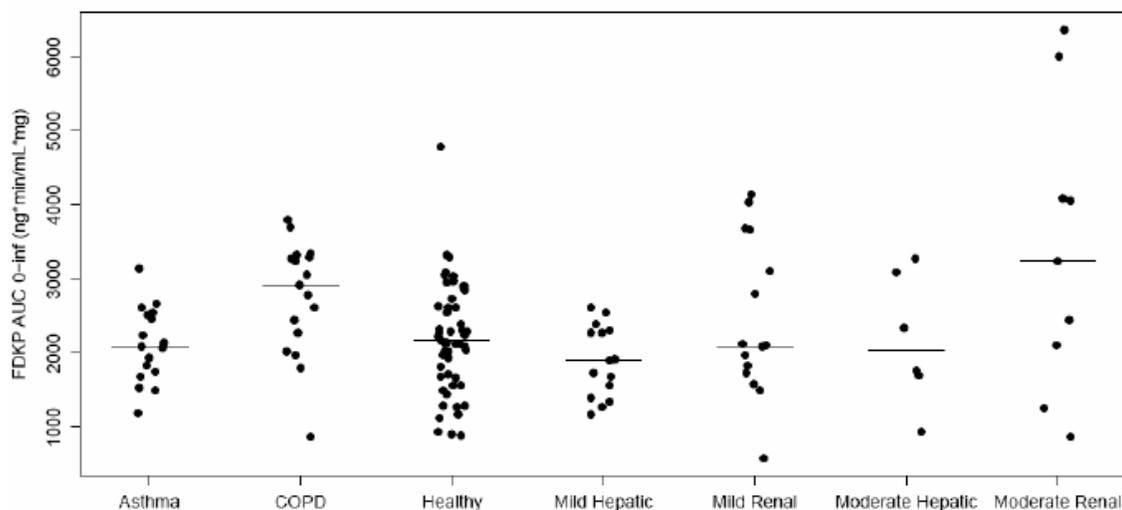
**Table 4** Urinary excretion of FDKP across studies

Study No.	Subgroup	% Dose Excreted	Collection End (min)	% Dose Excreted	Collection End (min)
MKC-T-017	Healthy	18	480	21	1440
	Mild renal impairment	18	480	21	1440
	Moderate renal impairment	14	480	20	1440
MKC-TI-111	Healthy	16	480	18	1440
	Mild hepatic impairment	22	480	25	1440
	Moderate hepatic impairment	17	480	20	1440
MKC-TI-015	Healthy	19	480	22	1440
	COPD	19	480	22	1440
MKC-TI-025	Cartridge Prototype A	NC	NC	22	1440
	Cartridge Prototype B	NC	NC	21	1440
MKC-TI-016	Smokers	12	480	NA	NA
	Nonsmokers	14	480	NA	NA

NC = not calculated; NA = not applicable or not available; COPD = chronic obstructive pulmonary disease.

It was concluded that FDKP pharmacokinetics was comparable among clinical pharmacology trials (Figure 17; Appendix 4.1.6)





**Figure 15** Dose-normalized FDKP Cmax (upper) and AUC (lower) in various populations

## 2.3 Intrinsic Factors

### 2.3.1 What intrinsic factors influence exposure?

The sponsor did not conduct trials evaluating the effect of gender and age on insulin and FDKP exposure. In addition, the sponsor did not evaluate the effect of renal and hepatic impairment on insulin but only on FDKP exposure.

- Disease

The effect of diseases such as COPD, asthma, and smoking on insulin and FDKP exposure following 30-U TI was evaluated as summarized in Table 5.

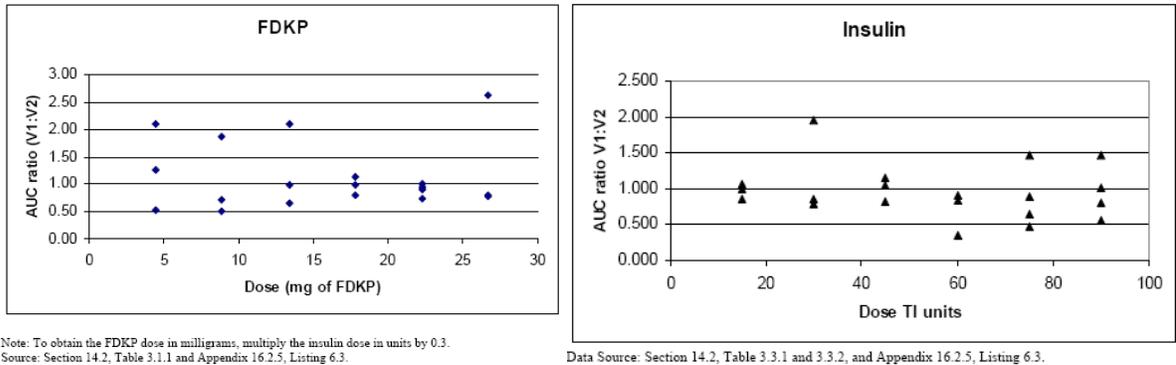
**Table 5** Summary of insulin and FDKP AUCs in control group versus disease or smoking group.

	Parameter		Control	Disease or smoking	Ratio <sup>#</sup>
<b>COPD*</b> (n=37 non-diabetics)	Insulin	AUC <sub>0-240</sub> (mU*min/L)	2117	1933	1.1 (0.888, 1.352)
	FDKP	AUC <sub>0-240</sub> (ng*min/mL)	16676	18821	0.89 (0.735, 1.067)
<b>Asthma**</b> (n=15 nonasthmatics, 5 asthmatic T2D)	Insulin	AUC <sub>0-360</sub> (mU*min/L)	2583	1823	0.71
	FDKP	AUC <sub>0-480</sub> (ng*min/mL)	15903	6833	0.43
<b>Smoking***</b> (n=24 T2D)	Insulin	AUC <sub>0-480</sub> (mU*min/L)	1677	2092	1.25
	GIR	AUC <sub>0-480</sub> (mg*min/kg)	362	490	1.35
	FDKP	AUC <sub>0-480</sub> (ng*min/mL)	17463	12376	0.71

\*: C-peptide baseline correction; clamp procedure

- \*\*.: baseline adjusted using  $t=0$ ; clamp procedure
- \*\*\*.: baseline adjusted using later time points; clamp procedure
- #.: arithmetic mean ratio (disease/control) except COPD as geometric mean ratio of control/disease with 90% confidence interval

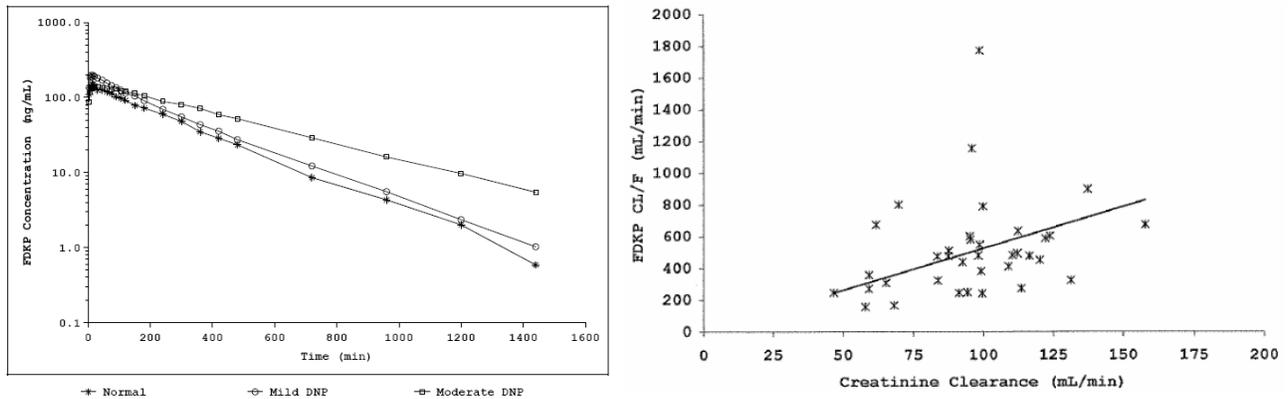
The effect of upper respiratory infection (URI) on exposure following TI dosing was evaluated (MKC-TI-112) but insulin pharmacokinetics were not characterized because of individualization of dose. Ratio of Visit 1 (before resolution of the URI) and Visit 2 (after resolution of the URI) was around 1 (no effect) and no systemic association between AUC ratio and doses (Figure 18).



**Figure 16** AUC ratio before (Visit 1) and after (Visit 2) resolution of URI for FDKP (left) and insulin (right)

- Renal impairment on FDKP

The effect of renal impairment on FDKP exposure was evaluated following 20-mg Technosphere<sup>®</sup> without insulin, and the results are summarized in Figure 19 and Table 6. The FDKP AUC<sub>0-480min</sub> and C<sub>max</sub> increased in mild renal impairment by 18% and 25%, respectively, without change in the amount excreted in urine. In moderate renal impairment, the FDKP AUC<sub>0-480min</sub> increased by 25% and C<sub>max</sub> decreased by 14% with 24% decrease in the amount excreted in urine (Ae<sub>0-480min</sub>) (Table 7).



**Figure 17** FDKP concentrations vs. time (left) and FDKP CL/F vs. creatinine clearance (right)

**Table 6 FDKP pharmacokinetic parameters in the renal impairment (top) and east square geometric mean ratio (bottom) (MKC-TY-017)**

Parameters <sup>a</sup>	Study Group			
	Normal (n = 12)	Mild DNP (n = 15)	Moderate DNP (n = 9)	Mild or Moderate DNP (n = 24)
AUC <sub>0-480</sub> (ng·min/mL)	30473.6 (31.8)	36089.9 (43.4)	38206.0 (53.8)	36869.3 (47.2)
AUC <sub>0-1440</sub> (ng·min/mL)	36840.0 (29.4)	43791.6 (43.1)	54631.1 (55.6)	47578.4 (51.1)
C <sub>max</sub> (ng/mL)	146.9901 (44.3)	184.1413 (54.7)	126.3733 (65.8)	159.8970 (59.4)
t <sub>max</sub> (min) <sup>b</sup>	12.0 (3-45)	15.0 (3-76)	30.0 (9-153)	16.0 (3-153)
t <sub>1/2</sub> (min) <sup>c</sup>	190.6 (51.66)	196.2 (45.67)	269.8 (64.61)	223.8 (63.60)
Ae <sub>0-480</sub> (mg) <sup>c</sup>	3.654 (1.2439)	3.664 (1.7139)	2.793 (1.7069)	3.338 (1.7282)
Ae <sub>0-1440</sub> (mg) <sup>c</sup>	4.190 (1.2437)	4.253 (1.8531)	3.909 (2.4583)	4.124 (2.0545)

<sup>a</sup> Parameters are presented as geometric mean (% coefficient of variation) unless otherwise indicated.

<sup>b</sup> Values presented are medians (range).

<sup>c</sup> Values presented are arithmetic means (SD).

Ae<sub>0-480</sub> = amount excreted in urine from time zero to 480 minutes after dosing; Ae<sub>0-1440</sub> = amount excreted in urine from time zero to 1440 minutes after dosing; AUC<sub>0-480</sub> = area under the serum concentration-time curve from time zero to 480 minutes after dosing; AUC<sub>0-1440</sub> = area under the serum concentration-time curve from time zero to 1440 minutes after dosing; C<sub>max</sub> = maximum concentration; DNP = diabetic nephropathy; t<sub>1/2</sub> = elimination half-life; t<sub>max</sub> = time at which maximum concentration was observed.

Parameter	Treatment Comparison	Least Squares Geometric Mean <sup>a</sup>		Least Squares Geometric Mean Ratio (90% CI)
		Test	Reference	
AUC <sub>0-480</sub> (ng·min/mL)	Mild or Moderate DNP: Normal	37133	30474	1.219 (0.900, 1.650)
C <sub>max</sub> (ng/mL)	Mild or Moderate DNP: Normal	153	147	1.038 (0.714, 1.508)
Ae <sub>0-480</sub> (mg) <sup>b</sup>	Mild or Moderate DNP: Normal	3.2	3.7	-0.4 (-1.4, 0.5)
Ae <sub>0-1440</sub> (mg) <sup>b</sup>	Mild or Moderate DNP: Normal	4.1	4.2	-0.1 (-1.2, 1.0)

<sup>a</sup> Least squares geometric mean based on ANOVA model is presented.

