FDA Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

April 1, 2014, 8:00 AM to 5:00 PM

The committee will discuss new drug application (NDA) 022472, proposed trade name AFREZZA (TECHNOSPHERE Insulin Inhalation System), 3 unit and 6 unit cartridges for oral inhalation, manufactured by MannKind Corporation. The proposed indication (use) for this application is to improve glycemic control in adult patients with type 1 or type 2 diabetes mellitus. FDA Briefing Document prepared March 7, 2014.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 022472 Afrezza (Technosphere insulin) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Division Director's Memo

Prepared by Jean-Marc Guettier, M.D.

Product:

Afrezza is a drug-device combination product consisting of a dry powder formulation of recombinant insulin (i.e., Technosphere Insulin) and an inhaler device (i.e., Gen2 inhaler).

The applicant has changed the device three times over the course of development. The three devices are referred to in the background package and are described below (refer to DPARP clinical background document for details).

1. **MedTone C inhaler**: Used in pivotal Phase 3 trials to support the original NDA.

2. **MedTone D inhaler:** (Abandoned)

3. **Gen2 inhaler**: Used in the two new pivotal phase 3 studies. This is the to-be-marketed device. In-vitro performance (particle size) and single dose comparative bioavailability (study: MKC-TI 142) suggest device design change would not affect efficacy. In light of these findings, data derived from Phase 3 trials performed with the MedTone C inhaler device although not pivotal may be thought of as providing supportive evidence to inform efficacy and safety of the product.

Regulatory History:

On March 16th, 2009 MannKind Corporation submitted a new drug application (NDA) for Afrezza. The applicant is seeking the following indication for Afrezza: *as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus and adult patients with type 1 diabetes mellitus.*

Afrezza has had a complex regulatory history including two previous cycles of review that resulted in issuance of Complete Response Letters on March 12, 2010 and January 18, 2011 due to multiple identified deficiencies in the application. The members of the committee should familiarize themselves with the regulatory history synopses provided in Section 1.2 of the clinical background document and Section II of the pulmonary consult review. On October 15, 2013 FDA received the re-submission for Afrezza. The response contained the results of two new clinical pharmacology studies (i.e., studies MKC-TI 176 and MKC-TI 177), a new pivotal Phase 3 trial in patients with type 1 diabetes mellitus (i.e., study 171: Afrezza versus aspart) and a new pivotal Phase 3 trial in patients with type 2 diabetes mellitus (i.e., study 175: Afrezza versus placebo).

Disease Burden:

In 2010, 19 million individuals were diagnosed with diabetes mellitus in the United States across all age groups[1]. It is estimated that approximately 90% of individuals with diabetes worldwide have type 2 diabetes mellitus[2].

Drugs Approved for the Treatment of Type 1 and 2 Diabetes:

Insulin and amylin agonists (i.e., pramlintide) are the only two classes of drugs approved and marketed for the treatment of patients with type 1 diabetes mellitus in the United States. There are 12 classes (insulin inclusive) of drugs approved and marketed for the treatment of patients with type 2 diabetes mellitus in the United States. Currently approved and marketed insulin therapies are administered only via the subcutaneous route (SC), often as multiple daily injections per day or through subcutaneous infusion using an insulin pump device. The only approved inhaled insulin, Exubera, was withdrawn from the market by Pfizer in 2007.

Intended Use and General Therapeutic Principles:

Afrezza was evaluated as a "meal time" insulin. Meal time insulins, also referred to as "prandial" or "short acting" insulins, are intended to cover meal time insulin requirements and are administered before each meal of the day.

As a matter of general principles, the pharmacokinetic profile of an ideal meal time insulin would match the glucose excursion profile that follows ingestion of macronutrients to ensure maximum benefit (i.e., glucose control) and minimum risk (i.e., hypoglycemia). The absorptive period which follows ingestion of a meal lasts for approximately 3 to 4 hours in normal individuals.

In diabetes, glucose levels are also elevated in the fasting state due to excessive glycogen breakdown (i.e., glycogenolysis) and/or de novo glucose formation (i.e., gluconeogenesis). Elevation in glucose that arise as a result of these biochemical processes are not directly linked to absorption of nutrients but rather to an absolute or relative absence of insulin. To cover glucose increases not linked to absorption of nutrients, a "basal" or "long-acting" insulin is administered.

Over a 24 hour period 50% of a healthy individual's insulin is secreted in the fasting state and 50% in the times that follow meals[3]. In patients with no or insufficient residual endogenous insulin, therapeutic interventions aim to approximate this pattern of secretion (e.g., basal to meal time ratio of 50:50 often time administered as one basal and three meal time injections).

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[1] Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

[2] http://www.who.int/mediacentre/factsheets/fs312/en/

[3] Polonsky et al. JCI. Volume 81, February 1988, 442-448

Recommended Glycemic Goals for Adults[4] with Diabetes:

The American Diabetes Association (ADA) and other professional societies, recommend targeting, individualized, but specific glycemic goals aimed at normalizing glucose levels. Specific ADA recommended goals and their rationale are reproduced below.

- *"Lowering A1C to below or around 7% has been shown to reduce microvascular complications of diabetes and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease. Therefore, a reasonable A1C goal for many nonpregnant adults is, 7%.*

- *Providers might reasonably suggest more stringent A1C goals (such as 6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD.*

- *Less stringent A1C goals (such as 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and in those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education (DSME), appropriate glucose monitoring, and effective doses of multiple glucose lowering agents including insulin."*

In general, every percentage point drop in HbA1c blood test results (e.g., from 8.0% to 7.0%) can reduce the risk of microvascular complications (eye, kidney, and nerve diseases) by 40%[5].

Indication for Insulin Products and Evidentiary Standard:

All currently approved insulins are indicated as: *an adjunct to diet and exercise to improve glycemic control in adults (+/- pediatric) patients with* ***type 1 diabetes mellitus*** *(Type 1 DM) and* ***type 2 diabetes mellitus*** *(Type 2 DM).*

For this indication, the applicants must typically demonstrate that the investigational agent offers superior (vs. placebo) or non-inferior (vs. active comparator) HbA1c reduction at ~ 6 months in adequate and well controlled trials (refer to section 14 of the full prescribing information of recently approved insulin products).

[4]Executive Summary: Standards of Medical Care in Diabetes 2014: Diabetes Care Volume 37, Supplement 1, January 2014

[5] Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

Reliance on HbA1c to establish efficacy of anti-diabetic drugs was based on results from the landmark Diabetes Control and Complications Trial (type 1 DM) and United Kingdom Prospective Diabetes Study (type 2 DM) trials which demonstrated that interventions aimed at normalizing glycemia using intensive glucose lowering strategies decreased microvascular disease complications (i.e., retinopathy, nephropathy and neuropathy). While intensive glucose lowering came at the cost of increased risk of hypoglycemia and weight gain, it is generally accepted that the net benefit of intensive treatment outweighs these risks.

Standard for Type 2 Diabetes Mellitus General Principles

Efficacy of a new agent for type 2 diabetes is demonstrated preferably against a placebo control +/- background agent at maximally effective doses. Several studies are needed in general to assess efficacy and risks with common co-administered drugs and in common clinical-use scenarios (e.g., add-on to metformin, add-on to sulfonylurea, add-on to dual therapy, add-on to insulin etc.). For injectable insulins, a study characterizing the risk benefit in the most likely use scenario is usually performed.

Standard for Type 1 Diabetes Mellitus General Principles

Efficacy of a new agent for type 1 diabetes is always demonstrated against an active comparator (for ethical reasons as these patients have an absolute requirement for insulin). The new agent is added to the background "other" insulin. (i.e., other = prandial or basal depending on what the investigational agent is).

Insulin Trials General Principles

Insulin trials are designed as "treat to target" trials. The question an insulin trial attempts to answer is not simply whether the titratable product lowers glucose but whether intensive treatment with the agent can result in glucose lowering that approaches the American Diabetes Association recommended glycemic goals safely (i.e., risk of hypoglycemia). To achieve this, intensive dose titration for at least 3 months is programmed into the protocols of insulin trials. Adherence to titration recommendations is usually monitored intensely by investigators and applicants in these trials. This design feature helps ensure that a robust, safe, glucose lowering response is elicited from both the new agent and the comparator.

Issues for Discussion and Background Package Orientation:

FDA has convened this committee to request advice on the following issues important in informing the risk benefit of Afrezza in patients with type 1 diabetes mellitus and in patients with type 2 diabetes mellitus:

Clinical Pharmacology:

Some of the clinical pharmacology findings are described in the "Clinical Pharmacology" background document and in the sponsor's background document. The pharmacology of any insulin is intimately linked to efficacy (e.g., glucose lowering) and safety (e.g., hypoglycemia). Identified clinical pharmacology issues to be considered include:

- *The novel pharmacokinetic and pharmacodynamic profile of Afrezza as it relates to meal time coverage*

- *Lower bioavailability compared to subcutaneous insulin:* The relative bioavailability of Afrezza is ~20-30% that of subcutaneous insulin. The applicant accounted for the lower bioavailability in pivotal trials using a dose conversion algorithm (i.e., 10 units of Afrezza for 4 units of subcutaneous insulin).

- *Atypical dose response relationship:* In some studies increasing doses of Afrezza did not increase glucose lowering effect. Study MKC-T1-176 (Gen-2 inhaler) showed less than dose proportional glucose lowering above 60 units (~20-24 units of SQ) in healthy subjects. In Study 005, a longer term forced dose titration study, performed early in product development also suggested a less than dose proportional HbA1c lowering response.

- *Specific issues related to method of drug delivery:* The inhaler is breath-powered. Particle size distribution studies suggest delivery of insulin to the systemic absorption site (i.e., lung) may be inhalation flow rate dependent (i.e., a decrease in particle size was observed with increased inhalation).

Efficacy New Trials:

Efficacy findings are described in details in the statistical review and clinical review clinical background documents. Committee members are asked to consider the efficacy finding in general (totality of the evidence) and related to the two new trials specifically.

In trial 175, Afrezza was shown to provide superior HbA1c lowering compared to placebo in patients with type 2 diabetes inadequately controlled on one or more oral anti-diabetic agent at 24 weeks. The response in the placebo arm was consistent with that seen in other programs (Refer to the stats and DMEP clinical background documents for details).

In trial 171, Afrezza was shown to provide statistically inferior HbA1c reduction compared to aspart in patients with type 1 diabetes but the upper 95% confidence interval around the difference in effect between arms remained within the pre-specified non-inferiority margin of 0.4%. (Refer to the statistical and clinical background documents for details). Factors identified in the reviews susceptible to affecting reliability of the estimate included baseline HbA1c that did not fully reflect impact of run-in phase, differential dropout rates and missing data, as well as inadequate optimization of insulins in the control arm. Analyses based on secondary glycemic endpoints (i.e., proportion of responders) and endpoints directly associated with insulin effectiveness (weight gain, hypoglycemia) were found to be consistent with the results of the primary analysis. (Refer to the statistical and clinical background documents for details).

Safety:

Clinical safety findings are described in details in the clinical review document, and pulmonary consultation background documents. A summary of the nonclinical carcinogenicity findings is described in the nonclinical review document. Details regarding the results of a post-marketing study to investigate a lung cancer imbalance for Exubera is summarized in the epidemiology review document. Advisors will be asked to provide input and weigh in on the following observed safety findings:

1. Pulmonary safety
2. Lung cancer risk
3. Disease specific safety issues

Afrezza – Draft Discussion Points

With regards to Afrezza's clinical pharmacology please comment on each of the following:

- Afrezza's clinical pharmacology profile as it relates to adequacy of mealtime coverage
- Your level of concern with regards to the less than dose proportional glucose lowering response observed in some studies and its potential impact on treatment
- Adequacy of the data to support the proposed 10:3 unit conversion algorithm to establish a safe starting dose for patients on an insulin regimen consisting of a short acting subcutaneous prandial insulin
- Other clinical pharmacology parameters susceptible to influencing dosing, efficacy or safety of the product (e.g., inhalation flow rate dependence, between subject variability, within subject variability etc.)

With regards to interpretation of the primary efficacy results in active comparator, non-inferiority trials, please comment on your level of concerns regarding issues identified in the review susceptible to influencing the accuracy of those results. Specifically but not necessarily limited to,

- Baseline Hba1c values that may not reflect the full effect of background therapy optimization in the run-in phase
- Differential dropout rates between Afrezza and comparator arms
- Missing data and assumptions made in the handling of missing data
- Potentially inadequate optimization of insulin therapies in the control arm (i.e., basal and prandial)

Based on the overall safety data in both the background package and presented at today's meeting please address each of the following

- Your level of concern with regards to the risk of acute bronchospasm in patients with asthma and COPD associated with Afrezza use.
- Your level of concern with regards to the risk of pulmonary function decline and chronic use of this product in patients with underlying lung disease
- The impact of smoking and intercurrent illness (i.e., upper respiratory tract infection) on efficacy and safety of the product
- Your level of concern with regards to the noted imbalance in cases of lung cancers not favoring Afrezza

- Your level of concern with regards to the noted imbalance in cases of diabetic ketoacidosis not favoring Afrezza in patients with type 1 diabetes mellitus
- Other safety concerns not covered in the above bullet points (e.g., tolerability issues)

Discuss mitigation strategies for the above listed risks

Based on data in both the background package and presented at today's meeting do you believe the applicant has demonstrated that Afrezza is safe and effective for the treatment of adult patients with type 1 diabetes mellitus to justify approval?

- If you have answered yes, please explain your rationale. Discuss your views regarding the role of Afrezza in the management of this disease.
- If you have answered no, please explain your answer. If you believe additional studies are needed before approval can be granted please describe which types of studies.

Based on the data in the background package and presented at today's meeting do you believe the applicant has demonstrated that Afrezza is safe and effective for the treatment of adult patients with type 2 diabetes mellitus to justify approval?

- If you have answered yes, please explain your rationale. Discuss your views regarding the role of Afrezza in the management of this disease.
- If you have answered no, please explain your answer. If you believe additional studies are needed before approval can be granted please describe which types of studies.

Advisory Committee Briefing Document Nonclinical Pharmacology & Toxicology Summary
Drug: Afrezza (recombinant human insulin + Technosphere carrier particles; TI)
Drug class: inhaled insulin
Clinical Indication: Diabetes

Afrezza or Technosphere insulin (TI) is inhaled as a dry powder with the aid of the Gen2 inhaler. Technosphere insulin is comprised of recombinant human insulin, and a proprietary carrier known as Technosphere. The formulation contains a novel excipient fumaryl diketopiperazine (FDKP) and polysorbate 80 (PS80). FDKP undergoes acid-induced intermolecular self-assembly in aqueous solution resulting in adsorption of insulin onto the Technosphere particles to form Technosphere insulin.

The proposed clinical indication is Type 1 and Type 2 diabetes with a maximum recommended human dose (MRHD) of 300 U of Afrezza daily or 99 mg TI (88.6 mg Technosphere + 10.4 mg insulin). This is an estimated MRHD, as diabetic, obese patients may require more insulin based on their body weight. TI is intended as rapid acting insulin. The pharmacokinetic profile and Technosphere particle size was designed by the sponsor for delivery into the lungs where it is absorbed. Different inhalational flow rates and variation in particle size may affect the amount of insulin absorbed. The mechanism involved in the rapid systemic absorption of insulin from Technospheres has not been established. Cell-based studies demonstrate that FDKP and TI do not disrupt cellular tight junctions and FDKP does not increase the permeability of cell membranes.

Nonclinical Development Program: The nonclinical development program for Afrezza focused on characterizing the local effects of inhaled insulin and on characterization of the toxicity profile of FDKP/Technospheres. FDKP is not metabolized and undergoes renal excretion, unchanged. The pharmacology/toxicology of inhaled human insulin has been well established in humans and animals over the last 90 years.

An important distinction in extrapolation of outcomes from animal exposure to human clinical exposure is the mode of administration. Afrezza is designed to be administered via an inhalational device (Gen2 inhaler) whereas administration of Technospheres with or without insulin in animals occurred from nose (i.e. rat, mouse) or nose and mouth (i.e. dog). These modes of exposure lead to exposure of the entire respiratory tract in animals which differs from humans based on the mean particle size of Afrezza. This is dissimilar to human exposure which is focused on distribution of Afrezza particles to the lung for rapid absorption. Dosimetry of inhalation toxicity studies are theoretical estimates because direct measurements of animal exposures are often impossible.

***Afrezza Carcinogenicity*:** The Sponsor performed a 2-year carcinogenicity study in rat and a subcutaneous transgenic mouse study (Tg.rasH2). The results of the carcinogenicity assessment with Technosphere (T) and TI indicate an absence of any drug-induced neoplastic findings with administration either via inhalation (2-year rat) or subcutaneous (Tg.rasH2 mouse) routes at systemic exposures of Technosphere (FDKP) 5X and 1X respectively, compared to the AUC at the MRHD (99 mg). Cell proliferation activity (proliferating cell nuclear antigen; PCNA) was confirmatory of the absence of neoplasias/pre-neoplastic signals as assessed in alveolar and bronchiolar cells across treatment and control groups from the rat carcinogenicity study.

The Sponsor assessed the genotoxicity of Technosphere and insulin in an Ames bacterial mutagenicity assay, chromosome aberration assay in human peripheral blood lymphocytes with and without metabolic activation as well as a mouse micronucleus assay with Technosphere alone. All genotoxicity studies were negative.

Carcinogenicity of Related Insulin Products: Exubera (NDA 21-868; approved 2006) was the first marketed recombinant human insulin in powdered form, delivered via a pulmonary inhaler. Marketing ceased in 2007 by Pfizer because the product failed to gain acceptance among patients and physicians. Carcinogenicity studies were not performed with Exubera. Recombinant human insulin is identical to the endogenous hormone and treatment is considered replacement therapy. Chronic toxicity studies indicated there was no effect on cell proliferation indices in alveolar or bronchiolar areas of the lung in either species. Compared to control animals, there were no drug-related adverse effects in either rats or Cynomolgus monkeys following 6-month duration repeat-dose chronic toxicity studies with regard to pulmonary function, gross or microscopic morphology of the respiratory tract or bronchial lymph nodes. The experience with Exubera is similar to Afrezza, with regard to the absence of a significant nonclinical pulmonary toxicity signal.

Lantus (NDA 21-081) is a recombinant human insulin analogue (insulin glargine) which is modified to slow the release of microprecipitated insulin glargine from the subcutaneous injection site. Two year life-time carcinogenicity bioassays with insulin glargine were performed in mice and rats at doses up to 0.455 mg/kg at exposures 10-times in the rat and 5-times in the mouse compared to human exposures at the starting dose of 10 IU (0.008 mg/kg/d) based on body surface area comparisons across species (mg/M^2). Female mice had survival issues during the study and the findings were inconclusive as a result of the excessive mortality in all dose groups attributable to hypoglycemia. Malignant histiocytomas were observed at the injection sites in male rats and male mice. The histiocytomas reached statistical significance in the male rats (2-fold human exposure at 10 IU) but was not statistically significant in the male mice. Histiocytomas were not observed in female rats, saline control, or in the insulin comparator group using a different (non-acidic) vehicle. Indices of mitogenicity and relative IGF-1 receptor binding were reported as slightly higher for insulin glargine compared to human insulin.

Afrezza General Toxicology: The chronic inhalational toxicology studies included 6-month rat and 9-month dog studies. Toxicology data with Technospheres suggest some potential for respiratory irritation with therapeutic use. The chronic toxicity studies (rat, dog) indicate minimal to mild respiratory irritation at ≤2X human systemic exposure. The respiratory irritation did not correlate to any preneoplastic or neoplastic findings as discussed previously.

In the 26-week chronic rat study with dose groups: 11.7 mg/kg/d for T, low dose (LD) TI (1.05 M, 0.404 F mg/kg/d) and high dose (HD) TI (1.91 M, 1.28 F mg/kg/d) administered by nose only inhalation, respiratory findings including increased lung weights, nasal cavity eosinophilic globules and epithelial degeneration were observed. These findings were recoverable in females but remained in the males following a 4-week drug withdrawal period. A slight increase in bronchiolar cell PCNA (but not alveolar cells) in the upper respiratory tract in T and in LD, HD TI groups may be associated with particulate impaction. This is in contrast to the results from the 2-year rat carcinogenicity study showing an absence of bronchiolar and alveolar cell PCNA. Insulin is known to have an adaptive effect on late phase G1 in conjunction with IGF-1, therefore an increased proliferation rate of exposed, regenerating cells such as the bronchial cells is not surprising. However since these cells did not show neoplastic findings and PCNA analysis was negative after lifetime exposure in rat, the slight increase in bronchiolar cell PCNA in the chronic rat study may be considered an adaptive response. These results showing a slight increase in the upper airway (bronchial) but not in the deep alveolar tissues probably reflects the rodent nose only dosing with particle distribution to the entire respiratory tract as compared to the proposed for human use with the inhaler directed into the lung tissue. In addition to pulmonary effects, approximately half the males treated with T (11.7 mg/kg/d) had evidence of myocardial degeneration/necrosis which was not observed in any TI treated groups nor was this observed in female rats or in the dog. The 2-year rat carcinogenicity study with lifetime exposure did not show any increase in treatment related cardiac findings above concurrent controls. The No Observed Adverse Effect Level (NOAEL) for the chronic rat toxicity study was 1.91 mg/kg/d in males and 1.28 mg/kg/d in females based on the findings noted above at higher exposures. Based on Technosphere exposure, the NOAEL was 2-fold greater than the maximum anticipated daily human therapeutic exposure (99 mg Afrezza) based on AUC.

In the 2-year rat carcinogenicity study, with nose only inhalation, the nasal cavity of the high dose (HD) Technosphere (41, 46 mg/kg/d) treated group had goblet cell hyperplasia of the respiratory epithelium, accumulation of eosinophilic droplets in the olfactory and respiratory epithelium. These findings were considered an adaptive response to chronic inhalation of Technospheres because they were seen at comparable severity/frequency in the control and TI treated groups. Consistent with this observation, is the minimal to slight mixed macrophage and neutrophils infiltrates and degenerative skeletal muscle myopathy seen in the subcutis in the SC transgenic mouse carcinogenicity study in all groups, including controls.

In the 39-week chronic dog study with administered doses of: LD T (2.4 mg/kg/d), HD T (10.9 mg/kg/d and LD TI (0.39 mg/kg/d) and HD TI (1.92 mg/kg/d) were tested using oral-nasal exposure. Respiratory findings included increased minimal to mild neutrophils infiltration of the lungs in the HD TI group which recovered following an 8-week drug withdrawal. Thymic atrophy and hypocellularity of the seminiferous epithelium and germ layer degeneration were observed in the T and TI groups. These findings are commonly associated with immature dogs, consistent with age 7-8 month old dogs at study initiation. These male reproductive effects were not observed in the subsequent reproductive toxicity test battery. The NOAEL for the chronic dog toxicity study was 1.92 mg/kg/d based on findings at higher exposures as described above. Based on Technosphere exposure this NOAEL provides an exposure margin less than the maximum anticipated daily human therapeutic exposure (99 mg Afrezza) based on AUC comparisons across species.

Conclusions:

The pharmacology and toxicology of insulin has been established over the last 90 years. Therefore the supporting nonclinical data for Afrezza have focused on the novel components of the inhalational Technosphere delivery system. A complete nonclinical development program of repeat-dose, genetic, reproductive/developmental, local tolerance, sensitization, immune toxicology and carcinogenicity studies have been performed. The results of these studies have suggested some potential for pulmonary irritation with Afrezza at maximum clinical exposures (99 mg Afrezza=TI =88.6 mg Technosphere + 10.4 mg insulin). This is based on minimal to mild respiratory irritation observed in rats and dogs following chronic exposure to Technospheres by inhalation at ≤2-fold higher exposures in animals relative to therapeutic exposure at the maximum clinical dose (99 mg Afrezza). These findings in test species did not have any functional significance on respiratory function. The respiratory irritation appeared to recover with discontinuation of Technosphere inhalation in animals. Evidence of pulmonary inflammation was not observed following chronic inhalational administration in rats and dogs, including lifetime exposure in rat. No evidence of lung neoplasia or pre-neoplastic signals was present in a lifetime rat carcinogenicity study or in a 6-month transgenic mouse carcinogenicity study following Afrezza exposure.

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1 Background

Throughout the clinical development program for TI inhaler there were modifications to 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), and CRL2 (dated 10/13/2013) are listed in Table 1. Table 1 also describes the bridging data used by the applicant and the related outcome.

Table 1 Summary of Key Background Information

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 response	Gen2	yes	Although Gen2 was tested in Phase 3 trials, the dosing regimen proposed in the label is different than what was tested in Phase 3 trials	

The applicant submitted 36 clinical pharmacology studies throughout the development of TI inhaler. These studies provided information on the relative bioavailability of Afrezza against subcutaneous insulin, dosing regimen for transfer from subcutaneous 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.

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.*"

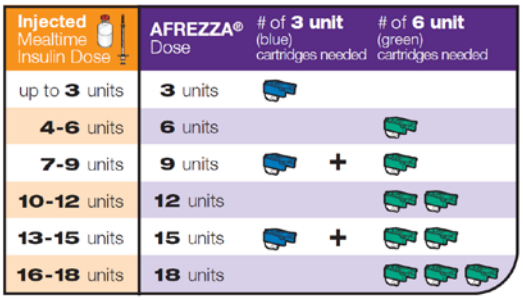

Figure 1: Afrezza dosage chart from the proposed label

However, note that the proposed dosing regimen and the dosing conversion factors 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.*"

***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-T1-176 and MKC-T1-177) 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 pharmacokinetic (PK) data (i.e., relative bioavailability estimates) to justify the proposed dosing conversion (Figure 2). However, FDA considers the corresponding pharmacodynamics (PD) effect to be equally or more important in evaluating the adequacy of the proposed dosing regimen because it is the PD effect that ultimately drives efficacy (i.e., HbA1c reduction). Considering this, we find 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).

The applicant also compares the overall mean daily prandial doses from the Phase 3 trial 171 in Type 1 diabetes mellitus (T1DM) to justify the proposed dosing (Figure 2). However, the approximation derived based on Phase 3 data makes several assumptions such as no differences in basal insulin dose and its effect between treatment groups, comparable titration between two arms, and a similar dose-response relationship for prandial insulin between treatment groups.

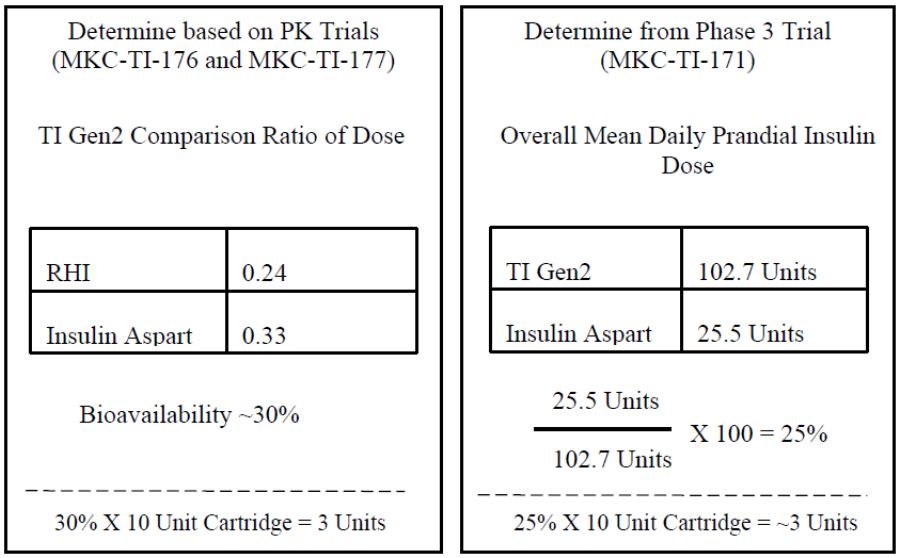

Figure 2 Summary of application's justification for the proposed dosing conversion

2.1 Assessment of Dosing Regimen Based on Clinical Pharmacology Data

The applicant conducted one dose-ranging study (i.e., study MKC-T1-176) 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 subcutaneous (SC) regular human insulin (15 U). In this study both PK and PD were assessed (Figure 3); however, in this section we only focus on PD data, and

PK data are discussed in section 3. In this clamp study, glucose infusion rate (GIR) was measured up to 240 minutes for Afrezza arms and up to 600 minutes for the subcutaneous insulin 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 is shown in Table 2.

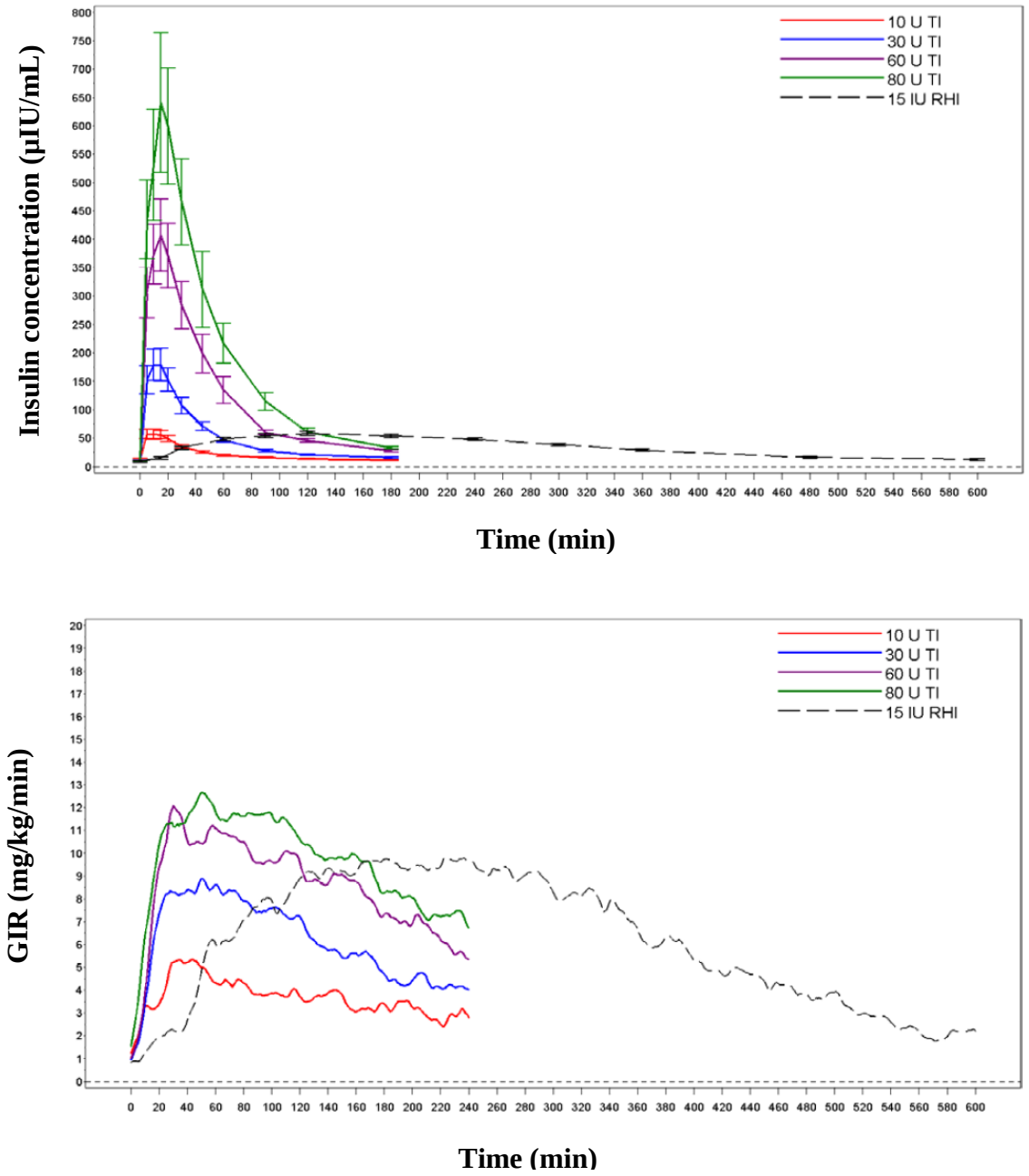

Figure 3 **Insulin concentration (upper) and GIR (lower) – time profiles in healthy subjects from study MKC-T1-176**

Table 2 Comparison of dosing conversion factors - estimation based on AUCGIR comparison vs. the proposed labeling

Dosing	Dose (U)	$AUCGIR_{0-240}$ (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	-
SC=subcutaneous insulin AUCGIR=area under the curve glucose infusion rate				

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

2.2 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 3), increase in PD (i.e., $GIRAUC_{0-240}$) was less than dose proportional (see Table 3). 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% intervals) and demonstrates that with an increase in median insulin AUC_{0-180} exposure from 7466 to 35261 µIU/mL*min (i.e., about 6.6 fold increase), median $AUCGIR_{0-240}$ only increased from 1542 to 2188 (i.e., 1.4 fold). Figure 5 is a scatter plot of insulin AUC_{0-180} vs. $AUCGIR_{0-240}$, which shows that (a) the variability in insulin exposure (AUC_{0-180}) for 60 and 80 U is high and (b) the PD response ($AUCGIR_{0-240}$) for these doses are largely overlapping. 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 subcutaneous insulin.

Table 3 Summary of Dose- $GIRAUC_{0-240}$ (Geometric mean)

Dose	10 U TI	30 U TI	60 U TI	80 U TI	Slope (90% CI)
N	32	32	32	32	
$GIRAUC_{0-240}$ (min*(mg/kg*min))	760.22	1342.52	1929.16	2188.60	0.512 (0.457, 0.567)
GIR_{max} (mg/kg*min)	7.52	11.20	14.41	15.48	0.352 (0.304, 0.401)

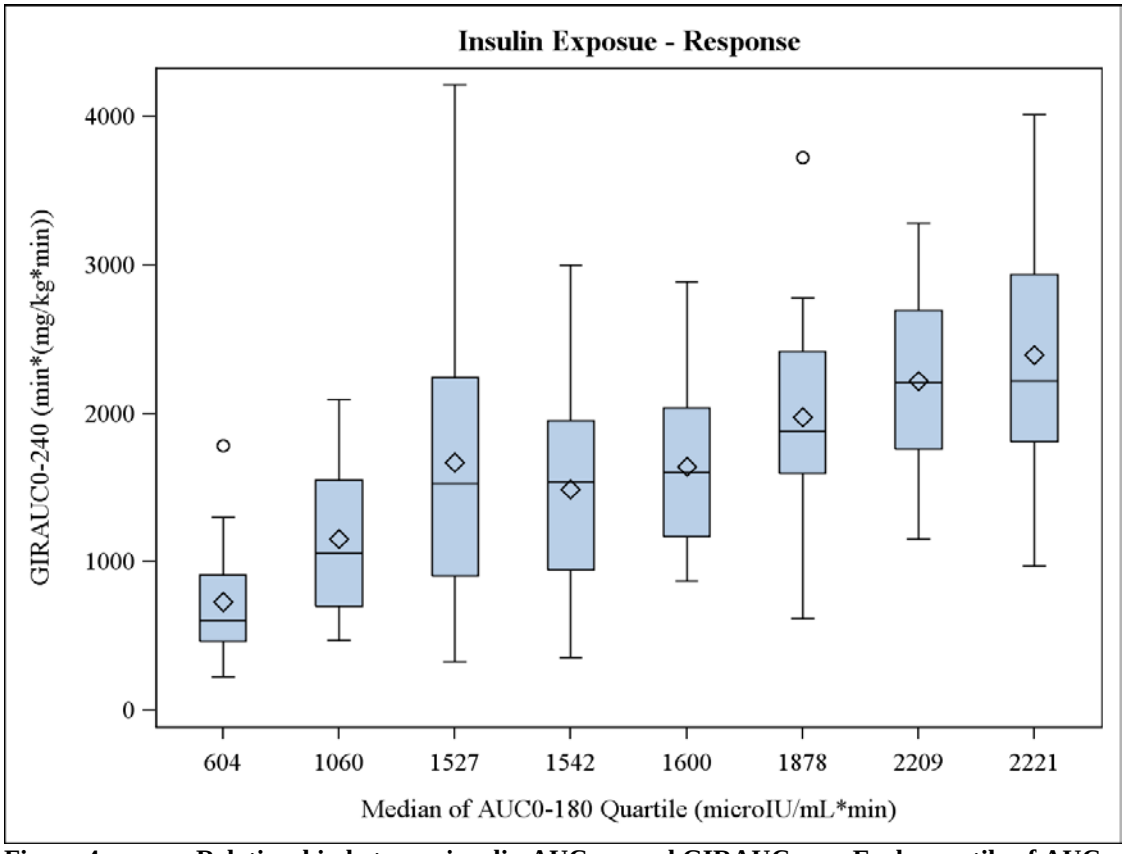

Figure 4 Relationship between insulin AUC_{0-180} and $GIRAUC_{0-240}$: Each quartile of AUC_{0-180} represents 12.5% interval (data source: Study MKC-TI-176)

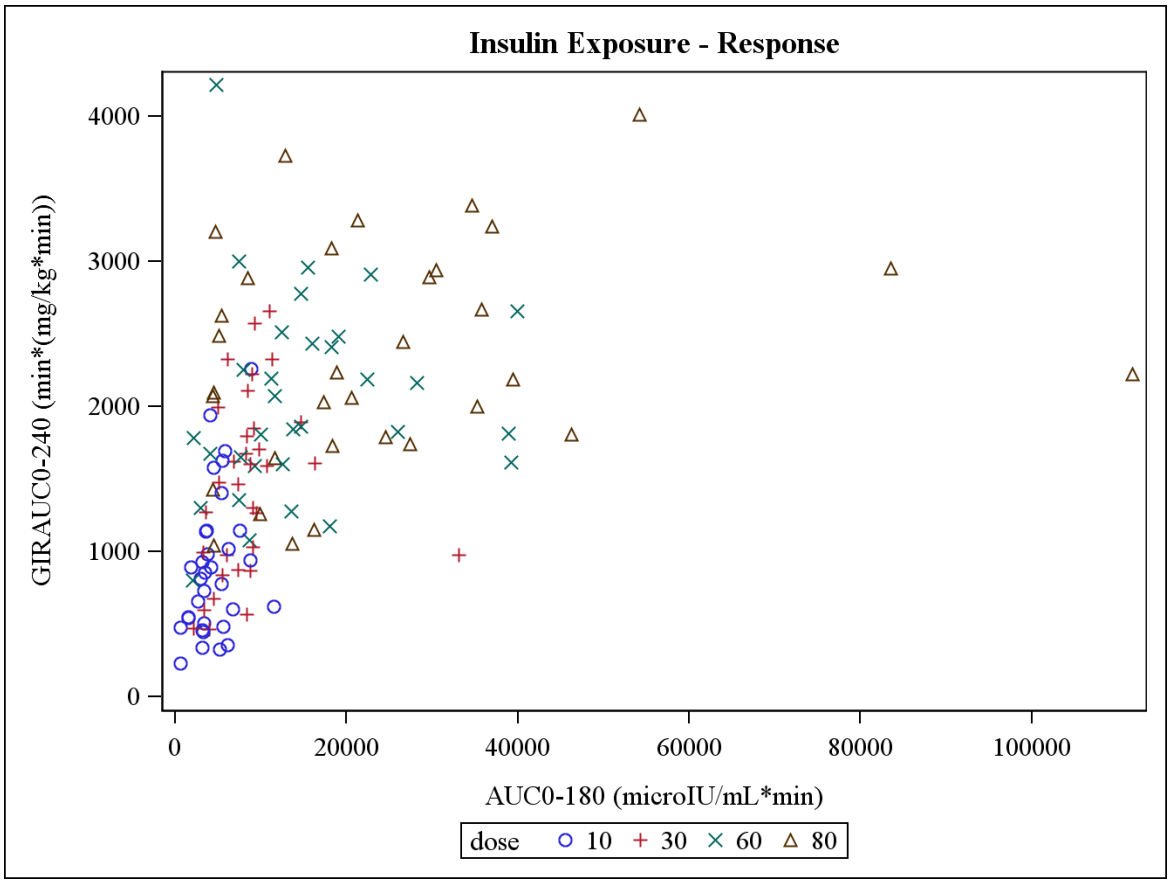

Figure 5 **Scatter plot for insulin $AUC_{0\text{-}180}$ vs.$GIRAUC_{0\text{-}240}$. (data source: Study MKC-TI-176)**

2.3 Assessment of PK Dose-Proportionality and Relative Bioavailability for Gen2Delivered 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_{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_{inf} and C_{max}, respectively, based on a power model[1]. PK profiles following Afrezza doses of 10, 30, 60 and 80 U are shown in Figure 3 of section 2.1.