<sup>b</sup> Arithmetic means and confidence intervals for difference in means are presented for untransformed Ae.

Ae<sub>0-480</sub> = amount excreted in urine from time zero to 480 minutes after dosing; Ae<sub>0-1440</sub> = amount excreted in urine from time zero to 1440 minutes after dosing; ANOVA = analysis of variance; AUC<sub>0-480</sub> = area under the serum concentration-time curve from time zero to 480 minutes after dosing; DNP = diabetic nephropathy.

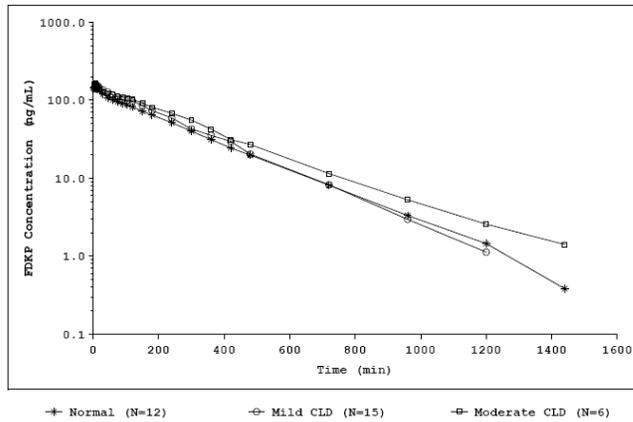
Data Source: Section 14.2, Table 14.2.4.

**Table 7 Arithmetic mean ratios of mild or moderate renal impairment to normal**

	Mild/Normal	Moderate/Normal
<b>AUC<sub>0-480 min</sub> (ng*min/mL)</b>	118%	125%
<b>AUC<sub>0-1440 min</sub> (ng*min/mL)</b>	119%	129%
<b>C<sub>max</sub> (ng/mL)</b>	125%	86%
<b>Ae<sub>0-480</sub> (mg)</b>	100%	76%
<b>Ae<sub>0-1440</sub> (mg)</b>	102%	93%

- Hepatic impairment on FDKP

Mild and moderate hepatic impairment effect on FDKP exposure was evaluated following 20-mg Technosphere<sup>®</sup> without insulin (Figure 20, Table 8), and the hepatic impairment did not significantly affect FDKP exposure (Table 9).



**Figure 18 FDKP plasma concentration-time profiles in subject with moderate hepatic impairment following Technosphere<sup>®</sup>**

**Table 8 FDKP pharmacokinetic parameters in the hepatic impairment (top) and east square geometric mean ratio (bottom) (MKC-TI-111)**

Parameters <sup>a</sup>	Study Group				
	Normal (n = 12)	Normal (n = 11) <sup>b</sup>	Mild CLD (n = 15)	Moderate CLD (n = 6)	Mild or Moderate CLD (n = 21)
AUC <sub>0-480</sub> (ng·min/mL)	26710.3 (34.8)	25489.5 (32.9)	31000.5 (26.1)	32699.6 (35.9)	31476.8 (28.8)
AUC <sub>0-1440</sub> (ng·min/mL)	32106.6 (33.6)	30735.4 (32.2)	36364.5 (25.8)	39757.4 (40.6)	37303.2 (31.2)
C <sub>max</sub> (ng/mL)	143.3656 (48.5)	133.5452 (44.3)	161.5196 (34.9)	156.7977 (42.1)	160.1562 (36.0)
t <sub>max</sub> (min) <sup>c</sup>	7.5 (3-20)	6.0 (3-20)	6.0 (3-60)	6.0 (3-45)	6.0 (3-60)
t <sub>1/2</sub> (min) <sup>d</sup>	190.073 (26.5098)	191.691 (27.1753)	172.766 (29.8315)	198.147 (45.0485)	180.018 (35.6135)
Ae <sub>0-480</sub> (mg) <sup>d</sup>	3.1938 (1.10824)	3.0290 (0.99617)	4.4578 (2.71886)	3.3608 (1.15451)	4.1444 (2.40117)

<sup>a</sup> Parameters are presented as geometric mean (%CV) unless otherwise indicated.

<sup>b</sup> Subject 260 was excluded because of quantifiable concentration before dosing.

<sup>c</sup> Values presented are median (range).

<sup>d</sup> Values presented are arithmetic mean (SD)

CV = coefficient of variation, CLD = chronic liver disease, SD = standard deviation

Data Source: Section 14.2, Table 14.2.3

Parameter	Treatment Comparison	Geometric Mean		Geometric Mean Ratio (90% CI)
		Test	Reference	
AUC <sub>0-480</sub> (ng·min/mL)	Mild or Moderate CLD: Normal	31476	26710	1.178 (0.958, 1.450)
C <sub>max</sub> (ng/mL)	Mild or Moderate CLD: Normal	160	143	1.117 (0.843, 1.481)
Ae <sub>0-480</sub> (mg) <sup>a</sup>	Mild or Moderate CLD: Normal	4.1	3.2	1.0 (-0.3, 2.2)

<sup>a</sup> Arithmetic means and confidence intervals for difference in means are presented for untransformed Ae.

ANOVA = analysis of variance, CI = confidence interval, CLD = chronic liver disease

Data Source: Section 14.2, Table 14.2.4

**Table 9 Arithmetic mean ratios of mild or moderate hepatic impairment to normal**

	Mild/Normal	Moderate/Normal
AUC <sub>0-480 min</sub> (ng·min/mL)	116%	122%
C <sub>max</sub> (ng/mL)	113%	109%
Ae <sub>0-480</sub> (mg)	140%	105%

• **Reviewer’s Comments on Intrinsic Factors:**

Insulin exposure was lower with COPD (91%) and asthma (71%), and it may not significant concern under the proposed titration dosing. Smoking increased insulin AUC by 25% and GIR by 35%. Therefore, dose titration should be cautious in subjects with smoking for an unexpected hypoglycemia potential. FDKP exposure change in the renal and hepatic impairment studies may not warrant dose adjustment because of no particular safety concern.

## 2.4 Extrinsic Factors

### 2.4.1 What are the drug-drug interaction studies?

The effect of inhaled albuterol and fluticasone on the insulin and FDKP exposure following TI was evaluated in a 3-way crossover study in healthy subjects (MKC-TI-114). The treatments were:

- Subject received 45-U TI during hyperinsulinemic (lisro)-euglycemic clamp procedure (Treatment 1).
- Subjects received 180- $\mu$ g albuterol as a single-dose 5 minutes after 45-U TI during hyperinsulinemic (lisro)-euglycemic clamp procedure (Treatment 2).
- The subjects received TI dose after 440- $\mu$ g fluticasone BID for a week. The fluticasone morning dose at Day 7 was 5 minutes after 45-U TI during hyperinsulinemic (lisro)-euglycemic clamp procedure (Treatment 3).

Insulin and FDKP concentrations were adjusted using the time matched C-peptide concentrations and detailed pharmacokinetic parameters are summarized in Appendix. Geometric mean ratios of PK parameters are in Tables 10 and 11. There were no clinically meaningful changes in insulin and FDKP pharmacokinetics.

**Table 10** Geometric mean ratio of insulin pharmacokinetic parameters

Parameter	Treatment Regimen Comparison	Geometric Mean <sup>a</sup>		Geometric Mean Ratio (%) (90% CI)	p Value
		Test	Reference		
AUC <sub>0-360</sub> (mU·min/L)	TI after albuterol : TI alone	4490.7	4819.8	93.17 (79.14 – 109.69)	0.4647
C <sub>max</sub> (mU/L)	TI after albuterol : TI alone	78.562	77.746	101.05 (86.05 – 118.66)	0.9122
t <sub>1/2</sub> (min)	TI after albuterol : TI alone	31.4	33.3 <sup>b</sup>	94.11 (78.45 – 112.90)	0.5721
AUC <sub>0-360</sub> (mU·min/L)	TI after fluticasone : TI alone	4414.7	4819.8	91.59 (77.80 – 107.83)	0.3656
C <sub>max</sub> (mU/L)	TI after fluticasone : TI alone	75.405	77.746	96.99 (82.60 – 113.89)	0.7469
t <sub>1/2</sub> (min)	TI after fluticasone : TI alone	30.8	33.3 <sup>b</sup>	92.48 (77.09 – 110.94)	0.4677

<sup>a</sup>N = 12 unless stated

<sup>b</sup>N = 10

Data Source: Section 14.3, Table 14.3.1

**Table 11** Geometric mean ratio of FDKP pharmacokinetic parameters

Parameter	Treatment Regimen Comparison	Geometric Mean <sup>a</sup>		Geometric Mean Ratio (%) (90% CI)	p Value
		Test	Reference		
AUC <sub>0-480</sub> (ng min/mL)	TI after albuterol : TI alone	42605.9	37099.4	114.84 (103.1 – 127.97)	0.0390
C <sub>max</sub> (ng/mL)	TI after albuterol : TI alone	232.556	191.459	121.47 (102.7 – 143.67)	0.0593
t <sub>1/2</sub> (min)	TI after albuterol : TI alone	152.5	159.9	95.36 (88.91 – 102.27)	0.2559
AUC <sub>0-480</sub> (ng min/mL)	TI after fluticasone : TI alone	38291.3	37099.4	103.21 (92.62 – 115.01)	0.6209
C <sub>max</sub> (ng/mL)	TI after fluticasone : TI alone	202.500	191.459	105.77 (89.42 – 125.10)	0.5722
t <sub>1/2</sub> (min)	TI after fluticasone : TI alone	168.1	159.9	105.13 (98.03 – 112.75)	0.2321

<sup>a</sup> N = 12 unless stated.

AUC<sub>0-480</sub> = area under the concentration-time curve from Time 0 to 480 minutes after dosing; C<sub>max</sub> = maximum observed concentration; t<sub>max</sub> = time to reach maximum concentration; t<sub>1/2</sub> = half-life; ANOVA = analysis of variance

Data Source: Section 14.3, Table 14.3.3

### Reviewer’s Comments:

Baseline adjustment for the endogenous insulin using C-peptide seems to be proper even under clamp procedure in healthy subjects because C-peptide concentration significantly fluctuate over the clamp procedure (Figure 21, MKC-TI-114). The baseline adjustment using average of predose or later phase insulin concentrations may have not reflected the change of endogenous insulin during the clamp procedure.

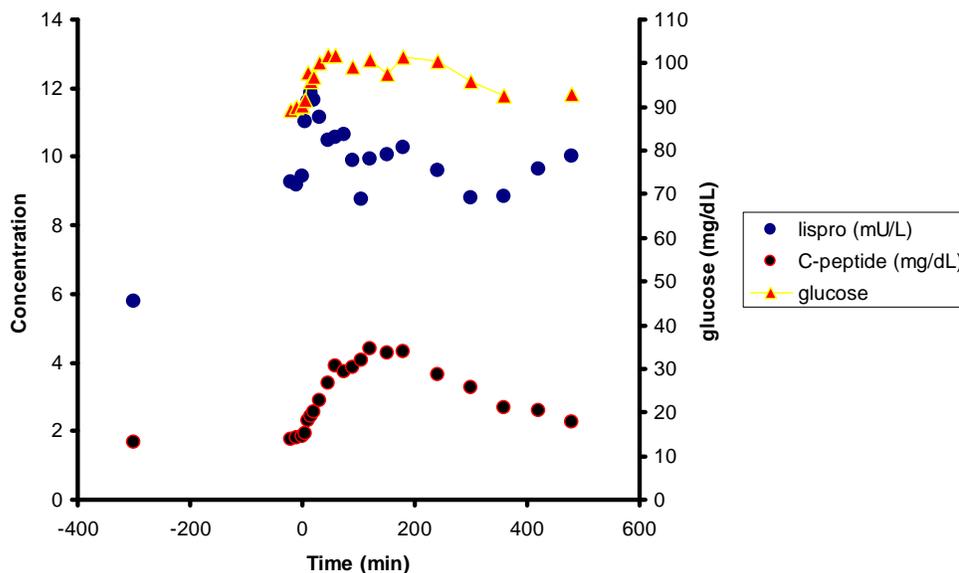


Figure 19 Mean lispro, C-peptide, and glucose concentration-time profiles following TI Inhalation Powder treatment

## 2.5 General Biopharmaceutics

### 2.5.1 *Was the proposed to-be-marketed formulation or inhaler properly bridged to those of pivotal clinical trial?*

There is no proposed change for the to-be-marketed TI formulation compared to that of the pivotal clinical trial formulation. However, the proposed to-be-marketed inhaler, Model D, is different from that (Model C) of pivotal clinical trial. Therefore, the sponsor conducted a BE study to evaluate comparability of Model D (test) to Model C (reference) (MKC-TI-138). I

(b) (4)

(b) (4)

**Reviewer's Comments:**

The review of DSI inspection on the pivotal BE study has not been completed at this moment, and the clinical pharmacology recommendation is pending on the results of DSI review.

**2.6 Analytical Section****2.6.1 *What bioanalytical methods are used to assess concentrations?***

Four bioanalytical methods were used for serum insulin measurement as follow:

- Roche E170 automated assay was used for detection of regular human insulin without cross-reactivity against insulin lispro. The validated range for the assay was 0.5  $\mu\text{U}/\text{mL}$  to 400  $\mu\text{U}/\text{mL}$ . This assay method was used for MKC-TI-110, 015, 113, 114, 116, 122, and 138. The validated range for the assay was 0.5  $\mu\text{U}/\text{mL}$  to 400  $\mu\text{U}/\text{mL}$ . The assay method used for MKC-TI-110, 015, 113, 114, 116, 122, and 138. The assay method seems to be acceptable with a reasonable precision and accuracy for the measurement of serum insulin (Table 15) with an assay sensitivity of 0.5 $\mu\text{U}/\text{mL}$  and

no cross-reactivity with insulin lispro. Serum insulin was stable throughout 3 freeze-thaw cycles and after 6 months of storage in frozen condition.

- The DCP Immulite 2000 automated assay (Abbott) was used for MKC-TI-03B, 016, 027, and 110. The dynamic range was 2 µU/mL to 300 µU/mL.
- LINCO RIA was used for MKC-TI-025.
- A radioimmunoassay was used for early phase of drug development studies – PDC-INS-0001 and 0002 with a dynamic range of 1.2 µU/mL to 200 µU/mL.

For FDKP, conventional LC/MS/MS method was used with the validated range of 1 ng/mL to 1000 ng/mL for plasma and serum and 10 ng/mL to 10000 ng/mL for urine.

**Reviewer’s Comments:**

Results of the validation report seem acceptable with reasonable accuracy and precision (Table 16 and 17).

**Table 15 Within day and between day insulin precision, and accuracy (% recovery) (Validation report: MKC-PC-2006-0042)**

Subject	Target Insulin	Mean Insulin	Within-day %CV <sub>w</sub>	Between-day %CV <sub>b</sub>	Overall %CV <sub>t</sub>	%Recovery
A	3,0 µU/mL	3,30 µU/mL	2,94%	0,67%	3,01%	110,15%
	50,0 µU/mL	48,08 µU/mL	1,47%	0,47%	1,55%	96,16%
	400,0 µU/mL	387,27 µU/mL	2,01%	0,96%	2,23%	96,82%
B	3,0 µU/mL	3,18 µU/mL	2,80%	0,71%	2,89%	105,96%
	50,0 µU/mL	47,28 µU/mL	1,11%	0,65%	1,29%	94,56%
	400,0 µU/mL	381,60 µU/mL	1,57%	1,33%	2,06%	95,40%

**Table 16 Validation report summary for FDKP (bioanalytical report for MKC-TI-116)**

Report Title	LC/MS/MS Assay Validation of FDKP in Human Serum
Report Number	(b) (4) 197-0602
Analyte Name	FDKP
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC/MS/MS
Extraction Method	Solid Phase Extraction
QC Concentrations	1, 3, 150 and 900 ng/mL
Standard Curve Concentrations	1, 3, 10, 30, 100, 300, 600 and 1000 ng/mL
Lower Limit Of Quantitation (ng/mL)	1 ng/mL
Upper Limit Of Quantitation (ng/mL)	1000 ng/mL
Average Recovery of Drug (%)	91.0
Average Recovery of Int. Std (%)	80.5
QC Intraday Precision Range (%CV)	2.6 to 6.0
QC Intraday Accuracy Range (%Diff)	-3.3 to 2.7
QC Interday Precision Range (%CV)	2.3 to 5.5
QC Interday Accuracy Range (%Diff)	-4.7 to 2.0
Stock Solution Solvent	H <sub>2</sub> O:Diethylamine (DEA) / 100:0.1
Master Stock Solution Stability in H <sub>2</sub> O:DEA/100:0.1 (v:v)	For at least 6.5 hours at Room Temperature <sup>a</sup>
Master Stock Solution Stability in H <sub>2</sub> O:DEA/100:0.1 (v:v)	For at least 188 days at -20°C <sup>b</sup>
Autosampler Stability in Reconstitution Solvent	For at least 158 Hours at Room Temperature
Benchtop Stability in Plasma	For at least 4.5 Hours
Freeze/thaw Stability in Serum	For at least 5 Cycles at -20°C and -70°C <sup>c</sup>
Long-term Storage Stability in Serum	198 Days at -20°C and -70°C <sup>d</sup>
Dilution Integrity (concentration tested/dilution factor)	5000 ng/mL diluted 10-fold
Selectivity	< 20% LLOQ for analyte; < 5% for IS

<sup>a</sup> Refer to 197-0602 report addendum 1, <sup>b</sup> Refer to 197-0602 report addendum 4  
<sup>c</sup> Refer to 197-0602 report addendum 3, <sup>d</sup> Refer to Sec 14.3 for more explanation

**Table 17**      **QC samples in human serum**

Run Date	Run ID	3.000 (ng/mL)	150.000 (ng/mL)	900.000 (ng/mL)
26-Jul-2008	1	2.938	153.632	890.304
		3.136	150.428	895.092
30-Jul-2008	2	3.273	153.449	847.312
		2.923	143.357	811.517
30-Jul-2008	3	3.116	158.153	890.038
		2.930	149.630	867.180
01-Aug-2008	4	3.088	153.391	909.777
		3.108	149.351	931.629
31-Aug-2008	5	3.103	156.442	950.473
		3.033	152.045	886.251
31-Aug-2008	6	2.828	153.469	872.057
		3.017	152.622	860.756
19-Sep-2008	7	#3.491	165.794	781.280
		3.215	137.009	845.348
03-Oct-2008	8	2.824	157.091	861.240
		2.552	151.559	783.822
20-Nov-2008	9	2.945	149.975	960.877
		2.912	156.130	873.101
20-Nov-2008	10	3.209	154.437	921.459
		2.860	151.479	951.864
Mean		3.025	152.472	879.569
S.D.		0.200	5.715	50.972
%CV		6.6	3.7	5.8
%RE		0.8	1.6	-2.3
n		20	20	20

# >15|%RE| from Nominal

### **3 Detailed Labeling Recommendations**

(Please refer attached file for clinical pharmacology labeling comments. ~~Strikethrough~~ indicates deletion and red underlined text indicates addition.)

The detailed labeling comments will be separately documented.

## 4 Appendices

### 4.1 Definition of hypoglycemia and hyperglycemia

- **Hypoglycemia:** Hypoglycemia was defined as a blood glucose concentration  $< 63$  mg/dL ( $< 3.5$  mmol/L) or the occurrence of hypoglycemia like symptoms (such as hypotonia, flush, weakness) that disappeared with appropriate caloric intake. Subjects were to be asked to document these events in the subject diary and, in the case of symptoms of hypoglycemia, to try to confirm the event with a blood glucose reading, also to be recorded in the diary. Subjects were instructed on measures to take in response to a suspected hypoglycemic occurrence, such as ingestion of glucose-containing material, and were to record such measures and the symptomatic response in the diary.
- **Severe Hypoglycemia:** Severe hypoglycemic episodes were to be recorded on the hypoglycemia page of the CRF, and were also to be recorded as SAEs. They were to be reported to the Investigator as soon as possible. Hypoglycemia was defined as severe if it required glucagon injection, glucose infusion, or assistance by a third party because of impaired consciousness or cognition or irrational behavior.
- **Hyperglycemia:** Hyperglycemia was defined as a FBG concentration  $> 270$  mg/dL ( $> 15.0$  mmol/L) or a nonfasting blood glucose  $> 396$  mg/dL ( $> 22$  mmol/L). Discontinuation of a subject's participation in the study because of hyperglycemia was at the discretion of the Investigator, except that any glucose concentration of  $> 495$  mg/dL ( $> 27.5$  mmol/L) was to result in immediate discontinuation. Hyperglycemia occurring after meal ingestion and treatment with the investigational drug might also be considered as lack of efficacy.

### 4.2 Dosing Guideline

#### T1D

##### TI starting dose

- Insulin naïve subjects typically started on 15 U of TI at each meal.
- Subjects who changed from insulin regimens that included short or longer acting insulin replaced half of their total daily insulin dose with a corresponding dose of TI that was divided between main meals (15 U of TI for each 3 IU of sc insulin, rounded down). The other half of the total dose of sc insulin was given as a long acting insulin.
- For subjects already on a prandial regimen, the short-acting insulin was replaced by TI using the same ratio of TI to sc insulin.

##### Dose adjustment: based on home blood glucose monitoring (HBGM)

- TI was adjusted in increments of 15 U up to a maximum of 90 U per meal as needed
  - Target BG goals
    - Premeal BG  $< 110$  mg/dL (6.1 mmol/L)
    - 2-hour postprandial BG  $< 140$  mg/dL (7.7 mmol/L)
  - Target HbA1c goals were  $< 7.0\%$  (ADA guidelines),  $< 6.5\%$  (AACE guidelines)
- Short-acting insulin was adjusted based on the same target BG for TI.

- Basal insulin such as insulin glargin QD at bedtime was adjusted based on HBGM at three fasting plasma glucose (FPG) levels for three days and other relevant laboratory or clinical findings
  - If FPG trend was > 110 mg/dL (6.1 mmol/L), basal insulin was increased by 2 - 4 IU
  - If FPG trend was < 70 mg/dL (3.9 mmol/L), basal insulin was decreased by 2 - 4 IU

## T2D

Adjustments beyond the starting dose could be made usually after 1 week, unless clinically indicated to do so earlier. TI Inhalation Powder and basal insulin doses were adjusted as clinically indicated on the basis of HBGM, as well as other relevant laboratory or clinical findings.

- TI Inhalation Powder doses were adjusted in 15 U increments.
- Target blood glucose goals included:
  - Pre-meal blood glucose of < 110 mg/dL (6.1 mmol/L)
  - 2-hour postprandial blood glucose of < 140 mg/dL (7.7 mmol/L)
- Target HbA1c goals were < 7.0% (ADA recommendation), < 6.5% (AACE recommendation).

In the case of intercurrent illness, including respiratory infections, if glycemic control was not maintained through adjustment of TI Inhalation Powder, temporary treatment with other anti-diabetic medication could be initiated at the discretion of the Investigator.