Systemic exposures for insulin (i.e., insulin AUC) from Afrezza doses were compared with the systemic exposure for insulin from subcutaneous 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.

[1] Power model to test dose-proportionality: PK parameter (AUC or C_{max}) = a*$Dose^{slope}$

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

3 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 T1D subjects (n=12) comparing Gen2 delivered Afrezza insulin (20 U) with insulin lispro (8 U, rapid acting analog (RAA)). Time profiles for insulin concentrations (upper panel) and glucose infusion rate (lower panel) are shown in the Figure 6 and PK data are presented in Table 4.

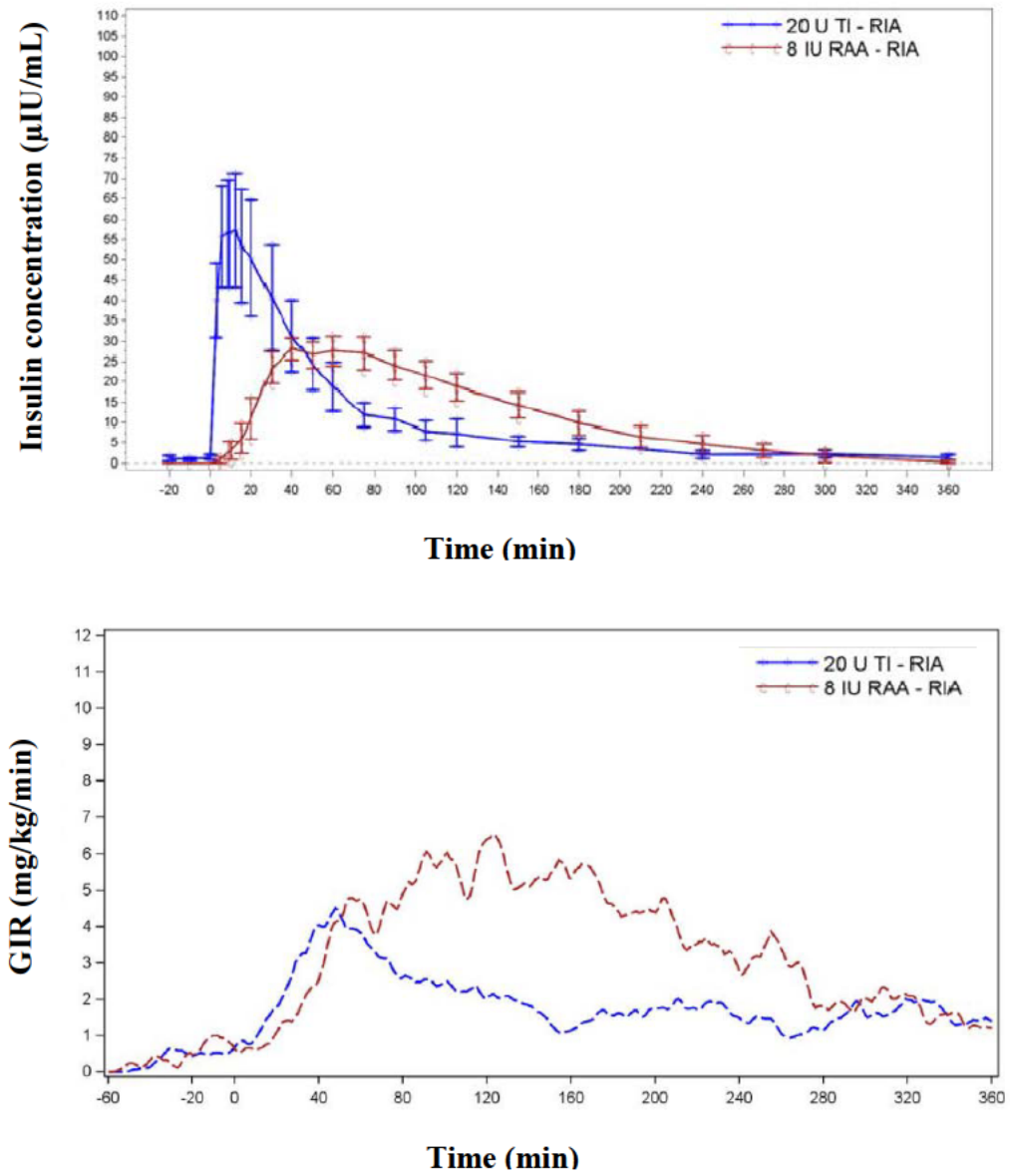

Figure 6: Insulin concentration (upper) and GIR (lower) – time profiles (TI – Gen2 delivered Afrezza, RAA –rapid acting analog insulin lispro)

Table 4: Summary of PK and PD parameters in T1D

PK	**Treatment**	**AUC_{0-360}**	**C_{max}**
	Afrezza	3684.9	60.8
	RAA	4341.9	36.0
PD	**Treatment**	**$AUCGIR_{0-360}$**	**GIR_{max}**
	Afrezza	522.8	6.1
	RAA	1007.2	9.4

As shown in Table 4, the relative bioavailability for Gen2 delivered insulin vs. insulin lispro (based on comparison of AUC_{360}) is about 33%. Relative PD effect for Gen2 delivered Afrezza is about 52% based on $AUCGIR_{240}$.

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, i.e., although insulin C_{max} for Afrezza is almost double the C_{max} for RAA, GIR_{max} for Afrezza is lower than RAA*
2. *PK comparison in this study may not provide meaningful information because the comparison is based on two different insulin molecules (i.e., regular human insulin for Afrezza and lispro). However, the 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. subcutaneous insulins might be different.*

4 Variability in Afrezza Insulin Pharmacokinetics and Pharmacodynamics

Between-subject Variability

Information on between-subject variability (BSV) in pharmacokinetics and pharmacodynamics of Gen2 delivered Afrezza insulin is obtained from the PK/PD Study in healthy subjects (MKC-TI-176). From the results shown in Table 5, it is evident that variability in PK parameters for Afrezza increased in a dose-dependent manner, with %CV of up to 90 to 103% for the 80U dose. Also the variability in PK parameters for Afrezza was higher than that observed for subcutaneous insulin. The route of administration and the need for administering multiple cartridges may in part explain this finding. The inhaler is breath-powered. For higher doses subjects need to inhale more than one cartridge to get the required dosage and possible differences in inhalation flow rates between actuations may introduce additional variability.

However, the trend for variability in PD parameters for Afrezza was opposite to the trend observed for the PK parameters, with decreasing variability at higher doses (Table 5). The relatively low variability for higher doses of Afrezza might be because of saturation in PD effect.

Table 5 Between-subject variability in PK and PD parameters (CV%) for Gen2 delivered Afrezza insulin (Study MKC-TI-176)

	Afrezza (Gen2)				Regular Human Insulin
	10 U	**30 U**	**60 U**	**80 U**	**15 U**
PK					
AUC_{0-180}	42.3%	61.1%	72.7%	89.6%	35.4%
C_{max}	69.9%	83.3%	81.4%	103.4%	32.2%
PD					
$AUCGIR_{0-240}$	56.7%	40.9%	34%	33.5%	36.9%
GIR_{max}	52.5%	42.7%	37.2%	34.5%	29.5%

Within-subject Variability

Assessment of within-subject variability (WSV) was not performed for Gen2 delivered Afrezza insulin. However, WSV was assessed for the MedTone Model C device in a replicated, crossover isoglycemic glucose clamp study in T2DM subjects (Study MKC-TI-00B2). WSV for Model C at the 48 U dose was found to be comparable to the variability observed for the subcutaneous insulin at 24 U dose.

Table 6 Within-subject variability (CV% [95% Confidence Interval]) in PK and PD parameters for MedTone Model C delivered Afrezza insulin (Study MKC-TI-00B2)

Parameter	**Afrezza MedTone C (48 U)**	**SC, Regular Human Insulin (24 U)**
PK		
$AUC_{0-120min}$	19.13 [11.32, 26.94]	27.12 [16.05, 38.19]
$AUC_{0-180min}$	18.21 [10.78, 24.64]	24.99 [14.79, 35.19]
$AUC_{0-540min}$	15.86 [9.39, 22.33]	14.68 [8.69, 20.67]
C_{max}	20.40 [12.07, 28.77]	29.22 [17.29, 41.25]
PD		
GIR $AUC_{0-120min}$	23.43 [13.86, 33.00]	39.22 [23.21, 55.23]
GIR $AUC_{0-180min}$	21.71 [12.85, 30.57]	33.41 [19.77, 47.05]
GIR $AUC_{0-540min}$	25.66 [15.18, 36.14]	18.10 [10.71, 25.94]
GIR_{max}	21.97 [13.00, 30.94]	17.32 [10.25, 24.39]

5 Clinical Pharmacology Findings from Previous Submissions

5.1.1 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_{max} 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_{max} 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_{max}
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_{max}
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, i.e., 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.

5.1.2 Insulin Exposure Following Multiple Doses (from the original submission)

The applicant evaluated insulin PK after multiple doses (7 days) in type 2 diabetes mellitus (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 nonasthmatic 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 in T2DM with and without asthma following multiple doses (Baseline-correction using previous concentrations)

	Visit 3 (1st dose)	Visit 4a (after 7 days)
$AUC_{0\text{-}6h}$ (min*mU/L)[b] (% CV) [b]	2583 (73.6)	3096 (83.1)
C_{max} (mU/L)[b] (% CV)[b]	31.8 (90.1)	38.5 (93.8)
T_{max} (min)	15	9

a: n=14; b: 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.

5.1.3 Intrinsic and Extrinsic Factors (from the original submission)

The 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. The 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 astmatics vs. nonasthmatics shows a decline in exposure by 57% (see Table 10).

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 anlaysis 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[#]**
COPD[*] (n=17 COPD; 19 non-COPD)	Insulin	AUC_{0-240} (mU*min/L)	2117	1933	1.1 (0.888, 1.352)
	FDKP	AUC_{0-240} (ng*min/mL)	16676	18821	0.89 (0.735, 1.067)
Asthma[**] (n=15 nonasthmatics, 5 asthmatic T2DM)	Insulin	AUC_{0-360} (mU*min/L)	2583[&] 3096[%]	1823[&] 1319[%]	0.71 0.43
	FDKP	AUC_{0-480} (ng*min/mL)	15903	6833	0.43
Smoking[***] (n=12 smokers, n=12 non-smokers T2DM)	Insulin	AUC_{0-480} (mU*min/L)	1677	2092	1.25
	GIR	AUC_{0-480} (mg*min/kg)	362	490	1.35
	FDKP	AUC_{0-480} (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 1st dose
%: after 7 days

In conclusion, the available data from clinical pharmacology studies for AFREZZ does not conclusively support 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 regular human insulin (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: In Afrezza program, 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 are considering a labeling recommendation suggesting that 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.

Reviewer's comment: Since there are insufficient data for assessment of impact of asthma and COPD on insulin exposures from clinical pharmacology perspective, it will be premature to consider dosing recommendations for coadministration with bronchodilators.

- The labeling proposed by the applicant for *Afrezza* for the specific populations (in the current submission) is compared with that for EXUBERA (from the approved label) in Table 11. Dosing recommendations for specific populations for Afrezza are yet to be finalized.

Table 11 Proposed labeling of *Afrezza* for specific populations compared to that of EXUBERA (internal memo)

	Afrezza	**EXUBERA**
Pediatric		In children (6–11 years) and adolescents (12–17 years) with type 1 diabetes, time to peak insulin concentration for EXUBERA was achieved faster than for subcutaneous regular human insulin, which is consistent with observations in adult patients with type 1 diabetes.
Geriatric		There are no apparent differences in the pharmacokinetic properties of EXUBERA when comparing patients over the age of 65 years and younger adult patients.
Gender		In subjects with and without diabetes, no apparent differences in the pharmacokinetic properties of EXUBERA were observed between men and women.
Race		A study was performed in 25 healthy Caucasian and Japanese non-diabetic subjects to compare the pharmacokinetic and pharmacodynamic properties of EXUBERA, versus subcutaneous injection of regular human insulin. The pharmacokinetic and pharmacodynamic properties of EXUBERA were comparable between the two populations.
Obesity		The absorption of EXUBERA is independent of patient BMI.
Renal	Exposure to the carrier was studied in patients with mild or moderate diabetic nephropathy (n=24) as compared with diabetic patients with normal renal function (n=12). The exposure ($AUC_{0\text{-}480\ min}$) of the carrier was 20% greater in patients with mild or moderate diabetic nephropathy. There is low potential for any accumulation of the carrier in patients with mild or moderate renal impairment.	The effect of renal impairment on the pharmacokinetics of EXUBERA has not been studied. Careful glucose monitoring and dose adjustments of insulin may be necessary in patients with renal dysfunction
Hepatic	No significant difference in exposure to the carrier was observed in patients with mild or moderate chronic liver disease (n=21) and patients with normal liver function (n=12) after a single dose of the carrier based on the primary PK parameter $AUC_{0\text{-}480\ min}$.	The effect of hepatic impairment on the pharmacokinetics of EXUBERA has not been studied. Careful glucose monitoring and dose adjustments of insulin may be necessary in patients with hepatic dysfunction
Pregnancy		The absorption of EXUBERA in pregnant patients with gestational and pre-gestational type 2 diabetes was consistent with that in non-pregnant patients with type 2 diabetes
Smoking	The overall pharmacokinetic profile of *Afrezza* in smokers (n=12) and non-smokers (n=12) was similar (AUC, C_{max} and T_{max}).	In smokers, the systemic insulin exposure for EXUBERA is expected to be 2 to 5 fold higher than in non-smokers. EXUBERA is contraindicated in patients who smoke or who have discontinued smoking less than 6 months prior to starting EXUBERA therapy. If a patient starts or resumes smoking, EXUBERA must be discontinued immediately due to the increased risk of hypoglycemia, and an alternative treatment must be utilized. In clinical studies of EXUBERA in 123 patients (69 of whom were smokers), smokersexperienced a more rapid onset of glucose-lowering action, greater maximum effect, and a greater total glucose-lowering effect (particularly during the first 2–3 hours after dosing), compared to non-smokers. Passive Cigarette Smoke In contrast to the increase in insulin exposure following active smoking, when EXUBERA was administered to 30 healthy non-smoking volunteers following 2 hours of exposure to passive cigarette smoke in a controlled experimental setting, insulin AUC and Cmax were reduced by approximately 20% and 30%, respectively. The pharmacokinetics of EXUBERA have not been studied in nonsmokers who are chronically exposed to passive cigarette smoke.
Asthma	In a study comparing *Afrezza* exposure in patients with (n=13) and without (n=12) asthma, there was an 18% lower systemic insulin exposure in patients with asthma compared with patients without. When these patients with asthma received a bronchodilator (short-acting beta-2 agonist) 5 minutes prior to administration of *Afrezza*, the systemic insulin exposure was comparable to that observed in healthy patients without asthma.	**Patients with Underlying Lung Diseases** The use of EXUBERA in patients with underlying lung disease, such as asthma or COPD, is not recommended because the safety and efficacy of EXUBERA in this population have not been established The use of EXUBERA is contraindicated in patients withunstable or poorly controlled lung disease, because of wide variations in lung function that could affect the absorption of EXUBERA and increase the

COPD	In a study comparing Afrezza exposure in patients with chronic obstructive lung disease (COPD; n=18) against patients without COPD (n=20), there were no statistically significant differences in systemic insulin exposure.	risk of hypoglycemia or hyperglycemia In a pharmacokinetic study in 24 non-diabetic subjects with mild asthma, the absorption of insulin following administration of EXUBERA, in the absence of treatment with abronchodilator, was approximately 20% lower than the absorption seen in subjects without asthma. However, in a study in 24 non-diabetic subjects with Chronic Obstructive Pulmonary Disease (COPD), the systemic exposure following administration of EXUBERA was approximately two-fold higher than that in normal subjects without COPD Administration of albuterol 30 minutes prior to administration of EXUBERA in non-diabetic subjects with both mild asthma (n=36) and moderate asthma (n=31) resulted in a mean increase in insulin AUC and C of between 25 and 50% compared to when EXUBERA was max administered alone
Respiratory Infections	The pharmacokinetics and pharmacodynamics of Afrezza were similar during and after resolution of a URI. No significant difference in exposure to insulin was observed in patients (n=20) treated with Afrezza who developed a URI during treatment.	

The blank fields in the table above indicate that no information was listed under those sections.

CLINICAL SUMMARY

EMDAC ADVISORY COMMITTEE MEETING
APRIL 1, 2014

Drug Established Name	Technosphere insulin inhalation powder
(Proposed) Trade Name	Afrezza
Therapeutic Class	Inhaled insulin
Applicant	MannKind
Formulation(s)	Inhalation powder (pre-metered)
Dosing Regimen	Dose-titrated prandial inhalation
Indication(s)	The treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia.
Intended Population(s)	Adults with Type 1 and Type 2 Diabetes Mellitus

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1 Introduction and Regulatory Background

1.1 Product Information

Afrezza is a drug-device combination product consisting of a dry powder formulation of recombinant regular human insulin [i.e., Technosphere Insulin (referred to as Afrezza TI)] and an 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).

Patients self-administer the insulin powder by oral inhalation. The insulin powder is pre-filled into cartridges packaged in blisters. Cartridges contain either 0.35 mg (10 units) or 0.7 mg (20 units) of insulin per cartridge. The patient uses the product by removing a cartridge from the blister package, inserting it into the inhaler, placing the inhaler in his/her mouth and inhaling the powder. The inhaler is breath-powered. Particle size distribution studies suggest delivery of insulin to the systemic absorption site (i.e., lung) is inhalation flow rate dependent (i.e., a decrease in particle size was observed increased inhalation).

1.2 Regulatory History

On March 31, 2009, MannKind Corporation submitted the original New Drug Application for Afrezza.

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

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

Another efficacy related issue identified in the Afrezza program arose from the unexpected results of a dose response study in patients with T2DM (Study 005). Insulin is a titratable

product and, in the clinical dosing range, increasing doses of insulin are expected to result in incremental glucose lowering. In this study, doses of insulin above 28 units did not result in incremental HbA1c lowering (see Table 2 below).

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

Product related safety issues identified in the review included tolerability (e.g., cough, irritation, throat paint) and pulmonary safety concerns (e.g., bronchospasm, and pulmonary function decline). These findings will be summarized in greater detail in the safety section of this document.

FDA issued a Complete Response letter on March 12, 2010, highlighting deficiencies related to efficacy, pulmonary safety and inhaler device related issues. Based on the efficacy results summarized above, FDA stated in the Complete Response letter that: *"these findings call into question the clinical utility of Afrezza to treat diabetes in an era where glycemic control has been established to reduce long-term complications of microvascular disease in both type 1 and 2 diabetes."*

At the End-of-Review meeting on June 9, 2010, the sponsor informed FDA of its plans to abandon the *MedTone* system and to submit a Complete Response to market Afrezza using an entirely new device (Gen-2 inhaler). At the meeting, the sponsor asserted that *in vitro* device performance studies and a PK study demonstrated the Gen2 and *MedTone* devices resulted in comparable delivery of the Afrezza drug product. The applicant was of the opinion that these studies were sufficient to permit reliance on efficacy and safety data derived with the *MedTone* C device to support approval of the Gen2 inhaler device.

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

A Complete Response on the re-submission was issued on 18 Jan 2011. The deficiencies were related to the lack of efficacy and safety data with the new device and to the inadequacy of

reliance on *in vitro* performance and single dose clinical pharmacology data to support approval of the Gen2 device.

In its decision FDA considered the following:

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

The information needed to resolve the deficiencies included two randomized, controlled phase 3 trials with the Gen2 device, one in patients with T1DM and the other in patients with T2DM. FDA requested that at least one of these trials should include a treatment group using the MedTone C inhaler so that a head-to-head comparison of the pulmonary safety data for the two devices could be obtained. FDA noted that these trials should be of sufficient duration to permit an adequate titration of study medication and that titration be followed by at least twelve weeks of relatively stable insulin doses to allow sufficient time for HbA1c to fully reflect the impact of the titration phase. FDA also noted these phase 3 trials with the Gen2 inhaler should ensure that appropriate titration of insulin doses occurs. For safety assessments, FDA asked for analysis of adverse events of interest in the Gen2 phase 3 trials including updated analyses of lung cancer cases, pulmonary safety (with pulmonary function testing), hypoglycemia, diabetic ketoacidosis, immunogenicity, eye events (given that there were numerically more cases of retinal detachment with Afrezza vs. comparator in the controlled phase 2/3 MedTone program), and device-related performance issues.

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

Note regarding nomenclature: In the sponsor's application, TI refers specifically to Technosphere insulin, the inhaled insulin powder. To improve readability of this document "TI" has been replaced by "Afrezza TI" in almost all instances with the exceptions of some tables. Afrezza TI across the program could have been delivered by any of the three devices used in development and where this is important the device is specifically referred to.

Efficacy: Type 1 Diabetes (MedTone C inhaler Trials)

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

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

This randomized, open-label trial enrolled patients with inadequately-controlled (HbA1c >7% to ≤11%) T1DM. At screening, most patients (85-90%) were using a fast-acting insulin with either an intermediate-acting insulin or long-acting insulin. Insulin dose titration was permitted throughout the treatment period and visits dedicated to insulin titration occurred during the first 10 weeks of the treatment period. Titration was to be based on results of 7-point meter glucoses obtained on any 3 days during the week immediately preceding the clinic visit. Part way through the trial, the sponsor started a "Glycemic Monitoring Program" that sent blinded summary HbA1c data for 451 patients to clinical sites on a monthly basis to provide investigators with information on how they were doing with respect to achieving glycemic goals.
The starting dose of Afrezza TI was based on the assumption that a 15 unit cartridge of Afrezza TI corresponds to 5 units of subcutaneous insulin. Afrezza TI was titrated in increments of 15 units up to a maximum dose of 90 units with meals.

The study was designed to have >90% power to show non-inferiority based on a margin of 0.4%, an HbA1c standard deviation of 1.2% and a 1-sided alpha of 0.025. A total of 590 patients were to be randomized to have 500 completers, assuming a 15% drop-out rate. A total of 539 patients were included in the primary efficacy analysis. Approximately 66% of the Afrezza TI-treated patients and 76% of the aspart-treated patients completed the trial. This differential dropout rate was predominantly driven by adverse events consistent with inadequate efficacy (e.g., hyperglycemia, blood glucose increased, diabetes mellitus inadequate control), which were reported as reasons for withdrawal in 7.6% of Afrezza TI-treated patients and 0.7% of aspart-treated patients. The high and differential dropout rate was also driven by other adverse events (excluding those suggestive of inadequate efficacy), which were reported in 6.6% of Afrezza TI-treated patients and 1.4% of aspart-treated patients.

As shown in Table 1, Afrezza TI was not non-inferior to insulin aspart because the upper bound of the 95% confidence interval for the HbA1c treatment difference was 0.404%, which is above the pre-specified non-inferiority margin of 0.4%. Similar results were obtained with various sensitivity analyses, including the completers analysis (of interest because of the high dropout rates), which had an upper bound of the 95% confidence interval for the HbA1c treatment difference of 0.45%. Furthermore, Afrezza TI is statistically worse (i.e., inferior) than insulin aspart because the lower bound of the 95% confidence interval for the HbA1c treatment difference was 0.1% (i.e., excludes 0%) for the primary efficacy analysis. Note that the mean treatment difference in HbA1c is small (~0.2%).

There was a treatment-by-gender interaction in this trial (p=0.01), which was not seen in the other phase 2/3 trials. For men, the mean change in HbA1c from baseline to Week 52 was 0.0% in the Afrezza TI treatment arm compared to -0.5% in the insulin aspart treatment arm. For women, the mean change in HbA1c from baseline to Week 52 was -0.2% in the Afrezza TI treatment arm and -0.3% in the insulin aspart treatment arm.

In the Afrezza TI treatment arm, the mean daily glargine dose increased from approximately 28 units at baseline to ~33 units by Week 8 and remained at ~33 units for the duration of the trial. In the aspart treatment group, the mean daily glargine dose increased from approximately 29 units at baseline to ~30 units by Week 12 and remained at ~30 units for the duration of the trial. Few patients in both treatment groups achieved HbA1c ≤7% at Week 52 based on the intent-to- treat analysis with last-observation-carried-forward (13.4% with Afrezza TI and 14.1% with insulin aspart).

An important limitation of the trial is that there was minimal titration of insulin doses during most of the treatment period. Had the insulins been better titrated, it is possible that there may have been even larger treatment differences favoring the aspart-treated group. For example, the mean total daily dose of insulin aspart increased from approximately 27 units at baseline to only ~31 units by Week 12 and remained at ~31 units for the duration of the trial. The mean total daily dose of Afrezza TI increased from approximately 80 units at baseline to ~150 units at Week 5 with little further change over the remainder of the treatment period. These mean doses of Afrezza TI are considerably lower than the maximum permitted dose of 270 units.

Note that in both treatment groups, the mean prandial insulin dose is similar to the mean glargine dose (150 units of Afrezza TI corresponds to approximately 40 units of subcutaneous insulin). Therefore, the prandial insulins comprised approximately 50% of the total daily insulin dose. Because patients with T1DM would not be expected to achieve adequate glycemic control on glargine alone, it may be reasonable to conclude that Afrezza (which comprised ~50% of the median total daily insulin dose) has demonstrated evidence of efficacy for some patients with T1DM.

Study 101 (12-week trial in type 1 diabetes)

Study 101 is not discussed in detail because it had a treatment period of only 12 weeks in duration and was likely underpowered for a non-inferiority assessment based on HbA1c as there were fewer than 60 patients per treatment group. In addition, HbA1c was a secondary endpoint with no prespecified non-inferiority margin (the primary endpoint was change in glucose following a standardized meal). Nonetheless, it is noteworthy that the HbA1c results in this study are consistent with the results in Study 009, with both trials showing that Afrezza TI + glargine is not non-inferior to insulin aspart + glargine. In Study 101, the upper bound of the 95% confidence interval for the treatment difference in HbA1c is 0.6% (Table 1), which exceeds the standard non-inferiority margin of 0.4% for insulins.

Interestingly, the within-group change from baseline in HbA1c was greater for both treatment groups in Study 101 than in Study 009 (Table 1). These larger within-group changes from baseline in HbA1c may be due to regression to the mean and are doubtfully related to the treatments themselves because there were modest, if any, changes in insulin doses over the course of the trial. For example, in the insulin aspart group (which had a mean change from baseline in HbA1c of 1%), the median daily glargine dose was 20 units at Week -3 (randomization visit) and 20 units at Week 8 and the median daily aspart dose was 20 units at Week -3 and 22 units at Week 8 (reliable data on insulin dose are only available up until Week

8 because patients switched back to their pre-treatment regimens immediately after the morning meal challenge at Week 12 and investigators did not reliably collect information on total daily insulin dose around the Week 12 visit). Similar findings with regard to total daily insulin doses were seen in the Afrezza TI treatment group.

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

Study	N	Baseline[1] mean ± SD	Change from baseline Adj. mean ± SE	Difference in adjusted mean change 95% CI	p-value
Study 009 (52-week phase 3 non-inferiority trial in type 1 diabetes)					
1-year data					
TI + glargine	277	8.4±0.9	-0.1±0.1	+0.2 (0.1, 0.404)	<0.01
Aspart + glargine	262	8.5±1.0	-0.4±0.1		
26-week data (post-hoc)					
TI + glargine	276	8.4±0.9	-0.1±0.1	+0.3 (0.1, 0.43)	<0.001
Aspart + glargine	261	8.5±1.0	-0.4±0.1		
Study 101 (12-week phase 2 trial in type 1 diabetes)					
TI + glargine	51	9.0±1.2	-0.8±0.1	+0.3 (-0.1, 0.6)	0.15
Aspart + glargine	56	8.9±1.2	-1.0±0.1		

[1]Baseline visit = Week -4 (screening visit) for Study 101 because TI was started during the 3-week (Week -3 to Week 0) substitution period to gradually replace subcutaneous prandial insulin in the TI + glargine group

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

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

The sponsor conducted six phase 2/3 trials in patients with T2DM, including two phase 2, double-blind, placebo-controlled trials (Study 0008 and Study 005) and three phase 3, open-label, active comparator-controlled trials (Study 014, Study 102, and Study 103). Study 026, another phase 2 trial, had only 15 patients in the control arm. This small sample size limits conclusions regarding efficacy. Therefore, this trial is not discussed here.

Note that the two phase 2 trials (studies 005 and 0008) used different formulations of Afrezza TI compared to the formulation used in the phase 3 trials and that these phase 2 formulations have not been bridged to the to-be-marketed formulation (no bioequivalence study and the changes to the manufacturing process are not biowaiverable). It is unknown whether these older formulations and the to-be-marketed formulation would yield similar efficacy findings.

<u>Study 005 (12-week placebo-controlled trial)</u>

This randomized, double-blind trial compared several doses of Afrezza TI (14 units, 28 units, 42 units, and 56 units) to placebo (Technosphere particles without insulin also called "TP") in patients with T2DM. Afrezza TI or TP were to be inhaled immediately prior to meals. To be eligible for enrollment, patients were to be treated for a minimum of 2 months with a stable dose of at least one oral anti-diabetic medication with or without glargine. The objective of the study was to show a relationship between Afrezza TI dose and glycemic response but the study design was not ideal. For example, within 1 month prior to the beginning of the 11-week treatment

period, all patients discontinued oral antidiabetic medications and glargine was initiated in the 80% of patients not already taking glargine. In addition, glargine could be titrated during the month preceding the 11-week treatment period or if there was inadequate glycemic control on the randomized dose of Afrezza TI. A more ideal trial design would have maintained stable doses of background anti-diabetic medications over the course of the trial. In addition, not all Afrezza TI treatment groups received 11 weeks of the randomized Afrezza TI dose. Instead, all patients randomized to Afrezza TI were initiated on 14 units that was force-titrated in weekly intervals by 14- unit increments to the goal Afrezza TI dose. Therefore, patients randomized to 56 units of Afrezza TI were treated for 1 week with 14 units, 1 week with 28 units, 1 week with 42 units, and only 8 weeks with 56 units. Therefore, the endpoint HbA1c value may not accurately reflect the full effect of the higher doses of Afrezza TI.

The placebo-corrected mean change in HbA1c was -0.5% with Afrezza TI 14 units and 0.7-0.8% with Afrezza TI 28-56 units, suggesting a plateau effect for pre-meal doses of Afrezza TI above 28 units (Table 2). This conclusion is limited by the trial design features described above. For example, there may have been more convincing evidence of a dose-response relationship had patients received the 56-unit dose for the entire 11-week treatment period.

The mean glargine dose increased in all treatment groups during the course of the trial. The mean glargine dose was 15 units at Week -1, 20 units at Week 0 and 27 units at Week 11 with comparable glargine doses across the treatment groups at the various timepoints. It is likely that the between-group changes from baseline in HbA1c would not be greatly affected by these somewhat comparable changes in glargine doses across treatment groups.

Study 0008 (12-week placebo-controlled trial)

This randomized, double-blind trial compared 12-weeks of treatment with Afrezza TI vs. TP in patients with T2DM. All enrolled patients were taking a stable dose of at least one oral anti-diabetic medication for at least 3 months. Patients assigned to Afrezza TI started 6 units with meals that was then titrated in increments of 6 units up to a maximum permitted dose of 48 units with meals. As shown in Table 2, the mean placebo-corrected reduction in HbA1c with Afrezza TI was -0.4% (95% confidence interval -0.6, -0.1; $p<0.01$). Of note, mean doses of Afrezza TI were 6 units at Week 0, 20 units at Week 4 and approximately 30 units at Weeks 8 and 12. Because the treatment period was only 12 weeks, this uptitration of Afrezza TI would not be fully reflected in the endpoint HbA1c, which may have resulted in underestimation of the treatment effect.

Study 014 (24-week open-label trial of Afrezza TI + glargine vs. insulin aspart + glargine)

This randomized, open-label, trial was conducted exclusively in Russia and compared 24-weeks of treatment with Afrezza TI + glargine vs. insulin aspart + glargine in patients with T2DM. All enrolled patients were to be taking subcutaneous insulin for at least 3 months prior to study entry. At Week -3, patients discontinued all anti-diabetic medications and initiated glargine 10 units or 20 units at bedtime. Aspart was substituted for previous prandial insulin. During these 3 weeks, glargine could be titrated weekly at the investigator's discretion based on fasting glucose

values. At Week 0, patients began pre-meal Afrezza TI (n=151) or insulin aspart (n=158). Afrezza TI-treated patients started 15 units with meals that could be titrated to a maximum of 60 units with meals. Aspart-treated patients started 4-8 units with meals and were titrated in increments of 2-4 units. Titration of both Afrezza TI and aspart occurred at the investigator's discretion based on clinic or home blood glucose monitoring data. Approximately 80% of Afrezza TI-treated patients and 97% of aspart-treated patients completed the 24-week treatment period. This differential dropout rate is driven predominantly by adverse events (10% with Afrezza TI – with more than one-half of these due to cough – and 0% with aspart) and by patient withdrawal of consent (6% with Afrezza TI vs. 0% with aspart).
Study 014 was designed as an equivalence trial. The sponsor specified that equivalence would be established if the lower bound of the 95% confidence interval for the treatment difference in HbA1c was greater than -0.4% and the upper bound was less than 0.4%. FDA also conducted a non-inferiority analysis using the standard margin for insulins of 0.4%.

Based on the sponsor's equivalence definition, the two treatment groups were not comparable using the intent-to-treat population with last-observation-carried forward. The sponsor concluded equivalence based on the intent-to-treat population without last-observation-carried forward. However, the FDA statistical reviewer noted that this analysis was biased because it excluded patients who had some missing data even though available data from these patients could contribute to the treatment estimates.

Based on a non-inferiority analysis, the FDA statistical reviewer noted that Afrezza TI add-on to glargine was not non-inferior to insulin aspart add-on to glargine because the upper bound of the 95% confidence interval for the HbA1c treatment difference was 0.6%, which is above the pre-specified non-inferiority margin of 0.4% (Table 2). Similar results were obtained using the completers analysis, which yielded an upper bound of the 95% confidence interval for the HbA1c treatment difference of 0.5%. In addition, Afrezza TI was statistically worse than insulin aspart because the lower bound of the 95% confidence interval for the HbA1c treatment difference for the intent-to-treat population using last-observation-carried-forward was 0.1% (i.e., excludes 0%).

The median total daily dose of Afrezza TI increased from 45 units at baseline to 135 units at Week 24. The median total daily dose of aspart increased from 22 units at baseline to 24 units at Week 24. In both treatment groups, the median glargine dose increased from 30 units at baseline to 35 units at Week 20. However, at Week 24, the median glargine dose was 40 units in the Afrezza TI group and 34 units in the aspart group. Because the glargine dose is comparable in both treatment groups for the majority of the treatment period, it may be reasonable to conclude that the between-group difference for HbA1c is not likely impacted substantially by the changes in glargine dose towards the end of the treatment period. However, the within-group change from baseline in HbA1c (e.g., reduction of 0.9% with Afrezza TI and reduction of 1.3% with aspart) likely overestimates the treatment effect of Afrezza TI and aspart because part of these reductions is driven by uptitration of the glargine dose both during the 3-week run-in period and during the 24- week treatment period.

Note that Afrezza TI was statistically worse than aspart even though the median aspart dose did not change appreciably (22 units at baseline vs. 24 units at Week 24) whereas the Afrezza TI dose increased 3-fold from 45 units at baseline (equivalent to ~12 subcutaneous units according to the sponsor) to 135 units at Week 24 (equivalent to ~36 subcutaneous units).

About 25% of Afrezza TI-treated patients and 33% of aspart-treated patients achieved HbA1c ≤7%.

At endpoint, the median Afrezza TI dose comprised ~50% of the median total daily insulin dose; however, it is not possible to determine from this trial the extent of incremental efficacy contributed by Afrezza TI over-and-above the efficacy resulting from uptitration of the glargine dose.

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

This multinational, randomized, open-label, trial compared 52 weeks of treatment with Afrezza TI + glargine vs. twice-daily NovoLog Mix 70/30 in patients with T2DM. To be eligible for enrollment, patients were to be on insulin with no more than 3 injections per day and a total daily insulin dose <1.4 units/kg. Oral anti-diabetic medications were permitted except for insulin secretagogues (sulfonylureas, glinides) and alpha glucosidase inhibitors. Doses of all background anti-diabetic medications were to be stable during the 6 weeks prior to screening.

For patients assigned to Afrezza TI, 50% of the total daily pre-randomization insulin dose was replaced with Afrezza TI and the remaining 50% was replaced by glargine. Afrezza TI was then uptitrated in 15-unit increments up to a maximum dose of 90 units with meals. Glargine was titrated based on fingerstick fasting glucoses. For patients randomized to NovoLog Mix 70/30, the initial dose of NovoLog Mix 70/30 depended on the type and doses of insulin used pre-randomization.