### Subsequent TI Inhalation Powder Adjustment

TI Inhalation Powder dose titration for a particular meal was based on *trends* of at least 3 recent HBGM values (for that meal) occurring over a period of 3 days (eg, the 3 days of 7-point blood glucose profiles, see Section 9.4.9.2):

- The pre-breakfast TI Inhalation Powder dose was titrated based on the subject's prelaunch blood glucose trend,
- The pre-lunch TI Inhalation Powder dose was titrated based on the subject's pre-supper blood glucose trend,
- The pre-supper TI Inhalation Powder dose was titrated based on the subject's bedtime blood glucose trend:
  - If the preprandial glucose trend of the next meal or bedtime glucose was > 110 mg/dL (6.1 mmol/L), TI Inhalation Powder was to be *increased* by 15 U, unless hypoglycemia had occurred in the postprandial period.
  - If the preprandial glucose trend of the next meal or bedtime glucose was ≤ 110 mg/dL (6.1 mmol/L), and > 80 mg/dL (4.5 mmol/L), no TI Inhalation Powder adjustment was necessary.
  - If the preprandial glucose trend of the next meal or bedtime glucose was < 80 mg/dL (4.5 mmol/L), TI Inhalation Powder was to be *reduced* by 15 U.
- The maximum TI Inhalation Powder dose was 90 U per meal. For most subjects, the requirement was likely to be the same for each meal; in some subjects, different doses were required for breakfast, lunch, or supper.
- Adjustment of mealtime TI Inhalation Powder dose may have required an adjustment of the basal insulin dose. FPG was closely monitored when dosing of TI Inhalation Powder was adjusted.

#### Recommendations for TI Inhalation Powder Dose Adjustments for Either a Low or Very High Preprandial Blood Glucose

- If preprandial HBGM was <70 mg/dL (3.9 mmol/L), the subject was instructed to reduce the dose of TI Inhalation Powder by 15 U (for that particular meal only);
- If preprandial HBGM was > 270 mg/dL (15 mmol/L), the subject was instructed to increase the dose of TI Inhalation Powder by 15 U (for that particular meal only).

#### Subsequent Basal Insulin Adjustment

The basal insulin dose was titrated based on the subject's HBGM measurement of fasting plasma glucose (FPG). The decision to increase, decrease or remain at the current dose of basal insulin was based on the *trends* of at least 3 recent FPG values occurring over a period of 3 days (eg, the 3 days of 7-point blood glucose profiles, see Section 9.4.9.2):

- If the FPG trend was > 110 mg/dL (6.1 mmol/L), basal insulin was to be increased by 2-4 IU;
- If the FPG trend was < 70 mg/dL (3.9 mmol/L), basal insulin was to be decreased by 2-4 IU.

#### Subsequent BPR 70/30 Dose Adjustment (Comparator Group)

Adjustments in BPR 70/30 insulin were done according to FPG and pre-supper glucose levels with an algorithm that was utilized in the INITIATE study.

- Any dose titration or adjustment was to be based on trends of at least 3 recent HBGM fasting and/or pre-supper values;
- BPR 70/30 was to be titrated and adjusted to achieve target FPG and pre-supper plasma glucose values of between 80-110 mg/dL (4.5-6.1 mmol/L); and
- BPR 70/30 pre-supper dose was to be titrated or adjusted based on FPG values while BPR 70/30 pre-breakfast dose was to be titrated or adjusted based on pre-supper plasma glucose. Pre-breakfast and pre-supper BPR 70/30 doses were adjusted *independently* of each other.

### **4.3 Representative Clamp Procedures**

#### **Glucose Monitoring**

The clamp procedure will begin at approximately 7:30am, with a target dosing time 4-6 hours after clamp start.

A Biostator<sup>®</sup> glucose-controlled insulin/glucose infusion system, (Life Science Instruments, Elkhart, Indiana, USA) will be employed. Subjects will lie in a supine position and remain fasting (only water is allowed) throughout the procedure. For blood glucose concentration measurements taken at one-minute intervals via the Biostator<sup>®</sup>, a wrist vein or hand vein of the arm will be cannulated in a retrograde manner for insertion of an 18-gauge PTFE double lumen catheter, which is connected to the glucose sensor of the Biostator<sup>®</sup>.

Another vein in the opposite forearm will be cannulated with an 18-gauge PTFE catheter for infusion of glucose (20% in water). In the same arm an insulin solution will be infused continuously from a syringe pump during the baseline period. Immediately after initiation of the procedure, the subjects will receive an intravenous insulin infusion (15 U

regular insulin in 50 mL physiological saline + 1 mL blood from the subjects) at a rate of at least 0.15 mU/kg/min via a precision pump.

The intravenous insulin infusion will start at least 4-6 hours before administration of the study drug. The goal is to reach a target blood glucose range of 100 mg/dL  $\pm$  18 mg/dL (6.7 mmol/L  $\pm$  1 mmol/L). Bolus injections of intravenous insulin may be given in order to reach the target blood glucose concentration, but no bolus injection is allowed in the last 3 hours before administration of the study drug. One hour prior to study drug administration, the insulin infusion rate will be lowered to a level where the blood glucose remains stable within the target range and the glucose infusion rate is as low as possible. The aim of this calibration/monitoring procedure is to ensure that subjects receive the minimal insulin infusion rate that maintains their blood glucose within the target range without requiring a substantial glucose infusion. It is necessary to maintain a low-level insulin infusion in order to suppress endogenous insulin secretion. The insulin infusion will be continued during study drug administration.

After the monitoring and calibration period, the study drug will be administered and will consist of 1 cartridge of 30 U of inhaled Technosphere<sup>®</sup>/Insulin administered by use of the MedTone<sup>™</sup> inhaler.

Blood glucose concentration will be kept within the target range by the Biostator<sup>®</sup>, which automatically calculates the appropriate adjustments of an intravenous glucose infusion rate. If a high glucose infusion rate is necessary, a part of the glucose infusion will be performed via an external pump. The glucose infusion rate (GIR) necessary to keep the blood glucose level within the target range during the subsequent 480 min (8 hours) will automatically be recorded every minute. (Settings for the Biostator<sup>®</sup> device are: clamp mode (mode 9:1) with a KS-value of 1.0). The infusion rate provided by the external pump will be added to the infusion rate of the Biostator<sup>®</sup> (GIR).

The blood glucose measurements of the Biostator<sup>®</sup> will be re-calibrated at regular intervals (up to 30 minute intervals) by blood glucose measurements performed with a laboratory device that employs the glucose oxidase method. A separate 18-gauge catheter will be placed in the cubital vein of the subject's arm. This catheter will be used to draw blood samples for the measurement of plasma glucose, serum insulin, and C-peptide. This line will be kept patent with a continuous infusion of 0.9% normal (0.15 mol/L) saline. The hand of the subjects will remain in a heated box ("Hot-Box") or under a heating pad throughout the trial. Temperature in this box / pad will be maintained at ~ 55°C by thermostatic regulation of an electric heating system. The heating of the hand results in an arterialization of the venous blood sampled by the retrograde catheter, due to an opening of arterio-venous shunts.

Blood samples for measurement of blood glucose by the glucose oxidase method will be drawn using standard operating procedures. The saline infusion will be stopped and ~ 1 mL of blood will be withdrawn. Blood samples for serum insulin, C-peptide, and FDKP measurements will be drawn according to the schedule in Section 7.6.1.

The procedure will be discontinued if blood glucose increases to >11.1 mmol/L (200 mg/dL) and the glucose infusion rate has been zero for approximately 30 minutes, or at 8 hours after dose administration at the latest. If the procedure is stopped before 8 hours a final blood sample will be collected. After the procedure has been completed,

subjects will take a dose of Technosphere/Insulin and will be served a light meal. This will be considered Day 1 of the 7-day dosing regimen. Vital signs will be measured.

At the end of the visit 3, the study physician will advise subjects on the dosage of Technosphere®/Insulin to be taken until the next clamp procedure. The study physician will also provide the following instructions:

- 1) Store the study drug refrigerated at home and remove the daily dose blister pack(s) from the refrigerator before the first meal of the day on which the study drug is to be used.
- 2) Administer the study drug **IMMEDIATELY (< 1 minute)** before the first mouthful of food at each regular meal.
- 3) Record FBG levels and blood glucose levels immediately prior to and 2 hours following each meal in the Patient Blood Glucose Diary.
- 4) Return all used (empty cartridges) and unused study drug at the next visit.
- 5) Contact a member of the study personnel staff in case of an emergency or if they have questions concerning their treatment.

Subjects will dose with Technosphere®/Insulin three to four times per day with meals for a total of seven days. Subjects will be given enough investigational drug to last until their next in-patient visit. In addition study subjects will also receive 2 MedTone™ inhalers, a glucose meter, glucose strips and a 7-day subject diary. Subjects will also be instructed on the use of a subjects' diary that will capture daily glucose readings, asthmatic episodes (if applicable), and daily study drug administration. The intention of the blood glucose diary is to provide the Investigator with information about the subjects' glycemic control.

Subjects will then be discharged from the site. Subjects will be contacted via telephone by study staff on day 3 and day 5 in order to monitor subject compliance and safety. At the end of 7 days of continuous treatment with Technosphere®/Insulin, subjects will return for the second euglycemic clamp procedure. Subjects should bring their study drug diaries and all study supplies to the next visit for review by the study personnel.

#### **Visit 4**

Study subjects will return to the unit with all of the supplies, study medication and diaries they were provided with at visit 3. The diaries will be reviewed with the subjects by the investigator or designee.

The second in-patient clamp procedure for Visit 4 will be identical to the first clamp procedure.

After the clamp procedure is completed, the investigator will advise subjects to resume their usual insulin therapy, and provide instructions for their final visit.

#### 4.4 Components and Composition of Meals used in Meal Challenges

Boos Plus®

Nutrient Composition of Vanilla Boost Plus®	
Nutrients	Per 12-fl oz
Calories	540
Calories from Fat	195
Protein	21 g
Fat	21 g
Saturated Fat	2.25 g
Trans Fat	0 g
Cholesterol	15 mg
Carbohydrate	67.5 g
Dietary Fiber	0 g
Sugars	33 g**
Water	277.5 g

\*\*Chocolate 24g; Strawberry 20g

Uncle Ben's Breakfast Bowl™ (PDC-INS-008)

Egg, Cheese, and Salsa Breakfast Bowl		
	Amount per Serving	% Daily Value <sup>a</sup>
Total Fat	21 g	32
Total Carbohydrates	16 g	5
Protein	14 g	-
Saturated Fat	4 g	20
Dietary Fiber	4 g	16
Cholesterol	270 mg	90
Sugars	3 g	-
Sodium	880 mg	37
Vitamin A	-	25
Calcium	-	15
Vitamin C	-	14
Iron	-	25
Thiamine	-	14
Folate	-	0

<sup>a</sup> % Daily Values are based on a 2000-calorie diet.

Meals in Study MKC-TI-025 (replicate PK study)

Lunch

Foods	Amount (g)	Energy (kcal)	CHO* (g)	Protein (g)	Fat (g)
Margarine	5	22.5	0.0	0.0	2.5
Fruit Cocktail	100	76.9	18.3	0.4	0.1
Mixed vegetables	125	80.0	15.6	2.8	0.6
Boiled potato	90	101.3	22.7	2.1	0.1
Brown rice	70	78.4	16.1	1.8	0.6
Chicken without skin	120	198.4	0.0	37.1	5.4
<b>Total</b>		557.5	72.7	44.2	9.30
% energy for mealtime			52.0	31.6	15.1
Data Source: Clinical Services Menu, Section 14: Investigator's File (Nurse's File)					
*Carbohydrate value includes fiber					

Snack (a)

Foods	Amount (g)	Energy (kcal)	CHO* (g)	Protein (g)	Fat (g)
Fat-free cottage cheese	100	70.2	2.7	12.4	1.0
Margarine	5	22.5	0.0	0.0	2.5
Pro-Vita	54	228.3	39.9	6.2	4.7
<b>Total</b>		321.0	42.6	18.6	8.2
% energy for mealtime			52.9	23.1	23.1
Data Source: Clinical Services Menu, Section 14: Investigator's File (Nurse's File)					
*Carbohydrate value includes fiber					

Snack (b)

Foods	Amount (g)	Energy (kcal)	CHO* (g)	Protein (g)	Fat (g)
Ham	30	38.1	0.3	5.8	1.5
Margarine	5	22.5	0.0	0.0	2.5
Brown bread rolls	60	155.1	30.4	5.2	1.2
<b>Total</b>		215.7	30.7	11.0	5.2
% energy for mealtime			56.9	20.3	21.8
Data Source: Clinical Services Menu, Section 14: Investigator's File (Nurse's File)					
*Carbohydrate value includes fiber					

Dinner

Foods	Amount (g)	Energy (kcal)	CHO* (g)	Protein (g)	Fat (g)
Raw apple with skin	100	63.8	15.3	0.2	0.1
Mixed salad	100	18.9	3.5	0.9	0.1
Mutton – loin chop	60	124.6	0.0	18.0	5.8
Brown bread rolls	60	155.1	30.4	5.2	1.2
Margarine	5	22.5	0.0	0.0	2.5
<b>Total</b>		384.8	49.2	24.3	9.7
% energy for mealtime			51.1	25.2	22.8
Data Source: Clinical Services Menu, Section 14: Investigator's File (Nurse's File)					
*Carbohydrate value includes fiber					

#### 4.5 Meal Challenge and Sampling Schedule

Time (minutes)	T/I Inhalation	Injection of rapid acting insulin	Standardized Liquid Meal	Plasma Glucose Venipuncture	Blood Glucose Meter Reading <sup>a</sup>
-30				X	X
-15		X			
0	X		X	X	X
30				X	
60				X	X
90				X	
105				X	
120				X	X
180				X	
240				X	
300				X	
360				X	

<sup>a</sup>Additional blood glucose readings may be obtained if the Principal Investigator deems it necessary.