Although the protocol contained fasting and post-prandial glycemic goals for investigators to target, titration was only prioritized early during the trial. The protocol stated that the insulin dose was titrated during the first 10 weeks of the treatment period with 3 telephone visits between Weeks 4 and 14 to further titrate the dose, if needed. Because this was a 52-week trial, titration should have been optimized until Week 40 (3 months prior to the endpoint HbA1c measurement).

Approximately 65% of the Afrezza TI-treated patients and 72% of the NovoLog Mix 70/30-treated patients completed the trial. This differential dropout rate was predominantly driven by patient withdrawal of consent (11.1% of Afrezza TI-treated patients and 8.2% of NovoLog Mix 70/30-treated patients) and by adverse events (excluding those suggestive of inadequate efficacy), which were reported in 9.6% of Afrezza TI-treated patients and 2.9% of NovoLog Mix 70/30-treated patients. Withdrawal due to adverse events suggestive of lack of efficacy (e.g., hyperglycemia, blood glucose increased, diabetes mellitus inadequate control) occurred in 4.2% of Afrezza TI-treated patients and 2.9% of NovoLog Mix 70/30-treated patients.

Afrezza TI + glargine was non-inferior to twice daily NovoLog Mix 70/30. The mean treatment difference for change from baseline in HbA1c was 0.1% (favoring NovoLog Mix 70/30) with an upper bound of the corresponding 95% confidence interval of 0.3%, which is less than the pre-specified margin of 0.4%. The completers analysis (of interest because of the high dropout rates) yielded similar results. The two treatment groups had superimposable HbA1c curves over time. Most of the reduction in HbA1c occurred during the first 14 weeks of the trial, which is consistent with the timing of titration.

Approximately 20% of Afrezza TI + glargine-treated patients and 23% of NovoLog Mix 70/30-treated patients achieved HbA1c ≤7% at Week 52 (intent-to-treat with last-observation carried forward).

In the Afrezza TI group, the mean dose of glargine increased from approximately 32 units at baseline to 44 units at Week 10 and 47 units at Week 52. The Afrezza TI mean total daily dose increased from approximately 80 units at baseline to ~185 units by Week 10 and ~198 units by Week 52. The NovoLog Mix 70/30 mean total daily dose was approximately 60 units at baseline, 80 units by Week 10, and 88 units by Week 52. Therefore, most of the increase in the insulin doses occurred during the first 10 weeks of the trial.

Of note, the glargine dose of 47 units at Week 52 is lower than the dose of the intermediate-acting-component of NovoLog Mix 70/30 at Week 52 (70% of 88 units or 62 units). The Afrezza TI dose of 198 units at Week 52 is approximately equivalent to ~50 units of subcutaneous insulin and is higher than the aspart component of NovoLog Mix 70/30 (30% of 88 units or 26 units). Therefore, the total daily dose of insulin at Week 52 is ~100 units in the Afrezza TI group and 88 units in the NovoLog Mix 70/30 group. Therefore, it appears that non-inferiority of Afrezza TI + glargine to NovoLog Mix 70/30 was established in the setting of a higher prandial insulin dose in the Afrezza TI group with a lower dose of glargine compared to the dose of the intermediate-acting component of NovoLog Mix 70/30. This provides reassurance that the non-inferiority finding is driven by Afrezza TI and not by glargine.

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

This randomized, open-label trial enrolled patients with T2DM and inadequate glycemic control (HbA1c 7.5-11%) on a stable dose (no change within the preceding 6 weeks) of metformin (≥1000 mg/day) and at least one-half the maximum-recommended dose of an insulin secretagogue (either sulfonylurea or glinide). No other anti-diabetic therapy was permitted.

Patients were randomized to 12 weeks of continued treatment with the secretagogue+metformin (n=170) or Afrezza TI + metformin (i.e., replacement of the insulin secretagogue with Afrezza TI; n=175) or Afrezza TI alone (i.e., discontinuation of the secretagogue and metformin and initiation of Afrezza TI; n=183). This treatment period was then followed by a 12-week non-randomized treatment period, which is not discussed in this document.

Patients randomized to a Afrezza TI-containing regimen started Afrezza TI at 15 units per meal and titrated, as needed, to a maximum dose of 90 units with meals. The protocol permitted adjustments of the metformin and insulin secretagogue doses.
Note that this study design is not ideal. Background anti-diabetic therapy should have remained constant and the controlled treatment period should have been longer (e.g., 24 weeks) to allow sufficient time for titration of Afrezza TI to be fully reflected in the endpoint HbA1c measurement.

The completion rate for the 12-week treatment period was 68% with Afrezza TI+metformin, 73% for Afrezza TI alone, and 89% for secretagogue+metformin. The sponsor reviewed the reasons for discontinuation and concluded that the premature discontinuations were predominantly driven by lack of efficacy (18% with Afrezza TI+metformin, 12% with Afrezza TI alone, and 1.2% with secretagogue+metformin) and patient withdrawal of consent (7% with Afrezza TI+metformin, 7% with Afrezza TI alone, and 6% with secretagogue+metformin).

The primary objective was to show superiority of Afrezza TI+metformin vs. secretagogue+metformin with respect to change in HbA1c from baseline to Week 12. Substitution of Afrezza TI for secretagogue and continued treatment with metformin was not superior to continued treatment with secretagogue+metformin (p=0.51). The mean reduction from baseline in HbA1c was -0.7% in the Afrezza TI+metformin group compared to -0.8% in the secretagogue+metformin group. The sponsor did not specify a non-inferiority margin. However, the FDA statistical reviewer noted that Afrezza TI+metformin was non-inferior to secretagogue+metformin when the standard margin of 0.4% for insulins is used (the upper bound of the 95% confidence interval for the treatment difference in HbA1c is 0.3%). Non-inferiority (and lack of superiority) was also shown when the completers population was used.

Note that the Afrezza TI alone group had a mean increase in HbA1c of 0.2% from baseline to Week 12. This is not necessarily surprising because two anti-diabetic medications were replaced by a single anti-diabetic medication in this treatment arm.

The sponsor calculated the median doses of study medication during Weeks 1-4, 5-8, and 9-12. In the Afrezza TI alone group, the median total daily Afrezza TI dose increased from ~100 units during Weeks 1-4 to ~200 units during Weeks 4-8, and ~240 units during Weeks 8-12.The metformin+ secretagogue arm had relatively stable doses of metformin (~2,000 mg daily) and insulin secretagogue throughout the treatment period, making it less likely that dose increases of the oral agents contributed to greater efficacy in this treatment group. In the Afrezza TI+metformin arm, the median dose of metformin was ~1700 mg during Weeks 1-4 and 2000 mg during Weeks 4-12, and the median daily dose of Afrezza TI was ~80 units during Weeks 1-4, 160 units during Weeks 4-8, and 190 units during Weeks 8-12.

Note that the trial design and implementation limits conclusions with respect to lack of superiority and the claim of non-inferiority. For example, for one-third of the treatment period, the Afrezza TI+metformin group had a lower median metformin dose (1700 mg) than the metformin+secretagogue group (2000 mg). In addition, the full effects of Afrezza TI titration were not reflected in the endpoint HbA1c measurement (titration mostly occurred during the

preceding 4-8 weeks). These findings may have contributed to the inability of Afrezza TI+metformin to show superiority against metformin+secretagogue. Also, the trial should not have compared a newly prescribed Afrezza TI regimen to continued treatment with metformin+insulin secretagogue. Patients newly starting the comparator medications would be expected to have an initial reduction in HbA1c whereas patients continuing the comparator medications may have stable or slowly increasing HbA1c values, making Afrezza TI appear more favorable than it otherwise is. This may limit a conclusion of non-inferiority.

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

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

Study	N	Baseline mean±SD	Change from baseline Adj. mean ± SE	Difference in adj. mean change with 95% CI	p-value
Study 005 (11-week phase 2, double-blind, placebo-controlled, forced-titration)					
TI 14 units	43	8.9±1.4	-0.3±0.1	-0.5 (-1.0, 0.0)	0.04
TI 28 units	43	8.6±1.4	-0.6±0.1	-0.8 (-1.3, -0.3)	<0.001
TI 42 units	41	8.7±1.2	-0.5±0.2	-0.7 (-1.2, -0.2)	<0.01
TI 56 units	42	8.8±1.2	-0.6±0.2	-0.8 (-1.3, -0.3)	<0.001
Placebo	41	8.7±1.3	0.2±0.2		
Study 0008 (12-week phase 2, double-blind, placebo-controlled)					
TI	58	7.9±1.2	-0.7±0.1	-0.4 (-0.6, -0.1)	<0.01
Placebo	61	7.8±1.1	-0.3±0.1		
Study 014 (24-week phase 3, open-label, with aspart + glargine comparator)					
TI + glargine	150	8.9±1.1	-0.9±0.1	+0.4 (0.1, 0.6)	<0.01
Aspart + glargine	155	9.0±1.3	-1.3±0.1		
Study 102 (52-week phase 3, open-label with NovoLog Mix 70/30 comparator)					
TI + glargine	302	8.7±1.1	-0.6±0.1	+0.1 (-0.1, 0.3)	0.16
BID NovoLog Mix 70/30	316	8.7±1.1	-0.7±0.1		
Study 103 (12-week phase 3, open-label comparison of TI + metformin to secretagogue + metformin					
TI alone	176	8.9±1.0	0.2±0.1	-	-
TI + metformin	169	9.0±1.0	-0.7±0.1	+0.1 (-0.1, 0.3)[1]	0.51
Secretagogue + metformin	162	8.9±0.9	-0.8±0.1		
[1]TI+metformin vs. secretagogue+metformin; study was designed to demonstrate superiority between these two treatment groups					

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

1.3 Important Safety Consideration for Inhaled Insulin Products

Lung Cancer Signal with Exubera

Exubera (Insulin Human [rDNA origin] Inhalation Powder) was approved by the FDA in January 2006 to improve glycemic control in adults with type 1 and type 2 diabetes. Exubera was later withdrawn by the sponsor (Pfizer) due to lower than expected sales. Because Exubera directly deposits insulin in the lung and insulin is a growth factor, there is a theoretical concern

for development of lung cancer with long-term treatment. At the time of the NDA filing in 2006, there was a known imbalance in lung cancers in Exubera-exposed participants in clinical trials.

To further assess lung cancer risk, the sponsor conducted a follow-up study (referred to as FUSE: An Observational Follow up Study of Patients Previously Enrolled in Exubera Controlled Clinical Trials) of participants who had been exposed to Exubera and comparison medications in pre-approval clinical trials and to standard of care after trial completion. In July 2012, FDA received the final study report for the FUSE Study. Significant imbalances in lung cancer mortality (6 cases in 12,605.9 Patient-Years (PYs) in the Exubera group and 2 cases in 11,802.5 PYs in the comparator group, Incidence Density Ratio: 2.81; 95% CI: 0.50-28.46) and lung cancer incidence (12 cases in 11,180.7 PYs in the Exubera group and 3 cases in 10,467.9 PYs in the comparator group, IDR: 3.75; 95% CI: 1.01-20.68) were seen.

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

Decline in Pulmonary Function with Exubera:

Another safety concern identified in the Exubera program of relevance is that Exubera-treated patients had a greater mean reduction in forced expiratory volume in 1 second (FEV1) and in diffusing capacity of the lung for carbon monoxide (DLCO) compared to control. This reduction occurred within the first few weeks of use but the mean treatment difference (~40 mL favoring comparator) persisted over 2 years of study. Based on these findings, the Exubera package insert recommended that patients undergo pulmonary function testing prior to initiating Exubera, after 6 months of treatment, then annually thereafter. Exubera was not recommended if the baseline FEV1 or DLCO was <70% predicted. Discontinuation of Exubera was recommended if there was a confirmed decline in FEV1 ≥20%.

Other Issues from the Exubera Clinical Development Program

• Insulin antibodies were increased in Exubera-treated patients compared to those only receiving subcutaneous insulin but no clinical consequences were identified.
• Efficacy and safety were not established in patients with underlying lung disease. Therefore, Exubera was not recommended for use in this patient population.
• Bronchospasm was reported as a serious adverse event in 1 (0.1%) Exubera-treated patient.
• Smokers had a 2-5-fold higher systemic insulin exposure compared to non-smokers

The Exubera program consisted of 7 phase 3 trials (two in T1DM and five in T2DM). The phase 3 trials were powered to rule out a non-inferiority margin of 0.5% for the treatment difference in HbA1c. Use of this less stringent margin did not ultimately affect approvability because in these trials Exubera was able to meet the 0.4% non-inferiority margin that is used by FDA for insulin trials.

Exubera was discussed at an advisory committee meeting where most (7 vs. 2) panel members agreed that it should be approved for the treatment of type 1 and type 2 diabetes. One of the

panel members who voted against approval raised concerns about how patients and healthcare providers will be adequately trained on the correct use of the device. The other panel member who voted against approval raised the need for more data to support pulmonary safety.

2. Description of Individual Studies/Clinical Trials

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

2.1. Information pertinent to both studies 171 and 175

Afrezza Dosing:

For both trials Afrezza dosing was as follows:

Timing of Administration

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

Conversion of "Afrezza units" to "subcutaneous units"

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

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

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

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

Afrezza Starting Dose

In trial 171 subjects who were randomized to Afrezza TI-Gen2C treatment group transferred to Afrezza TI Inhalation Powder as shown in Table 3.

Table 3 – Afrezza TI Dose Conversion for the Gen2 Inhaler

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

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

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

Prandial Insulin Titration

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

Afrezza prandial dose titration

Subjects were required to adhere to the subject-driven forced-titration algorithms for their inhaled prandial insulin treatment. During the first 12 weeks of the 24-week treatment phase of each study subjects titrated their study drug doses based on 7-point SMBG level determinations, according to the dosing guidelines shown in Table 4.

Table 4 – Recommended Afrezza TI Dose Adjustments for Gen2

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

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

Dose titration for the MedTone inhaler was similar except that <110 mg/dL=decrease dose by15 U Afrezza TI, and so on.

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

- Subjects with a 90-minute PPG level ≥ 180 mg/dL (10.0mmol/L) were to take a supplemental (after-meal) 10 U Gen2 or 15 U MedTone dose of Afrezza TI. Subjects who developed more

than 2 episodes of hypoglycemia after taking supplemental doses of Afrezza TI were to be instructed not to take additional supplemental doses of Afrezza TI and consult with the PI.

- Subjects who achieve 90-minute PPG levels of ≥ 110 mg/dL (6.1 mmol/L) to < 160 mg/dL (8.9 mmol/L) for a given meal (breakfast, lunch, or dinner), but have 2 out of 3 pre-prandial BG levels ≥ 160 mg/dL (8.9 mmol/L) for the subsequent SMBG 7-point measurement (before lunch, dinner, or bed time), were to take a supplemental dose of Afrezza TI on a regular basis 90 minutes after the start of the meal. If a regular supplemental dose was added, the mealtime insulin dose could be reduced at the PI's discretion.

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

During the second 12 weeks of the treatment phase, the study drug doses were kept stable unless a change was required for the safety of the subject. Subjects who had 90-minute PPG levels ≥180 mg/dL (10.0 mmol/L) were instructed to take a 10 U supplemental after-meal dose of study treatment at the time of the PPG reading (i.e., same day and time).

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

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

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

Afrezza maximal dose

The maximal recommended total daily dose of Afrezza TI was to be 6 U/kg bodyweight of Afrezza TI as delivered by the MedTone inhaler, or 4 U/kg body weight as delivered by the Gen2 inhaler (e.g., for a 75 kg adult, the maximum daily dose was 450 U delivered by MedTone

and 300 U delivered by Gen2). The total daily dose could be divided between different time points (different meal times and multiple dosing times for each meal). There was no maximum dose per meal.

Safety Assessments pertinent to both studies:

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

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

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

- Selected clinical laboratory evaluation included routine hematology, chemistry including liver tests, lipids, and urinalysis) (shift tables and descriptive statistics).

- Vital signs and 12-lead ECGs that were locally read were obtained.

- In addition to TEAE capture, for both phase 3 studies, safety parameters of special interest included: pulmonary function tests (PFTs), hypoglycemic events, and anti-insulin antibodies ([IAB] anti-insulin immunoglobulin G concentration). PFTs are discussed separately in the pulmonary section of the backgrounder. Hypoglycemia and IABs are discussed here.

Hypoglycemia definitions

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

Mild or moderate hypoglycemia was defined as a subject who experienced:
- SMBG levels <70 mg/dL AND/OR
- Symptoms of hypoglycemia relieved by self-administration of carbohydrates

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

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

Anti-insulin antibodies

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

Statistical Considerations Pertinent to Both Studies:

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

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

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

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

2.2 Study 171

(Afrezza TI + basal insulin vs. insulin aspart + basal insulin)

Title:

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

Sites:

91 principal investigators at 89 study sites in 4 countries (United States [US], Russia, Ukraine, and Brazil) screened 1 or more subjects in this study.

Study Objective:

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

Design:

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

1. Subcutaneous (SC) insulin aspart in combination with SC basal insulin
2. Afrezza TI administered using the Gen2 inhaler in combination with SC basal insulin (Afrezza TI Gen2)
3. Afrezza TI administered using the MedTone inhaler in combination with SC basal insulin (Afrezza TI MedTone)

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

Reviewer's comment: Trial 171 was designed to address the deficiency listed in the Cycle 2 Complete Response letter that one of the phase 3 studies with the Gen2 inhaler should include a MedTone arm so that pulmonary safety of the two inhalers could be directly

compared. The trial was not designed to directly compare the efficacy of Afrezza TI using the two devices. This approach was agreed upon at the Cycle 2 End-of-Review meeting held 4 May 2011.

Subjects:

Key Inclusion Criteria:

1. Men and women ≥18 years of age
2. Clinical diagnosis of type 1 DM for at least 12 months
3. Body mass index (BMI) ≤38 kg/m^2
4. Stable dose of basal/bolus insulin therapy for at least 3 months with an FPG consistently <220 mg/dL
    - Basal insulin included neutral protamine Hagedorn (NPH) insulin, insulin glargine, or insulin detemir
    - Bolus insulin was defined as 2 to 4 doses of regular human insulin or rapid-acting analog at meals
    - Subjects who were using PreMix insulin at least twice daily were allowed
5. HbA1c ≥7.5% and ≤10.0%
6. Fasting C-peptide ≤0.30 pmol/mL
7. Nonsmokers for the preceding 6 months
8. Met prespecified pulmonary function test cutoffs based on the Third National Health and Nutrition Examination Survey (NHANES III)

Key Exclusion Criteria:

1. Total daily insulin dose ≥2 IU/kg/day.
2. History of insulin pump use within 3 months of Screening or use of continuous glucose monitor (CGM) within 6 weeks of Screening.
3. History of use of pramlintide, oral antidiabetic drugs (OADs), or inhaled insulin in the previous 6 months.
4. Two or more unexplained severe hypoglycemic episodes within 3 months of Screening or an episode of severe hypoglycemia between Visit 1 and Visit 2. Unexplained refers to episodes of severe hypoglycemia that are not related to a dosing error, lack of or a change in meal size, or related to additional/unanticipated exercise.
5. Any hospitalization or emergency room visit due to poor diabetic control within 6 months of Screening, or hospitalization or emergency room visit due to poor diabetic control between Visit 1 and Visit 2.
6. Severe complications of DM, in the opinion of the PI, including symptomatic autonomic neuropathy; disabling peripheral neuropathy; active proliferative retinopathy; nephropathy with renal failure, renal transplant, or dialysis; non-traumatic amputations due to gangrene; or vascular claudication.
7. Allergy or known hypersensitivity to insulin or to any of the drugs to be used in the study, or a history of hypersensitivity to Afrezza TI or to drugs with a similar chemical structure.
8. History of recent blood transfusions (within previous 3 months), hemoglobinopathies, or any other conditions that affect HbA1c measurements.

9. History of chronic obstructive pulmonary disease (COPD), asthma, or any other clinically important pulmonary disease
(e.g., pulmonary fibrosis), or use of any medications for these conditions.
10. Any clinically significant radiological findings on screening chest x-ray.
11. Active respiratory infection within 30 days before Screening.
13. Current or previous chemotherapy or radiation therapy that could have resulted in pulmonary toxicity; treatment with amiodarone within 12 weeks of Screening.
14. Use of medications for weight loss (e.g., sibutramine, orlistat) within 12 weeks of Screening
15. Clinically significant abnormalities on Screening laboratory evaluation or chest x-ray.
16. Women who were pregnant, lactating, or planning to become pregnant during the clinical study period; women of childbearing potential not practicing adequate birth control.

Study Procedures and Visits:

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

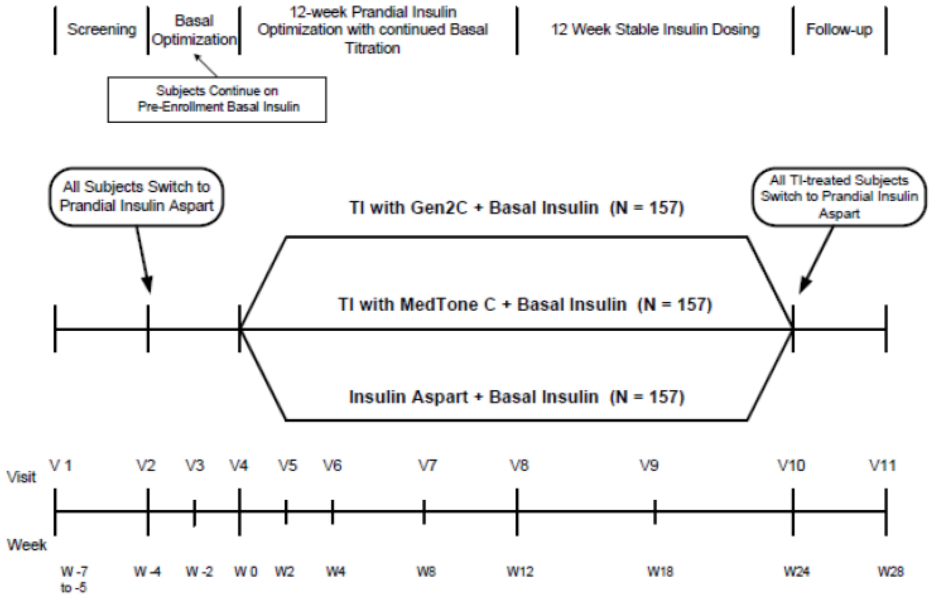
• Screening visit

• 4-week basal insulin optimization phase
Subjects not already using insulin aspart converted their mealtime insulin to insulin aspart and titrated their pre-enrollment basal insulin. All subjects remained on their pre-enrollment basal insulin (NPH, glargine, or detemir) throughout the study. Subjects were required to achieve an FPG value of ≤180 mg/dL measured at the central laboratory at the end of the 4-week basal optimization phase.

• 24-week randomized treatment phase consisting of:
-12-week prandial insulin optimization phase with continued basal titration: Subjects assigned to receive Afrezza TI using either the Gen2 or the MedTone inhaler converted their insulin aspart to Afrezza TI and continued to titrate their basal insulin dose as needed.
-12-Week stable insulin dose phase (with prandial and basal insulin doses remaining stable). During these 12 weeks, insulin doses could be adjusted only for safety reasons or because a subject's clinical condition (for example, the occurrence of an infection or other stress) changes.

• Follow-up visit

Figure 1 - Study 171 Schematic



Source: Figure 5, Study 171 CSR

Insulin Dosing and Titration:

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

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

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

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

Randomized Treatment Period Insulin Dosing

During the 12-week prandial insulin optimization phase with continued basal insulin titration, subjects could adjust their basal insulin doses once per week using the algorithm shown in Table 5. Titration was based on the median of the 3 most recent measurements within 7 days.

Table 5– Basal Insulin Titration Algorithm

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

Prandial Insulin Dosing

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

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

Adjustment of prandial doses of insulin aspart were to be based on subsequent premeal blood glucose values, (breakfast, lunch and dinner doses will be based on prelunch, predinner and bedtime blood glucose, respectively), as outlined below in Table 6. In addition to the recommended guidelines provided for dose initiation and subsequent dose adjustments described above, the PI may allow subjects to make additional dose adjustments/modifications (e.g., based on carbohydrate counting, meal size, SMBG results, snacks, PPG).

Table 6 – Insulin Aspart Dosing Algorithm

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

Endpoints:

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

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

2.3 Study 175

(Afrezza TI + OADs vs. placebo + OADs)

Title:

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

Study Sites:

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

Study Objective:

The primary study objective was to demonstrate that prandial Afrezza TI Gen2 is superior to TP (placebo) in reducing HbA1c levels when added to antidiabetic regimen of insulin-naive subjects with T2DM who are suboptimally controlled on optimal/maximally tolerated doses of metformin only or 2 or more OADs.

Design:

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

Reviewer's comment: This study design was recommended by FDA. This design was thought to be the most appropriate method for providing an unbiased evaluation of the administration of Afrezza TI via the Gen2 inhaler in subjects with T2DM. In addition, per recommendation of FDA, to characterize the population of subjects with T2DM who would

be likely to use Afrezza, only subjects on stable doses of either metformin monotherapy or 2 or more OADs were allowed to enroll in Study 175.

Subjects:

Key Inclusion Criteria:

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

Key Exclusion Criteria:

1. Treatment with glucagon like peptide-1 (GLP-1) analogs, thiazolidinedione (TZD) or weight loss drugs (e.g., sibutramine, orlistat) within 3 months of Screening
2. Two or more unexplained severe hypoglycemic episodes within 3 months of Screening. Unexplained refers to episodes of severe hypoglycemia that are not related to a dosing error, lack of or a change in meal size, or related to additional/unanticipated exercise
3. Any hospitalization or emergency room visit due to poor diabetic control within 6 months before Screening
4. Evidence of serious complications of diabetes in the opinion of the PI (proliferative retinopathy; autonomic neuropathy with symptoms of gastroparesis or cardiac arrhythmia; nontraumatic amputations due to gangrene; vascular claudication; sensory neuropathy) that made manipulation of the Gen2 inhaler difficult

5. History of COPD, clinically proven asthma, or any other clinically important pulmonary disease (e.g., pulmonary fibrosis)
6. Any clinically significant radiological findings on screening chest x-ray
7. Use of medications for asthma, COPD, or any other chronic respiratory conditions
8. Renal disease or renal dysfunction
   - For subjects who took metformin, serum creatinine levels ≥1.5 mg/dL in men, ≥1.4 mg/dL in women
   - For subjects who were not taking metformin, serum creatinine >2.0 mg/dL in men, >1.8 mg/dL in women; or blood urea nitrogen (BUN) >50 mg/dL
9. Significant cardiovascular dysfunction or history within 12 months of Screening
10. Allergy or known hypersensitivity to insulin or to any of the drugs to be used in the study, or a history of hypersensitivity to Afrezza TI or to drugs with a similar chemical structure
11. Active respiratory infection within 30 days before Screening (subject may return after 30 days from resolution for rescreening)
12. Major organ system diseases, including cancer (other than excised cutaneous basal cell carcinoma) within the past 5 years or any history of lung neoplasms
13. Women of childbearing potential, not using adequate contraception

Study Procedures and Visits:

The study consisted of 11 clinical visits (Figure 2).

• Visit 1: Screening (Week -8)

Eligibility was determined. See inclusion and exclusion criteria above.

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

After Screening, eligible subjects entered a 6-week run-in phase for baseline HbA1c stabilization, during which they continued their pre-enrollment OADs. Subjects received counseling regarding nutritional management and physical activity, and training in use of glucose meters, SMBG, and e-diaries.

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

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

• Visit 3b: Randomization visit (Week 0)

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

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

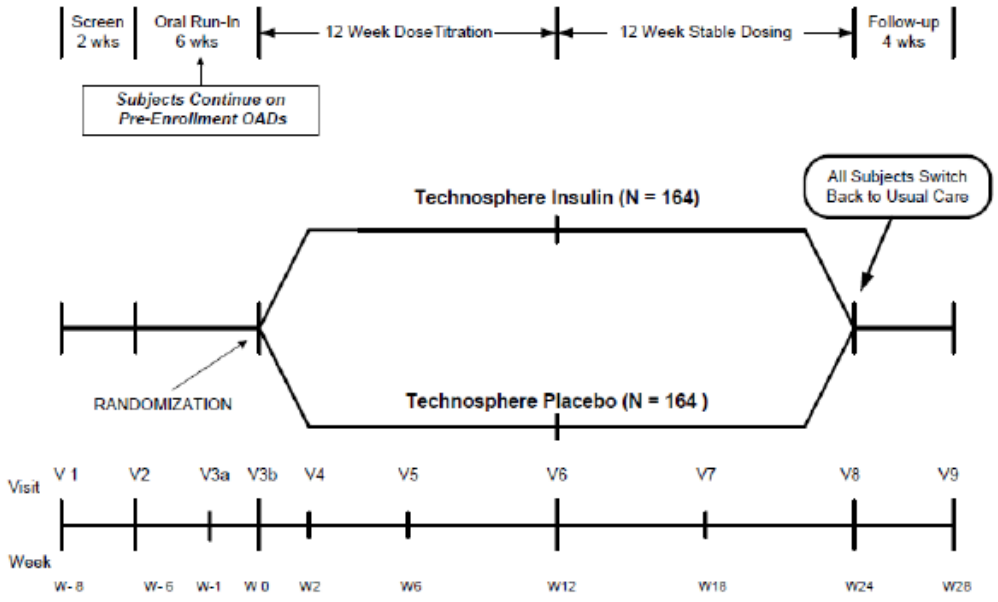
The randomized treatment phase was divided into two 12-week phases. In the first 12 weeks, subjects received study drugs with upward dose titration to achieve target blood glucose levels of 110-160 mg/dL. In the second 12 weeks, subjects were maintained on relatively stable dosing as established in the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

Also see description of Afrezza TI dosing above.

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

• Visit 9: Follow up visit (Week 28)
After completion of the 24-week randomized treatment phase, subjects were followed for safety for 4 weeks.

Figure 2– Study 175 Schematic



Source: Figure 5, Study 175 CSR

Rescue Therapy:

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

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

The algorithm for subjects to begin rescue therapy was:
• Between Randomization (Day 0) and through Week 6, if fasting SMBG levels measured on 3 different days within a week for at least 2 weeks were >270 mg/dL, the subject was instructed to notify the PI and have a central laboratory FPG test performed. If the FPG value from the central laboratory was >270 mg/dL, the subject began the appropriate rescue therapy.
• After Week 6 and through Week 12, the same procedure was used but cutoff level was FPG value from the central laboratory >240 mg/dL.
• After Week 12 and up to Week 24 (but not including the visit at Week 24), the same procedure was used but cutoff level was FPG value from the central laboratory >200 mg/dL.

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

Insulin dosing and titration:

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

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

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

Endpoints:

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

3 Review of Efficacy

3.1 Indication

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

3.1.1 Methods

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

3.1.2 Demographics

Study 171 – Type 1 Diabetes

Across the three randomized treatment groups, subjects had a mean age of 37-40 years, there were slightly more female than male subjects, the majority of subjects were White, and approximately 40% were from the U.S (Table 7). The duration of diabetes was 16 – 17 years on average, and subjects were, on average, mildly overweight (mean BMI approximately 26 kg/m^2).

Reviewer's comment: The three randomized treatment groups appear balanced with respect to demographic and baseline characteristics. The population is reasonably representative of the general population of patients with T1DM, although non-White subjects may be underrepresented.

Table 7 – Subject Demographics and Baseline Characteristics – Study 171

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

Demographic and Baseline Characteristics	TI Gen2 (N=174) n (%)	TI MedTone (N=173) n (%)	Insulin Aspart (N=171) n (%)
Sex			
Male	77 (44.3)	80 (46.2)	74 (43.3)
Female	97 (55.7)	93 (53.8)	97 (56.7)
Race			
White	164 (94.3)	166 (96.0)	167 (97.7)
Black Or African American	8 (4.6)	5 (2.9)	3 (1.8)
Asian	1 (0.6)	1 (0.6)	0
Native Hawaiian Or Other Pacific Islander	1 (0.6)	0	0
Other	0	1 (0.6)	1 (0.6)
Country			
USA	71 (40.8)	68 (39.3)	68 (39.8)
Russia	45 (25.9)	52 (30.1)	52 (30.4)
Ukraine	44 (25.3)	38 (22.0)	38 (22.2)
Brazil	14 (8.0)	15 (8.7)	13 (7.6)
Duration of DM (years)			
N	174	173	171
Mean (SD)	16.0 (10.27)	17.7 (10.69)	16.7 (10.01)
Median	13.8	15.2	16.0
Range	[1.1, 57.3]	[1.1, 49.5]	[1.0, 42.2]
Weight (kg)			
N	174	173	170
Mean (SD)	75.7 (15.75)	76.8 (14.87)	72.6 (15.24)
Median	74.4	76.3	69.7
Range	[41.7, 129.4]	[47.6, 124.0]	[46.6, 120.2]
BMI (kg/m^2)			
N	174	173	169
Mean (SD)	26.0 (4.48)	26.2 (3.74)	25.4 (4.10)
Median	25.7	26.0	24.5
Range	[16.6, 38.6]	[18.1, 36.4]	[17.4, 37.2]
HbA1c (%)			
N	172	171	168
Mean (SD)	7.98 (0.767)	7.99 (0.732)	7.88 (0.751)
Median	7.90	8.00	7.90
Range	[6.20, 10.60]	[6.10, 10.20]	[5.80, 10.10]
Fasting Plasma Glucose (mg/dL)			
N	174	173	171
Mean (SD)	155.0 (67.62)	143.9 (60.79)	151.6 (67.44)
Median	144.5	137.0	149.0
Range	[21.0, 403.0]	[43.0, 358.0]	[23.0, 375.0]

Source: Table 22, Study 171 CSR

At Screening, prior to the 4-week basal insulin optimization phase (i.e., Week -4), the mean HbA1c values were 8.50%, 8.65%, and 8.56%, respectively for subjects who were subsequently randomly assigned to the Afrezza TI Gen2, Afrezza TI MedTone, and insulin aspart groups. At

Baseline (i.e., Week 0), the mean HbA1c values were 7.98%, 7.99%, and 7.88%, respectively for the Afrezza TI Gen2, Afrezza TI MedTone, and insulin aspart groups.

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

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

Other relevant baseline characteristics - Study 171

The study design allowed patients to continue their pre-enrollment basal insulin to improve generalizability of study results. Table 8 shows that randomization was successful in creating three treatment groups, roughly equivalent in the percentages of patients on each type of basal insulin.

Table 8– Summary of Basal Insulin Stratification (Randomized Population)

	Afrezza TI Gen2	Afrezza TI MedTone	Insulin Aspart
		n (%)	
Insulin detemir	26 (14.9)	26 (14.9)	26 (15.3)
Insulin glargine	121 (69.5)	122 (70.1)	121 (71.2)
NPH insulin	27 (15.5)	26 (14.9)	23 (13.5)
Source: Table 24 Study CSR			

Study 175 – Type 2 Diabetes

As shown in Table 9, in the FAS population, the 2 treatment groups were generally balanced for the demographic characteristics of race, age, age category, country, and duration of diabetes as well as clinical characteristics of baseline HbA1c, FPG, BMI, and OAD therapy. The mean HbA1c at baseline was 8.26% in the Afrezza TI group and 8.35% in the placebo group.

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

Table 9– Subject Demographics and Baseline Characteristics – Study 175

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

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

Source: Table 18, Study 175 CSR

3.1.3 Subject Disposition

Study 171 – Type 1 Diabetes

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

Table 10 shows subject disposition for the randomized subjects in study 171.

Table 10– Subject Disposition Study 171

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

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

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

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

Reviewer's comment: There was an overall higher rate of subject discontinuation in the Afrezza TI groups. The reasons related to this imbalance appear to be clustered in the categories of adverse events, and subjects' choice – sometimes in relation to an adverse

experience or perceived lack of efficacy. This finding does not support a claim that patients prefer Afrezza TI over insulin aspart, at least in this particular study.

Study 175 – Type 2 Diabetes

The FAS population consisted of 353 subjects who were randomized to study treatment, 177 to the Afrezza TI Gen2 group and 176 subjects to the placebo group (Table 11).

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

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

Table 11– Subject Disposition Study 175

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

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

AEs accounted for 7 (4.0%) dropouts in the Afrezza TI Gen2 group and 9 (5.1%) dropouts in the placebo group. Discontinuations due to AEs are discussed in section 4 of this review. Subjects who discontinued the study with reasons in the "Withdrawal by Subject," "Physician Decision," or "Other" categories were reviewed by the Sponsor for verbatim explanation of discontinuation.

The most common reason was work/family conflict and relocation (Afrezza TI Gen2: 6; placebo: 6). "Persistently high FPG/PPG" was given as the reason by 3 placebo-treated subjects who withdrew from the study, and "Not satisfied with efficacy" was given as the reason for withdrawal by 1 placebo-treated subject and 1 Afrezza TI Gen2 subject.

3.1.4 Analysis of Efficacy Endpoint(s)

Please see the statistical section of this briefing document for the Agency's analysis of the primary endpoint for both studies 171 and 175. The analyses presented below are the Sponsor's analyses sourced from the Complete Study Reports for the studies.

3.1.4.1 Analysis of Primary Endpoint(s): Study 171 – Type 1 Diabetes

The primary efficacy endpoint was the change from the end of the basal insulin optimization phase at Randomization to Week 24 in HbA1c (%) between the Afrezza TI Gen2 and insulin aspart groups. In the Sponsor's analysis, the model-adjusted mean change (decrease) in HbA1c from the model-adjusted baseline values (7.94% in the Afrezza TI Gen2 group and 7.92% in the insulin aspart group) over 24 weeks was greater in the insulin aspart treatment group (-0.40%) than in the Afrezza TI Gen2 group (-0.21%), for a treatment difference of 0.19% (95% CI 0.02 to 0.36) (Table 12). The mean change in the Afrezza TI arm was statistically significantly less (or worse) than that in the aspart arm. Similar results were observed for the corresponding analyses of the PP population.

Table 12– Trial 171 ANCOVA of Mean Change from Baseline in HbA1c (%) at Week 24, MMRM Model, FAS Population

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

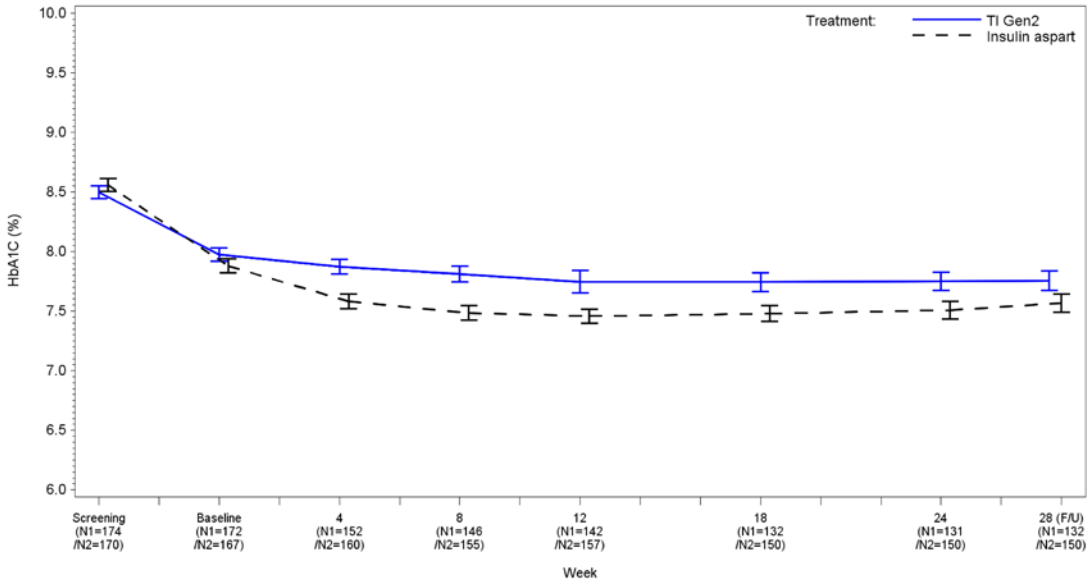
Reviewer's comment: The study results show that the primary objective of noninferiority of Afrezza TI Gen2 to insulin aspart was met (noninferiority margin 0.4%). However, Afrezza TI Gen2 was statistically worse than insulin aspart.

To put these results in perspective, they may be viewed in the context of the primary efficacy analysis of Study 009, the pivotal phase 3 study in T1DM conducted with the MedTone inhaler submitted with the original NDA which was summarized in section 1 of this briefing document. For study 009, the between-group difference in change from baseline in HbA1c was 0.24% (not favoring Afrezza TI) with a corresponding 95% CI of (0.08 to 0.40) not supporting a non-inferiority claim for Afrezza TI (inferiority margin < 0.4%).

It appears that the results of studies 009 and 171 are similar: note that the treatment difference in study 009 (0.24%) is very close to study 171 (0.22%) with both favoring the comparator, insulin aspart, the difference being that in Study 171 the non-inferiority margin was (barely) met, while in Study 009 it was narrowly missed. In a non-inferiority trial design the assessment of efficacy is based on 'implied' efficacy relative to a comparator that is assumed to also be effective, with a non-inferiority margin pre-specified based on historical data of how the comparator should perform.

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

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



Source: Figure 4 Study CSR

Analysis of Basal Insulin Doses Used - Study 171

The analysis of the primary efficacy endpoint cannot be fully interpreted without an examination of the relative insulin doses used by each study group, and a key component to an understanding

of the primary efficacy analysis is a comparison of the use of basal insulin between the two treatment groups.

Doses of basal insulin used were higher in the Afrezza TI groups than in the aspart group, whether examining the doses as means or medians, as shown in Figure 4 and Table 13. At Week 24 the median daily basal insulin dose for the Afrezza TI Gen2 group was 32 U (increased from 28 U at Baseline) and the median daily basal insulin dose for the insulin aspart group was 26 IU (increased from 25 U at Baseline). When examining change over time, the increase in dose was also higher for the Afrezza TI Gen 2 group. The change in median basal insulin dose from Week 1 to Week 24 was approximately 4 U in the Afrezza TI Gen 2 group and 1 IU in the insulin aspart group.

Data for the MedTone group are also shown in the Table 13.

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

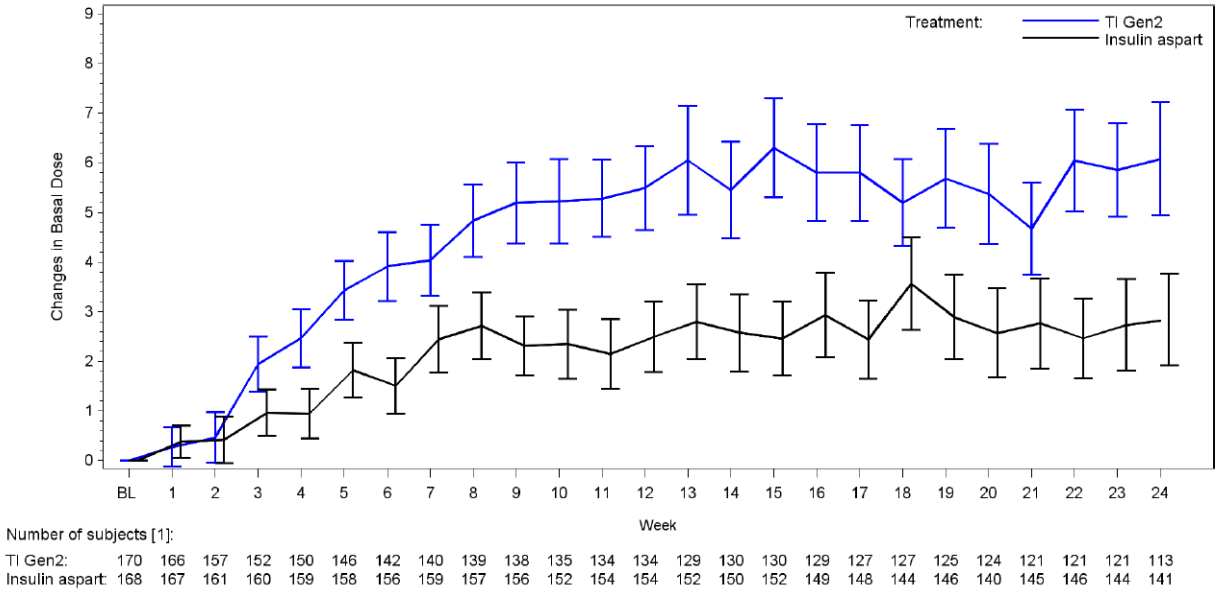


Table 13 - Study 171 –Average Daily Dose of Basal Insulin (IU/Day) Since Randomization by Time Periods (Safety Population)

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

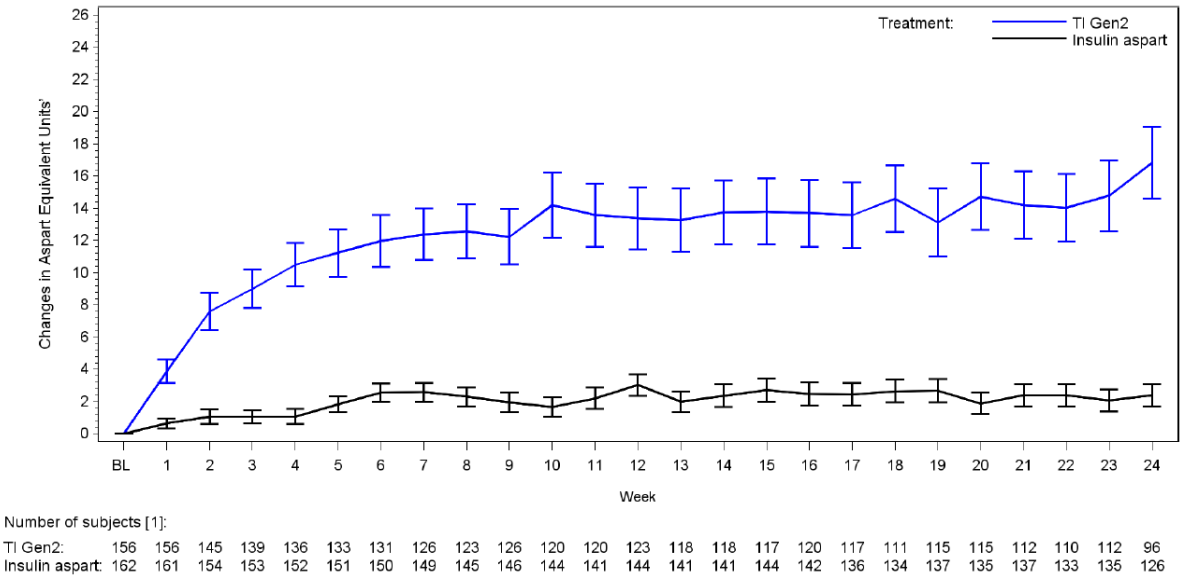
Source: Table 27 Study CSR

Reviewer's comment: The Afrezza TI Gen2 group's use of more basal insulin compared with the insulin aspart group is further evidence that Afrezza TI Gen2 is less effective than insulin aspart, at least as a substitute for prandial subcutaneously injected insulin, i.e. the manner in which Afrezza TI was studied in this trial. The higher basal insulin use the Afrezza TI group is also substantiated by the finding of a lower FPG in the Afrezza TI group at Week 24 compared with the insulin aspart group (see Secondary Endpoints).

Analysis of Prandial Insulin Doses Used – Study 171

The mean daily doses of inhaled prandial insulin increased throughout the randomized treatment phase (from 84.7 U at Week 1 to 115.4 U at Week 24 in the Afrezza TI Gen2 group and from 117.5 U at Week 1 to 137.7 U at Week 24 in the Afrezza TI MedTone group) (Figure 5 and Table 14). In contrast, in the insulin aspart group, the mean daily dose of insulin aspart showed only a slight increase (24.3 U at Week 1 and 25.9 U at Week 24).

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



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

Table 14- Study 171 - Average Daily Dose of Prandial Insulin since Randomization by Time Periods (Safety Population)

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

	Range	[30, 360]	[45, 420]	[8, 103]

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

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

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

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

It is notable that the aspart group experienced an improvement in HbA1c from Baseline to Week 24 of -0.40% with virtually no increase in the average dose of prandial insulin. Given that the basal insulin optimization phase was only 4 weeks in duration, the effect of basal insulin titration would not be expected to be fully reflected in the Baseline HbA1c. Therefore, the improvement in HbA1c from Baseline to Week 24 was likely driven, in part, by previous titration of basal insulin. Consequently, it is difficult to determine whether there was a reasonable contribution of prandial insulin to the improvement in HbA1c in either treatment arm.

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

Sensitivity Analyses of the Primary Endpoint – Study 171

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

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

Responder Analysis – Study 171

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

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

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

Fasting Plasma Glucose – Study 171

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

Reviewer's comment: The relative reductions in FPG from baseline to Week 24 may be largely due to the differences in the amount of basal insulin used between the treatment groups (which was higher in the Afrezza TI arm).

Body Weight – Study 171

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

Reviewer's comment: Analysis of body weight is difficult to interpret in light of the difference in efficacy between Afrezza TI and insulin aspart seen in the trial.

3.1.4.3 Subpopulations: Study 171 – Type 1 Diabetes

Females in the insulin aspart group had the greatest reduction compared to insulin aspart treated males, Afrezza TI treated females, and Afrezza TI treated males (Table 15).

Table 15– Study 171: Efficacy Results for HbA1c (%) by Sex

FAS Gender	Change from Baseline at Week 24 : LS Mean ± SE (N)		Treatment Difference	
	Afrezza TI-Gen2	IAsp	LS Mean ± SE	95% CI
Male	-0.21 ± 0.14 (58)	-0.18 ± 0.14 (65)	-0.03 ± 0.14	(-0.31, 0.25)
Female	-0.17 ± 0.09 (73)	-0.58 ± 0.09 (82)	0.41 ± 0.10	(0.20, 0.61)
The results were obtained using ANCOVA on subjects who had a baseline and Week 24 HbA1c values. Similar findings were observed when MMRM approach was employed.				

Source: reproduced from the FDA statistician' review

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

3.1.4.4 Analysis of Primary Endpoint: Study 175 – Type 2 Diabetes

The adjusted mean change in HbA1c from baseline to Week 24 for subjects who received Afrezza TI Gen2 in addition to OADs was -0.82% versus subjects who received placebo and OADs (-0.42); This difference was statistically significant (95% confidence interval [CI]: -0.57, -0.23; p < 0.0001) (Table 16). The results in the PP population were consistent with those seen in the FAS population.

Table 16– Study 175 –Analysis of Primary Endpoint – Change in HbA1c from Baseline to Week 24 -MMRM Analysis with FAS Population

Time Point	Statistic	Afrezza TI+OADs	Placebo+OADs	Afrezza TI+OADs-Placebo+OADs
Baseline	N	176	176	
	LS Mean (SE)	8.25 (0.057)	8.27 (0.058)	
Week 24	N	139	129	
	LS Mean (SE)	7.43 (0.061)	7.85 (0.062)	
Treatment Difference	LS Mean Change	-0.82 (0.061)	-0.42 (0.062)	-0.40
	95% CI			-0.57 – (-0.23)
	p value			<0.0001
Source: Table 23 Study CSR				

Reviewer's comment: To put these results into context, Table 17 shows the HbA1c reduction achieved in reviewed (labeled) studies of antidiabetes drugs representing various classes, studied in combination with metformin alone and at least two other OADs. While cross-study comparison is difficult and generally not recommended, on its face, the magnitude of the effect size achieved with Afrezza TI in comparison to these other antidiabetes agents is surprisingly modest, especially in light of the fact that Afrezza TI can be titrated.

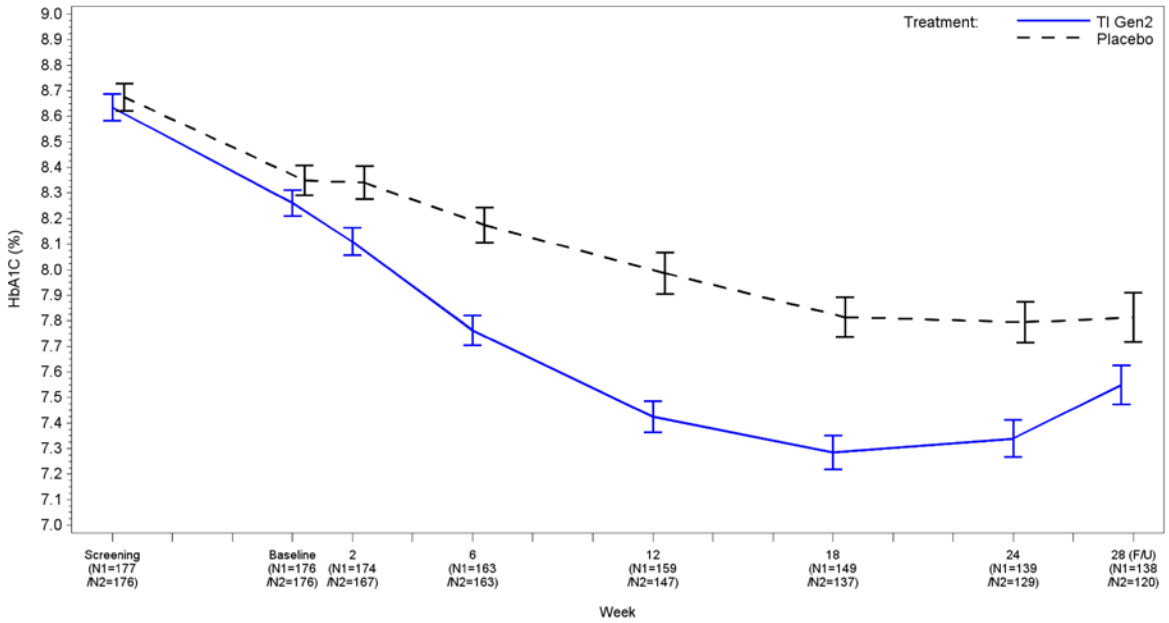
Table 17– Efficacy of Non-titratable Antidiabetes Drugs on a Background of Metformin or at Least Two Other Oral Antidiabetes Drugs

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

Observed Mean HbA1c over Time During the Randomized Treatment Phase – Study 175

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

Figure 6– Mean HbA1c Change over Time, Study 175



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

Sensitivity Analyses of the Primary Endpoint – Study 175

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

The FDA statistician also performed extensive sensitivity analyses for study 175 and verified the Sponsor's sensitivity analyses. In brief, the FDA statistician concluded that sensitivity analyses supported the superiority finding.

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

Responder Analysis – Study 175

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

The FDA statistical reviewer also examined these data including non-rescued patients with missing data at Week 24 and rescued patients as non-responders. As shown in Table 18, results were similar.

Table 18– Study 175 (T2DM): Responder Rate for HbA1c at Week 24 (from the FDA reviewer's statistical review)

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

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

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

Fasting plasma glucose – Study 175

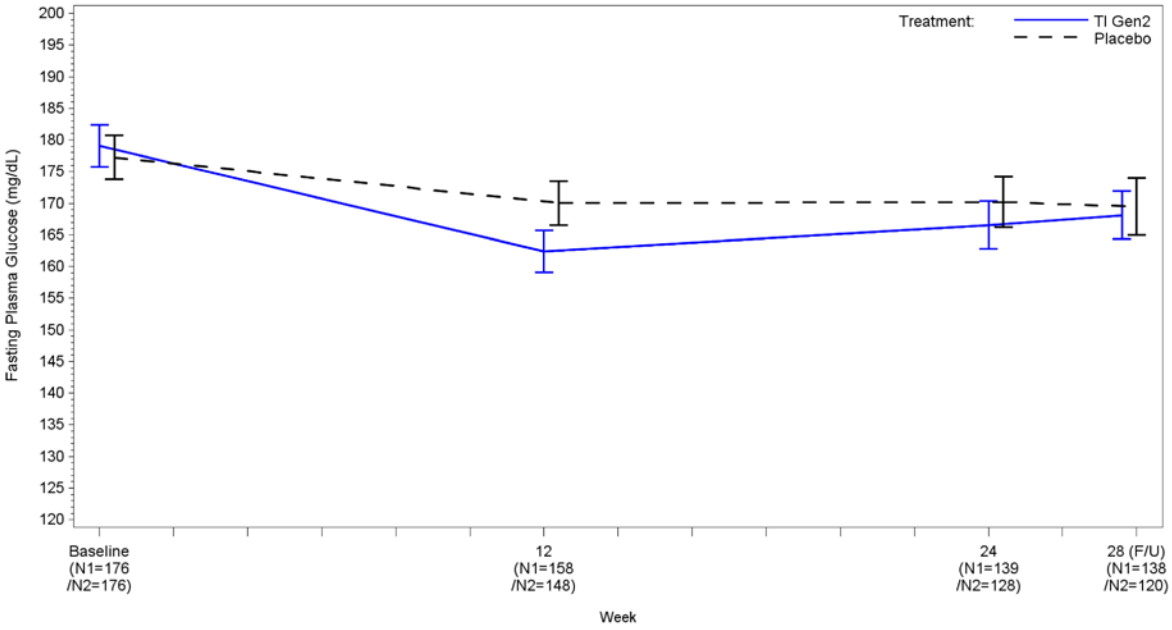
FPG appeared to decrease slightly in both groups, with the greatest difference between the groups at Week 12, and then increase in the Afrezza TI group and remain stable in the placebo group, such that by Week 24, the mean FPG in the treatment groups was similar (Figure 7).

In the Sponsor's analysis, at Week 24, the adjusted mean change of FPG was a decrease of 11.20 mg/dL from baseline in the Afrezza TI Gen2 group and a decrease of 3.78 mg/dL from baseline in the placebo group. The treatment difference between the groups in FPG reduction was 7.42 mg/dL, (95% CI: -18.03, 3.18; p = 0.1698). The FDA statistical reviewer's analysis used a

different methodology but the results were similar, i.e. no significant difference between Afrezza TI and placebo.

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

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



Source: Sponsor's CSR for study 175

Reviewer's comment: The explanation for this finding is likely that Afrezza TI, used as prandial insulin, is not having a significant impact on FPG; the mean reduction in HbA1c compared to placebo observed in the study is likely due to a decrease in average post-prandial glucose.

Body Weight – Study 175

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

Reviewer's comment: This result is not remarkable given that insulin is known to cause body weight gain. A less effective insulin product would be expected to cause less weight gain.

Rescue therapy and time to rescue – Study 175

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

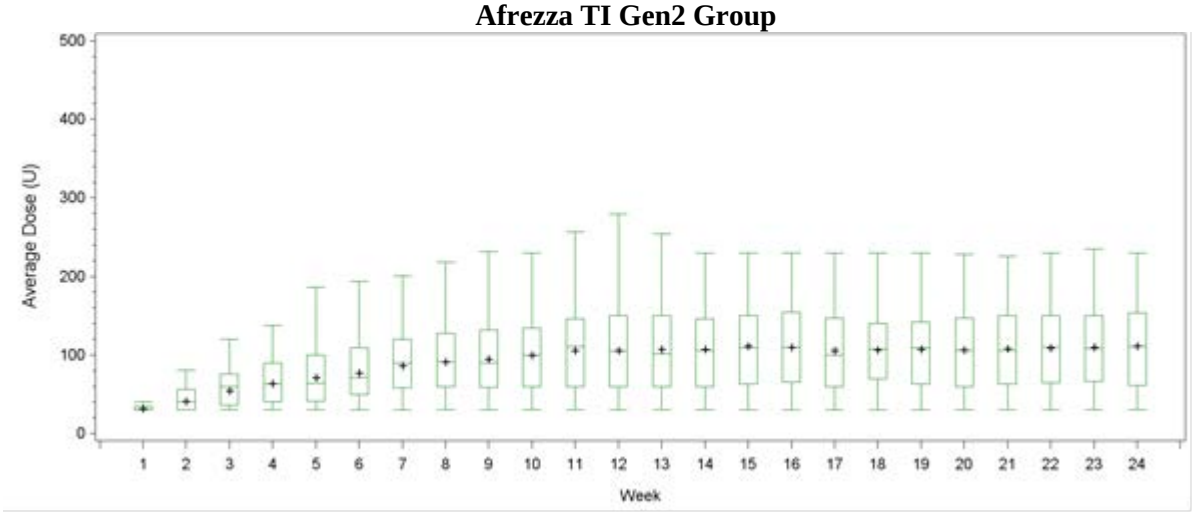
Both the Sponsor's analyses and the FDA's analyses showed no difference in time to rescue between the Afrezza TI and placebo group. However, the numbers of rescued subjects were small in the two groups. The FDA statistician noted that when time to rescue was included as an additional covariate in the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

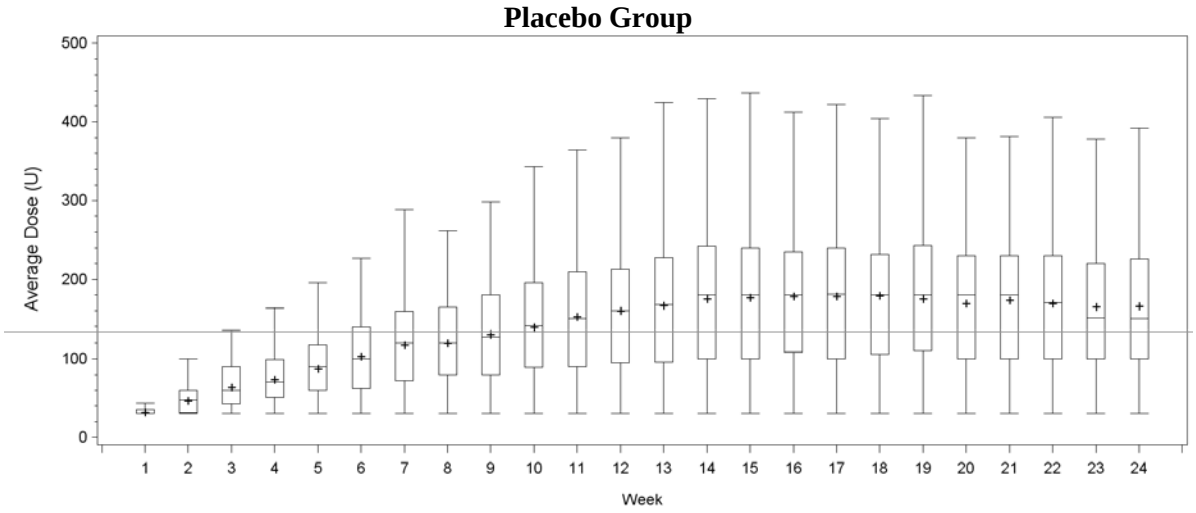
3.1.4.6 Other Endpoints: Study 175 – Type 2 Diabetes

Doses of trial product achieved – Study 175

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

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





Source: Figure 3 Study CSR

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

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

3.1.4.7 Subpopulations: Study 175 – Type 2 Diabetes

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

4 Review of Safety

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

4.1 Methods

The Sponsor pooled data from both inhalation systems for the 2013 Resubmission, presenting general safety data for each device separately and for both devices combined.

4.1.1 Pooling of Data across Studies to Estimate and Compare Incidence

Information for comparison of incidence of safety findings was obtained from the pooled controlled Phase 2 and Phase 3 study data.

As in the original NDA submission, the pooling strategy applied for the Integrated Summary of Safety in this resubmission was:

- Completed Phase 2/3 controlled trials - a completed trial was considered one with a completed data base lock at the cut-off date
- Adult subjects with T1DM or T2DM
- Continuous duration of exposure for ≥ 14 days

Table 19 shows the number of subjects in pooled, controlled phase 2/3 clinical studies in the 2009 Original NDA, the 2010 Resubmission, and the current Resubmission. As already noted, the new safety data included in the pooled database was generated primarily from the two new controlled clinical studies of Afrezza TI with the Gen2 inhaler (Study 171 in subjects with T1DM and Study 175 in subjects with T2DM).

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

Table 19 - Number of Subjects in Pooled, Controlled Phase 2/3 Clinical Studies

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

Source: Sponsor's Table 3, ISS

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

4.2 Adequacy of Safety Assessments

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

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

Demographics of pooled safety population

T1DM
Table 20 shows the demographic and baseline disease characteristics of the T1DM pooled controlled phase 2/3 trials safety population in the 2013 Resubmission. There are no important differences between the previously reviewed pooled T1DM safety populations and the current 2013 T1DM safety population. Note that only new study (Study 171) that qualified for pooling was completed since the 2010 Resubmission.

Table 20 Demographic and Baseline Disease Characteristics of the T1DM Pooled Controlled Phase 2/3 Trials Safety Population of 2013 Resubmission

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

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

T2DM

Table 21 shows the demographic and baseline disease characteristics of the T2DM pooled controlled phase 2/3 trials safety population in the 2013 Resubmission.

Table 21 – Demographic and Baseline Disease Characteristics of the T2DM Pooled Controlled Phase 2/3 Trials Safety Population of 2013 Resubmission

	Afrezza TI Gen2 (n=196)	Afrezza TI Med Tone (n=1795)	TP (n=290)	Comparator (n=1363)

Sex				
• % Male	47 %	51%	48%	51 %
Race				
• Caucasian	65 %	81 %	71 %	80 %
• Black or African American	12 %	5 %	6 %	5 %
• Hispanic	22 %	10 %	19 %	11 %
• Asian	0.5%	2 %	2 %	3 %
• Other	0.5%	1 %	1 %	2 %
Age (years)				
• Mean (SD)	57 (9)	56 (9)	56 (9)	56 (9)
• Median	57.5	57	57	56
• Range	27 - 75	19 - 82	26 - 79	18 - 78
Age Group				
• 18 – 64 years	78 %	83 %	80 %	84 %
• 64 – 74 years	22 %	16 %	18 %	15 %
• > 74 years	1 %	1 %	2 %	1 %
BMI (kg/m^2)				
• Mean (SD)	32 (5)	31 (5)	32 (5)	31 (5)
• Median	31.5	31	31	31
• Range	19 - 45	15 - 56	21 - 44	19 - 64
Duration of Diabetes (years)				
• Mean (SD)	10 (6)	11 (7)	9 (5)	11.5 (7)
• Median	9.5	9.5	8	10
• Range	1 - 36	0 - 45	1 - 29	0.3 - 52

Source: ISS Tables 16 and 22
Comparator group includes both non-insulin and other insulin drugs
Key: TP=Technosphere Powder Placebo using either inhaler

As expected for a population of T2DM subjects, the mean age is older than the T1DM subjects and BMI is higher with the mean/median BMI in the obese category, i.e. > 30 kg/m^2.

The T2DM population had an average duration of diabetes of roughly 10-11 years suggesting in general subjects were not recently diagnosed. This seems appropriate for clinical studies investigating an insulin product, i.e. insulin is not typically first line therapy for the treatment of T2DM.

In comparison to the original NDA, the major difference the demographic and baseline disease characteristics of the T2DM pooled safety population appears to be a greater proportion of Black or African American and Hispanic subjects included.

Reviewer's comment: The demographic and baseline disease characteristics of the T2DM safety population in the Afrezza TI development program appear reasonably representative of T2DM patients who may be expected to use an insulin product.

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

4.3 Major Safety Results

4.3.1 Deaths

At the time of NDA submission a total of 16 subjects with T1DM or T2DM who participated in the Afrezza TI program had died. Of the 16 subjects who died, 14 were included in the pooled database for the Phase 2/3 controlled trials. Of the 14 subjects who died in the pooled phase 2/3 controlled trials, 9/2409 (0.4%) received Afrezza TI and 5/1944 (0.3%) received comparator.

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

Table 22 shows deaths occurring in the Afrezza TI development program for all controlled and uncontrolled trials.

Table 22 - Deaths Listing[1] for Afrezza TI and Comparator

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

010/009/0246				MedTone		prostate CA
MKC-TI-010/403/2782	60	M	2	270 U MedTone	372	Metastatic pancreatic adenocarcinoma
MKC-TI-139/011	64	F	2	45-90 U Gen2	233	Acute leukemia
Comparator						
MKC-TI-030/174/1783	50	M	1	SC insulin	261	Road traffic accident
MKC-TI-030/912/3282	56	M	2	OADs	603	Cardiac arrest
MKC-TI-030/537/0308	51	F	2	SC insulin	399	Acute coronary syndrome
MKC-TI-102/322/1772	68	F	2	SC insulin	76	Cardiac arrest
MKC-TI-014/534/678	74	F	2	SC insulin	167	Acute coronary syndrome
MKC-TI-014/524/074	72	M	2	SC insulin	298	Acute cardiac failure
MKC-TI-171/1413	26	M	1	SC insulin	45	Accidental drowning

1 - Includes all deaths that occurred during drug exposure; or within 30 days following discontinuation from drug; or later but resulting from adverse events that had onset during drug exposure or had onset within 30 days following drug exposure
2 – Last dose prior to discontinuation if on Afrezza TI or type of therapy if on comparator
3 – Days on treatment before death

Narratives for these deaths are included in the Clinical Briefing Document Appendices (section 5.1).

As concluded during the first two review cycles, again, there do not appear to be any deaths that can be directly attributed to study treatment (such as death from diabetic ketoacidosis or hypoglycemia).

Reviewer's comment: In summary, death rates were low, causes of death do not suggest relationship to Afrezza TI treatment, and there is no apparent imbalance between Afrezza TI and comparator based on controlled clinical data.

4.3.2 Nonfatal Serious Adverse Events

In the original NDA review, because serious adverse event (SAE) rates were low, the controlled phase 2/3 trials for T1DM and T2DM were pooled to improve the likelihood of detecting potentially important imbalances between treatment groups. In the pooled phase 2/3 dataset, the overall incidence of SAEs was 8.3% (11.1 per 100 patient-years) with Afrezza TI and 9.4% (8.9 per 100 patient-years) with comparator. Most of the SAEs were reported in only 1-2 patients; among T2DM subjects there was no pattern of a single type of SAE that occurred with significantly greater frequency among Afrezza TI-treated subjects than among comparator-treated subjects. However, among T1DM subjects, there was a higher rate of diabetic ketoacidosis (DKA) seen in Afrezza TI-treated subjects vs. comparator-treated subjects. DKA is discussed in more detail in section 4.3.5 along with other adverse events of special interest.

As requested by the FDA, in the re-submission the Sponsor presented tabulations by system organ class and preferred term of the new safety data combined with the original NDA data and 2010 Resubmission data and included tables that compared frequencies of safety data in the original NDA and 2010 Resubmission with the re-tabulated frequencies.

Results of the new analyses are similar to those of the original NDA. For T1DM patients, the incidence of SAEs in both the Afrezza TI group and the comparator group was similar between the 2010 Resubmission (11.6% for both groups) and the 2013 Resubmission (9.1% for Afrezza TI Inhalation Powder and 9.9% for comparator treatment). For T2DM, the incidence of SAEs in the Afrezza TI group between the 2013 Resubmission and the original NDA (note the 2010 Resubmission did not add any T2DM patients to the pooled Phase 2/3 Safety Population) also remained similar (120/1991 [6.0%] and 114/1795 [6.4%], respectively). In the Afrezza TI Placebo group, the incidence of SAEs was 11/290 (3.8%) in the 2013 Resubmission compared to 2/114 (1.8%) in the original NDA. The incidence of SAEs in the Comparator group between 2013 and 2009 was the same (106/1363 [7.8%] and 105/1345 [7.8%]).

Table 23 shows the incidence of SAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) for both diabetes types combined in the pooled phase 2/3 safety database in the current Resubmission.

Table 23–Serious Adverse Events by System Organ Class and Preferred Term for T1DM and T2DM Combined, Pooled Phase 2/3 Safety Population, 2013 Resubmission

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

Pericarditis	0	1 (0.0)	1 (0.0)	0	0	0	0
Ventricular tachycardia	0	1 (0.0)	1 (0.0)	0	0	0	0
Acute myocardial infarction	0	0	0	0	0	0	1 (0.0)
Angina pectoris	0	0	0	1 (0.6)	0	1 (0.3)	3 (0.1)
Atrial flutter	0	0	0	0	0	0	1 (0.0)
Bundle branch block left	0	0	0	0	0	0	1 (0.0)
Coronary artery insufficiency	0	0	0	0	0	0	2 (0.1)
Cyanosis	0	0	0	1 (0.6)	0	1 (0.3)	0
Hypertensive heart disease	0	0	0	0	0	0	1 (0.0)
Sinus tachycardia	0	0	0	0	0	0	1 (0.0)
Supraventricular tachycardia	0	0	0	0	0	0	3 (0.1)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	0	1 (0.6)	0	1 (0.3)	0
Skull malformation	0	0	0	1 (0.6)	0	1 (0.3)	0
EAR AND LABYRINTH DISORDERS	0	0	0	0	0	0	1 (0.0)
Meniere's disease	0	0	0	0	0	0	1 (0.0)
ENDOCRINE DISORDERS	0	0	0	0	0	0	1 (0.0)
Myxedema	0	0	0	0	0	0	1 (0.0)
EYE DISORDERS	0	5 (0.2)	5 (0.2)	0	0	0	3 (0.1)
Retinal detachment	0	3 (0.1)	3 (0.1)	0	0	0	0
Retinal disorder	0	1 (0.0)	1 (0.0)	0	0	0	0
Vitreous hemorrhage	0	1 (0.0)	1 (0.0)	0	0	0	0
Diabetic retinopathy	0	0	0	0	0	0	1 (0.0)
Eye hemorrhage	0	0	0	0	0	0	2 (0.1)
Glaucoma	0	0	0	0	0	0	1 (0.0)
Optic atrophy	0	0	0	0	0	0	1 (0.0)
Optic neuropathy	0	0	0	0	0	0	1 (0.0)
GASTROINTESTINAL DISORDERS	0	15 (0.6)	15 (0.5)	0	1 (0.9)	1 (0.3)	14 (0.6)
Pancreatitis acute	0	4 (0.2)	4 (0.1)	0	0	0	0
Gastritis	0	2 (0.1)	2 (0.1)	0	0	0	2 (0.1)
Abdominal hernia	0	1 (0.0)	1 (0.0)	0	0	0	0
Anal fistula	0	1 (0.0)	1 (0.0)	0	0	0	0
Colitis ulcerative	0	1 (0.0)	1 (0.0)	0	0	0	0
Constipation	0	1 (0.0)	1 (0.0)	0	0	0	0
Duodenal ulcer	0	1 (0.0)	1 (0.0)	0	0	0	0
Erosive esophagitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Gastric ulcer	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Gastritis erosive	0	1 (0.0)	1 (0.0)	0	0	0	0
Gastrointestinal hemorrhage	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Intestinal obstruction	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Large intestine perforation	0	1 (0.0)	1 (0.0)	0	0	0	0
Esophageal ulcer	0	1 (0.0)	1 (0.0)	0	0	0	0
Pancreatic cyst	0	1 (0.0)	1 (0.0)	0	0	0	0
Pancreatitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Retroperitoneal hemorrhage	0	1 (0.0)	1 (0.0)	0	0	0	0
Vomiting	0	1 (0.0)	1 (0.0)	0	0	0	0
Abdominal discomfort	0	0	0	0	0	0	1 (0.0)
Abdominal pain	0	0	0	0	0	0	1 (0.0)
Abdominal pain upper	0	0	0	0	0	0	1 (0.0)
Colonic polyp	0	0	0	0	0	0	1 (0.0)
Gastroduodenitis	0	0	0	0	0	0	1 (0.0)
Gastroesophageal reflux disease	0	0	0	0	0	0	2 (0.1)
Hematemesis	0	0	0	0	0	0	1 (0.0)
Hiatus hernia	0	0	0	0	0	0	1 (0.0)
Inguinal hernia, obstructive	0	0	0	0	1 (0.9)	1 (0.3)	0
Esophagitis	0	0	0	0	0	0	1 (0.0)
Pancreatic necrosis	0	0	0	0	0	0	1 (0.0)
Pancreatitis chronic	0	0	0	0	0	0	1 (0.0)
Small intestinal obstruction	0	0	0	0	0	0	1 (0.0)