#### 4.6 Unique pivotal trial design and discontinuation

The pivotal trials were conducted in an open-label design because

- individual insulin dose adjustments comparing two prandial insulin therapies with different action profiles (e.g., basal insulin such as insulin glargine QD at bedtime + prandial TI immediately before main meals vs. basal insulin QD + prandial sc rapid-acting insulin such as aspart insulin immediately before main meals),
- the use of long-term multiple daily injection of placebo SC was not well accepted,
- a placebo inhalation treatment with proven safety following long-term multiple daily administration was not available.

The incidence of discontinuation for any reason from the trials was 870/2409 (36.1%) in the TI group and 455/1944 (23.4%) in the combined comparator groups. The sponsor concluded that changes in HbA1c did not attribute the drop-out in the Phase II/III trials and disproportionate rate of early discontinuations did not affect the efficacy.

#### 4.7 Sponsor's C-peptide baseline correction method (Excerpt from Study MKC-TI-114)

The protocol stated that major protocol violations would be described in further detail in the SAP and identified before database lock. The SAP did not include any additional details of protocol violations specific to this study. However, the SAP defined the process that was used before database lock for identifying major protocol violations as part of defining the evaluable analysis population. (See Section 9.7.1.1.) Violations to eligibility criteria, failure to obtain adequate consent, and evidence of falsification of data would be considered major violations for the purpose of determining the PK Population. The protocol did not include any correction of serum insulin for endogenous insulin. The SAP stated that PK parameters would be derived based upon Baseline-corrected serum insulin. The actual analysis was done using C-peptide-corrected insulin concentrations. In the following text, the term "insulin concentrations" means "C-peptide corrected insulin concentrations." It was apparent from the individual C-peptide concentrations that after administration of TI Inhalation Powder either alone or after albuterol or fluticasone, there was considerable production of C-peptide during the study. C-peptide is a marker for endogenous insulin; therefore, the considerable increase in C-peptide concentrations corresponded to considerable production of endogenous insulin during the study. The design of the study included a background infusion of insulin lispro that ran from approximately 120 minutes before through 480 minutes after administration of TI Inhalation Powder at each of the visits. The purpose of this background infusion was to suppress endogenous production of insulin. From the observed C-peptide concentrations, it appeared that the amount of lispro infused during the study in the majority of cases was not sufficient to suppress endogenous production of insulin. This was reflected in the measured insulin lispro concentrations, where approximately 10% of samples were below the 5-mU/L LLOQ and approximately 30% of samples were measured to be within 5 mU/L of the LLOQ. A maximal insulin lispro concentration of approximately 10 times the LLOQ was observed. The measured serum insulin concentrations in this study represent the exogenous insulin administered via TI Inhalation Powder and also endogenous insulin. Consequently, serum insulin concentrations needed to be corrected to account for the amount of endogenous insulin. In the SAP, serum insulin concentrations were to be baseline corrected before PK analysis. It was decided that planned baseline correction of insulin concentrations was no longer appropriate in light of the considerable amounts of endogenous concentrations released at time points after administration of TI Inhalation Powder. A C-peptide correction of insulin concentrations was used that provided a more realistic indication of serum insulin concentrations as a result of TI Inhalation Powder administration. C-peptide correction of serum insulin concentrations was performed as follows: C-peptide and serum insulin levels that were taken before administration of TI Inhalation Powder and more than 6 hours after administration of TI Inhalation Powder were analyzed for each subject. Six hours was chosen because in previous studies in healthy volunteers, exogenous insulin levels were at or near the level of detection due to the relatively rapid clearance of insulin in these subjects when insulin was given via inhalation of TI Inhalation Powder. A mixed-effect linear regression model was then used in the program NONMEM VI Level 2.03 running on an HP xw-4500 Workstation with Windows XP Professional to determine the slope and intercept

for each subject's C-peptide-insulin relationship as per the equation below, where  $i$  is each subject and  $j$  is each measurement within that subject.

$$\text{Insulin } i, j = \text{Intercept } i + \text{Slope } i \times \text{C-peptide } i, j$$

The best fit was found to be that of an additive error model (intersubject variability) for the slope term and the intercept term was modeled to be the same for each subject (ie, no error term). Insulin assay error was modeled with a combined constant %CV model and an additive model. The output from this analysis contained each subject's slope and intercept (the intercept was found to be best modeled as the same between subjects). The slope and intercept were then used to predict the endogenous insulin for each subject. The predicted endogenous insulin concentration was then subtracted from the measured serum insulin concentration to provide the estimated exogenous insulin or, using the different nomenclature, the C-peptide-corrected insulin concentration.

$$\text{C-peptide- corrected Insulin } i, j = \text{Serum Insulin } i, j - \text{Predicted Endogenous Insulin } i, j$$

Following correction, several subjects had negative C-peptide-corrected insulin concentrations that were set to zero. (To account for the number of subjects who had negative C-peptide corrected insulin concentrations, see "Insulin Concentration Data" in Section 11.4.1.1). The NONMEM code, output and predicted endogenous insulin concentrations are presented in Appendix 16.2.5, Listing 16.2.5.12. The protocol did not define the statistical analysis required for the secondary endpoints,  $t_{max}$  and  $t_{1/2}$  of serum insulin and FDKP. Secondary endpoints were summarized with descriptive statistics only and were not analyzed. Inspection of the subject BG concentration-time profiles (Appendix 16.2.5, Figure 16.2.5.10) indicated that BG concentrations were not satisfactorily maintained during this glucose clamp study, as BG concentrations were rarely within the specified upper and lower concentration limits. In addition, the endogenous insulin released during the study, as indicated by the C-peptide concentrations, together with the administered TI Inhalation Powder, were responsible for the amount of BG administered during the study. Subsequently, the GIR data associated with the glucose-lowering effect of the administered TI Inhalation Powder were indistinguishable from the GIR data associated with the glucose-lowering effect of the endogenous insulin. Consequently, it was decided that the GIR analysis specified in the SAP would not be performed because the accuracy and significance of any of the derived additional endpoints would be questionable as a consequence of high endogenous insulin concentrations and the inability to keep BG concentration within concentration limits. Therefore, only a listing of GIR is presented in this CSR with GIR values presented as both mL/h and mg/kg/min. Both serum C-peptide and BG concentration-time profiles are presented to indicate the problems associated with the GIR data from this study.

NONMEM Code





## 4.8 Sponsor's summary on PK parameters among studies

### Insulin t<sub>max</sub>

Study	Population	t <sub>max</sub> (min)	Dose (Units)	Device	Lot Numbers
PDC-INS-0001	Healthy	13	100	BI Handihaler	043.98.004
PDC-INS-0001A	Healthy	15	25	Alpha	043.00.02
PDC-INS-0002	Healthy	12	25, 50	Alpha	P99.007
		20	100		043.98.004
PDC-INS-0003	Type 2	19	100	Alpha	043.98.004
PDC-INS-0003A	Type 2	25	48	CTT	043.01.006
MKC-TI-03B	Type 2	25	48	Model C	3023A, 3023B
MKC-TI-003B2	Type 2	16.7	48	Model C	3262A
MKC-TI-015	Healthy	12	30	Model C	D060023
	COPD	15	30		D060023
MKC-TI-016	Type 2 Non-smokers	12	30	Model C	X4232A
	Type 2 Smokers	20	30		X4232A
MKC-TI-025	Type 1	8.75	30	Model C Prototype A	4173A
		10	30	Model C Prototype B	X4232A
MKC-TI-027	Type 2 Nonasthmatic Single dose	15	30	Model C	X4232A
	Type 2 Nonasthmatic Subchronic dose	9	30		
MKC-TI-110 <sup>a</sup>	Type 1	10	30	Model C	D050010
		12.5	60		D050010
MKC-TI-112	Type 1 and 2	10-15	Varied doses	Model C	Supplied from MKC-TI-030
MKC-TI-113	Healthy, TI alone	12	45	Model C	D070058 D070059
	Healthy, TI plus salbutamol	15	45		
	Asthmatic, TI alone	10	45		
	Asthmatic, TI plus salbutamol	20	45		
	Asthmatic, MCT plus TI	10	45		
MKC-TI-114	Healthy, TI alone	16	45	Model C	D070058 D070059
	Healthy, TI plus albuterol	16	45		
	Healthy, TI plus fluticasone	14	45		
MKC-TI-116	Type 1	10	2 by 15	Model D	PPT2008.09
		10	30		PPT2008.10
MKC-TI-122	Healthy	14	60	Model C	D070058
MKC-TI-138	Type 1	(b) (4)	30	Model C	CLM8211A
			30	Model D	CLM8227A

COPD = chronic obstructive pulmonary disease; MCT = methacholine challenge test; TI = Technosphere Insulin.

<sup>a</sup> Only TI Inhalation Powder "D" is reported here.

## Insulin Cmax

Study	Population	C <sub>max</sub> (µIU/mL)	Dose (Units)	Device	Lot Number
PDC-INS-0001	Healthy	371	100	BI Handihaler	043.98.004
PDC-INS-0001A	Healthy	6.3 (dose normalized)	25	Alpha	043.00.02
PDC-INS-0002	Healthy	55	25, 50	Alpha	P99.007
		110	50		043.98.004
		189	100		043.98.004
PDC-INS-0003	Type 2	219	100	Alpha	043.98.004
PDC-INS-0003A	Type 2	147	48	CTT	043.01.006
MKC-TI-03B	Type 2	99.5	48	Model C	3023A, 3023B
MKC-TI-003B2	Type 2	123.6	48	Model C	3262A
PDC-INS-0011	Type 1	179 – 215 (Isocaloric meal)	32	Model C	2305A 2269A 2269B
		137 – 211 (Hypercaloric meal)	53		
MKC-TI-015	Healthy	39.5	30	Model C	D060023
	COPD	34.7	30		D060023
MKC-TI-016	Type 2 Smokers	23	30	Model C	X4232A
	Type 2 Nonsmokers	25	30		X4232A
MKC-TI-025	Type 1	50.75	30	Model C Prototype A	4173A
		51.98	30	Model C Prototype B	X4232A
MKC-TI-027	Type 2 Non-asthmatic Single dose	32	30	Model C	X4232A
	Type 2 Non-asthmatic Subchronic	39	30		
MKC-TI-110	Type 1	54	30 Powder D	Model C	D050010
		100	60 Powder D		D050010
MKC-TI-112	Type 1 and 2	10 (during URI) 15 (after URI)	Varied doses	Model C	Supplied from MKC-TI-030
MKC-TI-113	Healthy, TI alone	98	45	Model C	D070058 D070059
	Healthy, TI plus salbutamol	83	45		
	Asthmatic, TI alone	73	45		
	Asthmatic, TI plus salbutamol	85	45		
	Asthmatic, MCT plus TI	94	45		
MKC-TI-114	Healthy, TI alone	78	45	Model C	D070058 D070059
	Healthy, TI plus albuterol	79	45		
	Healthy, TI plus fluticasone	75	45		
MKC-TI-116	Type 1	66	2 × 15	Model D	PPT2008.09
		69	30		PPT2008.10
MKC-TI-122	Healthy	138	45	Model C	D070058, D070059
MKC-TI-138	Type 1	(b) (4)	30	Model C	CLM8211A
			30	Model D	CLM8277A

COPD = chronic obstructive pulmonary disease; MCT = methacholine challenge test; TI = TI inhalation Powder.