Umbilical hernia	0	0	0	0	0	0	1 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	6 (0.2)	6 (0.2)	0	0	0	3 (0.1)
Chest pain	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Generalized edema	0	2 (0.1)	2 (0.1)	0	0	0	0
Chest discomfort	0	1 (0.0)	1 (0.0)	0	0	0	0
Edema peripheral	0	1 (0.0)	1 (0.0)	0	0	0	0
Non-cardiac chest pain	0	0	0	0	0	0	1 (0.0)
Pyrexia	0	0	0	0	0	0	1 (0.0)
HEPATOBILIARY DISORDERS	0	9 (0.3)	9 (0.3)	0	0	0	7 (0.3)
Cholecystitis	0	3 (0.1)	3 (0.1)	0	0	0	3 (0.1)
Cholecystitis acute	0	2 (0.1)	2 (0.1)	0	0	0	0
Cholelithiasis	0	2 (0.1)	2 (0.1)	0	0	0	3 (0.1)
Drug-induced liver injury	0	1 (0.0)	1 (0.0)	0	0	0	0
Hepatitis toxic	0	1 (0.0)	1 (0.0)	0	0	0	0
Cholecystitis chronic	0	0	0	0	0	0	1 (0.0)
Gallbladder disorder	0	0	0	0	0	0	1 (0.0)
Hepatocellular injury	0	0	0	0	0	0	1 (0.0)
IMMUNE SYSTEM DISORDERS	0	1 (0.0)	1 (0.0)	0	0	0	0
Autoimmune disorder	0	1 (0.0)	1 (0.0)	0	0	0	0
INFECTIONS AND INFESTATIONS	2 (0.5)	27 (1.0)	29 (1.0)	0	0	0	29 (1.3)
Urinary tract infection	1 (0.3)	2 (0.1)	3 (0.1)	0	0	0	1 (0.0)
Diabetic gangrene	0	2 (0.1)	2 (0.1)	0	0	0	0
Furuncle	0	2 (0.1)	2 (0.1)	0	0	0	0
Pneumonia	0	2 (0.1)	2 (0.1)	0	0	0	5 (0.2)
Wound infection	0	2 (0.1)	2 (0.1)	0	0	0	0
Appendicitis	0	1 (0.0)	1 (0.0)	0	0	0	5 (0.2)
Carbuncle	0	1 (0.0)	1 (0.0)	0	0	0	0
Cellulitis	0	1 (0.0)	1 (0.0)	0	0	0	4 (0.2)
Cellulitis streptococcal	0	1 (0.0)	1 (0.0)	0	0	0	0
Cytomegalovirus infection	1 (0.3)	0	1 (0.0)	0	0	0	0
Diabetic foot infection	0	1 (0.0)	1 (0.0)	0	0	0	0
Diverticulitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Gastroenteritis viral	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Hepatitis viral	0	1 (0.0)	1 (0.0)	0	0	0	0
Injection site cellulitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Localized infection	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Osteomyelitis	0	1 (0.0)	1 (0.0)	0	0	0	2 (0.1)
Otitis media acute	0	1 (0.0)	1 (0.0)	0	0	0	0
Parotitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Perirectal abscess	0	1 (0.0)	1 (0.0)	0	0	0	0
Pulmonary tuberculosis	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Pyelonephritis chronic	0	1 (0.0)	1 (0.0)	0	0	0	0
Rectal abscess	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Staphylococcal infection	0	1 (0.0)	1 (0.0)	0	0	0	0
Upper respiratory tract infection	0	1 (0.0)	1 (0.0)	0	0	0	0
Arthritis bacterial	0	0	0	0	0	0	1 (0.0)
Bacterial sepsis	0	0	0	0	0	0	1 (0.0)
Bronchitis	0	0	0	0	0	0	1 (0.0)
Gangrene	0	0	0	0	0	0	1 (0.0)
Infection	0	0	0	0	0	0	1 (0.0)
Pelvic abscess	0	0	0	0	0	0	1 (0.0)
Peritonitis	0	0	0	0	0	0	1 (0.0)
Pilonidal cyst	0	0	0	0	0	0	1 (0.0)
Postoperative wound infection	0	0	0	0	0	0	1 (0.0)
Pyelonephritis	0	0	0	0	0	0	2 (0.1)
Sepsis	0	0	0	0	0	0	1 (0.0)

Staphylococcal scalded skin syndrome	0	0	0	0	0	0	1 (0.0)
Subcutaneous abscess	0	0	0	0	0	0	1 (0.0)
Tonsillitis	0	0	0	0	0	0	1 (0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (0.5)	16 (0.6)	18 (0.6)	1 (0.6)	0	1 (0.3)	19 (0.9)
Facial bones fracture	0	2 (0.1)	2 (0.1)	0	0	0	0
Rib fracture	1 (0.3)	1 (0.0)	2 (0.1)	0	0	0	1 (0.0)
Road traffic accident	0	2 (0.1)	2 (0.1)	0	0	0	4 (0.2)
Accidental overdose	0	1 (0.0)	1 (0.0)	0	0	0	0
Ankle fracture	0	1 (0.0)	1 (0.0)	0	0	0	4 (0.2)
Concussion	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Electric shock	0	1 (0.0)	1 (0.0)	0	0	0	0
Fall	0	1 (0.0)	1 (0.0)	0	0	0	5 (0.2)
Hand fracture	0	1 (0.0)	1 (0.0)	0	0	0	0
Injury	0	1 (0.0)	1 (0.0)	0	0	0	0
Jaw fracture	0	1 (0.0)	1 (0.0)	0	0	0	0
Joint dislocation	1 (0.3)	0	1 (0.0)	0	0	0	1 (0.0)
Limb injury	0	1 (0.0)	1 (0.0)	0	0	0	0
Meniscus lesion	0	1 (0.0)	1 (0.0)	0	0	0	0
Overdose	0	1 (0.0)	1 (0.0)	0	0	0	0
Patella fracture	0	1 (0.0)	1 (0.0)	0	0	0	0
Upper limb fracture	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Brain contusion	0	0	0	0	0	0	1 (0.0)
Cerebral hemorrhage traumatic	0	0	0	0	0	0	1 (0.0)
Delayed recovery from anesthesia	0	0	0	0	0	0	1 (0.0)
Femur fracture	0	0	0	0	0	0	1 (0.0)
Fibula fracture	0	0	0	0	0	0	1 (0.0)
Foot fracture	0	0	0	0	0	0	1 (0.0)
Hip fracture	0	0	0	0	0	0	2 (0.1)
Humerus fracture	0	0	0	1 (0.6)	0	1 (0.3)	0
Intentional overdose	0	0	0	0	0	0	1 (0.0)
Lower limb fracture	0	0	0	0	0	0	1 (0.0)
Multiple fractures	0	0	0	0	0	0	1 (0.0)
Procedural complication	0	0	0	0	0	0	1 (0.0)
Spinal fracture	0	0	0	0	0	0	1 (0.0)
Tendon rupture	0	0	0	0	0	0	1 (0.0)
Thoracic vertebral fracture	0	0	0	0	0	0	1 (0.0)
INVESTIGATIONS	0	1 (0.0)	1 (0.0)	1 (0.6)	0	1 (0.3)	1 (0.0)
International normalized ratio increased	0	1 (0.0)	1 (0.0)	0	0	0	0
Blood potassium increased	0	0	0	0	0	0	1 (0.0)
Heart rate decreased	0	0	0	1 (0.6)	0	1 (0.3)	0
METABOLISM AND NUTRITION DISORDERS	2 (0.5)	66 (2.5)	68 (2.3)	0	0	0	65 (3.0)
Hypoglycemia	2 (0.5)	47 (1.8)	49 (1.6)	0	0	0	49 (2.2)
Diabetic ketoacidosis	0	10 (0.4)	10 (0.3)	0	0	0	4 (0.2)
Hyperglycemia	0	4 (0.2)	4 (0.1)	0	0	0	2 (0.1)
Ketoacidosis	0	4 (0.2)	4 (0.1)	0	0	0	1 (0.0)
Dehydration	0	2 (0.1)	2 (0.1)	0	0	0	0
Diabetes mellitus inadequate control	0	2 (0.1)	2 (0.1)	0	0	0	6 (0.3)
Ketosis	0	1 (0.0)	1 (0.0)	0	0	0	0
Diabetic complication	0	0	0	0	0	0	1 (0.0)
Metabolic syndrome	0	0	0	0	0	0	1 (0.0)
Obesity	0	0	0	0	0	0	1 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	14 (0.5)	14 (0.5)	1 (0.6)	1 (0.9)	2 (0.7)	12 (0.5)

Osteoarthritis	0	4 (0.2)	4 (0.1)	0	0	0	2 (0.1)
Intervertebral disc degeneration	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Intervertebral disc protrusion	0	2 (0.1)	2 (0.1)	0	0	0	3 (0.1)
Rotator cuff syndrome	0	2 (0.1)	2 (0.1)	0	0	0	0
Back pain	0	1 (0.0)	1 (0.0)	1 (0.6)	0	1 (0.3)	2 (0.1)
Intervertebral disc disorder	0	1 (0.0)	1 (0.0)	0	0	0	0
Musculoskeletal chest pain	0	1 (0.0)	1 (0.0)	0	0	0	0
Musculoskeletal pain	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Rheumatoid arthritis	0	1 (0.0)	1 (0.0)	0	0	0	0
Spinal osteoarthritis	0	1 (0.0)	1 (0.0)	0	0	0	2 (0.1)
Tenosynovitis	0	1 (0.0)	1 (0.0)	0	0	0	0
Arthritis	0	0	0	0	0	0	1 (0.0)
Osteochondrosis	0	0	0	0	0	0	1 (0.0)
Polyarthritis	0	0	0	0	1 (0.9)	1 (0.3)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.3)	13 (0.5)	14 (0.5)	1 (0.6)	0	1 (0.3)	10 (0.5)
Breast cancer	0	3 (0.1)	3 (0.1)	0	0	0	1 (0.0)
Prostate cancer	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Basal cell carcinoma	0	1 (0.0)	1 (0.0)	0	0	0	0
Benign salivary gland neoplasm	0	1 (0.0)	1 (0.0)	0	0	0	0
Breast cancer stage iii	0	1 (0.0)	1 (0.0)	0	0	0	0
Gastrointestinal cancer metastatic	0	1 (0.0)	1 (0.0)	0	0	0	0
Ovarian epithelial cancer	0	1 (0.0)	1 (0.0)	0	0	0	0
Pituitary tumor benign	0	1 (0.0)	1 (0.0)	0	0	0	0
Prostate cancer metastatic	0	1 (0.0)	1 (0.0)	0	0	0	0
Rectal cancer	1 (0.3)	0	1 (0.0)	0	0	0	1 (0.0)
Uterine leiomyoma	0	1 (0.0)	1 (0.0)	0	0	0	3 (0.1)
Adrenal adenoma	0	0	0	0	0	0	1 (0.0)
Benign pancreatic neoplasm	0	0	0	0	0	0	1 (0.0)
Cervix carcinoma	0	0	0	0	0	0	1 (0.0)
Colon cancer	0	0	0	0	0	0	1 (0.0)
Pancreatic carcinoma	0	0	0	0	0	0	1 (0.0)
Squamous cell carcinoma	0	0	0	1 (0.6)	0	1 (0.3)	0
NERVOUS SYSTEM DISORDERS	2 (0.5)	34 (1.3)	36 (1.2)	1 (0.6)	0	1 (0.3)	29 (1.3)
Loss of consciousness	0	13 (0.5)	13 (0.4)	0	0	0	9 (0.4)
Hypoglycemic unconsciousness	1 (0.3)	6 (0.2)	7 (0.2)	0	0	0	4 (0.2)
Hypoglycemic seizure	1 (0.3)	5 (0.2)	6 (0.2)	0	0	0	6 (0.3)
Transient ischemic attack	0	2 (0.1)	2 (0.1)	0	0	0	0
Ataxia	0	1 (0.0)	1 (0.0)	0	0	0	0
Carotid artery stenosis	0	1 (0.0)	1 (0.0)	0	0	0	0
Convulsion	0	1 (0.0)	1 (0.0)	0	0	0	0
Dizziness	0	1 (0.0)	1 (0.0)	0	0	0	0
Encephalopathy	0	1 (0.0)	1 (0.0)	0	0	0	0
Epilepsy	0	1 (0.0)	1 (0.0)	0	0	0	0
Third nerve paralysis	0	1 (0.0)	1 (0.0)	0	0	0	0
Multiple sclerosis	0	1 (0.0)	1 (0.0)	0	0	0	0
Pre-syncope	0	1 (0.0)	1 (0.0)	0	0	0	0
Cerebrovascular accident	0	0	0	0	0	0	5 (0.2)
Hypoglycemic coma	0	0	0	0	0	0	2 (0.1)
Ischemic stroke	0	0	0	1 (0.6)	0	1 (0.3)	1 (0.0)
Neuritis	0	0	0	0	0	0	1 (0.0)
Radiculitis lumbosacral	0	0	0	0	0	0	1 (0.0)
Sciatica	0	0	0	0	0	0	1 (0.0)

Syncope	0	0	0	0	0	0	1 (0.0)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	0	0	0	0	0	0	1 (0.0)
Pregnancy	0	0	0	0	0	0	1 (0.0)
PSYCHIATRIC DISORDERS	0	2 (0.1)	2 (0.1)	0	0	0	3 (0.1)
Depression	0	1 (0.0)	1 (0.0)	0	0	0	0
Psychotic disorder	0	1 (0.0)	1 (0.0)	0	0	0	0
Mental status changes	0	0	0	0	0	0	1 (0.0)
Suicide attempt	0	0	0	0	0	0	2 (0.1)
RENAL AND URINARY DISORDERS	0	4 (0.2)	4 (0.1)	0	0	0	6 (0.3)
Hydronephrosis	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Renal failure acute	0	2 (0.1)	2 (0.1)	0	0	0	1 (0.0)
Calculus bladder	0	1 (0.0)	1 (0.0)	0	0	0	0
Nephrolithiasis	0	1 (0.0)	1 (0.0)	0	0	0	3 (0.1)
Calculus ureteric	0	0	0	0	0	0	1 (0.0)
Renal colic	0	0	0	0	0	0	1 (0.0)
Renal failure	0	0	0	0	0	0	1 (0.0)
Urethral stenosis	0	0	0	0	0	0	1 (0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	4 (0.2)	4 (0.1)	0	0	0	2 (0.1)
Adenomyosis	0	1 (0.0)	1 (0.0)	0	0	0	1 (0.0)
Benign prostatic hyperplasia	0	1 (0.0)	1 (0.0)	0	0	0	0
Cervical polyp	0	1 (0.0)	1 (0.0)	0	0	0	0
Prostatomegaly	0	1 (0.0)	1 (0.0)	0	0	0	0
Uterine prolapse	0	0	0	0	0	0	1 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.3)	7 (0.3)	8 (0.3)	0	0	0	2 (0.1)
Asthma	0	1 (0.0)	1 (0.0)	0	0	0	0
Atelectasis	0	1 (0.0)	1 (0.0)	0	0	0	0
Bronchial hyperreactivity	1 (0.3)	0	1 (0.0)	0	0	0	0
Bronchial obstruction	0	1 (0.0)	1 (0.0)	0	0	0	0
Cough	0	1 (0.0)	1 (0.0)	0	0	0	0
Dyspnea	0	1 (0.0)	1 (0.0)	0	0	0	0
Hemoptysis	0	1 (0.0)	1 (0.0)	0	0	0	0
Orthopnea	0	1 (0.0)	1 (0.0)	0	0	0	0
Vocal cord polyp	0	1 (0.0)	1 (0.0)	0	0	0	0
Hydrothorax	0	0	0	0	0	0	1 (0.0)
Pulmonary edema	0	0	0	0	0	0	1 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	2 (0.1)	2 (0.1)	2 (1.1)	0	2 (0.7)	2 (0.1)
Angioedema	0	1 (0.0)	1 (0.0)	1 (0.6)	0	1 (0.3)	0
Hyperhidrosis	0	1 (0.0)	1 (0.0)	1 (0.6)	0	1 (0.3)	0
Skin ulcer	0	0	0	0	0	0	1 (0.0)
Urticaria	0	0	0	0	0	0	1 (0.0)
VASCULAR DISORDERS	0	6 (0.2)	6 (0.2)	0	0	0	4 (0.2)
Aortic stenosis	0	2 (0.1)	2 (0.1)	0	0	0	0
Deep vein thrombosis	0	1 (0.0)	1 (0.0)	0	0	0	0
Hypertension	0	1 (0.0)	1 (0.0)	0	0	0	0
Hypertensive crisis	0	1 (0.0)	1 (0.0)	0	0	0	0
Hypotension	0	1 (0.0)	1 (0.0)	0	0	0	0
Essential hypertension	0	0	0	0	0	0	1 (0.0)
Extremity necrosis	0	0	0	0	0	0	1 (0.0)
Peripheral arterial occlusive disease	0	0	0	0	0	0	1 (0.0)
Thrombosis	0	0	0	0	0	0	1 (0.0)

Source: Table G.3.9.6.1.1, ISS

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

A listing of patients with SAEs (other than hypoglycemia-related SAEs) occurring after randomization (n=9 for Afrezza TI and n=13 for comparator) newly reported for the pooled Phase 2/3 Safety population (all from either study 171 or study 175) in the current 2013 Resubmission is shown in Table 24. Again, there is no apparent pattern of SAEs, as they cover a range of SOCs/PTs. Many of the events in the T2DM trial were cardiovascular events which is not unexpected for this population.

Table 24– Listing of Patients with Non-hypoglycemic Serious Adverse Events (SAEs) Occurring after Randomization in the Pooled Phase 2/3 Population since the 2010 Resubmission cutoff - T1DM and T2DM combined

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

*verbatim from investigator: Large dihiscence of the tegmen mastoideum secondary to a congenital abnormality of the tegmen plate causing an acute CSF leak in left ear)
Source: ISS

Selected narratives for Afrezza TI-treated patients experiencing SAEs (including narratives of interest from the Original NDA and 2010 Resubmission) are listed in the Appendices of this briefing document (section 5.2).

Table 25 shows that there were fewer SAEs among Afrezza TI-treated patients than among placebo-treated patients in study 175, although the power to detect differences in Afrezza TI vs. placebo regarding the incidence of SAEs in study 175 alone is limited by small numbers.

Table 25– SAEs during the Randomized Treatment Phase of Study 175

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

Source: Table 37, study 175 CSR

Reviewer's comment: Overall, it appears that SAEs (non-hypoglycemic/non-pulmonary) were rare with Afrezza TI treatment and did not suggest any important safety signal. Pulmonary adverse events are discussed in a separate section of this briefing document.

4.3.3 Dropouts and/or Discontinuations

In the original NDA, premature discontinuation from clinical trials was higher among Afrezza TI-treated subjects for both T2DM and T1DM populations: the pooled phase 2/3 database for T1DM and T2DM combined showed that adverse events leading to discontinuation occurred in 7.7% of Afrezza TI-treated patients and 1.2% of comparator-treated patients. This difference was driven predominantly by discontinuations due to adverse events in the Respiratory, Thoracic, and Mediastinal Disorders SOC (4.2% with Afrezza TI vs. 0.1% with comparator). Cough was the only adverse event leading to discontinuation that occurred in >1% of Afrezza TI-treated patients

in the controlled phase 2/3 database. Most of the other reported adverse events leading to discontinuation occurred in isolated Afrezza TI- or comparator-treated patients. The higher rate of withdrawals for non-pulmonary adverse events was possibly due, in part, to the open-label nature of the trial designs because an examination of the incidence rate of adverse events overall showed no difference between Afrezza TI and comparators suggesting that subjects treated with Afrezza TI were dropping out at a higher rate for essentially the same adverse events.

T1DM

In the current Resubmission, dropouts due to AEs were more frequent among T1DM Afrezza TI-treated patients (9.2% for Gen2, 6.1% for MedTone and 0.5% for comparator) (Table 26). Again, the dropouts appear to be driven predominantly by discontinuations due to adverse events in the Respiratory, Thoracic, and Mediastinal Disorders SOC, (4.4% with Afrezza TI vs. 0% with comparator), primarily cough. The rate of dropout was higher among Gen2 treated patients than MedTone treated patients; this finding appears to be driven by a higher rate of withdrawal for cough and dyspnea. AEs leading to dropout that occurred in more than one subject in the Afrezza TI Total group were cough (3.3%); dyspnea (0.6%); hyperglycemia diabetes mellitus inadequate control, hypoglycemia, bronchial obstruction, and headache (each in 0.3%).

The Sponsor tabulated the incidence of AEs leading to dropout among the T1DM population for the 2010 Resubmission, the current 2013 Resubmission, and the difference totals. Comparison of AEs leading to discontinuation among subjects with T1DM in the 2010 Resubmission with those in the 2013 Resubmission showed no important differences.

Table 26– Adverse Events Leading to Dropout –T1DM – 2013 Resubmission

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

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

Source: Table 62, ISS

T2DM

In the T2DM population, dropouts due to AEs were also more frequent among Afrezza TI-treated patients (3.6% for Gen2, 7.9% for MedTone [7.5% Total Afrezza TI] and 1.5 % for comparator) (Table 27). Total TP placebo had an incidence of dropout of 3.4%. The most common AEs that led to discontinuation in the Afrezza TI group were: cough in 2.5%, hyperglycemia in 0.5%, and dyspnea in 0.5%.

The Sponsor tabulated the incidence of AEs leading to dropout among the T2DM population for the 2010 Resubmission, the current 2013 Resubmission, and the difference totals. These are similar.

The pattern of dropouts observed for the T2DM population appears similar to the T1DM population. One notable difference, however, is that, in contrast to the T1DM patients, the incidence of dropout is higher for MedTone-treated patients compared with Gen2-treated patients.

Again, although the overall power to detect differences in Afrezza TI vs. placebo in the incidence of dropout due to AEs in study 175 alone is limited by small numbers, examination of the data from this trial alone allows a comparison of Afrezza TI vs. placebo for a the Gen 2 device, and shows that the incidence of AEs leading to dropout was similar: 4.0% in the Afrezza TI group, and 5.1% in the TP group.

Table 27- Adverse Events Leading to Dropout –T2DM – 2013 Resubmission

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

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

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

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

Source: Table 64, ISS

T1DM and T2DM populations combined

Overall, for the pooled phase 2/3 data the cumulative incidence of discontinuations due to adverse events was 47/679 subjects (6.9%) for Afrezza TI and 4/664 (0.6%) for comparator which is similar to the results for the pooled phase 2/3 data from previous submissions.

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

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

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

4.3.4 Significant Adverse Events

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

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

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

In the Afrezza TI development program, four cases of lung malignancy were reported: two in the clinical program reported in the 2009 Original NDA and two spontaneously reported after the subjects' completion of participation in clinical trials (Table 28). Narratives for these patients are located in the Appendices (section 5.2).

Table 28 – Lung Cancer Cases in Afrezza TI-Treated Patients

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

Source: Adapted from FDA DOP2 consult report

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

A summary of lung cancer cases in Afrezza TI exposed patients versus comparators is presented in Table 29. In the pooled phase 2/3 safety database the exposure-adjusted incidence rate of lung cancer was 0.05% in the Afrezza TI group. In a database that includes all Phase 2/3 controlled and uncontrolled studies of >14 days duration, the exposure-adjusted incidence rate of lung cancer was 0.07% in the Afrezza TI group because of the additional case of the patient in uncontrolled study 010.

Table 29 –Lung Cancer in the Afrezza TI Program

	AFREZZA TI	COMPARATOR
Pooled phase 2/3 safety database		
N (SYE)	3017 (2052)	2488 (2250)*
Events of lung cancer	1	0
Percent with event	0.03%	0%
Exposure-adjusted incidence (per 100 SYE)	0.05	0
Phase 2/3 controlled and uncontrolled studies of >14 days duration		
N (SYE)	3283 (2747)	2494 (2267)
Events of lung cancer	2	0
Percent with event	0.06%	0
Exposure-adjusted incidence (per 100 SYE)	0.07	0
All exposed patients^		
Events of lung cancer	4	N/A

*Includes 290 subjects and 98 SYE exposed to Technosphere Placebo
^Incidence rates not calculated because two cases are spontaneous reports
SYE=Subject year exposure

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

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

4.3.5 Submission Specific Primary Safety Concerns

Based on FDA request, adverse events of special interest were summarized individually by the Sponsor. Those discussed in this section include:

- Diabetic ketoacidosis (DKA)
- Cardiovascular
- Malignancy (general)
- Immunogenic

- Eye events
- Hypoglycemia
- Anti-insulin antibodies

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

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

Diabetic Ketoacidosis (DKA) in Patients with T1DM

There were no additional cases of DKA identified in the new Phase 3 studies (recall that only one new study was performed in T1DM patients in the resubmission).

In the original NDA, DKA occurred with greater frequency in Afrezza TI arms in patients with T1DM (13 subjects in the Afrezza TI group and 3 in the comparator group). In the original dataset, using exposure adjusted incidence rates, DKA occurred 4.8 times more frequently in Afrezza TI treated patients than comparator treated patients (2.4 per 100 patient-years versus 0.4 per 100 patient years for Afrezza TI versus comparator).

Review of the narratives for these cases suggested that most identified episodes were triggered by infections. (Narratives of interest are presented in the Appendices [section 5.4]).There was one event of DKA that was directly attributed to improper use of the inhaler, but the narrative contained insufficient details to tell whether the subject actually had DKA or just severe hyperglycemia. One case occurred in a patient stopping the subcutaneous basal insulin on her own accord without consulting with her physician. One case was associated with an overdose of paracetamol and ensuing illness. The cases of DKA occurred as early as 3 days after start of Afrezza TI treatment up to > 400 days after start of Afrezza TI treatment with no temporal apparent pattern. Basal insulin alone in sufficient doses should be adequate to prevent DKA, and the narratives suggested that some DKA events were due to missed doses of all insulins as well as infections. In general, however, narratives are insufficiently detailed to determine whether Afrezza TI, through under-insulinization, contributed to these events.

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

Reviewer's comment: The Resubmission does not change the overall review findings for DKA, in that a higher incidence of DKA was observed among Afrezza treated patients. DKA and glycemic control are linked, and in light of the observed worse efficacy of Afrezza

TI compared with insulin aspart as a prandial insulin for glycemic control in T1DM patients, the possibility exists that Afrezza TI contributed to this observed imbalance.

Cardiovascular Safety

In December 2008 FDA published a Guidance for Industry entitled Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. This guidance document requests that sponsors of new pharmacologic therapies for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. Note that this recommendation generally does not apply to insulin products because insulin is the only life-saving treatment available for patients with T1DM and is the last-line treatment for patients with T2DM who have failed all other available therapies. The Afrezza TI development program was not designed to evaluate cardiovascular safety by the manner suggested in the Guidance, e.g. the study designs did not contain prespecified and prospectively adjudicated cardiovascular endpoints, and the studies did not selectively recruit high risk patients. Nonetheless, the Sponsor submitted an analysis of cardiovascular safety which evaluated cardiovascular events identified through an independent blinded MedDRA search strategy. In the Sponsor's analysis, multiple MedDRA system organ classes were inspected for all cardiac and/or vascular terminology including:

- Cardiac disorders
- General and administration site conditions
- Nervous system disorders
- Surgical and medical procedures
- Vascular disorders

In the original NDA the incidence of any cardiovascular and/or cerebrovascular AEs in subjects with T1DM and T2DM was comparable between treatment groups with 198/2409 subjects (8.2%, incidence rate =10.9 per 100 SYE) in the Afrezza TI group and 171/1944 subjects (8.8%, incidence rate = 8.3 per 100 SYE) in the comparator group.

Caveats to this analysis include the observation that the Sponsor did not include terms from Investigations such as ECG-related preferred terms and Creatine Kinase-related preferred terms, and that this analysis should not be considered a "MACE" (major adverse cardiovascular events) analysis because the analysis included such terms representing arrhythmias, cardiac valvular disorders, and venous diseases among others, which are not considered MACE endpoints. However, the number of subjects with ischemic events (e.g., angina pectoris, angina unstable, myocardial infarction, and myocardial ischemia) was low and similar between treatment groups suggesting no evidence in the phase 2/3 program of excess cardiovascular risk.

In the current 2013 Resubmission, the Sponsor updated their previous analyses and also performed a custom analysis of MACE "FDA custom MACE" which they based on the FDA review of other non-insulin therapies that were already under development at the time of issuance of the 2008 Guidance. Note that this "FDA Custom MACE" is not necessarily a

preferred or standard approach to MACE analysis, but was rather a unique approach crafted for applications 'caught in the middle' of product development and release of the Guidance.

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

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

Malignancy

In the 2013 Resubmission, events reported as neoplasms were identified using the same MedDRA search strategy as used in the 2009 Original NDA and were summarized by SOC, including the PT that referred to either a benign or malignant neoplastic disease. These terms were reviewed to identify malignant and benign neoplasms.

In the original NDA controlled phase 2/3 database, there were 40 (1.7%) Afrezza TI-treated patients and 30 (1.5%) comparator-treated patients with reported neoplasms. Based on an analysis of malignant tumors, there were 12 (0.5%) events with Afrezza TI and 7 (0.4%) events with comparator. In this analysis, breast cancer (n=4 with Afrezza TI vs. n=2 with comparator) and prostate cancer (n=3 with Afrezza TI vs. n=1 with comparator) were the only malignant tumors reported in more than one Afrezza TI-treated patient. The conclusion was that there were very few events and that the available data did not support an association between Afrezza TI and malignancies.

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

Twenty-one malignant neoplasms were included in the analysis (excluding the 5 cases of basal cell carcinoma and 1 case of squamous cell carcinoma of the nose): 13 of 3017 subjects (0.43%)

who received Afrezza TI, 1 of 290 subjects (0.3%) who received TP (placebo), and 7 of 2198 subjects (0.32%) who received comparator treatment (Table 30).

Table 30–Reported Malignancies in Type 1 or Type 2 Subjects, Excluding Non-Melanoma Skin Malignancies (Pooled Safety Population)

	All Malignancies			Malignancies with Latency ≥ 90 days	
	Afrezza TI (N=3017)	TP (N=290)	Comparator (N=2198)	Afrezza TI (N=3017)	Comparator (N=2198)
Breast cancer	4		2	4	2
Colon cancer	1		1	1	1
Ovarian epithelial cancer	1			1	
Bile duct cancer	1				
Prostate cancer	3		1	2	1
Cervix carcinoma			1		1
Rectal cancer	1		1		
Metastatic gastric cancer	1			1	
Pancreatic carcinoma			1		
Neuroendocrine oat cell type (small cell) lung cancer	1			1	
Squamous cell carcinoma of the hard palate		1			
Total	13	1	7	10	5

Source: Reviewer's table

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

Immunogenic

Insulins, including Humulin R and Novolin R are labeled for allergic reactions, including severe, life-threatening, generalized allergy (e.g., anaphylaxis). Although human insulin and the insulin in Humulin R, Novolin R and Afrezza have identical amino acid sequences, expression systems in bacteria or yeast likely alter other characteristics of these products that predispose to allergy. Based on our knowledge of allergic reactions with currently available insulins, Afrezza TI is expected to have potential for hypersensitivity reactions.

Potentially immune-related events were identified and summarized from a predefined set of MedDRA codes. This list of events was agreed upon with FDA prior to initiation of the two Gen2 phase 3 studies 171 and 175.

Table 31 summarizes adverse events potentially related to allergic reactions in the combined T1DM and T2DM population using the pre-specified MedDRA terms and using all available pooled phase 2/3 data as of the 2013 Resubmission. Similar to the original NDA event rates were low and generally comparable between Afrezza and comparator (which mostly included other insulin therapies): 2.4% (73/3017) in the Afrezza TI group, 1.5% (33/2198) in the comparator group, and 2.4% (7/290) in the TP group. Some of these adverse events (e.g., laryngospasm, throat tightness) may be related to a non-allergic mechanism (e.g., irritation) from inhalation of Afrezza.

Table 31–Potentially Immunogenic Adverse Events – T1DM and T2DM Combined (2013 Resubmission Safety Population)

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

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

Source: Sponsor's Table 88, ISS

Reviewer's comment: Although incidence comparisons do not suggest a greater incidence of potentially immunogenic adverse events when compared to placebo or comparator, findings of hypersensitivity reactions with Afrezza are supported by some events in the NDA, such as a patient who developed facial edema and respiratory difficulties after the second dose of Afrezza TI. Labeling for Afrezza would be expected to include information about hypersensitivity reactions in Warnings and Precautions because of the life-threatening nature of some potential reactions and the likelihood that they are causally related to the product to align with other insulin products.

Eye events

In the original NDA, when including all adverse events (serious and non-serious) in the pooled phase 2/3 trials there were 5 cases of retinal detachment (all with Afrezza TI) and 17 cases of intraocular hemorrhage (5 with Afrezza TI vs. 12 with comparator). Therefore, retinal detachment or intraocular hemorrhage occurred in a total of 10 Afrezza TI-treated patients (0.4%; 0.55 per 100 patient-years) and 12 comparator-treated patients (0.6%; 0.59 per 100 patient-years). Given the 5 to 0 imbalance in cases of retinal detachment with Afrezza TI vs. comparator, the Sponsor was asked to provide an updated analysis of eye events in the 2013 Resubmission.

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

Reviewer's comment: The new data in the 2013 Resubmission do not change the previous observation of an imbalance of retinal detachment not favoring Afrezza.

Hypoglycemia

Hypoglycemia was reviewed thoroughly in the original NDA; analysis of hypoglycemia was challenging because each of the studies included somewhat different definitions of hypoglycemia, and different trial designs (some with forced titration and some with treat-to-target designs). For example, FDA review noted a drastic difference in the overall incidence of severe hypoglycemia in the two T1DM trials submitted with the original NDA (0% in Study 101 vs. ~35% in Study 009), which is, at least in part, due to the different definitions of severe hypoglycemia. An FDA statistician analyzed the hypoglycemia data (with a focus on severe hypoglycemia) to determine whether there was sufficient evidence to support the Sponsor's assertion that fewer hypoglycemic events are seen with Afrezza TI compared to insulin controls.

The FDA statistician's approach to evaluate hypoglycemia in the individual trials and not to pool the data given that the trials had different comparators and used different definitions of hypoglycemia. General observations from these analyses were:

- The incidence of hypoglycemia was numerically higher with Afrezza TI than placebo in placebo-controlled studies, which is expected based on Afrezza TI's mechanism of action (an insulin) and the better glycemic control achieved in the Afrezza TI group (the placebo group was not randomized to active anti-diabetic therapy).
- In active comparator studies where Afrezza TI was compared with another insulin, the incidence of hypoglycemia was generally lower for Afrezza TI than comparator, but in these studies the comparator groups had better glycemic efficacy than the Afrezza TI groups, confounding the hypoglycemia analyses.

The FDA statistician noted that that Study 102 (Afrezza TI + glargine vs. 70/30 insulin in T2DM) was the only study that statistically clearly showed a lower incidence of protocol-defined severe hypoglycemia (14/323 or 4.3% in the Afrezza TI group vs. 33/331 or 10% in the NovoLog Mix 70/30 group; $p<0.01$). In this study, Afrezza TI+glargine was shown to be noninferior to NovoLog Mix 70/30; therefore, differences in glycemic control do not explain these findings. However, cases of hypoglycemia with a blood glucose <37 mg/dL were classified as severe (regardless of symptoms), and this is not a typical definition for severe hypoglycemia. In fact, most of the patients classified as having severe hypoglycemia (12/14 for Afrezza TI and 30/33 for comparator) had a blood glucose <37 mg/dL and did not require the assistance of another person and did not have accompanying cognitive neurological symptoms. When severe hypoglycemia was more typically defined, the incidence is low and comparable between treatment groups – only 3 Afrezza TI+glargine-treated patients and 5 NovoLog Mix 70/30-treated patients required the assistance of another person to treat and had at least 1 cognitive neurological symptom.

For the new data since the 2010 Resubmission, definitions of hypoglycemia were applied consistently across both studies 171 and 175 and were appropriately based on the ADA definitions (definitions are listed in section 2 above). The two new studies are analyzed separately because of the difference in diabetes type and comparator between the two studies.

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

Study 171 – T1DM

Event rate analyses

The event rates for hypoglycemia in study 171 since randomization performed by the Sponsor are presented in Table 32. The Sponsor also performed analyses of event rate by demographic variables, by week, and by final HbA1c at Week 24. These analyses should be considered exploratory and are not discussed here.

Table 32 – Event Rates for Hypoglycemia Events – Study 171

Category	TI Gen2 (N=174)	TI MedTone (N=173)	Insulin aspart (N=171)	TI Gen2 - Insulin aspart *P*-value [1]
All Hypoglycemia				
Number of Subjects at Risk	174	173	171	
Number of Subjects with Events (%) [2]	167 (96.0)	166 (96.0)	170 (99.4)	
Number of Events	7919	8764	12571	
Exposure Time in Subject-Month	807.7	850.7	899.6	
Event Rate (per Subject-Month)	9.80	10.30	13.97	<.0001
Mild or Moderate Hypoglycemia				
Number of Subjects at Risk	174	173	171	
Number of Subjects with Events (%) [2]	166 (95.4)	166 (96.0)	170 (99.4)	
Number of Events	7854	8679	12441	
Exposure Time in Subject-Month	807.7	850.7	899.6	
Event Rate (per Subject-Month)	9.72	10.20	13.83	<.0001
Severe Hypoglycemia				
Number of Subjects at Risk	174	173	171	
Number of Subjects with Events (%) [2]	32 (18.4)	37 (21.4)	50 (29.2)	
Number of Events	65	85	130	
Exposure Time in Subject-Month	807.7	850.7	899.6	
Event Rate (per 100-Subject-Month)	8.05	9.99	14.45	0.1022
Hypoglycemia with Glucose <= 36 mg/dL				
Number of Subjects at Risk	174	173	171	
Number of Subjects with Events (%) [2]	41 (23.6)	45 (26.0)	63 (36.8)	
Number of Events	94	111	230	
Exposure Time in Subject-Month	807.7	850.7	899.6	
Event Rate (per 100-Subject-Month)	11.64	13.05	25.57	0.0009

Source: Table 54, Study 171 CSR

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

Incidence Rates Analyses

The incidence of any hypoglycemia during the randomized treatment period of the study was comparable in the Afrezza TI Gen2 (167 subjects, 96.0%) and the Afrezza TI MedTone (166 subjects, 96.0%) groups and in the insulin aspart group (170 subjects, 99.4%) (Table 33). The exposure-adjusted incidence per subject-month was similar across groups for any hypoglycemia and mild/moderate hypoglycemia.

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

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

Table 33– Incidence of Hypoglycemia – Trial 171

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

Study 175 – T2DM
The risk of hypoglycemia is expected to be higher with Afrezza vs. placebo; therefore, a brief summary of the Sponsor's analyses of hypoglycemia is presented here.

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

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

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

Reviewer's comment: For the T1DM trial, conclusions regarding hypoglycemia are confounded by the difference in efficacy observed between the two study arms and are entirely consistent with the fact that Afrezza was demonstrated to be less effective than comparator. For the T2DM trial, the result of greater hypoglycemia risk vs. placebo is expected.

4.4 Supportive Safety Results

4.4.1 Common Adverse Events

For analysis of common adverse events in the original NDA, the most common adverse events were analyzed separately for each of the main phase 3 trials in patients with T2DM. These data were not pooled because these trials used different comparators. The phase 2 and phase 3 T1DM trials were pooled because these trials used similar treatments. Tables 34 and 35 show the findings for common adverse events in the T1DM and T2DM populations, respectively. Note that all of these trials used the MedTone inhaler.

Table 34– Common Adverse Events (incidence >2% and occurring ≥0.5% more frequently with Afrezza TI than comparator) in the Original NDA phase 2/3 trials in patients with T1DM, excluding cough and hypoglycemia

Preferred Term	TI + glargine N=614	Aspart + glargine N=599
	n (%)	n (%)
Any	544 (89)	539 (90)
Headache	33 (5.4)	19 (3.2)
Pulmonary function test decreased	27 (4.4)	8 (1.3)
Pharyngolaryngeal pain	23 (3.7)	9 (1.5)
Hyperglycemia	16 (2.6)	9 (1.5)

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

Table 35– Common Adverse Events (incidence >2% and occurring ≥0.5% more frequently with Afrezza TI than comparator) in the Original NDA main phase 3 trials in patients with T2DM, excluding cough and hypoglycemia

Study 014	**TI + glargine N=151**	**Aspart + glargine N=158**
Any	67 (44)	71 (45)
Upper respiratory tract infection	5 (3.3)	3 (1.9)
Osteochondrosis	5 (3.3)	1 (0.6)
Pyelonephritis	3 (2.0)	2 (1.3)
Study 102	**TI + glargine N=323**	**NovoLog Mix 70/30 N=331**
Any	272 (84)	296 (89)
Upper respiratory tract infection	39 (12.1)	24 (7.3)
Nasopharyngitis	30 (9.3)	28 (8.5)
Headache	18 (5.6)	12 (3.6)
Back pain	16 (5.0)	9 (2.7)
Bronchitis	16 (5.0)	7 (2.1)
Diarrhea	13 (4.0)	9 (2.7)
Throat irritation	11 (3.4)	0
Pharyngitis	10 (3.1)	8 (2.4)
Pharyngolaryngeal pain	10 (3.1)	8 (2.4)
Nausea	9 (2.8)	6 (1.8)
Muscle cramp	9 (2.8)	2 (0.6)
Fatigue	9 (2.8)	1 (0.3)
Blood creatine phosphokinase increased	8 (2.5)	2 (0.6)
Hyperglycemia	7 (2.2)	3 (0.9)
Abdominal pain upper	7 (2.2)	3 (0.9)
Study 103	**TI alone or TI + met N=355**	**Insulin secretagogue + met N=166**
Any	201 (57)	73 (44)
Headache	10 (2.8)	2 (1.2)
Hyperglycemia	9 (2.5)	1 (0.6)
Study 030	**TI N=656**	**Comparator N=678**
Any	**512 (78)**	**451 (67)**
Nasopharyngitis	48 (7.3)	41 (6.0)
Arthralgia	28 (4.3)	22 (3.2)
Influenza	27 (4.1)	23 (3.4)
Diarrhea	20 (3.0)	15 (2.2)
Pharyngolaryngeal pain	18 (2.7)	2 (0.3)
Throat irritation	17 (2.6)	1 (0.1)
Bronchitis	14 (2.1)	11 (1.6)
Headache	16 (2.4)	9 (1.3)
Fatigue	16 (2.4)	7 (1.0)
Nausea	16 (2.4)	7 (1.0)
Dyspnea	14 (2.1)	2 (0.3)

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

For the 2013 Resubmission, there were only one new phase 3 study in each diabetes type; therefore, each trial is analyzed individually.

Table 36 shows the most common adverse events occurring in ≥2% of Subjects in trial 171, and occurring more frequently with Afrezza TI than comparator. Afrezza TI-treated patients reported more cough, upper respiratory tract infection, headache, dyspnea, bronchitis, and throat irritation than did insulin aspart-treated patients. For comparison, headache was also commonly reported by T1DM patients treated with the MedTone device in previous studies, as was pharyngolaryngeal pain which may be similar to throat irritation. Dyspnea was not reported commonly with the MedTone device. Note that none of the events of dyspnea were serious, although 4 led to premature study discontinuation.

Table 36- Common Adverse Events Occurring in ≥2% of Subjects in Trial 171 and Occurring More Frequently with Afrezza TI than Comparator

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

Source: Adapted from Table 37, Study 171 CSR

Table 37 shows the most common adverse events occurring in ≥2% of Subjects in trial 175, and occurring more frequently with Afrezza TI than comparator. Because the placebo in trial 175 was Technosphere Powder, many of the adverse events related to inhaling a dry powder appear to be common in the placebo group as well. Therefore, events from the Respiratory, Thoracic, and Mediastinal Disorders System-Organ Class are shown in the table as well, regardless of whether the event was more common in the Afrezza TI or TP group. The only additional event to which this approach applies is Bronchitis.

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

Table 37- Common Adverse Events Occurring in ≥2% of Subjects in Trial 175 and Occurring More Frequently with Afrezza TI than Placebo and all Events from the Respiratory, Thoracic, and Mediastinal Disorders System-Organ Class Occurring in ≥2% of Subjects

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

Source: Adapted from Table 30, Study 175 CSR

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

4.4.2 Laboratory Findings

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

For the original NDA submission, the mean changes, shift analyses, and outlier analyses for hematology and chemistry data (including liver and renal parameters) for the controlled phase 2/3 trials in patients with T1DM and T2DM showed no clinically meaningful changes in these parameters with Afrezza compared to control. In the phase 2/3 program, elevations in ALT were balanced between Afrezza TI and comparator groups.

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

4.4.3 Vital Signs

In the two new phase 3 studies, vital signs obtained at all in-clinic visits included temperature, blood pressure (in the supine position), pulse, and respiratory rate. Similar to the original NDA there were no clinically meaningful changes in heart rate or blood pressure with Afrezza TI or comparators in the controlled phase 2/3 trials in patients with T1DM and T2DM.

4.4.4 Electrocardiograms (ECGs)

In the two new phase 3 studies, standard 12-lead ECGs were recorded with the subject in the supine position at Screening and study end. The PI determined whether any abnormal values were to be documented as clinically significant or not clinically significant. This methodology is similar to that of the original NDA submission in which ECGs were reviewed by investigators and were not read centrally by cardiologists, which limits conclusions. The investigators classified the electrocardiogram as “normal”, “abnormal not clinically significant” or “abnormal clinically significant”. These categories are broad and somewhat subjective (e.g., criteria for assessing clinical significance varies from one investigator to the next). Therefore, the ECG analyses have limited utility. The sponsor could be asked to have the ECGs reanalyzed centrally by cardiologists; however, there is no basis for doing so based on the currently available data - there were no concerning findings in the non-clinical trials, the Thorough QT Study, or based on reported cardiovascular adverse events. In addition, there is extensive history with insulin products administered via other routes of administration (including intravenously), which have higher bioavailability than that achieved with Afrezza TI.

4.4.5 Special Safety Studies/Clinical Trials

Study 171 was designed so that a head-to-head comparison of pulmonary safety could be obtained between the MedTone and Gen2 devices. Therefore, this study provides opportunity to examine non-pulmonary safety comparing the two devices. Note that this section discusses primarily exploratory analyses and/or observations that the trial was not designed to assess.

There were no deaths in Afrezza TI-treated patients. The incidence of SAEs was low in both treatment groups but higher in the MedTone group: Gen2, 5 subjects (2.9%); MedTone, 9 subjects (5.2%). Table 38 displays the SAEs by MedDRA PT.

Table 38– Serious Adverse Events in Trial 171

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

Source: Adapted from Table 45, Study 171 CSR

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

In regards to withdrawals due to adverse events, the proportion of subjects who withdrew from the study due to an adverse event was higher in the Gen 2 group (16 subjects [9.2%] vs. 9 subjects [5.2%] in the MedTone group) (Table 39). It appears that discontinuations for cough were twice as frequent with Gen2 (10 vs. 5 patients). The second most common cause of discontinuation in the Gen2 group was dyspnea (including exertional) (5 patients vs. none). Note that no subject discontinued due to an AE in the insulin aspart group. The most frequent AE leading to subject discontinuations in the Afrezza TI Inhalation Powder group was Respiratory Events with Cough, accounting for 10 of the 16 subjects in the Afrezza TI Gen2 group, and 5 of the 9 subjects in the Afrezza TI MedTone group. Other AEs that led to early discontinuation in the Afrezza TI Gen2 group were dyspnea (4 subjects), and 1 subject each due to bronchial hyperreactivity, hypoglycemia, exertional dyspnea, and eye pruritis. AEs that led to early discontinuation in the Afrezza TI MedTone group were bronchial obstruction, inadequate diabetes control, dizziness, drug hypersensitivity, nausea, and sensation of foreign body in throat.

Table 39– Adverse Events Leading to Discontinuation in Trial 171

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

Source: Adapted from Table 48, Study 171 CSR

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

A similar proportion of subjects in each Afrezza TI treatment group experienced any AEs during the randomized treatment period: (58.0%) in the Afrezza TI Gen2 group and 104 (60.1%) in the Afrezza TI MedTone group. Table 40 displays common adverse events occurring in ≥2% of subjects during the randomized treatment period.

Table 40– Common Adverse Events Occurring in ≥2% of Subjects in Trial 171

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

Source: Adapted from Table 37, Study 171 CSR

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

Possible immunogenic events based on prespecified MedDRA preferred terms:
4 events were reported in the Afrezza TI MedTone group (2 drug hypersensitivity, 1 myalgia, 1 wheezing) and none were reported in the Afrezza TI Gen2 group.

There are no notable differences between Gen2 and MedTone in terms of vital signs, routine laboratory assessments, ECGs, or anti-insulin antibodies. The risk of hypoglycemia also appears similar between the two inhalers whether analyzing by numbers of subjects with events, or event rate; the numbers of subjects with events and the event rates were all slightly numerically lower for Gen2 compared to MedTone, but a statistical comparison was not performed.

Pulmonary function tests (spirometry): please see the pulmonary safety section of this briefing document. The Sponsor concluded that" Head-to head comparison between Afrezza TI Gen2 and Afrezza TI MedTone showed that there were no significant differences in the change from baseline to Week 24 in FEV1 or FVC. The overall magnitude and pattern of changes in lung function (FEV1, FVC and FEV1/FVC ratio) over a 24 week treatment period were similar between Afrezza TI Gen2 and Afrezza TI MedTone groups."

Reviewer's comment: Overall, the results of these analyses suggest no difference in safety between Gen2 and MedTone except for a higher rate of cough and dyspnea, with some events leading to dropout, with the Gen2 device. One caveat is that there are small numbers of events limiting conclusions. Given the small numbers, and because objective data is more sensitive and specific for picking up differences in safety issues compared with adverse event reporting, more weight should be given to review of the spirometry data in comparing pulmonary safety between the two devices.

4.4.6 Immunogenicity

The Agency requested that immunogenicity be assessed in the two requested Phase 3 clinical trials. The validated Kronus radioimmunoassay used to measure IAB levels (IgG, exclusively) was to be the same as used in the original NDA. FDA agreed with this proposal.

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

In sum, there was no identifiable relationship between insulin antibody concentrations and efficacy or selected safety (e.g., hypoglycemia, allergic reactions) findings. Of note, Exubera was also associated with higher antibody concentrations compared to controls in patients with T1DM and T2DM with greater increases seen in patients with T1DM. Similarly, as noted above, the higher antibody concentrations with Exubera did not have a clinical correlate.

5 Appendices

5.1 Deaths Narratives

Controlled phase 2/3 trials

MKC-TI-030/857/3469: A 59-yo Caucasian male in the Ukraine with type 1 DM received Afrezza TI 60 U prandially TID and basal insulin 40 IU subcutaneous (sc) QD. The duration of treatment at the onset of the event was 479 days. Patient was found dead at his desk. Blood glucose on the scene was 90 mg/dL. Autopsy showed coronary atherosclerosis. The cause of death was listed as acute cardiovascular collapse.

MKC-TI-030/458/3254: A 67-yo Caucasian female in Poland with type 2 DM, received Afrezza TI Inhalation 75 U prandially BID with the addition of 60 U QD day; and insulin glargine (Lantus) subcutaneous (sc) 16 IU QD. The duration of treatment at the onset of the event was 167 days. The patient was hospitalized for abdominal pain and diagnosed with cholangiocarcinoma. The patient died 5 months later while undergoing chemotherapy.

MKC-TI-030/526/0539: A 60-yo Caucasian female in Russia with type 2 DM complicated by retinopathy and neuropathy, HTN, received Afrezza TI 30 U TID prandially and insulin isophane, human biosynthetic (Protaphan), 34 IU subcutaneous (sc) QD as basal coverage. The duration of treatment at the onset of event was 109 days. The patient was hospitalized with neurologic symptoms and diagnosed with acute ischemic stroke. EKG also noted acute MI. Patient died 8 days later.

MKC-TI-102/483/2524: A 56-yo multiracial male in Brazil with type 2 DM complicated by retinopathy, HTN, dyslipidemia received Afrezza TI 75 U prandially at breakfast and lunch and 60 U at dinner and insulin glargine 50 IU subcutaneous (sc) QD. The duration of treatment at the onset of the event was 217 days. The subject's antidiabetic regimen also included metformin 850 mg po BID since 2001. Patient presented to hospital with hypertensive emergency and died of hemorrhagic stroke.

MKC-TI-030/031/0237: A 55-yo (year old) Caucasian female in the U.S. with type 2 DM received Afrezza TI 30 U prandially TID. The subject's antidiabetic regimen also included metformin 1000 mg BID since 2001, glyburide 10 mg BID since 1990, and rosiglitazone 8 mg QD since 2005. The duration of treatment at the onset of the event was 67 days. The dose had been increased 45 days prior to the event. The patient experienced sudden cardiac arrest while on a bus and could not be resuscitated. Patient had known coronary artery disease. No autopsy was performed. Cause of death was listed as cardiac arrest.

MKC-TI-030/162/0611: A 58-yo Caucasian male in the U.S. with type 2 DM received Afrezza TI 60 U TID prandially. Type of basal insulin not reported. The duration of treatment at the onset of the event was 178 days. The patient experience left sided hemiparesis and died in the hospital after progressive deterioration. According to the narrative the death certificate listed the cause of death as respiratory failure, CVA, congestive heart failure and diabetes mellitus type 2.

MKC-TI-102/523/2158: A 72-yo Caucasian male in Russia with type 2 DM and known coronary artery disease with history of previous MI received Afrezza TI 60 U TID prandially and insulin glargine 35 IU subcutaneously daily. The duration of treatment at the onset of event was 34 days. The patient complained of chest pain and died at home. An autopsy reported the cause of death as coronary heart disease.

MKC-TI-102/488/2219: A 64-yo Caucasian male in Brazil with type 2 DM received Afrezza TI 90 U prandially TID and insulin glargine 62 IU subcutaneously (sc). The duration of treatment at the onset of the event was 163 days. The patient was known to have arterial hypertension, surgery for peripheral arterial insufficiency, and dyslipidemia, but no history of previous MI. The patient experienced epigastric pain at home for 2 days and then collapsed. He was pronounced dead upon arrival to the hospital. Autopsy showed the cause of death to be acute MI.

MKC-TI-102/508/2981: A 50-yo Caucasian male in Russia with type 2 DM received Afrezza TI 90 U prandially TID and insulin glargine 48 IU subcutaneous (sc) QD. The duration of treatment at the onset of the event was 306 days. The subject's antidiabetic regimen also included metformin 850 mg BID po since 2003. Patient admitted with fever and died of overwhelming sepsis likely from a gangrenous toe. No hypoglycemia occurred.

MKC-TI-102/067/2909: A 62-yo Caucasian male in Argentina with T2DM. Afrezza TI 90 U at breakfast, 30 U at lunch and 90 U at dinner was administered between 07 Aug 2007 and 21 Dec 2007 when the subject was discontinued due an abnormal chest CT (this event was reported originally to the NDA as a discontinuation due to an adverse event) and was eventually diagnosed with biopsy proven neuroendocrine tumor with lung involvement. The subject died in (b) (6) due to the neuroendocrine tumor.

Uncontrolled, Long term safety study, on Afrezza TI

MKC-TI-010/409/1854: A 75-yo Caucasian male in the Czech Republic with type 2 DM. Afrezza TI 30 U was administered via inhalation QID. The duration of Afrezza TI Inhalation Powder treatment at the onset of event was 756 days. The subject's antidiabetic regimen also included insulin glargine 24 IU sc QD and metformin 1.5 g TID. Illnesses present at the onset of the events and other relevant medical history included dyslipidemia, coronary artery disease with angina pectoris New York Heart Association Class I to II, hypertension, hyperuricemia, and chronic LBBB. The patient experienced acute dyspnea, diagnosed with acute MI at hospital; complicated hospital course. Patient died 12 days later of cardiac failure.

MKC-TI-010/407/3316: A 67-yo Caucasian male in the Czech Republic with T2DM. He received Afrezza TI Inhalation Powder 45 U TID via inhalation starting on 22 Mar 2005 and was administered 30 U TID from 01 Nov 2005 to 13 Dec 2006. The subject's antidiabetic regimen also included glibenclamide and metformin. On 07 Dec 2006 while undergoing diagnostic tests for an anemia workup, he underwent a CT scan of the lungs, which showed two areas measuring 12 × 19 × 20 mm and 19 × 14 × 20 mm in segment S2 in the right side of the lungs which was

eventually (Feb 2007) confirmed to be bronchogenic carcinoma non-small-cell (T4N2M0). The patient's medical history was notable for tobacco use (40 cigarettes per day for 20 years) until 1985.

MKC-TI-010/009/0246: 73-yo Caucasian male in the United States with T2DM treated with Afrezza TI 90 U TID prandially starting 04 Aug 2004. The patient also used glargine since 20 Dec 2005. Patient was diagnosed with metastatic prostate cancer to the bone on 06 Jan 2006. The patient had a history of elevated PSA since 1993. The last dose of study drug was on 06 Jun 2006. The patient died on (b) (6). Cause of death was metastatic prostate cancer to the bone.

MKC-TI-010/403/2782: A 60-yo Caucasian male in the Czech Republic with T2DM treated with Afrezza TI 90 U TID from 20 Apr 2005 to 19 Apr 2006. The patient also took metformin. The patient began having nonspecific symptoms of dyspepsia and weight loss 10 Mar 2006 and was diagnosed with pancreatic CA on 27 Apr 2006 which resulted in discontinuation of Afrezza TI. The patient died on (b) (6) from metastatic adenocarcinoma of the pancreas.

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

<u>Death in Named Compassionate Use Program</u>

MK201000002 Compassionate Use Program Switzerland

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

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

5.2 Serious Adverse Event Narratives (Selected)

From the original NDA

T1DM Narratives from the Original NDA

Colon cancer with hepatic metastasis MKC- TI-009 186/1011: A 56-yo Caucasian male in the United States with type 1 diabetes mellitus was undergoing the screening phase of the trial and was not randomized into the study. Before he completed his screening visit he was diagnosed with metastatic colon cancer.

Hemoptysis and cough MKC- TI-009 237/1207: A 45-yo Caucasian female in the United States was receiving Afrezza TI 90 U before breakfast, 60 U before lunch and before dinner, and insulin glargine 30 IU daily subcutaneously (sc). On day 121 of treatment the subject reported episodes of coughing up blood (without sputum) for approximately the past 2 weeks that usually occurred 20 minutes after every Afrezza TI Inhalation Powder treatment. Afrezza TI Inhalation Powder was interrupted and the subject was given a prescription for insulin lispro (Humalog) 3 to 6 IU before each meal and instructed to continue insulin glargine 30 IU daily. Chest x-ray showed no abnormalities and PFTs were essentially unchanged. The symptoms resolved 11 days later. The subject discontinued from the trial due to the SAE.

Cerebral concussion MKC-TI-009 505/2090: A 23-yo Caucasian male in Russia received Afrezza TI 60 U at breakfast and 30 U at lunch and at dinner and insulin glargine 24 U QHS. The duration of treatment at the onset of the event was 205 days. The subject experienced a cerebral concussion after hitting his head on the steering wheel during a car accident. The subject experienced nausea and dizziness and lost consciousness for several minutes. The event was not

recorded as a hypoglycemic event because the blood glucose that morning before the subject was driving was normal. However, there is no report of a blood glucose being measured on the scene of the accident. The subject restarted Afrezza TI after hospital discharge.

Seizure MKC-TI-030 092/2391: A 49-yo Caucasian male in the United States received Afrezza TI 30 U TID from 22 Aug 2006 and insulin glargine (Lantus) 55 IU QD subcutaneously (sc) from 03 Aug 2006. The duration of treatment at the onset of the event was 6 days. On the morning of 27 Aug 2006, the subject was walking and noticed that his left hand was twitching. The subject's companions stated that he appeared to have had a seizure as his body was twitching. The subject spontaneously awoke from the incident, lying on the ground. His blood glucose was 146 mg/dL that morning before breakfast. No hypoglycemia was documented. No cause for the seizure was found. The extent of the workup for seizure is not described in the narrative. The subject continued in the trial.

Loss of consciousness/Epilepsy MKC-TI-030 406/2706: A 45-yo Caucasian male in the Czech Republic received Afrezza TI 30 U TID from 02 Sep to 18 Sep 2006 and then was increased to 45 U TID starting 19 Sep 2006. On 24 Sep the subject lost consciousness while driving and crashed into the car in front of him. He awoke on his own and drank cola prior to any emergency services arriving. He had not missed a meal. Hypoglycemia was never documented. In fact his blood glucose was 440 mg/dL on the scene. The subject remained in the trial. The subject apparently had a history of occasional loss of consciousness events prior to trial enrollment.

T2DM Narratives from the Original NDA

Polyarthritis MKC-TI-005/101/4920: A 67-year-old (yo) Caucasian type 2 diabetic female in Germany was hospitalized for polyarthritis 58 days after starting Afrezza TI. The pain was located in the back, hands, shoulders, and knees and lasted for several days. There was no action taken with study treatment and the subject completed the trial.

Pericarditis MKC-TI-005 302/2981: A 56-yo Caucasian type 2 diabetic male in Bulgaria received Afrezza TI and glargine. He was hospitalized for pericarditis 90 days after initiation of Afrezza TI. No action was taken with study drug and the subject completed the trial.

Multiple sclerosis MKC-TI-030 048/1962: A 55-yo Caucasian male in the United States received Afrezza TI and oral diabetic agents for the treatment of type 2 diabetes mellitus. Afrezza TI 60 U TID was administered from 28 Jul 2006 to 05 Apr 2008. On (b) (6), the subject was hospitalized due to complaints of multiple falls and left lower extremity weakness with difficulty getting out of bed. MRI findings were consistent with demyelinating plaques. He was diagnosed with new onset multiple sclerosis (MS), and was started on intravenous (IV) methylprednisolone (Solu-Medrol) with improvement in strength. The subject was withdrawn from the study.

Pituitary tumor benign (MKC-TI-030 095/0918: A 58-yo Caucasian male in the U.S. received Afrezza TI 30 U BID and 15 U QD from (b) (6) to (b) (6). Other medications

included pioglitazone and metformin. Duration of treatment at the onset of the event was 137 days. The patient was hospitalized with a severe headache on (b) (6) and was diagnosed with a pituitary macroadenoma with apoplexy which was surgically removed. The subject recovered with sequelae on (b) (6). The subject continued in the trial.

Essential thrombocythemia MKC-TI-030 508/1183: A 47-yo Caucasian female in Russia received Afrezza TI 30 U TID and metformin 850 PO BID both started on 29 May 2006. Isophane insulin 18 to 20 IU subcutaneously BID was started on an unknown date in 2007. The duration of treatment at the onset of the event was 311 days. On (b) (6), the subject was hospitalized for examination and treatment of unspecified diabetic complications. A high platelet count was noted. Bone marrow biopsy confirmed essential thrombocythemia. The patient was discontinued from the trial due to the development of myeloproliferative disorder.

Pharyngeal abscess MKC-TI-030 539/1292: A 58-yo Caucasian female in Russia was randomized to the Afrezza TI group. She received the TP alone for training on 02 Jun 2006. A few hours after administration of TP she became ill with symptoms of throat pain and edema and was diagnosed with pharyngeal abscess. She recovered but withdrew from the study due to the SAE.

Rheumatoid arthritis MKC-TI-030 853/3356: A 69-year-old Caucasian female in the Ukraine received Afrezza TI 30 U inhaled at breakfast and 45 U inhaled at lunch and dinner from 04 Oct 2006 to 02 Oct 2007; intermediate acting insulin was administered 26 IU subcutaneously (sc) at breakfast and 22 IU sc at dinner from 04 May 2006 onward, and metformin was administered 850 mg po BID was administered from 25 Oct 2006 onward. The duration of treatment at the onset of the event was 365 days. The subject was hospitalized for signs and symptoms consistent with rheumatoid arthritis. The subject withdrew from the study.

Diabetic ketoacidosis MKC-TI-030 907/2979: A 58-yo Caucasian female in Canada received Afrezza TI 90 U TID from 12 Sep 2006 to 11 Feb 2008; insulin detemir (Levemir) 22 IU QAM subcutaneously (sc) and 42 IU sc QHS was administered from 28 Sep 2007 to 11 Feb 2008, and Metformin 500 mg po BID was administered from 2000 to 11 Feb 2008. The duration of treatment at the onset of the first event was 339 days. The subject experienced DKA related to a URI and noncompliance related to depression. She permanently discontinued Afrezza TI and withdrew from the study.

Reviewer's comment: DKA is very unusual in T2DM raising the question of whether this was truly a case of DKA or perhaps whether this patient actually has T1DM.

Facial fracture and possible seizure MKC-TI-102 188/2450: A 60-yo Caucasian female in the United States received Afrezza TI 15 U prandially TID from (b) (6) onward. Insulin glargine 30 IU QD was administered subcutaneously (sc) from 30 Apr 2007 onward. Pioglitazone (Actos) 22.5 mg po QD was administered from 23 Jul 2007 onward. The duration of treatment at the onset of the event was 172 days. On (b) (6), the subject experienced a fall at home in her living room, where she hit a window ledge with her left eye bone and lost consciousness. She was subsequently brought to the hospital. The subject stated she did not

know why she fell; she thought she had a seizure but was unsure. Discharge diagnoses included syncope, status post fall, with probable seizure episode versus hypoglycemic episode. No blood glucose levels were reported. The event was not coded as hypoglycemia. The subject remained in the trial.

Acute hepatitis (viral) MKC-TI-102 247/1687: A 44-yo Caucasian male in the United States received Afrezza TI 75 U TID and insulin glargine 50 IU QHS subcutaneously (sc) from 13 Dec 2006 onward. The duration of treatment at the onset of the event was 121 days. On 12 Apr 2007, the subject experienced acute hepatitis. He presented to the emergency room on (b) (6) with nausea, vomiting, runny nose, diffuse myalgia, and arthralgia. He had a fever of 100.2. Alanine transaminase (ALT) was 1415, aspartate transaminase (AST) was 850, and alkaline phosphatase was 517. An Epstein-Barr virus serology was positive for viral capsid AB IgG and viral capsid AB IgM suggesting a recent infection. Acute viral hepatitis due to Epstein-Barr virus infection was the final diagnosis. On 23 Apr 2007, he followed up with his attending physician. Total protein was 7.8, albumin 4.0, A/G ratio 1.1, unconjugated bilirubin 1.0, total bilirubin 1.0, AST 59, ALT 325, and alkaline phosphatase 448. A hepatitis panel was negative for A, B, and C viruses.

Toxic hepatitis MKC-TI-030-3363: A 59-yo Caucasian male in Poland received Afrezza TI and Lantus since 25 Sep 2006. On 14 Feb 2008, at day 506 of treatment the subject had an adverse event reported by the Investigator as toxic hepatitis due to intake of Chinese herbs. A medical history revealed that the subject had been taking several doses of the herbal preparation for weight loss. His GGT was 2288 IU/L (normal range 10-249 IU/L). He was subsequently hospitalized on (b) (6) due to the event, however details of hospitalization were not provided. Additional liver enzymes confirming the diagnosis of toxic hepatitis were not reported by the Investigator. No action was taken with the study medications in response to the event. The event resolved on (b) (6) and the subject was discharged from the hospital on the same date.

Acute renal failure MKC-TI-102 289/3066: A 69-yo Caucasian female in the United States received Afrezza TI 15 U at breakfast, 45 U at lunch, and 90 U at dinner and Insulin glargine 22 IU at bedtime from (b) (6) onward. The duration of treatment at the onset of the event was 254 days. On (b) (6), the subject experienced shortness of breath, acute renal failure supratherapeutic INR, and urinary tract infection and was hospitalized. Creatinine was 4.1 mg/dL. The renal failure was attributed to lisinopril possibly in the setting of a gram-negative urinary tract infection. The subject did not discontinue from the trial.

Autoimmune disorder MKC-TI-102 507/2532: A 50-yo Caucasian female in the Ukraine received Afrezza TI U TID from (b) (6) onward. Insulin glargine (Lantus) 35 IU subcutaneously QD in the evening was administered from 22 Aug 2007 onward. The duration of treatment at the onset of the event was 155 days. On (b) (6), the subject was diagnosed with an unspecified autoimmune disorder during a planned hospitalization that began on (b) (6) due to deterioration in vertebral osteoarthrosis since May 2007. The vertebral osteoarthrosis began in 1980 with pain in the lumbar spine followed by intense headache, vertigo, with a history of multiple hospitalizations for this condition. On 30 Nov 2007, diagnostic

results included a higher titer of anti-DNA antibodies and isolated lupus erythematosus (LE) cells. No other clinical manifestations of systemic lupus erythematosus (SLE) were found. The subject was hospitalized again on (b) (6) for joint complaints. On 20 Mar 2008, results of an immunoassay included circulating immune complex 148 units, C-reactive protein 3.01 mg/dL, antibodies to cardiolipin IgG 32.5 GPL, and antibodies to cardiolipin IgM 21.2 MPL, LE cells negative, antibodies to DNA and rheumatoid factor both within normal limits. On 09 Jul 2008, during a follow-up, the subject's general condition was satisfactory, but pain and joint stiffness remained. The subject's medical history is notable for an erythematous rash on the skin of abdomen, chest, and neck, as well as swelling of the joints that occurred in 2004. The subject did not discontinue from the trial.

Deep vein thrombosis MKC-TI-103 484/1823: A 41-yo Black female in Brazil received Afrezza TI 30 U TID since (b) (6), and metformin 850 mg po TID since 01 Oct 2006. The duration of treatment for Afrezza TI Inhalation Powder at the onset of the event was 87 days. On (b) (6) the subject was hospitalized for a deep vein thrombosis. No etiology was identified and there is not enough information in the narrative to identify a cause. The subject did not discontinue due to this SAE.

Fall/Ankle fracture MKC-TI-103 852/2536: A 54-yo Caucasian female subject in Ukraine received Afrezza TI TID (90 U with breakfast, 75 U with lunch and60 U with supper) from 04 Jul 2007 to 08 Nov 2007 and 90 U at breakfast and lunch and 75 U at supper from 08 Nov 2007 to 10 Jan 2008, and metformin po BID (850 mg and 1850 mg) starting 04 Jul 2007. The duration of treatment at the onset of the first event was 141 days. On 21 Nov 2007, the subject fell down damaged stairs at home while on the way to work. There was no blood glucose measurement at the time and no loss of consciousness.

Angioneurotic edema MKC-TI-014 514/984: A female subject with history of allergy to insulin and multiple prior episodes of angioedema upon ingestion of apples, nuts, and pears. The adverse event occurred with the first dose of Afrezza TI and the subject was discontinued from the study.

Erosive esophagitis MKC-TI-030 001/0600: A 57 yo Caucasian male in the U.S. received Afrezza TI for 39 days before experiencing nausea and vomiting. He was hospitalized and found to have moderate erosive esophagitis on endoscopy. The subject recovered and resumed Afrezza TI treatment as the investigator did not think the event was related to Afrezza TI use, although an alternate causality was not found.

Esophageal ulcer MKC-TI-030 162/0465: A 55 yo Caucasian male in the U.S. while several months into Afrezza TI treatment experienced recurrent acute pancreatitis with a prolonged medical course complicated by recurrent hospital admissions for surgical complications, infections and pancreatic cysts. The subject was found to have small esophageal ulcers on one of the later admissions that appears to be due to the complications related to pancreatitis/recurrent emesis and abdominal pain. The ulcers are most likely not directly related to Afrezza TI inhalation.

Significant SAE narratives for trial 010 – uncontrolled safety trial not included in pooled safety data.

Meningioma MKC-TI-010 309/4411: A 61-yo Caucasian type 2 diabetic female in Bulgaria diagnosed with benign meningioma. The duration of treatment at the onset of the event was 729 days.

Renal carcinoma MKC-TI-010 403/2595: A 63-yo Caucasian type 2 diabetic male subject in the Czech Republic diagnosed with carcinoma in situ of the left kidney. The duration of treatment at the onset of the event was 548 days. The subject's antidiabetic regimen also included metformin and glimepiride.

Syncope MKC-TI-010 007/0215: A 52-yo Hispanic type 2 diabetic male in the United States received Afrezza TI 60 U TID from 14 Jul 2004 onward. The duration of treatment at the onset of the event was 1193 days. The subject's antidiabetic regimen also included insulin glargine 45 IU subcutaneously (sc) QD, metformin 1000 mg po BID, and rosiglitazone 8 mg po QD. On 19 Oct 2007, the subject was at work on a conference call when he suddenly passed out and fell on the floor. The subject lost consciousness for approximately 3 to 4 minutes. He had no sweating, dizziness, or weakness and had not had syncopal episode before in his life. He did report that prior to this syncopal episode, he had some numbness and tingling in his right arm. He had never had a hypoglycemic episode. His blood glucose level that morning was reported to be 89. No reason for the syncopal episode was ever found.

From the 2010 Resubmission

Hypoglycemia requiring assistance
Site Number/Subject ID Number: 028/0214
A 52-year-old Caucasian female in the U.S. received Afrezza TI and Lantus for T1DM in trial 117. The subject was treated with Afrezza TI 15 U to 60 U TID before meals and 15 U to 30 U at one other time during the day beginning 16 Jul 2009, and Lantus 14 IU sc QD at 9 AM since 2007. The duration of treatment from the start of therapy with Afrezza TI until the onset of the event was 30 days. On 14 Aug 2009 while at home, the subject experienced hypoglycemia. Her morning blood glucose level at 09:47 was 299 mg/dL. She took Afrezza TI 45 U and ate half a bagel. The subject was very busy that day with errands and cleaning. Her blood glucose level at 18:17 was 59 mg/dL. She ate 15 grams of carbohydrate and did not recheck her blood glucose. Her blood glucose at 20:13 was 163 mg/dL. She took Afrezza TI 15 U before dinner, which consisted of chicken and cheese. Subject stated she does not remember what happened next. She lives in a duplex and her neighbors heard some noise and called 911. The subject slid to the floor and paramedics found her sitting awake on the floor. The investigator confirmed the subject did not lose consciousness. The paramedics gave the subject oral carbohydrates and orange juice and the event resolved. No glucagon or i.v. dextrose was given. The subject was under a lot of stress, with increased activity for the day, the duplex was warm, and she had consumed no carbohydrates with dinner. The subject took Afrezza TI 4 minutes before eating dinner. The subject has a history of 4 severe hypoglycemic episodes since being diagnosed in 1959. The last severe hypoglycemia episode was August 2007.

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

Hypoglycemia
Site Number/Subject ID Number**:** 017/0013
A 60-year-old Caucasian male in the U.S. with T2DM was treated with Afrezza TI 15 U TID from 23 Jul 2009 to 10 Sep 2009 in Study 119 (an uncontrolled phase 2 pharmacodynamic study). The duration of treatment at the onset of the event was 45 days. The subject's antidiabetic regimen included glimepiride 4 mg po QD since 1997, metformin 2000 mg po QD since 2000, pioglitazone (Actos) 45 mg po QD since 2002, and sitagliptin 100 mg po QD since Feb 2009. On 05 Sep 2009, the subject experienced possible hypoglycemia although alcohol intoxication is possible alternate explanation for his symptoms. He was attending a wine tasting party and had not eaten a meal since 09:00. He inhaled 15 U Afrezza TI at 22:00 after consuming wine and cheese but without eating a meal, and felt light-headed, dizzy, and confused. He did not check his blood glucose level at that time. The subject fell asleep at the party and awoke on 06 Sep 2009 at 03:00. He returned home and checked his blood glucose level via finger stick, obtaining a result greater than 100 mg/dL at 10:00 but not recording the result. At that time, the subject felt nauseous and vomited a pink clear liquid. After that, the subject felt better and ate a meal, inhaling 15 U Afrezza TI before the meal. The subject felt fully recovered after eating the meal at 11:30 on 06 Sep 2009. The subject stopped taking Afrezza TI Inhalation Powder on 10 Sep 2009 at Visit 17 of the trial per the protocol.

Bradycardia
Site Number/Subject ID Number**:** 017/0014
A 63-year-old Caucasian male in the U.S. with T2DM in Study 119 (an uncontrolled phase 2 pharmacodynamic study) received Afrezza TI 30 U TID prandially from 23 Jul 2009 to 10 Sep 2009. The subject's antidiabetic regimen also included metformin 2 g po QD.
On (b) (6), the subject had an ECG as part of the study procedures during the last study visit and was found to have a heart rate of 44 bpm. He was referred to the ER for further evaluation. He was admitted the same day with a diagnosis of symptomatic bradycardia secondary to 2nd degree AV block. Symptoms reported were mild tingling of the fingers and toes, mild exercise intolerance, and mild fatigue. An ECG on the same day showed changes consistent with 2 to 1 AV block, right bundle branch block, and left anterior ventricular block. Troponin series were negative. He underwent an adenosine thallium stress test with normal results (LVEF 79%); he had no chest pain during the test and there was no significant myocardial perfusion defect. Oxygen saturation was 100% on 2 L nasal cannula. The subject underwent dual pacemaker placement on (b) (6) and subsequently noticed substantial improvement in energy level and well-being and noted that his hands and feet felt warmer. He was discharged and the event was considered resolved as of (b) (6). Discharge diagnosis included sinus bradycardia secondary to 2 to 1 AV block and left anterior hemiblock. The subject's medical history was significant for right bundle branch block since screening, but his heart rate was always > 60 bpm. The subject had no referable symptoms except, in retrospect, fatigue.

Renal papillary necrosis
Site Number/Subject ID Number**:** 017/0021
A 66-year-old Caucasian male in the U.S. in study 119 (an uncontrolled phase 2 pharmacodynamic study) received prandial Afrezza TI for T2DM. The subject's first dose of Afrezza TI was on 09 Feb 2010 at 15 U with meals, and was increased to 30 U at meals on 16 Mar 2010. The last dose of study drug in trial MKC-Afrezza TI-119 was on 20 Apr 2010. The subject was initiated into the extension trial MKC-Afrezza TI-158, receiving the first dose of Afrezza TI in that protocol on 21 Apr 2010. The duration of treatment at the onset of the event was 94 days. Afrezza TI was permanently discontinued as of 13 May 2010. The subject's antidiabetic regimen also included metformin 1 g po QD and subcutaneous insulin glargine 70 IU BID.
On (b) (6), the subject went to the emergency room (ER) with symptoms of kidney stones (right lower quadrant pain) and was diagnosed with right-sided renal papillary necrosis by the ER physician. The narrative does not mention analgesic use. Diagnostic laboratory results on (b) (6) included glomerular filtration rate estimated at 43 ml/min/1.73m2 (reference range: > 60 ml/min/1.73m2). Urinalysis showed a urine protein of 100 mg/dL (reference range: <20 mg/dL) and urine ketones of 40 mg/dL (reference: negative). Findings of a CT IVP urogram included significant right perinephric stranding with mild right hydronephrosis and hydroureter and delayed excretion of the right kidney. Laboratory results showed a blood urea nitrogen (BUN) of 31 mg/dL (reference range: 8 – 25 mg/dL) and serum creatinine of 1.6 mg/dL (reference range: 0.7 – 1.3 mg/dL). Treatment included hydrating with 2 L of normal saline, and the subject received 1 acetylcysteine (Mucomyst) dose and 3 doses to go home. The subject was discharged from the ER pain free and alert, with normal oxygen saturation on (b) (6). Serum creatinine had dropped to 0.8 mg/dL as of 12 May 2010. Follow-up with a urologist was planned. The subject was withdrawn from the study due to a renal dysfunction exclusion criterion on 13 May 2010.
The renal papillary necrosis was reported resolved on 13 May 2010.