# Insulin AUC

Study	Population	AUC ( $\mu\text{IU}\cdot\text{min}/\text{mL}$ ) (interval in minutes)	Dose (Units)	Device	Lot Numbers
PDC-INS-0001	Healthy	16982 (0-360)	100	BI Handihaler	043.98.004
PDC-INS-0001A	Healthy	353 (Dose normalized) (0-360)	25	Alpha	043.00.02
PDC-INS-0002	Healthy	3502 (0-360)	25	Alpha	P99.007
		6504 (0-360)	50		043.98.004
		11718 (0-360)	100		043.98.004
PDC-INS-0003	Type 2	12322 (0-360)	100	Alpha	043.98.004
MKC-TI-03B (Baseline adjusted)	Type 2	8187 (0-240)	48	Model C	3023A, 3023B
MKC-TI-003B2 (Baseline adjusted)	Type 2	11800 (0-540)	48	Model C	3262A
MKC-TI-015 (C-peptide corrected)	Healthy	2279 (0-240)	30	Model C	D060023
	COPD	2037 (0-240)	30		D060023
MKC-TI-016	Type 2 Smokers	2092 (0-480)	30	Model C	X4232A
	Type 2 Non-smokers	1677 (0-480)	30		
MKC-TI-025	Type 1	3848 (0-240)	30	Model C Prototype A	4173A
		4101 (0-240)	30	Model C Prototype B	X4232A
MKC-TI-027 (Baseline corrected)	Type 2 Nonasthmatic single dose	2583 (0-360)	30	Model C	X4232A
	Type 2 Nonasthmatic Subchronic	3096 (0-360)	30		
MKC-TI-110 (Baseline corrected)	Type 1	3366 (0-360)	30	Model C	D050010
		7523 (0-360)	60		D050010
MKC-TI-112	Type 1 and 2	NA	Varied doses	Model C	Supplied from MKC-TI-030
MKC-TI-113	Healthy, TI alone	5365 (0-360)	45	Model C	D070058 D070059
	Healthy, TI plus salbutamol	4912 (0-360)	45		
	Asthmatic, TI alone	4397 (0-360)	45		
	Asthmatic, TI plus salbutamol	5500 (0-360)	45		
	Asthmatic, MCT plus TI	5835 (0-360)	45		
MKC-TI-114	Healthy, TI alone	4820 (0-360)	45	Model C	D070058 D070059
	Healthy, TI plus albuterol	4491 (0-360)	45		
	Healthy, TI plus fluticasone	4415 (0-360)	45		
MKC-TI-116	Type 1	3337 (0-360)	2 × 15	Model D	PPT2008.09
		3397 (0-360)	30		PPT2008.09
MKC-TI-122 (Uncorrected)	Healthy	6781 (0-235)	45	Model C	D070058 D070059
MKC-TI-138 (Baseline corrected)	Type 1	(b) (4)	30	Model C	CLM8211A
		(b) (4)	30	Model D	CLM8277A

COPD = chronic obstructive pulmonary disease; MCT = methacholine challenge test; TI = TI Inhalation Powder

FDKP t<sub>max</sub>

Study	Population	t <sub>max</sub> (min)	TI Inhalation Powder Dose (Units)
MKC-TI-3B2	Type 2	15	48 <sup>a</sup>
MKC-TI-015	Healthy	9	30
	COPD	20	30
MKC-TI-016	Type 2, nonsmokers	12	30
	Type 2, smokers	16	30
MKC-T-017	Normal renal function	12	60 <sup>a</sup>
	Type 2, mild diabetic nephropathy	15	60 <sup>a</sup>
	Type 2, moderate diabetic nephropathy	30	60 <sup>a</sup>
MKC-TI-025	Type 1, Prototype A	6.3	30
	Type 1, Prototype B	5	30
MKC-TI-027	Type 2, nonasthmatic, single dose	25	30
	Type 2, nonasthmatic, subchronic dose	25	30
MKC-TI-110	Type 1	5	30
		6.3	60
MKC-T-111	Healthy	7.5	60 <sup>b</sup>
	Mild Hepatic Impairment	6	60 <sup>b</sup>
	Moderate Hepatic Impairment	6	60 <sup>b</sup>
MKC-TI-112	Type 1 and 2 during URI	7.5	Different doses
	Type 1 and 2 after URI	10	Different doses
MKC-TI-113	Healthy, TI alone	8.5	45
	Healthy, TI plus salbutamol	18	45
	Asthmatic, TI alone	18	45
	Asthmatic, TI plus salbutamol	20	45
	Asthmatic, MCT plus TI	20	45
MKC-TI-114	Healthy, TI alone	16	45
	Healthy, TI plus albuterol	8	45
	Healthy, TI plus fluticasone	13	45
MKC-TI-116	Type 1	10	2 × 15 U
		10	30 U
MKC-T-122	Healthy	14	60
MKC-T-131	Healthy	10	60 <sup>b</sup>
		10	120 <sup>c</sup>

COPD = chronic obstructive pulmonary disease; MCT = methacholine challenge test; TI = Technosphere® Insulin Inhalation Powder.

FDKP C<sub>max</sub>

Study	Population	C <sub>max</sub> (ng/mL)	Dose (Units)
MKC-TI-003B2	Type 2	160 <sup>a</sup>	48
MKC-TI-015	Healthy	93	30
	COPD	95	30
MKC-TI-016	Type 2, nonsmokers	75	30
	Smokers	72	30
MKC-T-017	Type 2, normal renal function	147	60 <sup>a</sup>
	Type 2, mild diabetic nephropathy	184	60 <sup>a</sup>
	Type 2, moderate diabetic nephropathy	126	60 <sup>a</sup>
MKC-TI-025	Type 1, Prototype A	95	30
	Type 1, Prototype B	95	30
MKC-TI-027	Type 2, nonasthmatic, single dose	74	30
	Type 2, nonasthmatic, subchronic dose	94	30
MKC-TI-110	Type 1	131 <sup>b</sup>	30
		171 <sup>b</sup>	60
MKC-T-111	Healthy	143 <sup>c</sup>	60 <sup>a</sup>
	Mild Hepatic Impairment	162 <sup>c</sup>	60 <sup>a</sup>
	Moderate Hepatic Impairment	157 <sup>c</sup>	60 <sup>a</sup>
MKC-TI-112	Type 1 and 2 during and after a URI	NA	Varied doses
MKC-TI-113	Healthy, TI alone	283	45
	Healthy, TI plus salbutamol	265	45
	Asthmatic, TI alone	197	45
	Asthmatic, TI plus salbutamol	258	45
	Asthmatic, MCT plus TI	258	45
MKC-TI-114	Healthy, TI alone	191	45
	Healthy, TI plus albuterol	233	45
	Healthy, TI plus fluticasone	203	45
MKC-TI-116	Type 1	118	2 × 15 U
		131	1 × 30 U
MKC-TI-122	Healthy	268	60
MKC-T-131	Healthy	247 <sup>c</sup>	60 <sup>c</sup>
		781 <sup>d</sup>	120 <sup>d</sup>

COPD = chronic obstructive pulmonary disease; URI = upper respiratory infection; MCT = methacholine challenge test; TI = Technosphere<sup>®</sup> Insulin Inhalation Powder.

## FDKP AUC

Study	Population	AUC (ng-min/mL)	Dose (Units)
MKC-TI-003B2	Type 2	28818 (0-540)	48
MKC-TI-015	Healthy	17399 (0-480)	30
	COPD	19756 (0-480)	30
MKC-TI-016	Type 2, smokers	12318 (0-480)	30
	Type 2, nonsmokers	17495 (0-480)	30
MKC-T-017	Type 2, normal renal function	30474 (0-480)	60 <sup>a</sup>
	Type 2, mild diabetic nephropathy	36090 (0-480)	60 <sup>a</sup>
	Type 2, moderate diabetic nephropathy	38206 (0-480)	60 <sup>a</sup>
MKC-TI-025	Type 1, Prototype A	20353 (0-240)	30
	Type 1, Prototype B	20237 (0-240)	30
MKC-TI-027	Type 2, nonasthmatic, single dose	15903 (0-480; baseline-corrected)	30
	Type 2, nonasthmatic, subchronic dosing	20658 (0-480; baseline-corrected)	30
MKC-TI-110	Type 1	14017 <sup>c</sup> (0-360)	30 <sup>c</sup>
		23715 <sup>c</sup> (0-360)	60 <sup>c</sup>
MKC-T-111	Healthy	26710 (0-480)	60 <sup>a</sup>
	Mild hepatic impairment	31001 (0-480)	60 <sup>a</sup>
	Moderate hepatic impairment	32700 (0-480)	60 <sup>a</sup>
MKC-TI-112	Type 1 and 2, during and after a URI	NA	Different doses
MKC-T-113	Healthy, TI alone	40517 (0-480)	45
	Healthy, TI plus salbutamol	38978 (0-480)	45
	Asthmatic, TI alone	30034 (0-480)	45
	Asthmatic, TI plus salbutamol	39821 (0-480)	45
	Asthmatic, MCT plus TI	40491 (0-480)	45
MKC-TI-114	Healthy, TI alone	37099 (0-480)	45
	Healthy, TI plus albuterol	42606 (0-480)	45
	Healthy, TI plus fluticasone	38291 (0-480)	45
MKC-TI-116	Type 1	19552 (0-480)	2 × 15
		21059 (0-480)	30
MKC-TI-122	Healthy	42375 (0-475)	60
MKC-T-131	Healthy	46860	60 <sup>b</sup>
		94515	120 <sup>d</sup>

COPD = chronic obstructive pulmonary disease; URI = upper respiratory infection; MCT = methacholine challenge test; TI = Technosphere<sup>®</sup> Insulin Inhalation Powder.

FDKP t1/2

Study	Population	Half-life (min)	Dose (Units)
MKC-TI-003B2	Type 2	157	48
MKC-TI-016	Type 2, smokers	NC	30
	Type 2, nonsmokers	NC	30
MKC-T-017	Type 2, normal renal function	191	60 <sup>a</sup>
	Type 2, mild diabetic nephropathy	196	60 <sup>a</sup>
	Type 2, moderate diabetic nephropathy	270	60 <sup>a</sup>
MKC-TI-025	Model C, Prototype A	165	30
	Model C, Prototype B	170	30
MKC-TI-027	Type 2, nonasthmatic, single dose	158	30
	Type 2, nonasthmatic, subchronic dosing	158	30
MKC-TI-110 <sup>c</sup>	Type 1	126	30
	Type 1	135	60
MKC-TI-015	Healthy	156	30
	COPD	185	30
MKC-T-111	Healthy	190 <sup>b</sup>	60 <sup>a</sup>
	Mild hepatic impairment	173 <sup>b</sup>	60 <sup>a</sup>
	Moderate hepatic impairment	198 <sup>b</sup>	60 <sup>a</sup>
MKC-TI-112	Type 1 and 2 during URI	163	Different doses
	Type 1 and 2 after URI	175	Different doses
MKC-TI-113	Healthy, TI alone	117	45
	Healthy, TI plus salbutamol	114	45
	Asthmatic, TI alone	134	45
	Asthmatic, TI plus salbutamol	121	45
	Asthmatic, MCT plus TI	121	45
MKC-TI-114	Healthy, TI alone	160	45
	Healthy, TI plus albuterol	153	45
	Healthy, TI plus fluticasone	168	45
MKC-TI-116	Type 1	161	2 × 15 U
		165	30 U
MKC-TI-122	Healthy	148	60
MKC-T-131	Healthy	152 <sup>e</sup>	60 <sup>b</sup>
		164 <sup>e</sup>	120 <sup>d</sup>

NC = not calculated; COPD = chronic obstructive pulmonary disease; MCT = methacholine challenge test; TI = Technosphere® Insulin Inhalation Powder.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	INSULIN HUMAN (RDNA ORIG)INH POWDER

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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SANG M CHUNG  
12/16/2009

SALLY Y CHOE  
12/18/2009  
Please see Team Leader memorandum.