Syncope
Site Number/Subject ID Number: 626/0004
A 52-year-old Caucasian male in the U.S. with T1DM in trial 139 (an uncontrolled phase 3 device study) received prandial Afrezza TI 45 U at breakfast, 60 U at lunch, and 75 U at dinner beginning (b) (6). The duration of treatment at the onset of the event was 97 days. On (b) (6), the subject experienced severe back pain, went to the emergency room, and was treated with Percocet (oxycodone hydrochloride, paracetamol) 5/325 for the pain. The subject experienced near syncope secondary to the pain medication and was hospitalized overnight for observation. The subject was discharged the next day. The event of syncope was considered mild in severity and resolved on (b) (6). No relevant tests were performed and no action was taken with Afrezza TI.

Abdominal discomfort
Site Number/Subject ID Number: 631/0011
A 63-year-old Caucasian female in the U.S. in trial 139 (an uncontrolled phase 3 device study) started treatment with Afrezza TI beginning on (b) (6). Current daily dosage was prandial Afrezza TI 15 U at breakfast and lunch, and 30 U at dinner for diabetes mellitus (unreported

type). Treatment duration at the onset of the event was 87 days. The subject's antidiabetic medication also included glimepiride (Amaryl) 0.5 mg po, metformin 1000 mg po, and sitagliptin phosphate (Januvia) 100 mg po daily.
On (b) (6), the subject experienced lower abdominal discomfort one day after receiving a transfusion for myelodysplasia and was hospitalized for unspecified treatment. An abdominal CT scan was negative, and the subject was referred to neurology for evaluation for neuropathic pain. No action was taken with Afrezza TI; the subject continued Afrezza TI treatment throughout hospitalization. The subject was subsequently discharged from the hospital on (b) (6); the event had resolved. Final diagnosis and outcome were unknown at the time of this report.

Atrial fibrillation
Site Number/Subject ID Number: 624/005
A 56-year-old Caucasian female in the U.S. with T1DM in trial 139 (an uncontrolled phase 3 device study) began treatment with prandial Afrezza TI on (b) (6) at 30 U TID and 15 to 30 U as needed for other meals or snacks. Afrezza TI dosing was increased to 45 to 60 U at each meal, beginning 18 Jul 2009. Treatment with Afrezza TI was interrupted on 20 Dec 2009 due to the onset of bronchitis, which resolved on 15 Jan 2010. In the interim, the subject received subcutaneous (sc) insulin aspart (Novolog) and sc insulin glargine (Lantus) on a sliding scale. Treatment with Afrezza TI subsequently resumed on 16 Jan 2010 at 45 to 60 U TID at meals with dosage depending on glucose levels. The duration of treatment prior to the onset of the event was 196 days.
On (b) (6) while at home, the subject experienced a sudden episode of "fluttering" and was sent to the emergency room by her internist. The diagnosis was atrial fibrillation of mild severity. Per hospital records, the subject presented with chest pain and palpitations with no peripheral edema; shortness of breath with no cough; dyspnea on exertion; no abdominal pain, nausea, vomiting, diarrhea nor rectal bleeding; no fever, chills, nor sweating; and no recent increase in alcohol or caffeine use. The subject also presented with elevated blood glucose (BG) of 400 mg/dL that had been present over the previous 5 days and was not lowered through self-titrated insulin.
Later that day pulse was elevated at 131. The subject was subsequently diagnosed with atrial fibrillation with rapid ventricular response and treated with Diltiazem 125 mg until conversion to normal sinus rhythm. Anticoagulants were not used because of the significant contraindication of spontaneous subconjunctival hemorrhage in left eye within 24 hours of presenting to the ER. The subject was admitted to telemetry for observation and was kept overnight for observation and released in the morning. No further episodes were reported. The subject had no cardiac history and had never experienced atrial fibrillation prior to (b) (6).

Anal fistula
Site Number/Subject ID Number: 023/3012
A 61-year-old Asian male in the U.S. in trial 159 (an uncontrolled phase 2 device use study) received Afrezza TI for T2DM. Prandial Afrezza TI 10 U TID was administered from 09 Mar 2010 to 18 Apr 2010. The subject's antidiabetic regimen also included sitagliptin phosphate (Januvia) 100 mg po QD, pioglitazone hydrochloride (Actos) 45 mg po QD, and glimepiride 4 mg po QD.

On (b) (6), after completing the treatment period of the trial, the subject saw his proctologist for follow up on hemorrhoids. He was diagnosed with an anal fistula and admitted to the hospital for surgery. Diagnostic tests and results were unknown at the time of this report. The event resolved and the subject was discharged on (b) (6) after unspecified treatment.

Diabetic ketoacidosis/acute renal failure
Site Number/Subject ID Number: Not applicable
A 31-year-old Caucasian female with T1DM in the United Kingdom was participating in a Compassionate Use Program of Afrezza TI due to severe needle phobia. Afrezza TI was administered daily at 15 U with breakfast, 45 U with lunch, and 60 U with dinner beginning on 22 Oct 2009. The duration of treatment at the onset of the event was 9 days. The patient's antidiabetic regimen included an unknown basal dose of insulin detemir (Levemir) by subcutaneous injection. On the evening of 31 Oct 2009, the patient drank alcohol. The patient missed the daytime Afrezza TI and Levemir doses on 01 and 02 Nov 2009 because she felt unwell. She was subsequently hospitalized and refused blood testing and intravenous cannulation due to her needle phobia and remained in severe metabolic acidosis (pH 6.94, BE 28.7). Glasgow Coma was reported as 12. She recovered on (b) (6) and was extubated on (b) (6). The investigator reported the ketoacidosis and acute renal failure as severe and life-threatening and confirmed that the patient recovered from both events without sequelae. Per the patient, her new physician confirmed that she would be able to restart Afrezza TI.

Selected SAE Narratives of Interest from the Current 2013 Resubmission

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

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

171/210/1913 – Bronchial hyperreactivity 58 yo man randomized to Gen2 arm. The subject received Afrezza TI, 10 – 20 U at mealtimes plus 10 U supplemental doses as needed, for approximately 3 weeks when he experienced cough, chest pain and difficulty breathing and was hospitalized with the diagnosis of reactive airway disease. On hospital admission, the subject had a respiratory rate of 16 breaths per minute and oxygen saturation of 97%. The subject's chest x-ray showed a tall hyperinflated lung with a slender heart, and a flattened hemidiaphragm consistent with the pattern of hyperinflation. The study medication was discontinued and the subject was treated with oral Albuterol 2.5 mg per 3 mL four times daily and oral Tussionex 8-10 mg per 5 mL every 12 hours for 10 days. The subject was discharged from the hospital in stable condition after 3 days. Levosalbutamol tartrate (Xopenex HFA) as needed for shortness of breath

was started 10 days later. The subject was withdrawn from the study due to the reactive airway disease, which was considered resolved with sequelae. FEV1 was 3.39 L (85% predicted) at the screening visit and 3.45 L (87% predicted) at the baseline. FVC at these visits were 4.56 L (87% predicted) and 4.56 L (87% respectively. FEV1 and FVC testing was not conducted at the early termination visit.

Reviewer's comment: It is unclear from the narrative whether the SAE experienced by this patient, which appears to be causally related, could have been foreseen by the investigator. The patient's smoking history is not reported.

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

Reviewer's comment: Chest tightness in a diabetic patient on exertion is suspicious for cardiac ischemia. A pulmonary focused workup was not described. A chest x-ray to rule out mass was either not performed, or the results not reported. However, based on the narrative provided, a causal relationship between the event and Afrezza TI is unlikely.

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

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

5.3 Lung Cancer Narratives

Subject ID 102/2909: a 62-year-old Caucasian male with T2DM was enrolled in study 102. The subject received Afrezza TI inhalation powder from an unknown date through December 21, 2007. The patients' past medical history included stage 3A rectal carcinoma treated with surgery, radiation and 5-flurouracil eight years prior to study entry and a 20 cigarettes per day smoking history for 41 years (from 1959 to 2000). On December 5, 2007, 200 days after initiation of Afrezza TI, the patient was found to have elevated an elevated serum CEA and enlarged neck lymph nodes, a right upper lung lesion and enlarged mediastinal lymph nodes. A subsequent biopsy revealed neuroendocrine carcinoma (oat cell type) with immunohistochemistry positive for synaptophysin, chromogranin, CK, Ki76 60% and negative for ACL. The investigator considered the tumor as a second primary and initiated chemotherapy with carboplatin and

etoposide. The patient subsequently died on (b) (6) due to disease progression. The investigator assessed causality as not related to the study drug and considered the medical history of cancer and heavy smoking as possible causes.

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

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

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

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

with Afrezza TI. No further interaction occurred with the subject until spontaneous reporting of the event from the clinical site on 05 Mar 2012.

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

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

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

Subject ID 0008/358: a 59 -year-old Caucasian male initially participated in trial 0008 from11JUN2004 and received Technosphere Placebo. At the conclusion of the 0008 trial the subject enrolled into the open label uncontrolled extension trial 010 on 22OCT2004. The subject received Technosphere Insulin 15 U QD (22Oct2004 - 21Nov2004), 30 U QD (22Nov2004 - 02Mar2005), 15 U QD (03Mar2005 - 20Aug2006), 90 U QD (21Aug2006 - 21Apr2008). The duration of treatment was 3 years, 5 months, and 30 days. The subject completed the study and the last study visit was on 22Apr2008. Since then (for a total duration of 2 years, 7 months, and 16 days) the subject did not receive any treatment with Afrezza TI.

On 20Dec2010, the study coordinator was informed by the subject of his appointment with an oncologist for possible lung cancer. Per the study coordinator, subject developed symptoms of cough, throat tickle, intermittent fever and hoarseness of voice on 16Nov2010. The subject was initially treated with antibiotics, first with doxycycline, then azithromycin (29Nov2010), and subsequently with benzonatate, levaquin and oral prednisone (initiation date: 3Dec2010; doses and duration unknown). As the hoarseness of voice persisted, the subject was referred to an otolaryngologist. Otolaryngologist upon examination on 03Dec2010, found paralysis of the left vocal cord; the rest of the physical examination was unremarkable. CT of neck and chest was

ordered and was performed on 07Dec2010. CT of the chest revealed large mass in the middle mediastinum at the level of carina extending into AP window and azygous and subcarinal lymph nodes. There were areas of hypodensity in the mass which may indicate necrosis – finding concerning for neoplasm particularly lymphoma, primary mediastinal tumor or metastatic disease. The lungs appeared well aerated without evidence of focal consolidation, volume loss or pleural effusion. No evidence of mass or nodules identified. Small hiatal hernia was identified and a small renal cyst. Neck CT, performed on 07Dec2010, revealed soft tissue thickening of the left maxillary sinus. Remaining of the paranasal sinuses and mastoid air cells were well aerated. Visualized intracranial structures were unremarkable. Parotid, submandibular glands and epiglottis appear normal. The left vocal cord appear midline. The thyroid gland appeared unremarkable. The vascular structures at the base of neck appear unremarkable. The aortic arch and its vessel branches appear unremarkable.

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

Past medical history was significant for type 2 diabetes mellitus, obesity, hypertension, hyperlipidemia; history of colon polyp from 07 Feb 1992 to 28 June 2004; pharyngouvuloplasty for sleep apnea (b) (6), cholecystectomy in 1990, depression, penicillin allergy, bronchitis, non-smoker (experimented with smoking cigarettes first 2 years of college (> 40 year ago) and has never smoked over 5 packs total in lifetime), and seborrheic keratosis. Significant family history included father with a history of colon cancer died at age 51, brother with history of prostate cancer at age 76, mother with the diagnosis of tuberculosis, and sister with asthma. The investigator reported not having complete information about the subject at this time and assigned the causality for the event as possibly related to the Afrezza TI the subject received during the trial. Alternate causality was not reported. There were no apparent environmental or other causal factors.

5.4 Diabetic Ketoacidosis Narratives

Note: many of the narratives did not provide laboratory evidence of DKA.

Diabetic ketoacidosis MKC-TI-009 189/1283: A 33-yo African American female using Afrezza TI Inhalation Powder 60 U TID and insulin glargine 30 IU QHS experienced headache, nausea,

vomiting, and tachycardia without respiratory distress and was admitted to the hospital with DKA.The investigator reported that there were no missed doses of insulin. The duration of treatment at the onset of the event was 146 days. The subject discontinued the trial due to the SAE.

Diabetic ketoacidosis MKC-TI-009 229/1931: A 35-yo Caucasian male in the U.S. receiving Afrezza TI 90 U at breakfast, 60 U at lunch, 60 U at dinner, and 15 U PRN, and insulin glargine 11 IU QHS hospitalized with DKA likely due to a viral illness associated with vomiting. The blood glucose was 700 mg/dL on admission. The subject reported not taking any insulin for three days after the illness began, before the hospital admission. The duration of treatment at the onset of the event was 346 days.

Diabetic ketoacidosis MKC-TI-009 118/1546: A 42-yo African American male received Afrezza TI 60 U at breakfast, 45 U at lunch, and 60 U at dinner. The insulin glargine dose was 28 IU in the morning and 14 IU at bedtime. The duration of treatment at the onset of the event was 205 days. On 12 Jul 2007, after eating some fish, the subject experienced nausea and vomiting and was found confused and disoriented in his apartment. The subject was living alone and was not appropriately hydrated during acute illness. Subsequently he was taken to the hospital and was diagnosed with diabetic ketoacidosis (DKA) with a pH of 7.16 and a blood glucose level of 888 mg/dL. The subject recovered and did not discontinue from the trial.

Diabetic ketoacidosis MKC-TI-009 313/1683: A 22-yo Caucasian male in Poland received Afrezza TI 60 U at breakfast, 45 U at lunch, and 90 U at dinner, and insulin glargine 23 IU QHS. The duration of treatment at the onset of the event was 260 days. At a routine trial visit, the subject was noted to have elevated blood glucose, nausea and vomiting and tachypnea. The subject was hospitalized with confirmed DKA with a pH of 7.23 and blood glucose > 500 mg/dL. A precipitating cause was described as “dietary mistake”. Afrezza TI was restarted upon discharge at the same dosing prior the event. The subject completed the trial.

Diabetic ketoacidosis MKC-TI-009 484/2303: A 26-yo Caucasian female in Brazil received Afrezza TI 30 U at breakfast, 90 U at lunch, and 75 U at dinner, and insulin glargine 38 IU QHS. The duration of treatment at the onset of event was 362 days. The subject was hospitalized with DKA [(nausea and abdominal pain associated with excess food intake and a missed dose of “insulin” (not clear if Afrezza TI or basal insulin)]. The investigator noted that in the discharge summary the pH at the time of admission was reported to be 7.11. The subject recovered in one day and did not discontinue from the trial.

Diabetic ketoacidosis MKC-TI-009 486/2242: A 23-yo Caucasian male in Brazil received Afrezza TI 90 U at breakfast, 90 U at lunch, and 90 U at dinner, and insulin glargine 48 IU QHS. The duration of treatment at the onset of event was 265 days. The subject was hospitalized with DKA likely related to gastroenterocolitis associated with nausea, diarrhea and vomiting. The pH on admission was 7.35 with blood glucose of 511 mg/dL. Ketones were 2+. The subject recovered after one dose of bolus 10 IU rapid acting insulin subcutaneously; no changes were made with respect to study drugs, and the subject did not discontinue from the trial.

Ketoacidosis MKC-TI-009 495/1748: A 23-yo female Caucasian in Poland was started on Afrezza TI Inhalation Powder 15 U TID plus 22 IU of insulin glargine (Lantus) at bedtime. On the day of study entry the subject experienced hyperglycemia (up to 380 mg/dL) and was hospitalized. It was presumed due to inappropriate use of the inhaler. Although the subject was hospitalized the narrative states that there was no evidence of metabolic acidosis so whether or not this was DKA is not clear. The patient was retrained on the use of the inhaler and completed the trial.

Reviewer's comment: This is likely not a true case of DKA.

Diabetic ketoacidosis MKC-TI-009 181/1522: A 19-yo African American female received Afrezza TI 30 U TID starting (b) (6). The subject received insulin glargine 35 IU subcutaneously at bedtime which was administered starting 20 Dec 2006. The duration of treatment at the onset of event was 3 days. On (b) (6), the subject presented to the emergency room (ER) with symptoms of nausea and vomiting for 2 days. The subject was found to have a buttock abscess, and urinary tract infection, and was in DKA with a pH of 7.05 and blood glucose of 400 mg/dL. The patients HbA1c was found to be 17.9%. The subject withdrew consent from the study after hospital discharge.

Reviewer's comment: This patient had an HbA1c of close to 18% three days after starting Afrezza TI. Clearly she should not have been enrolled in the clinical trial, i.e. she did not meet the inclusion criteria for HbA1c. This patient presumably has a history of non-adherence to her insulin regimen (hence the extremely high HbA1c) and this behavior likely contributed to her episode of DKA.

Diabetic ketoacidosis MKC-TI-030 029/2970: A 29-yo Caucasian female in the United States received Afrezza TI 60 U at breakfast and 75 U at lunch and dinner starting 07 Sep 2006 and subcutaneous insulin glargine (Lantus) 46 IU QD starting 1999. The duration of treatment at the onset of the event was 56 days. The subject was hospitalized with DKA. She admitted to stopping her basal insulin. She did not indicate that she thought she could get all the insulin she needs from Afrezza TI so it is unclear why she stopped the basal insulin. The medical history notes that the subject had a history of prior hospitalizations for DKA and a history of depression. She did not discontinue from the trial.

Diabetic ketoacidosis MKC-TI-030 406/3031: A 24-yo Caucasian female in the Czech Republic received Afrezza TI 75 U at breakfast and lunch, 90 U at dinner, and 15 U at other unspecified time from 03 Jul 2007 to 12 Nov 2007. Insulin glargine was administered sc 26 IU QD from 03 Jul 2007 onward. The duration of treatment at the onset of the first event was 421 days. On 13 Nov 2007, the subject experienced diabetic ketoacidosis (DKA) likely due to gastritis. She had another episode of DKA on 25 Feb 2008 associated with acute pancreatitis. She recovered and did not discontinue from the trial for these SAEs.

Diabetic ketoacidosis and hepatotoxicity due to paracetamol overdose MKC-TI-030 461/2708: A 42-yo Caucasian female in Poland received Afrezza TI 30 U TID from 22 Jan 2007 to 02 Feb 2008. Insulin glargine was administered 18 IU QD from 13 Aug 2007 onward. The

duration of treatment at the onset of the first event was 372 days. She recovered and did not discontinue from the trial for these SAEs.

Diabetic ketoacidosis MKC-TI-030 858/2805: A 31-yo Caucasian female in the Ukraine received Afrezza TI 30 U TID from 04 Sep 2006 to 15 May 2007 was hospitalized with DKA associated with acute cholecystitis. She recovered and did not discontinue from the trial for this SAE.

Diabetic ketoacidosis MKC-TI-030 912/3493: A 19-yo Caucasian female in Canada received Afrezza TI 60 U TID from 02 Oct 2006 to 07 Nov 2006, and insulin isophane injection (NPH insulin) 22 IU QD subcutaneously (sc) at bedtime starting in year 2000 onward. Duration of treatment at the onset of the event was 33 days. The subject had DKA related to influenza. She recovered but discontinued Afrezza TI due to the event.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL SUMMARY

NDA/Serial Number:	22-472/SN-0074 (SDN 79)
Drug Name:	AFREZZA (insulin human [rDNA origin]) Inhalation Powder with Gen2 Inhaler
Indication(s):	Treatment of Diabetes Mellitus in Adults
Applicant:	MannKind Corporation
Date(s):	Received 10/15/13; user fee (6 months) 04/15/14
Review Priority:	Priority due to Class 2 Resubmission
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1. INTRODUCTION

MannKind Corporation is developing AFREZZA for the treatment of hyperglycemia associated with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) in adults. It is a drug and device combination product and consists of Technosphere Insulin (TI) Inhalation Powder, a dry powder formulation of recombinant human insulin, pre-metered into single unit dose cartridges and administered by means of a reusable, breath-powered inhaler. TI is intended for use as a prandial insulin and is dosed at each meal.

The sponsor submitted the original NDA on 03/16/2009 (SN 0000) and received a Complete Response (CR) letter from the Agency on 03/12/2010 (Cycle 1). The NDA was resubmitted on 06/29/2010 (SN 0045) and the Agency issued another CR letter on 01/18/2011 (Cycle 2). In the Cycle 1 and Cycle 2 submissions, the MedTone inhaler was used in the clinical trials. However, the Gen2 inhaler, developed in 2010, is the to-be-marketed product. Therefore, the sponsor was asked in the 01/18/2011 CR letter to conduct two additional Phase 3 clinical trials with the Gen2 inhaler (one for T1DM and the other for T2DM). In addition, at least 1 of the studies should include a treatment group using the MedTone inhaler so that a head-to-head comparison of the pulmonary safety data from the two devices can be performed. The sponsor is now submitting the results from two confirmatory Phase 3 trials (MKC-TI-171 for T1DM and MKC-TI-175 for T2DM) where the Gen2 inhaler was used.

Throughout this report, the prefix before numbers in each study name will be omitted for the ease of discussions. For example, Study MKC-TI-171 will be referred as Study 171.

1.1 Summary of Results and Issues

Study 171

Study 171 was a randomized (1:1:1), open-label, active-controlled, multinational (Brazil, Russia, Ukraine, USA), forced-titration trial in subjects with T1DM. This study had 518 subjects randomized across three treatment arms of TI-Gen2, TI-MedTone, and insulin aspart. Subjects were treated over a 24-week period (12-week prandial and basal insulin titration phase + 12-week stable dosing phase). The primary endpoint was HbA1c change from baseline to 24 weeks with a non-inferiority comparison of TI-Gen2 to insulin aspart based on a non-inferiority margin of 0.4%.

The following bullets summarize the results and issues for HbA1c change from baseline to 24 weeks.

- The difference in mean HbA1c change from baseline to 24 weeks between the TI-Gen2 and insulin aspart groups was

- 0.22% with 95% confidence interval of (0.08%, 0.37%).

- The criterion was met for TI-Gen2 being non-inferior to insulin aspart in HbA1c change from baseline to 24 weeks (the upper limit of the above confidence interval of 0.37% < 0.4%). The criterion was also met for TI-Gen2 being inferior to insulin aspart in HbA1c change from baseline to 24 weeks (the lower limit of the above confidence interval of 0.08% > 0).

- The missing data rates on the Week 24 HbA1c in the primary analysis were 25% in the TI-Gen2 arm and 12% in the IAsp arm.

- A sensitivity analysis that incorporated multiple imputation under the non-inferiority null led to a difference in mean HbA1c change from baseline to 24 weeks between the TI-Gen2 and insulin aspart groups of 0.31% with 95% confidence interval of (0.15%, 0.48%). For this sensitivity analysis, the non-inferiority criterion was not met.

- All subjects were switched to prandial insulin aspart use four weeks prior to randomization/baseline. How this affects the effect of insulin aspart on HbA1c change from baseline should be considered when evaluating the results on HbA1c change from baseline from Study 171.

- Among the subjects treated with TI-Gen2 and insulin aspart, 55% and 73%, respectively, had a known improvement in HbA1c change at 24 weeks.

- 14% of subjects in the TI-Gen2 group achieved HbA1c $\leq$ 7.0% at Week 24 when compared with 27% in the IAsp group.

- There was a significant treatment-by-sex interaction observed based on the available data at Week 24 (p-value = 0.01).

    - Among female patients in the IAsp group, there was a 0.58% mean reduction in HbA1c change from baseline to 24 weeks, while around 0.2% of mean reduction was seen in each of the TI-Gen2 male, TI-Gen2 female, and IAsp male groups.
    - A significant treatment-by-sex interaction was also observed in Study 009 in the original NDA submission (p = 0.01), however in the opposite direction as in Study 171. There was a greater mean reduction in HbA1c in the male

patients in the IAsp + Lantus group (the adjusted mean change from baseline at Week 52 in the TI + Lantus and IAsp + Lantus groups were -0.00% and -0.47% for the males, respectively; and -0.19% and -0.26% for the females, respectively).

- Severe hypoglycemic episodes were more prevalent on the insulin aspart arm.

    - Incidence rates of 18.4% and 29.2% for the TI-Gen2 and insulin aspart arms, respectively.
    - Event rates of 0.08 and 0.14 per month for the TI-Gen2 and insulin aspart arms, respectively.

Other findings and issues

- In an exploratory analysis: The mean duration of exposure in years appears to be different between the TI-Gen2 and IAsp groups (0.39 and 0.44 years [4.6 and 5.3 months], respectively).

- During the 24-week treatment period, the average daily basal and prandial insulin doses used in the TI-Gen2 group were consistently higher than those used in the IAsp group. See Figures 12 and 13 in Section 3.5.1 of this review for further details. [Note that the dosage units for prandial TI and IAsp were U and IU, respectively. In order to compare the dose levels between the 2 treatment groups, a rough conversion of 10 U of TI-Gen2 to 4 IU of IAsp (i.e., 2.5 U of TI-Gen2 ≈ 1 IU of IAsp, as implied in the sponsor's clinical study report page 46 conversion table) was applied in Figure 13 in Section 3.5.1.]

    - There may be an issue on whether insulin aspart was optimally given in the control arm.

- For the exploratory endpoint of Body Weight: At 24 weeks, the TI-Gen2 group had a mean weight change of -0.5 kg compared to a mean weight change of +0.9 kg for the IAsp group.

- For the exploratory endpoint of Fasting Plasma Glucose (FPG (mg/dL)): During the 12-week titration period, there was little change in FPG in both the TI-Gen2 and IAsp groups. The mean reduction at Week 24 was greater in the TI-Gen2 group than in the IAsp group by a difference of -31.7 mg/dL.

The robustness of the primary analysis result is an issue. There was only one confirmatory study submitted for TI-Gen2 in type 1 diabetes mellitus. Risk-benefit evaluations should also consider the comparability of TI-Gen2 and insulin aspart doses as well as safety factors. Further details on the design, conduct, and results of Study 171 can be found in Sections 2 and 3 of this review.

Study 175

Study 175 was a randomized (1:1), double-blind, placebo-controlled, multinational (Brazil, Russia, Ukraine, USA) trial in insulin naïve subjects with T2DM. After a 6-week run-in period, 353 subjects were randomized to either TI Inhalation Powder delivered through the Gen2 inhaler (TI-Gen2) or T Inhalation Powder (placebo, without insulin). Subjects were then treated over a 24-week period (12-week prandial titration phase + 12-week stable dosing phase). The primary endpoint was HbA1c change from baseline (i.e., randomization) to 24 weeks.

The following bullets summarize the results and issues for HbA1c change from baseline to 24 weeks.

- The difference in mean HbA1c change from baseline to 24 weeks between the TI-Gen2 and placebo groups was
    - -0.42% with 95% confidence interval of (-0.58%, -0.27%).
- The criterion was met for TI-Gen2 being superior to placebo in HbA1c change from baseline to 24 weeks.
- The missing data rates on the Week 24 HbA1c in the primary analysis were 21% in the TI-Gen2 arm and 27% in the placebo arm.
- Among the subjects treated with TI-Gen2 and placebo, 86% and 72%, respectively, had a known improvement in HbA1c change at 24 weeks.
- 32% of subjects in the TI-Gen2 group achieved HbA1c $\leq$ 7.0% at Week 24 when compared with 15% in the placebo group.
- Severe hypoglycemic episodes were more prevalent on the TI-Gen2 arm.
    - Incidence rates of 5.1% and 1.7% for the TI-Gen2 and placebo arms, respectively.

- Event rates of 0.024 and 0.006 per month for the TI-Gen2 and placebo arms, respectively.

Other findings and issues

- During the 24-week treatment period, the average daily prandial doses used in the TI-Gen2 group were consistently lower than those used in the placebo group (see Figure 14 in section 3.5.2).

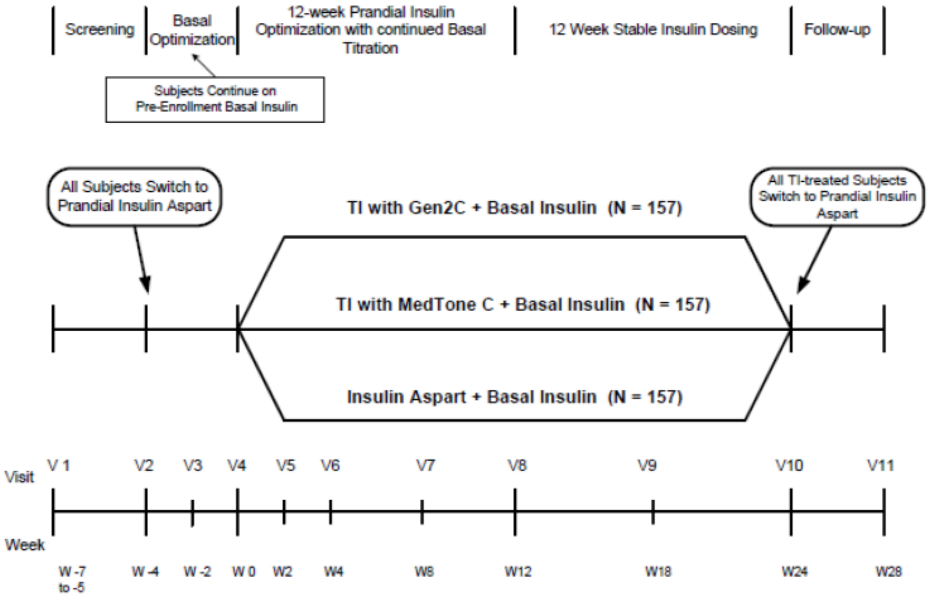
- For the exploratory endpoint of Body Weight: At 24 weeks, the TI-Gen2 group had a mean weight change of +0.5 kg compared to a mean weight change of -1.2 kg for the placebo group.

There was only one confirmatory study submitted for TI-Gen2 in type 2 diabetes mellitus. Risk-benefit evaluations should consider safety factors. Further details on the design, conduct, and results of Study 175 can be found in Sections 2 and 3 of this review.

2. STUDY DESIGN AND ENDPOINTS

Study 171 (09/19/2011 – 05/31/2013) was a Phase 3, randomized (1:1:1), open-label, active-controlled, 3-parallel-group, multicenter, multinational (Brazil, Russia, Ukraine, USA), forced-titration trial, evaluating the efficacy and safety of TI Inhalation Powder with Gen2 inhaler in subjects with T1DM over a 24-week treatment period (12-week prandial and basal insulin titration phase + 12-week stable dosing phase, see Figure 1 below for study design schema). After a 4-week basal insulin optimization phase where subjects converted their mealtime insulin to aspart insulin and titrated their pre-enrollment basal insulin, subjects were randomized to 1 of the 3 treatment groups: TI Inhalation Powder delivered through the Gen2 inhaler (TI-Gen2), TI Inhalation Powder delivered through the MedTone inhaler (TI-MedTone), and insulin aspart administered through subcutaneous injection (IAsp), all in combination with a basal insulin. Randomization was stratified by region (North America, Latin America, and Eastern Europe) and basal insulin (insulin glargine, insulin detemir, and NPH insulin). The inclusion criterion for HbA1c was $\geq 7.5\%$ and $\leq 10.0\%$.

Figure 1 – Design Schema for Study 171 (sponsor's figure)



Source: Figure 1 in Study 171 clinical study report
N = 157 was the planned sample size per treatment arm.

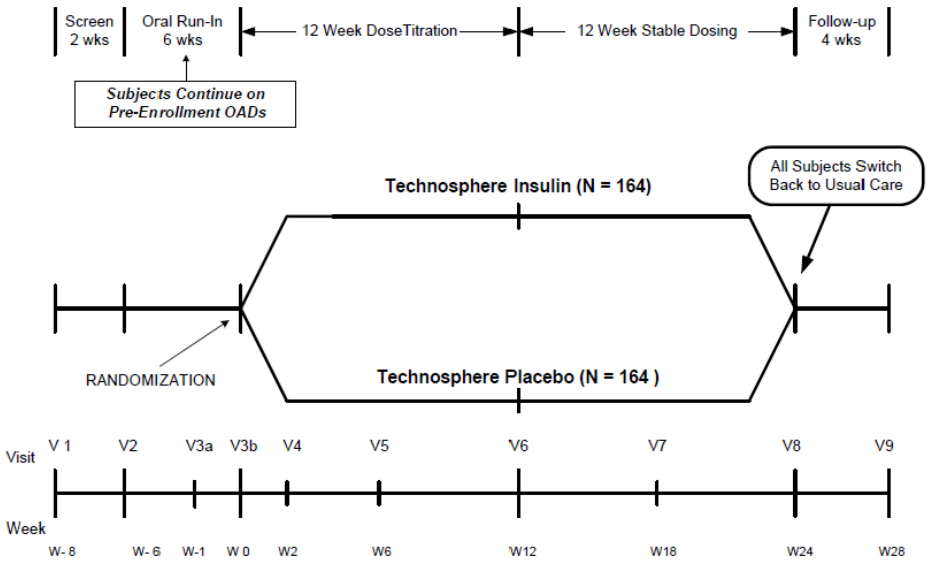
The primary objective of this study was to demonstrate that TI Inhalation Powder administered using the Gen2 inhaler in combination with a basal insulin was non-inferior to insulin aspart in combination with a basal insulin in improving HbA1c levels in subjects with T1DM whose disease was suboptimally controlled with their current insulin regimens. The primary efficacy endpoint was the change from the end of the basal insulin optimization phase at Visit 4 (Week 0, Randomization) to Visit 10 (Week 24) in HbA1c (%) between the TI-Gen2 and insulin aspart groups. The post-baseline HbA1c measurements were collected at Weeks 4, 8, 12, 18, 24, and 28 (follow-up). Comparison of the changes from baseline to the final treatment visit in FEV_1 between the TI-Gen2 and TI-MedTone groups was the main safety objective but is not a focus of this review.

Study 175 (11/30/2011 – 06/17/2013) was a Phase 3, randomized (1:1), double-blind, placebo-controlled, 2-parallel-group, multicenter, multinational (Brazil, Russia, Ukraine, USA) trial, evaluating the efficacy and safety of TI Inhalation Powder with Gen2 inhaler in insulin naïve subjects with T2DM over a 24-week treatment period (12-week prandial dose titration phase + 12-week stable dosing phase, see Figure 2 below for study design schema). After a 6-week run-in period, subjects were randomized to 1 of the 2 treatment groups: TI Inhalation Powder delivered through the Gen2 inhaler (TI-Gen2) and T Inhalation Powder (placebo, without insulin). Randomization was stratified by region (North America, Latin America, and Eastern Europe) and oral therapy at time of entry (metformin only; metformin + sulfonylurea; metformin + DPP-4 inhibitor; metformin + 1 or more oral antidiabetic drugs

(OADs) not specified above; 2 or more OADs not including metformin). All subjects continued to take their pre-trial OADs throughout the study without dose modification unless it was necessary. The inclusion criterion for HbA1c was ≥ 7.5% and ≤ 10.0%.

During the 24-week treatment phase, subjects whose hyperglycemia persisted or worsened beyond pre-specified thresholds received open-label rescue therapy (i.e., glimepiride for subjects entering the study on metformin only or insulin glargine for subjects entering the study on 2 or more OADs) in addition to their study treatment.

Figure 2 – Design Schema for Study 175 (sponsor's figure)



Source: Figure 1 in Study 175 clinical study report
N = 164 was the planned sample size per treatment arm.

The primary objective of this study was to demonstrate that TI Inhalation Powder administered using the Gen2 inhaler was superior to placebo in reducing HbA1c levels when added to antidiabetic regimen of subjects with T2DM who were suboptimally controlled on optimal/maximally tolerated doses of metformin only or 2 or more OAD agents. The primary efficacy endpoint was the mean change in HbA1c value (%) from Randomization (Week 0) to Week 24 between the TI-Gen2 and placebo groups. The post-baseline HbA1c measurements were collected at Weeks 2, 6, 12, 18, 24, and 28 (follow-up).

In both studies, several secondary efficacy endpoints (e.g., responders of Week 24 HbA1c ≤ 7.0% or 6.5%, change in FPG, change in body weight) were listed, but no statistical testing procedure to control the Type 1 error rate was planned.

3. STATISTICAL EVALUATION

3.1 Statistical Methods

For both Study 171 (T1DM) and Study 175 (T2DM), the primary efficacy analysis was performed on the Full Analysis Set (FAS) population which consisted of all randomized subjects. All data up to the initiation of rescue medication (for T2DM only) or discontinuation/end of study treatment were used and analyzed using a Mixed Model Repeated Measures (MMRM) approach with terms for treatment, visit, region, basal insulin (for T1DM) or OAD (for T2DM) stratum, and treatment by visit interaction as fixed factors and baseline HbA1c as a covariate. Subject was included in the model as a random effect. An autoregression (1) [AR(1)] covariance structure was used. As stated in the statistical analysis plan of the T2DM trial, the OAD strata of metformin + DPP-4 inhibitor, metformin + 1 or more OADs not specified above, and 2 or more OADs not including metformin were pooled in the analyses as each of them had sample size ≤ 20. Note that the sponsor used the HbA1c measurements including baseline (Week 0) as the dependent variable values. However, as per agreement with the Agency, change from baseline in HbA1c should be the dependent variable. Therefore, I reanalyzed the model using the change data as the dependent variable values.

For the T1DM trial, the primary comparison was to show non-inferiority (NI) of T1-Gen2 to IAsp in change from baseline in HbA1c at Week 24 with a pre-defined NI margin (0.4%). If non-inferiority was demonstrated (i.e., upper bound of the two-sided 95% CI of the treatment difference [TI-Gen2 minus IAsp] < 0.4%), then superiority was tested.

For the T2DM trial, the primary comparison was to show superiority (SUP) of TI-Gen2 to placebo in change from baseline in HbA1c at Week 24.