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
<b>NDA/BLA Number</b>	22472	<b>Brand Name</b>	AFRESA and AFRESA inhaler
<b>OCP Division (I, II, III, IV, V)</b>	II	<b>Generic Name</b>	Insulin monomer human [rDNA origin]
<b>Medical Division</b>	DMEP	<b>Drug Class</b>	
<b>OCP Reviewer</b>	Sang M. Chung, Ph.D.	<b>Indication(s)</b>	treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia
<b>OCP Team Leader</b>	Wei Qiu, Ph.D. (Acting)	<b>Dosage Form</b>	Powder inhaler
<b>Pharmacometrics Reviewer</b>		<b>Dosing Regimen</b>	<ul style="list-style-type: none"> <li>• AFRESA should be administered at the beginning of a meal.</li> <li>• Insulin naïve patients: a 4 unit dose at each meal and titrate to the dose necessary to control blood sugar.</li> <li>• Patients transitioning from other insulins: replace 50% of the total daily dose with a corresponding AFRESA divided between main meals and additional doses may be taken to accommodate additional meals. The remaining 50% of the total dose of sc insulin should be given as longer acting insulin.</li> </ul>
<b>Date of Submission</b>	March 16, 2009	<b>Route of Administration</b>	Oral inhalation
<b>Estimated Due Date of OCP Review</b>	December 7, 2009 (TL DFS)	<b>Sponsor</b>	MannKind
<b>Medical Division Due Date</b>	December 21, 2009	<b>Priority Classification</b>	Standard
<b>PDUFA Due Date</b>	January 6, 2010		

***Clin. Pharm. and Biopharm. Information***

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
<b>Table of Contents present and sufficient to locate reports, tables, data, etc.</b>	X			
<b>Tabular Listing of All Human Studies</b>	X			
<b>HPK Summary</b>	X			
<b>Labeling</b>	X			
<b>Reference Bioanalytical and Analytical Methods</b>	X			
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>	X			97% in the urine after IV, 97.1% in the feces after oral administration of <sup>14</sup> C-FDKP(MKC-T-123) T1/2=114-198 minutes
<b>Isozyme characterization:</b>	X			FDKP
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>	X			FDKP
<b>Pharmacokinetics (e.g., Phase I) -</b>	X			
<b>Healthy Volunteers-</b>	X			
single dose:	X			
multiple dose:	X			
<b>Patients-</b>	X			

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:	X		
multiple dose:	X		
<b>Dose proportionality -</b>	<b>X</b>		Linear following 25 U, 50 U, 100U (PDC-INS-002) Linear following 30 U, 60 U (MKC-TI-110)
fasting / non-fasting single dose:	X		
fasting / non-fasting multiple dose:			
<b>Drug-drug interaction studies</b>	<b>X</b>		
In-vivo effects on primary drug:	X		No effect by albuterol, fluticasone (MKC-TI-114)
In-vivo effects of primary drug:			
In-vitro:			
<b>Subpopulation studies -</b>	<b>X</b>		Smoker (no clinical significance; MKC-TI-016), asthma (25% lower exposure; MKC-TI-027), COPD (no effect; MKC-TI-015), upper respiratory infection (no effect)
ethnicity:			
gender:			
pediatrics:			
geriatrics:			
renal impairment:	X		Mild to moderate (MKC-T-017, FDKP only)
hepatic impairment:	X		Mild to moderate (MKC-TI-111; FDKP only)
<b>PD -</b>	<b>X</b>		
Phase 2:	X		
Phase 3:			
<b>PK/PD -</b>	<b>X</b>		
Phase 1 and/or 2, proof of concept:	X		
Phase 3 clinical trial:			
<b>Population Analyses -</b>			
Data rich:			
Data sparse:			
<b>II. Biopharmaceutics</b>			
<b>Absolute bioavailability</b>	<b>X</b>		14.7% by AUC0-180 following 100U vs. 5 IU RHI (PDC-INS-0001)
<b>Relative bioavailability -</b>	<b>X</b>		
solution as reference:			
alternate formulation as reference:	X		21% vs. sc lispro (MKC-TI-116) 14%-27% vs. sc RHI (PDC-INS-002, MKC-TI-03B2, -025, -110, -116) 21-25% vs. sc RHI (MKC-TI-03B2)
<b>Bioequivalence studies -</b>	<b>X</b>		
traditional design; single / multi dose:	X		BE between 15 U cartridges and 30 U cartridge (MKC-TI-116) BE between Model C (pivotal trials) and Model D (TBM) (MKC-TI-138) (glucose AUC ?)
replicate design; single / multi dose:			
<b>Food-drug interaction studies</b>			
<b>Bio-waiver request based on BCS</b>			
<b>BCS class</b>			
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>			
<b>III. Other CPB Studies</b>			
<b>Genotype/phenotype studies</b>			
<b>Chronopharmacokinetics</b>			
<b>Pediatric development plan</b>			
<b>Literature References</b>	X		
<b>Total Number of Studies</b>	<b>31</b>		27 using inhaled Technosphere Insulin inhalation powder and 4 using Technosphere Powder without insulin

\*: FDKP: fumaryl diketopiperazine – insulin carrier excipient

RHI: regular human insulin

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	✓			BE in T1D (insulin antibody lower than 17.3 Kronus units/mL; MKC-TI-116)
2	Has the applicant provided metabolism and drug-drug interaction information?	✓			Inhaled albuterol and fluticasone (MKC-TI-114)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	✓			F=14.7%-14.9% (PDC-INS-000); 14-27% vs. RHI or lispro
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	✓			
5	Has a rationale for dose selection been submitted?	✓			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	✓			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	✓			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	✓			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	✓			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			✓	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	✓			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	✓			Initial dose targeting endogenous insulin levels and titrated to appropriately control blood glucose
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	✓			Dose is titrated to appropriately control blood glucose. The total amount of glucose administered is directly related to the overall effect of the insulin administered according to the euglycemic

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

					glucose clamp studies and postprandial glucose excursion studies.
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	✓			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			✓	Deferral
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			✓	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	✓			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	✓			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		✓		

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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Reviewing Clinical Pharmacologist

Date

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Team Leader/Supervisor

Date

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## DSI inspection request on the pivotal BE study

Quality of the study results is critical for the approvability. Therefore, the DSI inspection is requested for the study sites of clinical and bioanalytical studies (i.e., insulin, glucose and fumaryl diketopiperazine) in the pivotal BE study. The brief study information is as follows:

Study Report: MKC-TI-138

Title: A Phase 1, Open-Label, Randomized, 2-Way Crossover Clinical Trial to Compare Insulin Pharmacokinetics Following Technosphere® Insulin Inhalation Powder Administration Via 2 MedTone® Inhaler Models in Subjects With Type 1 Diabetes Mellitus

Lot numbers: Technosphere® Insulin Inhalation Powder for MedTone® Inhaler, Model C: CLM8211A  
Technosphere® Insulin Inhalation Powder for MedTone® Inhaler, Model D: CLM8227A  
Technosphere® Inhalation Powder: D070032

Principal Investigators:

**Professor Vladimir Yakusevich, MD**

MHI “Clinical Hospital for Emergency Care n.a. N.V. Soloviev”  
11, Zagorodny Sad str  
Yaroslavl, 150003, Russia

**Professor Vladimir G. Kukes, MD**

SI “Research Centre of Biomedical Technology of RAMS”  
Branch “Clinical Pharmacology” SHI of Moscow “City Clinical Hospital #23 honoured  
by Red Labour Flag Order, Named After Medsantrud”  
11, Yauzskaya str  
Moscow, 109240, Russia

Sponsor:

MannKind Corporation 61 South Paramus Road Paramus, New Jersey 07652  
(201) 983-5000

Responsible Medical Officer:

Anders H. Boss, MD, MFPM

Central laboratory:

(b) (4)

Analytical (for serum insulin):

(b) (4)

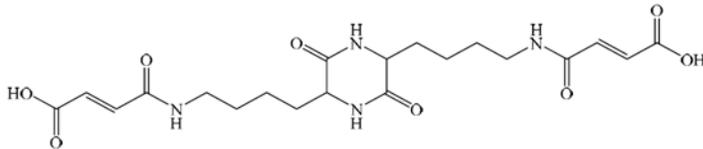
# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Filing memo (Internal Memo)

The sponsor submitted NDA 22-472 for AFRESA<sup>®</sup> (insulin monomer human [rDNA origin]) Inhalation Powder and the AFRESA<sup>®</sup> Inhaler as a 505(b)(1).

### 1. Formulation

AFRESA consists of Technosphere<sup>®</sup> Insulin (TI) Inhalation Powder pre-metered into unit dose cartridges and the MedTone<sup>®</sup> Inhaler. The TI is comprised primarily of insulin and fumaryl diketopiperazine (FDKP, Figure 1), a new insulin carrier excipient. FDKP is crystallized by the acid and the FDKP crystals are self-assembled into Technosphere<sup>®</sup> particles with spherical shape. The TI is formed by adsorbing insulin onto the surfaces of Technosphere<sup>®</sup> particles and the TI is about 2.5 μm for inhalation into the deep lung. The TI particles dissolve at physiological pH and both of insulin and FDKP are absorbed systematically. FDKP is renally excreted without being metabolized. Formulations of TI contained up to 20% insulin by weight (Table 1).



**Figure 1** Chemical structure of FDKP (M.W.=452.46)

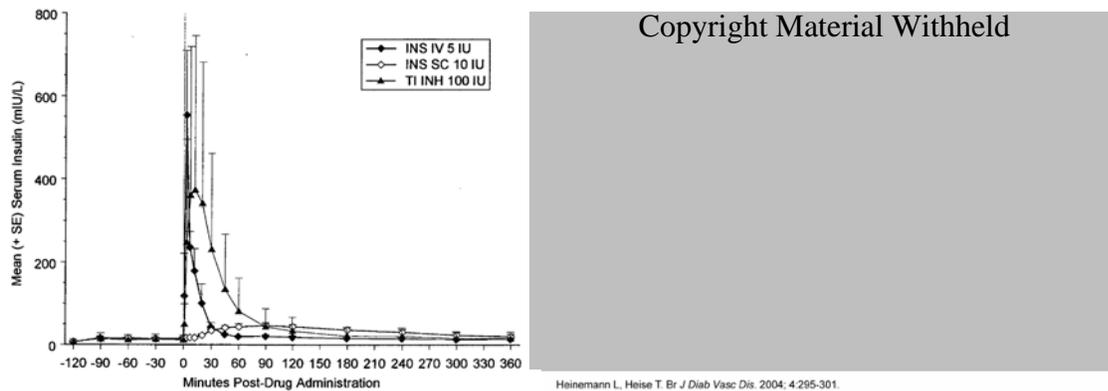
**Table 1** Components and composition of TI powder

Component	Grade	Quantity (per mg of formulation)	Function
Insulin Human Recombinant	USP	3.0 U <sup>a</sup>	Drug Substance
Fumaryl Diketopiperazine (FDKP)	In-house	(b) (4)	Raw material to form carrier particle
Polysorbate 80	NF	(b) (4)	(b) (4)
(b) (4)			

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## 2. Major pharmacokinetic properties

A total of 31 clinical pharmacology studies were conducted (Table 2-5) and representative plasma concentration-time profiles and glucose profiles following AFRESA<sup>®</sup> are shown in Figure 2. The ranges of time to reach maximum insulin concentration (t<sub>max</sub>) following the TI were 10-20 minutes in healthy volunteers, 9-15 minutes in Type 1 Diabetes (T1D), 9-25 minutes in Type 2 Diabetes (T2D), and 9-20 minutes in subject with asthma or in smoking subjects. Insulin concentrations were generally returned to the baseline in 180 minutes. The t<sub>max</sub> for FDKP ranged from 5 to 30 minutes. The mean t<sub>1/2</sub> of FDKP ranged from 114 to 198 minutes. The t<sub>max</sub> of regular human insulin (RHI) and rapid acting insulin analogue (RAA) following subcutaneous injection were 110 and 60 minutes, respectively. The insulin relative bioavailability following TI was 21% to RAA and 14-27% to RHI. Insulin metabolism and elimination was not studied. FDKP was mainly eliminated into urine (97% of dose) following IV dose and oral absorption was about 3%. Following TI, about 20% of FDKP dose was eliminated into urine.



**Figure 2** Mean plasma concentration-time profiles following TI inhalation, sc RHI, and IV insulin (left panel) and glucose infusion rates following TI inhalation and comparators (right panel)

## 3. Phase 3 studies

The primary efficacy endpoint was the change in hemoglobin A1c (HbA1c). The efficacy of TI was evaluated in 7 pivotal trials;

- placebo-controlled studies in T2D (PDC-INS-0008, MKC-TI-005),
- TI+a basal insulin vs. RAA+a basal insulin (MKC-TI-014, MKC-TI-102 in T2D MKC-TI-009 in T1D),
- TI along vs. TI+oral anti-diabetics in T2D (MKC-TI-026, MKC-TI-103)

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

**Table 2 Clinical pharmacology trials to characterize the pharmacokinetic and pharmacodynamic properties of TI Inhalation powder**

Study Type	Protocol Number
PK/PD - Normal	PDC-INS-0001, PDC-INS-0002,
PK/PD - Type 1	MKC-TI-025, MKC-TI-110, MKC-TI-116, MKC-TI-138
PK/PD - Type 2	PDC-INS-0003, PDC-INS-0003A, MKC-TI-03B, MKC-TI-003B2, PDC-INS-0004A, PDC-INS-0011, MKC-TI-016, MKC-TI-027
Postprandial control	MKC-TI-03B
Timing of dosing	PDC-INS-0011
Intrasubject variability	PDC-INS-0003A, MKC-TI-003B2, MKC-TI-025
Pulmonary distribution	PDC-INS-0007, MKC-TI-122

**Table 3 Clinical pharmacology trials to evaluate pharmacokinetic characteristics or for exploratory purposes**

Study Type	Protocol Number
Single dose	PDC-INS-0001, PDC-INS-0001A, PDC-INS-0002, PDC-INS-0003, MKC-TI-110, MKC-TI-116, MKC-TI-138,
Multiple dose	PDC-INS-0004A, MKC-TI-027
Bioequivalence	MKC-TI-025, MKC-TI-116, MKC-TI-138

**Table 4 Clinical pharmacology in special populations**

Study Type	Protocol Number
Smokers	MKC-TI-016
Renal disease	MKC-T-017 <sup>a</sup>
Liver disease	MKC-T-111 <sup>a</sup>
Asthma	MKC-TI-027, MKC-TI-113
Chronic obstructive pulmonary disease	MKC-TI-015
Upper respiratory infection	MKC-TI-112

<sup>a</sup> These studies evaluated FDKP only.

**Table 5 Other studies**

Study Type	Protocol Number
Drug-drug Interaction	MKC-TI-113, MKC-TI-114
ADME	MKC-T-123 <sup>a</sup>
Lung residence time	MKC-TI-122
QT Prolongation	MKC-T-131 <sup>a</sup>

<sup>a</sup> These studies evaluated FDKP only.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## 4. Bioanalytical Methods

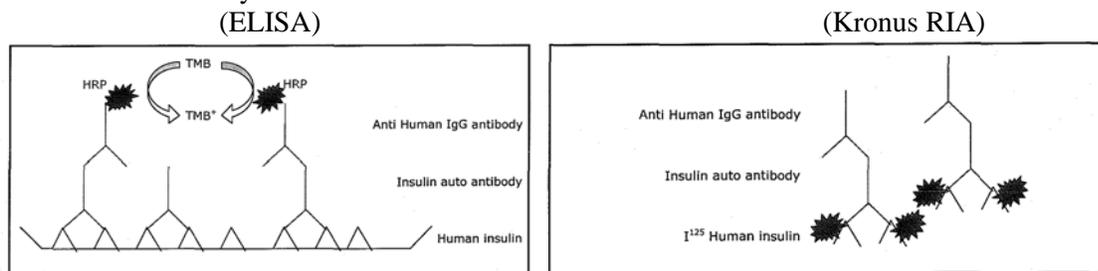
The sponsor submitted validations for 3 bioanalytical methods used throughout AFRESA development as follows:

### 4-1. Insulin

- Radioimmunoassay (RIA) for PDC-INS-0001 and -002: dynamic range of 1.2 to 200  $\mu\text{U/mL}$ .
- DCP Immulite 2000 automated assay (Abbott) for MKC-TI-03B, -03B2, -016, -027, and Cohort 1 of MKC-TI-110: dynamic range of 2 to 300  $\mu\text{U/mL}$ .
- Roche E170 automated insulin assay for MKC-TI-110 (Cohort 2), -015, -113, -114, -116, -122, and -138
  - Serum-based, electrochemiluminescence immunoassay
  - No cross-reactivity to insulin lispro (or insulin aspart)
  - Validated based on the Guidance with range of 0.5 to 400  $\mu\text{U/mL}$ .
- Lispro radioimmunoassay (Lispro Insulin RIA kit) for MKC-PC-2006-0042 without cross-reactivity with RHI in the range of 2.5 to 200  $\mu\text{U/mL}$ .

### 4-2. Insulin antibodies

Kronus radioimmunoassay (MKC-PC-2006-0043) for all studies except a serum-based enzyme-linked immunosorbent assay for PDC-INS-0008.



### 4-3. Fumaryl Diketopiperazine

LC/MS for plasma, serum (1 to 1000ng/mL), and urine (10 to 10000ng/mL)

## Potential Review issues (Internal Memo):

- Pivotal BE study
  - Study population: The Agency recommended conducting the pivotal BE study in healthy volunteers, Type 1 Diabetes who do not have anti-insulin antibodies, or provide that the PK assessments are not affected by endogenous anti-insulin antibodies because anti-insulin antibodies may impact insulin PK assessment (refer to the section 2.5 of preNDA meeting minute). The sponsor concluded that “the neither the presence of insulin antibodies nor their concentration influenced glycemic control, the incidence of hypoglycemia, or pulmonary function parameters” (page 33 of Study report MKC-TI-138).
  - PD as a primary endpoint: The Agency recommend including PK and PD parameters as primary endpoints. However, the sponsor did not analyze PD parameters because additional insulin analogue was injected during the study per protocol and it affected postprandial glucose concentrations as follows;  
*“By protocol, the site was allowed to administer RAA to subjects whose blood glucose was above 270 mg/dL. A majority of the subjects entered the meal challenge with blood glucose concentrations approaching 270 mg/dL. On Day 1, after the meal and administration of TI Inhalation Powder, 19*

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*subjects had blood glucose concentrations above 270 mg/dL and received RAA within 90 minutes of administration of TI Inhalation Powder. On Day 2, the corresponding number was 43 subjects. Because the RAA and TI Inhalation Powder both affected postprandial glucose concentrations, the interpretation of blood glucose concentrations as a PD marker for these subjects was unreliable. To meet the objective of evaluating the effect of TI Inhalation Powder on glucose excursions, AUC0-120 was calculated for subjects who had not received RAA within 90 minutes after starting the meal challenge. Fifty-five profiles were evaluable on Day 1, and 31 on Day 2.”*

- Baseline correction; various baseline correction methods can be employed in insulin PK assessment and its impact on insulin PK assessment is unknown:
  - AFRESA (e.g., -120, -90, -60, -30, 0)
  - EXUBERA (e.g., correction with C-peptide, or -30, -15, 0)
- TQT, renal, and hepatic impairment studies were conducted only for FDKP.
- The sponsor concluded that variability on insulin exposure following AFRESA was less compared to that of sc or EXUBERA (Table 6) through cross study comparison and the conclusion should be confirmed because of significant labeling impact related to product promotion.

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Table 5. Comparison between AFRESA and EXUBERA

	<b>AFRESA</b>	<b>EXUBERA</b>
<b>Absolute bioavailability</b>	14.7%	NA
<b>Relative bioavailability</b>	21% vs. sc lispro 14%-27% vs. sc RHI	About 10% (5-15%) vs. RHI
<b>Dose proportionality</b>	Proportional after 25, 50, and 100 U 30 and 60 U	Exposure increased with doses (1, 2, 3, 4, and 6mg) but did not meet criteria for dose proportionality and variability may contribute (e.g., 45 $\mu$ U min/mL vs. 3870 $\mu$ U min/mL following 1mg replicate study)
<b>Smoking</b>	no clinical significance (MKC-TI-016)	2-5-fold higher in chronic smokers 20-30% lower in passive smoking
<b>Asthma</b>	25% lower exposure (MKC-TI-027)	Decrease in exposure
<b>Obstructive pulmonary disease (COPD)</b>	no effect (MKC-TI-015)	Higher exposure but inconclusive because of high variability
<b>Rhinovirus infection</b>	upper respiratory infection	Inconclusive because of high variability
<b>Gender/Race</b>	No study	No study; No effect in cross study comparison
<b>Pregnancy</b>	No study	No effect
<b>Obese</b>	No study	Higher exposure and lower sc insulin exposure may contribute
<b>DDI</b>	Albuterol/fluticasone; no effect	25% and 50% increase in insulin exposure after albuterol with mild and moderate asthma, respectively; No fluticasone effect on insulin
<b>Variability</b>	ISV was 14.1% for 48 U of TI and 16.9% for 15 IU of RHI (repeated single-dose; MKC-TI-0003A). 28.8% for TI vs. 33.9% CV of AUC for RHI CV of insulin AUC was lower after TI than that of sc RHI	Insulin variability was higher following EXUBERA compared to that of sc, BSV; 14%-103% (AUC), 18-123% (Cmax) for EXUBERA vs. 23%-84% (AUC), 31-148% (Cmax) for sc ISV; 20% (AUC), 60% (Cmax) in helathy Glucose-lowering activity was comparable to that of sc.
<b>Antibody formation</b>	8-fold over the study period vs. 2-fold for comparators. Baseline for T1D is about 2-fold higher than that of T2D; with AFRESA 3-4 times greater than their baseline values. The absolute level did not associate with clinical outcomes such as HbA1c, hypoglycemia, insulin dose, serious and non-serious AEs.	30-fold increase over 6 months treatment vs. no following sc administration. No apparent glucose intolerance or loss of glycemic control associated with insulin resistance with neutralizing Ab over 24 wks trt with either inhaled or sc insulin
<b>Particle size</b>	2.5 $\mu$ m	(b) (4)
<b>BE</b>	Clinical vs. TBM; BE based on PK	Clinical vs. TBM; BE based on PK
<b>Lung deposition</b>	Tc deposition; (b) (4) lung, (b) (4) oropharyngeal	(b) (4)

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<b>Components and composition</b>	<b>Component</b>	<b>Grade</b>	<b>Quantity (per mg of formulation)</b>	<b>Function</b>
	Insulin Human Recombinant	USP	3.0 U <sup>a</sup>	Drug Substance
	Fumaryl Diketopiperazine (FDKP)	In-house	(b) (4)	Raw material to form carrier particle
	Polysorbate 80	NF	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Formulation Code No.: 97060/97063			
Name of Ingredient	Unit Formula (mg/blister)	Function	Reference to Standard
Insulin, Human Recombinant	(b) (4)	Active	USP/Ph. Eur./Aventis (b) (4)
Sodium Citrate, Dihydrate	(b) (4)		
Mannitol	(b) (4)		
Glycine	(b) (4)		
Sodium Hydroxide	(b) (4)		
Dose Blister			
Total Weight		5.10	
<sup>a</sup> Based on sodium ion			
<sup>b</sup> (b) (4)			
N/A = Not Applicable			

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/s/

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Sang Chung  
5/8/2009 01:39:47 PM  
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5/8/2009 02:23:27 PM  
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