To evaluate the impact of missing data on the results of the primary MMRM analysis, the sponsor performed sensitivity analyses using multiple imputation under the null hypothesis method for both studies. Specifically, for Study 171, the imputation under the non-inferiority null would involve adding 0.4% to the imputed values in the TI-Gen2 group.

FPG data were analyzed using the method similar to the primary efficacy endpoint. Body weight data were analyzed using an ANCOVA model. Hypoglycemic episodes were analyzed by a negative binominal regression model as well as Fisher's exact test.

3.2 Subject Disposition

For Study 171 (T1DM), a total of 518 subjects were randomized. Overall, about 19% of the randomized subjects discontinued from the study. The dropout rates were higher in the two TI groups (25% for the Gen2 group and 21% for the MedTone group) than in the IAsp group

(11%). As Table 1 shows, the most recorded reasons for discontinuation were "Withdrawal by Subject" and "Adverse Event". Specifically, there were 9% randomized patients in the TI-Gen2 group and 5% in the TI-MedTone group withdrawn due to adverse event while none in the IAsp group. Among the reported adverse events in the two TI groups, the most recorded reason leading to withdrawal was cough, accounting for 10 of the 16 TI-Gen2 treated subjects and 5 of the 9 TI-MedTone treated subjects. The proportion of subjects remaining in the study over time (calculated as study discontinuation/completion date minus randomization/treatment start date) is shown for all 3 treatment groups in Figure 3 below.

Figure 3

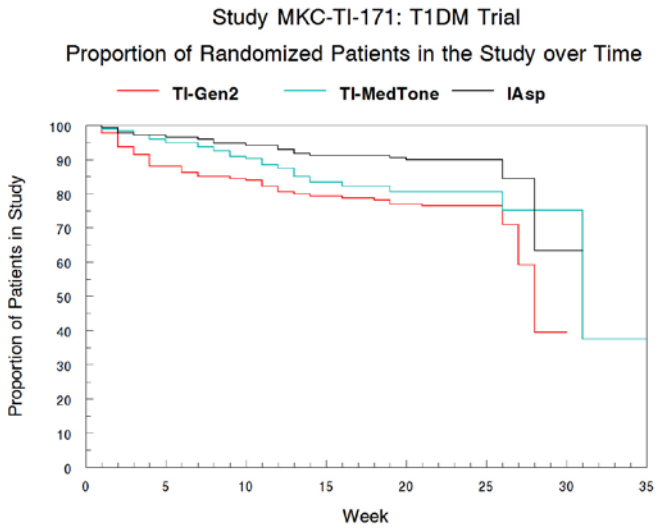


Table 1 – Study 171 (T1DM): Subject Disposition (extracted from sponsor's table)

Description	TI Gen2 n (%)	TI MedTone n (%)	Insulin Aspart n (%)	Total n (%)
Randomized Subjects [4]	174	174	170	518
Safety Population [5]	174	173	171	518 (100)
Full Analysis Set	174 (100)	174 (100)	170 (100)	518 (100)
Per-Protocol Population	130 (74.7)	136 (78.2)	147 (86.5)	413 (79.7)
Randomized Treatment Phase Completers	130 (74.7)	138 (79.3)	151 (88.8)	419 (80.9)
Follow-Up Completers [6]	130 (74.7)	135 (77.6)	151 (88.8)	416 (80.3)
Prematurely Discontinued during Randomized Treatment Phase	44 (25.3)	36 (20.7)	19 (11.2)	99 (19.1)
Reasons for Discontinuation from Study [4]				
Adverse Event	16 (9.2)	9 (5.2)	0	25 (4.8)
Protocol Violation	2 (1.1)	2 (1.1)	2 (1.2)	6 (1.2)
Withdrawal by Subject	21 (12.1)	16 (9.2)	8 (4.7)	45 (8.7)
Physician Decision	3 (1.7)	1 (0.6)	0	4 (0.8)
Lost to Follow-up	1 (0.6)	2 (1.1)	4 (2.4)	7 (1.4)
Non Compliance With Study Drug	1 (0.6)	2 (1.1)	0	3 (0.6)
Pregnancy	0	1 (0.6)	4 (2.4)	5 (1.0)
Study Terminated by Sponsor	0	0	0	0
Death	0	0	1 (0.6)	1 (0.2)
Other	0	3 (1.7)	0	3 (0.6)

[4] All subsequent percentages are based on the total number of randomized subjects in each treatment group.
[5] Subject 2042 was randomized to TI MedTone but was dispensed Insulin aspart since Day 1 until end of study.
[6] Follow-up completers are the subjects who completed both treatment phase and the follow-up visit.
Source: Extracted from Table 19 in Study 171 clinical study report

For Study 175 (T2DM), a total of 353 subjects were randomized. Among them, 29 (8%) subjects received rescue medication during the 24-week treatment phase. Of which, 27 completed the randomized treatment. If rescued patients were treated as non-completers, about 26% of the randomized subjects discontinued from the study (21% and 30% in the TI-Gen2 and placebo groups, respectively). When the 27 rescued and completed subjects were taken into account, the overall study dropout rate was 18% (15% and 21% in the TI-Gen2 and placebo groups, respectively). As Table 2 shows, the most recorded reasons for discontinuation were "Withdrawal by Subject" and "Adverse Event". Among the reported adverse events in the two study groups, the most recorded reason leading to withdrawal was cough, accounting for 2 of the 7 TI-Gen2 treated subjects and 6 of the 9 placebo treated subjects. The proportion of subjects remaining in the study over time (calculated as study discontinuation/completion date minus randomization/treatment start date) is shown for both treatment groups in Figure 4 below. (Note that there was one placebo-treated subject who was randomized in April, 2012 and discontinued from the study in March, 2013, resulting in being in the study for 48 weeks long. The treatment end date for this subject, however, was in September, 2012.)

For the 29 subjects receiving rescue therapy during the 24-week treatment phase, 12 (6.8%) were TI-Gen2 treated patients and 17 (9.7%) were placebo treated patients. Kaplan-Meier curves for the time to rescue for the two study groups are provided in Figure 5.

Figure 4

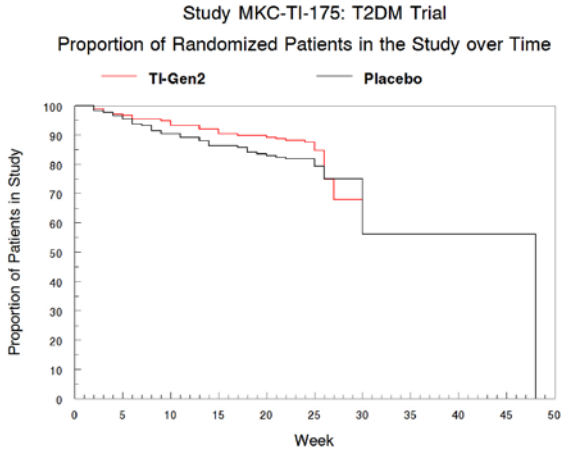


Figure 5
Time to Rescue

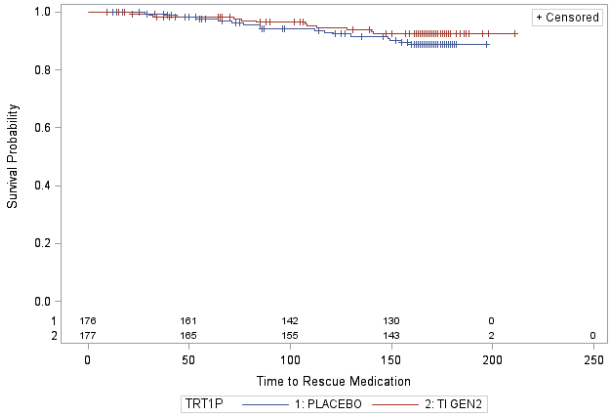


Table 2 – Study 175 (T2DM): Subject Disposition (extracted from sponsor's table)

	Subjects, n (%)		
Disposition	**TI Gen2 n (%)**	**Placebo n (%)**	**Total n (%)**
Randomized Subjects [5]	177	176	353
Safety Population	177 (100.0)	176 (100.0)	353 (100.0)
Subjects who received rescue therapy	12 (6.8)	17 (9.7)	29 (8.2)
Subjects received glimepiride as rescue therapy	4 (2.3)	2 (1.1)	6 (1.7)
Subjects received insulin glargine as rescue therapy	8 (4.5)	13 (7.4)	21 (5.9)
Other rescue medication	0	2 (1.1)	2 (0.6)
Subjects who did not receive any rescue therapy	165 (93.2)	159 (90.3)	324 (91.8)
Full Analysis Set	177 (100.0)	176 (100.0)	353 (100.0)
Per-Protocol Population	144 (81.4)	131 (74.4)	275 (77.9)
Subjects who completed randomized treatment phase	150 (84.7)	139 (79.0)	289 (81.9)
Subjects who completed randomized treatment phase and received rescue therapy	11 (6.2)	16 (9.1)	27 (7.6)
Subjects who completed randomized treatment phase without receiving any rescue therapy	139 (78.5)	123 (69.9)	262 (74.2)
Subjects who completed follow-up visit	149 (84.2)	138 (78.4)	287 (81.3)
Subjects who withdrew during randomized treatment phase	27 (15.3)	37 (21.0)	64 (18.1)
Reasons for Discontinuation from Study [5]			
Adverse Event	7 (4.0)	9 (5.1)	16 (4.5)
Protocol Violation	1 (0.6)	2 (1.1)	3 (0.8)
Physician Decision	1 (0.6)	1 (0.6)	2 (0.6)
Withdrawal by Subject	10 (5.6)	14 (8.0)	24 (6.8)
Death	0	0	0
Non Compliance With Study Drug	1 (0.6)	3 (1.7)	4 (1.1)
Pregnancy	0	0	0
Study Terminated By Sponsor	0	0	0
Lost To Follow-Up	6 (3.4)	4 (2.3)	10 (2.8)
Other	1 (0.6)	4 (2.3)	5 (1.4)

[5] All subsequent percentages are based on the total number of randomized subjects in each treatment group.
Source: Extracted from Table 14 in Study 175 clinical study report

3.3 Demographic and Baseline Characteristics

In both trials, the treatment groups were similar with respect to demographic and baseline characteristics such as age, gender, race, ethnic, country, region, basal insulin or OAD type, duration of the disease, baseline BMI, baseline HbA1c, and baseline FPG (Tables 3 and 4).

Table 3 – Study 171 (T1DM): Demographic and Baseline Characteristics (extracted from sponsor's tables)

Demographic Characteristics	Category/ Statistics		TI Gen2 [N=174] n (%)	TI MedTone [N=174] n (%)	Insulin aspart [N=170] n (%)
Country	United States		71 (40.8)	69 (39.7)	67 (39.4)
	Russia		45 (25.9)	52 (29.9)	52 (30.6)
	Ukraine		44 (25.3)	38 (21.8)	38 (22.4)
	Brazil		14 (8.0)	15 (8.6)	13 (7.6)
Gender	Male		77 (44.3)	80 (46.0)	74 (43.5)
	Female		97 (55.7)	94 (54.0)	96 (56.5)
Race	White		164 (94.3)	167 (96.0)	166 (97.6)
	Black or African American		8 (4.6)	5 (2.9)	3 (1.8)
	American Indian or Alaska Native		0	0	0
	Asian		1 (0.6)	1 (0.6)	0
	Native Hawaiian or Other Pacific Islander		1 (0.6)	0	0
	Other		0	1 (0.6)	1 (0.6)
Ethnic Group	Hispanic or Latino		17 (9.8)	22 (12.6)	18 (10.6)
	Not Hispanic or Latino		157 (90.2)	152 (87.4)	152 (89.4)
Age	N		174	174	170
	Mean		37.0	39.8	39.1
	SD		12.42	13.36	12.63
	Median		36.0	38.5	36.5
	Range		[18, 71]	[18, 76]	[18, 76]
Age Group (yrs)	18 - 30		56 (32.2)	48 (27.6)	46 (27.1)
	31 - 49		93 (53.4)	84 (48.3)	88 (51.8)
	50 - 64		18 (10.3)	33 (19.0)	28 (16.5)
	65+		7 (4.0)	9 (5.2)	8 (4.7)
Duration of Diabetes (yrs)	N		174	174	170
	Mean		16.0	17.7	16.7
	SD		10.27	10.66	10.04
	Median		13.8	15.2	16.0
	Range		[1.1, 57.3]	[1.1, 49.5]	[1.0, 42.2]
Basal Stratum		Insulin detemir	26 (14.9)	26 (14.9)	26 (15.3)
		Insulin glargine	121 (69.5)	122 (70.1)	121 (71.2)
		NPH insulin	27 (15.5)	26 (14.9)	23 (13.5)
Weight (kg)		N	174	174	169
		Mean	75.7	76.8	72.6
		SD	15.75	14.84	15.28
		Median	74.4	76.2	69.9
		Range	[41.7, 129.4]	[47.6, 124.0]	[46.6, 120.2]
Height (cm)		N	174	174	169
		Mean	170.2	170.8	168.8
		SD	9.82	9.34	9.76
		Median	169.0	171.0	168.0
		Range	[150.0, 200.0]	[151.0, 194.0]	[149.0, 196.0]
BMI (kg/m^2)		N	174	174	168
		Mean	26.0	26.2	25.4
		SD	4.48	3.73	4.11
		Median	25.7	25.9	24.5
		Range	[16.6, 38.6]	[18.1, 36.4]	[17.4, 37.2]
Fasting Plasma Glucose (mg/dL)		N	174	174	170
		Mean	155.0	144.3	151.2
		SD	67.62	60.90	67.43
		Median	144.5	137.5	148.0
		Range	[21.0, 403.0]	[43.0, 358.0]	[23.0, 375.0]
HbA1c (%)		N	172	172	167
		Mean	7.98	8.00	7.88
		SD	0.767	0.731	0.753
		Median	7.90	8.00	7.90
		Range	[6.20, 10.60]	[6.10, 10.20]	[5.80, 10.10]

Note(s): Percentages are based on the number of subjects in each treatment group in the Full Analysis Set (N).
SD = Standard Deviation.

Source: Extracted from Table 14.1.2.2 and Table 14.1.3.2 in Study 171 clinical study report

Table 4 – Study 175 (T2DM): Demographic and Baseline Characteristics (extracted from sponsor's tables)

		TI Gen2			Placebo		
Demographic Characteristics	Category/ Statistics	Not Rescued (N=165)	Rescued (N=12)	All (N=177)	Not Rescued (N=159)	Rescued (N=17)	All (N=176)
Age (yrs)	N	165	12	177	159	17	176
	Mean	56.8	55.9	56.7	56.6	56.8	56.7
	SD	9.20	7.96	9.10	8.53	8.62	8.51
	Median	57.0	55.0	57.0	57.0	54.0	57.0
	Range	[27.0, 75.0]	[45.0, 69.0]	[27.0, 75.0]	[36.0, 79.0]	[42.0, 73.0]	[36.0, 79.0]
Age Group (yrs)	18 - 30	1 (0.6)	0	1 (0.6)	0	0	0
	31 - 49	35 (21.2)	2 (16.7)	37 (20.9)	31 (19.5)	2 (11.8)	33 (18.8)
	50 - 64	95 (57.6)	7 (58.3)	102 (57.6)	99 (62.3)	11 (64.7)	110 (62.5)
	>=65	34 (20.6)	3 (25.0)	37 (20.9)	29 (18.2)	4 (23.5)	33 (18.8)
Gender	Female	87 (52.7)	8 (66.7)	95 (53.7)	92 (57.9)	10 (58.8)	102 (58.0)
	Male	78 (47.3)	4 (33.3)	82 (46.3)	67 (42.1)	7 (41.2)	74 (42.0)
Race	White	142 (86.1)	9 (75.0)	151 (85.3)	138 (86.8)	17 (100)	155 (88.1)
	Black or African American	18 (10.9)	3 (25.0)	21 (11.9)	17 (10.7)	0	17 (9.7)
	American Indian or Alaska Native	1 (0.6)	0	1 (0.6)	1 (0.6)	0	1 (0.6)
	Asian	1 (0.6)	0	1 (0.6)	2 (1.3)	0	2 (1.1)
	Other	3 (1.8)	0	3 (1.7)	1 (0.6)	0	1 (0.6)
Ethnic Group	Hispanic or Latino	39 (23.6)	4 (33.3)	43 (24.3)	37 (23.3)	4 (23.5)	41 (23.3)
	Not Hispanic or Latino	126 (76.4)	8 (66.7)	134 (75.7)	122 (76.7)	13 (76.5)	135 (76.7)
Country	USA	80 (48.5)	8 (66.7)	88 (49.7)	79 (49.7)	8 (47.1)	87 (49.4)
	Russia	55 (33.3)	0	55 (31.1)	49 (30.8)	7 (41.2)	56 (31.8)
	Ukraine	16 (9.7)	3 (25.0)	19 (10.7)	17 (10.7)	2 (11.8)	19 (10.8)
	Brazil	14 (8.5)	1 (8.3)	15 (8.5)	14 (8.8)	0	14 (8.0)
OAD Type	Metformin Only	38 (23.0)	4 (33.3)	42 (23.7)	37 (23.3)	3 (17.6)	40 (22.7)
	Metformin Plus Sulfonylurea	107 (64.8)	7 (58.3)	114 (64.4)	102 (64.2)	13 (76.5)	115 (65.3)
	Metformin Plus DPP-4 Inhibitor	9 (5.5)	0	9 (5.1)	8 (5.0)	1 (5.9)	9 (5.1)
	Metformin Plus 1 or More OADs Not Specified Above	8 (4.8)	1 (8.3)	9 (5.1)	9 (5.7)	0	9 (5.1)
	2 or More OADs Not Including Metformin	3 (1.8)	0	3 (1.7)	3 (1.9)	0	3 (1.7)
Duration of Diabetes (yrs)	N	165	12	177	158	17	175
	Mean	9.7	9.5	9.7	9.4	7.8	9.2
	SD	5.84	5.22	5.79	5.44	4.60	5.38
	Median	9.0	8.9	9.0	8.6	6.2	8.3
	Range	[1.1, 34.7]	[2.1, 22.2]	[1.1, 34.7]	[1.0, 28.8]	[1.8, 18.7]	[1.0, 28.8]
Weight (kg)	N	165	12	177	159	17	176
	Mean	90.5	84.8	90.2	90.6	92.4	90.8
	SD	17.43	13.50	17.22	17.71	13.70	17.34
	Median	89.0	80.5	88.4	87.5	95.0	88.6
	Range	[54.0, 142.3]	[64.5, 116.4]	[54.0, 142.3]	[58.0, 136.6]	[70.0, 111.2]	[58.0, 136.6]
Height (cm)	N	165	12	177	159	17	176
	Mean	168.2	166.6	168.1	167.2	167.0	167.1
	SD	9.68	9.86	9.68	9.81	9.64	9.77
	Median	167.6	165.0	167.5	166.0	170.0	166.2
	Range	[146.0, 188.0]	[153.3, 186.5]	[146.0, 188.0]	[143.0, 196.8]	[152.0, 179.0]	[143.0, 196.8]
BMI (kg/m^2)	N	165	12	177	159	17	176
	Mean	31.9	30.6	31.8	32.3	33.2	32.4
	SD	4.97	4.24	4.92	5.07	4.42	5.00
	Median	31.3	30.3	31.3	31.5	32.0	31.6
	Range	[21.6, 44.6]	[24.3, 37.4]	[21.6, 44.6]	[21.1, 44.4]	[26.1, 40.7]	[21.1, 44.4]
HbA1c (%)	N	164	12	176	159	17	176
	Mean	8.23	8.68	8.26	8.27	9.06	8.35
	SD	0.658	0.861	0.680	0.747	0.674	0.775
	Median	8.10	8.65	8.10	8.20	9.30	8.30
	Range	[6.60, 10.10]	[7.00, 10.10]	[6.60, 10.10]	[5.10, 10.90]	[7.60, 9.90]	[5.10, 10.90]
Fasting Plasma Glucose (mg/dL)	N	164	12	176	159	17	176
	Mean	176.6	213.1	179.1	173.8	209.0	177.2
	SD	43.11	38.85	43.72	45.95	38.81	46.40
	Median	170.5	212.5	172.0	166.0	212.0	171.5
	Range	[49.0, 306.0]	[140.0, 270.0]	[49.0, 306.0]	[54.0, 316.0]	[137.0, 295.0]	[54.0, 316.0]

Note(s): Percentages are based on the number of subjects in each combination of treatment and rescue status in the Full Analysis Set (N). Subjects never received rescue therapies during the study are counted under Not Rescued column. Subjects received rescue therapies during the study are counted under Rescued column.
SD = Standard Deviation.

Source: Extracted from Table 14.1.2.2 and Table 14.1.3.2 in Study 175 clinical study report

3.4 Efficacy Results and Discussion

In general, I was able to verify the sponsor's primary analysis results for both studies. Unless otherwise noted, the following results and discussions are based on my own analyses.

3.4.1 Type 1 Diabetes Mellitus (T1DM) – Study 171

HbA1c (%). The baseline HbA1c in the TI-Gen2 and IAsp groups were both around 8.0%. The mean reduction in HbA1c from baseline to Week 24 in the TI-Gen2 group (-0.20%) was statistically significantly less than that in the IAsp group (-0.42%). The treatment difference (TI-Gen2 minus IAsp) was +0.22% and its two-sided 95% CI was (0.08%, 0.37%), as shown in Table 5. The non-inferiority of TI-Gen2 to IAsp in reducing HbA1c was demonstrated since the upper bound (0.37%) of the 95% CI of the treatment difference was < 0.4%, the pre-defined non-inferiority margin. Also, as the 95% confidence interval was entirely greater than zero, TI-Gen2 was inferior to IAsp in reducing HbA1c from baseline to 24 weeks. Additionally, the dropout rate was higher in the TI-Gen2 arm (25%) than in the IAsp arm (11%) in this open-label inhalation vs. subcutaneous injection study. Therefore, several sensitivity analyses were performed to evaluate the impact of missing data on the results of the primary analysis.

Table 5 – Study 171 (T1DM): Summary of Statistical Results

FAS Population	LS Mean Change from baseline ± SE (N)		Treatment Difference	95% CI
	TI-Gen2	Insulin Aspart		
Change in HbA1c (%)	-0.20 ± 0.06 (131)	-0.42 ± 0.06 (147)	0.22 ± 0.07	(0.08, **0.37**)
Male	-0.21 ± 0.14 (58)	-0.18 ± 0.14 (65)	-0.03 ± 0.14	(-0.31, 0.25)
Female	-0.17 ± 0.09 (73)	-0.58 ± 0.09 (82)	0.41 ± 0.10	(0.20, 0.61)

Change in HbA1c was analyzed using MMRM with terms for baseline, treatment, region, basal insulin type, visit, and treatment by visit interaction.

My analysis using the completers cohort (Figure 6) had similar non-inferiority findings to the primary analysis based on the overall population. The discontinued patients in the TI-Gen2 group had mean increases in HbA1c from baseline during the 12-week titration period while mean decreases were observed in the IAsp group (Figure 7), which resulted in a bigger difference between the two treatment arms. If all the dropouts had stayed in the study and continued contributing data, one may wonder whether the overall treatment difference would have been larger than the 0.2% shown in the primary analysis.

Figure 6

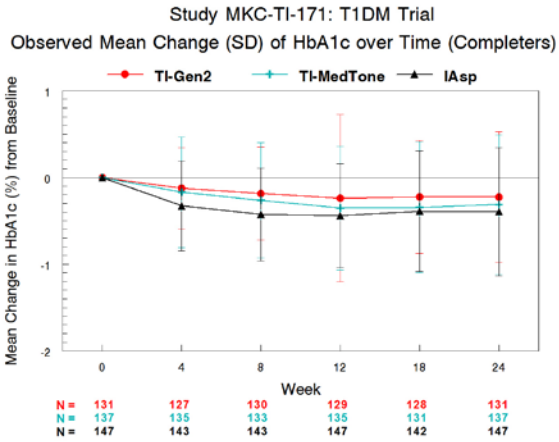
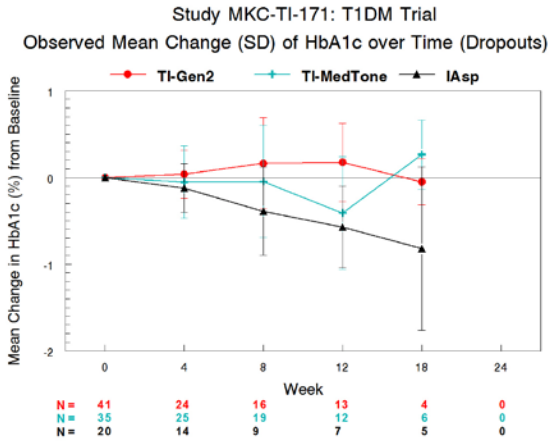


Figure 7



The sponsor performed the following 4 multiple imputation analyses based on different assumptions for missing data. The first sensitivity analysis involves an imputation under the non-inferiority null hypothesis.

1. Assumed all TI Gen2 discontinued subjects were missing not at random (MNAR) and added 0.4% to the Week 24 HbA1c of these subjects. This serves as the most conservative approach against TI Gen2.

2. Adjudicated the reasons for discontinuation among TI Gen2 subjects and identified subjects who were likely to be MNAR, and added 0.4% to the Week 24 HbA1c for these TI Gen2 subjects.

3. Used post-meal glucose as a predictor variable in the PROC MI (a SAS software procedure) to impute missing HbA1. The post-meal glucose is utilized as the indicator of treatment effect of prandial insulin.

4. Assumed all discontinued subjects were missing at random (MAR). This serves as a MAR sensitivity analysis to compare with the original primary analysis, MMRM.

As shown in Table 6 below, the results from Analysis 2, 3, and 4 met the non-inferiority criterion, while Analysis 1 fails to meet the non-inferiority criterion since the upper bound of the 95% CI of the treatment difference was 0.48%, > 0.4%, the pre-specified non-inferiority margin. Note that in Analysis 2, there were only 5 TI-Gen2 treated subjects identified as missing due to lack of efficacy and none identified as missing due to AE in the sponsor's adjudication (5 in total treated as MNAR). Additionally, in every case, the 95% confidence

interval was entirely greater than zero, meeting the criterion that TI-Gen2 was inferior to IAsp in reducing HbA1c from baseline to 24 weeks.

Table 6 – Study 171 (T1DM): HbA1c Change from Baseline with Multiple Imputation (sponsor's table)

Method	Statistics	TI Gen2	Insulin aspart	Treatment difference TI - Aspart
Analysis 1 0.4% was added to every discontinued TI subject	LSMean (SE)	-0.07 (0.078)	-0.38 (0.079)	0.31 (0.085)
	95% CI	(-0.22, 0.08)	(-0.54, -0.23)	(0.15, 0.48)
Analysis 2 0.4% was added to MNAR TI subjects	LSMean (SE)	-0.14 (0.077)	-0.37 (0.078)	0.23 (0.084)
	95% CI	(-0.30, 0.01)	(-0.52, -0.22)	(0.06, 0.39)
Analysis 3 No margin added. Post-meal glucose as predictor	LSMean (SE)	-0.17 (0.078)	-0.39 (0.079)	0.21 (0.083)
	95% CI	(-0.33, -0.02)	(-0.55, -0.23)	(0.05, 0.38)
Analysis 4 No margin added. Missing at Random	LSMean (SE)	-0.15 (0.077)	-0.37 (0.077)	0.22 (0.083)
	95% CI	(-0.30, -0.00)	(-0.52, -0.22)	(0.05, 0.38)

Source: Table 2 in February 10th, Sequence No. 0077 submission

Among the subjects treated with TI-Gen2 and insulin aspart, 55% and 73%, respectively, had a known improvement in HbA1c change at 24 weeks.

The lesser mean reduction in HbA1c at Week 24 in the TI-Gen2 group also reflected a smaller proportion of subjects (14%) achieving HbA1c ≤ 7.0% at Week 24 when compared with the IAsp group (27%).

FPG (mg/dL). During the 12-week titration period, there was little change in FPG in both the TI-Gen2 and IAsp groups. However, after Week 12, the mean FPG was gradually decreased through Week 24 in the TI-Gen2 group, while it was gradually increased in the IAsp group. The mean reduction at Week 24 was markedly greater in the TI-Gen2 group than in the IAsp group, resulting in a treatment difference of -31.7 mg/dL with 95% CI = (-48.1 mg/dL, -15.3 mg/dL).

Body Weight (kg). After 24 weeks of treatment, the TI-Gen2 group showed a slight weight loss (-0.5 kg), while the IAsp group showed an increase (+0.9 kg). The difference in weight change between the 2 treatment groups favored the TI-Gen2 group.

3.4.2 Type 2 Diabetes Mellitus (T2DM) – Study 175

HbA1c (%). The baseline HbA1c in the TI-Gen2 and placebo groups were both around 8.0%. The mean reduction in HbA1c from baseline to Week 24 in the TI-Gen2 group (-0.84%) was statistically significantly greater than that in the placebo group (-0.41%). The treatment difference (TI-Gen2 minus placebo) was -0.42% and its two-sided 95% CI was (-0.58%, -0.27%), as shown in Table 7. The superiority of TI-Gen2 over placebo in reducing HbA1c was clinically and statistically demonstrated since the upper bound (-0.27%) of the 95% CI of the treatment difference was < 0%, the pre-defined superiority margin. The dropout rate was lower in the TI-Gen2 arm (21% or 15% when rescued and completed patients were discounted) than in the placebo arm (30% or 21% when rescued and completed patients were discounted). Sensitivity analyses were performed to evaluate the impact of missing data on the results of the primary analysis.

Table 7 – Study 175 (T2DM): Summary of Statistical Results

FAS Population	LS Mean Change from baseline ± SE (N)		Treatment Difference	95% CI
	TI-Gen2	Placebo		
Change in HbA1c (%)	-0.84 ± 0.07 (138)	-0.41 ± 0.07 (129)	-0.42 ± 0.08	(-0.58, -0.27)

Change in HbA1c was analyzed using MMRM with terms for baseline, treatment, region, OAD type, visit, and treatment by visit interaction.

Data collected after initiation of rescue therapy were excluded from the analysis.

My analysis using the completers cohort (Figure 8) had similar superiority findings to the primary analysis based on the overall population. The discontinued patients in the placebo group showed almost no changes in mean HbA1c during the 12-week titration period while mean decreases were observed in the TI-Gen2 group (Figure 9). If all the dropouts had stayed in the study and continued contributing the data, one may wonder whether the overall treatment difference would have been larger than the -0.4% shown in the primary analysis.

Figure 8

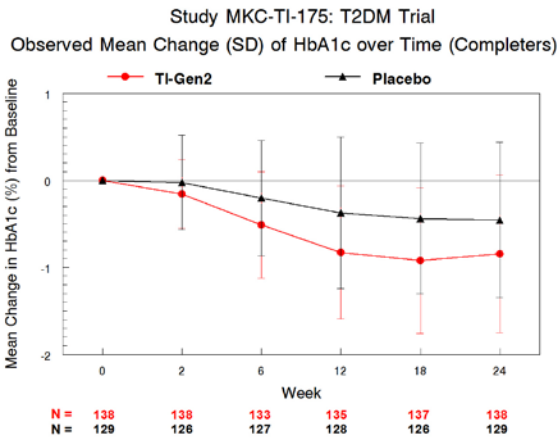
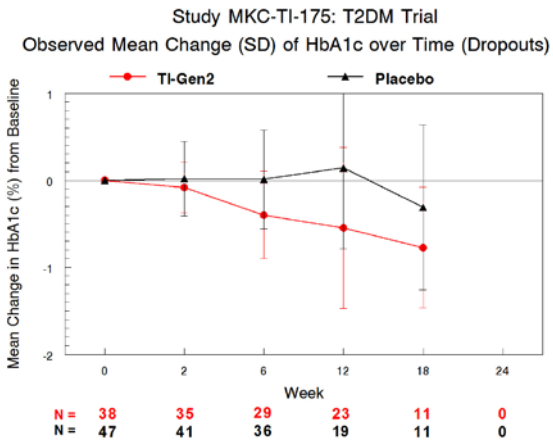


Figure 9



There were 12 (6.8%) TI-Gen2 treated and 17 (9.7%) placebo treated patients meeting the rescue criterion and given rescue medication. When I used the primary analysis model to analyze the data including rescue, similar results to the primary analysis were observed (treatment difference = -0.41%, 95% CI = (-0.56%, -0.25%)).

The sponsor performed the following multiple imputation analyses and both of them consistently demonstrated superiority of TI-Gen2 over placebo in HbA1c lowering (Table 8).

- All HbA1c measurements collected before initiation of rescue therapy, with post-rescue measurements set to missing
- All HbA1c measurements including those collected after initiation of rescue therapy (a rescue status (Y/N) was added as an additional covariate to indicate if subject received rescue therapy or not during the study)

Table 8 – Study 175 (T2DM): HbA1c Change from Baseline with Multiple Imputation (sponsor's table)

Data	Statistics	TI Gen2	Placebo	Treatment difference TI Gen2 – Placebo
Post-rescue data were excluded	LSMean Change (SE)	-0.83 (0.11)	-0.42 (0.11)	-0.41 (0.10)
	95% CI	(-1.05, -0.62)	(-0.64, -0.20)	(-0.62, -0.21)
	p-value			<0.0001
Post-rescue data were included	LSMean Change (SE)	-0.82 (0.14)	-0.42 (0.14)	-0.40 (0.10)
	95% CI	(-1.09, -0.55)	(-0.70, -0.15)	(-0.59, -0.20)
	p-value			<0.0001

Source: Table 4 in February 10th, Sequence No. 0077 submission

Among the subjects treated with TI-Gen2 and placebo, 86% and 72%, respectively, had a known improvement in HbA1c change at 24 weeks.

The greater mean reduction in HbA1c at Week 24 in the TI-Gen2 group also reflected a larger proportion of patients (32%) achieving HbA1c ≤ 7.0% at Week 24 when compared with the placebo group (15%).

FPG (mg/dL). During the 12-week titration period, there was more decrease in FPG in the TI-Gen2 group than in the placebo group. After Week 12, the mean FPG was slightly increased in the TI-Gen2 group, while it was sustained in the placebo group. Nevertheless, there was a numerically greater mean reduction in FPG at Week 24 in the TI-Gen2 group when compared with the placebo group (treatment difference = -4.9 mg/dL, 95% CI = (-14.4 mg/dL, 4.5 mg/dL)).

Body Weight (kg). Unlike the case in the T1DM trial, after 24 weeks of treatment, the TI-Gen2 group showed a slight weight gain (+0.5 kg), while the placebo group showed a decrease (-1.2 kg). The difference in weight change between the 2 treatment groups favored the placebo group.

3.4.3 Findings in Special/Subgroup Populations

For Study 171 (T1DM), treatment effects on mean change from baseline in HbA1c at Week 24 between the TI-Gen2 and IAsp groups were consistent across the subgroups defined by age (< 65 years or ≥ 65 years), race, region, country, ethnic, basal insulin type, and baseline HbA1c (≤ 8.0% or > 8.0% as defined by the sponsor), as no significant treatment-by-subgroup interactions were observed (all p > 0.10). However, there was a significant treatment-by-sex interaction observed based on the available data at Week 24 (p = 0.01). As shown in Table 5 above, the greater mean reduction in HbA1c at Week 24 in the IAsp group than in the TI-Gen2 group was mainly driven by the female patients in the IAsp group in which a 0.58% reduction was observed, while around 0.2% of reduction was seen in each of the TI-Gen2 male, TI-Gen2 female, and IAsp male groups. This significant treatment-by-sex interaction was also observed in Study 009 in the original NDA submission (p = 0.01), but there the greater mean reduction in HbA1c was mainly driven by the male patients in the IAsp + Lantus group (the adjusted mean change from baseline at Week 52 in the TI + Lantus and IAsp + Lantus groups were -0.00% and -0.47% for the males, respectively; and -0.19% and -0.26% for the females, respectively).

For Study 175 (T2DM), treatment effects on mean change from baseline in HbA1c at Week 24 between the TI-Gen2 and placebo groups were consistent across the subgroups defined by age (< 65 years or ≥ 65 years), gender, race, region, country, ethnic, OAD type, and baseline HbA1c (≤ 8.0% or > 8.0% as defined by the sponsor), as no significant treatment-by-subgroup interactions were observed (all p > 0.10).

Figures 10 and 11 below depict that the higher the baseline HbA1c, the greater the mean reduction from baseline to 24 weeks for each treatment group in both trials.

Figure 10

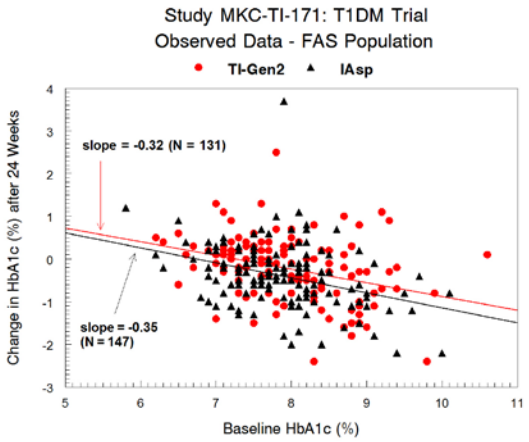
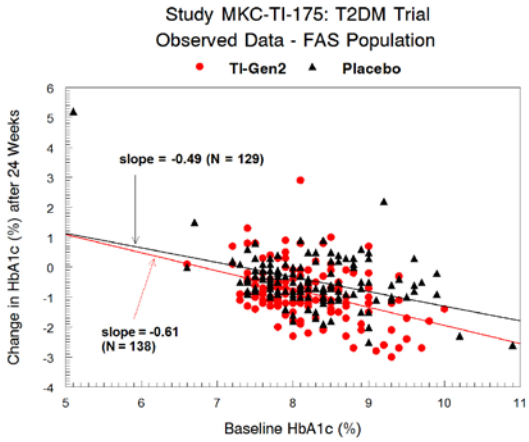


Figure 11



3.5 Evaluation of Safety

My statistical analysis results of hypoglycemic episodes and insulin dose for each trial are summarized briefly in this section.

3.5.1 Type 1 Diabetes Mellitus (T1DM) – Study 171

The mean duration of exposure in years appears to be different between the TI-Gen2 and IAsp groups (0.39 and 0.44 years [4.6 and 5.3 months], respectively).

Hypoglycemic Episodes. For any definition of hypoglycemic episodes (e.g., severe, mild/moderate, and all), numerically lower incidence rate (proportion of patients with at least 1 specific episode) and event rate per subject-month were consistently seen in the TI-Gen2 group when compared with the IAsp group (Table 9).

Table 9 – Study 171 (T1DM): Hypoglycemic Episodes

Safety Population Type of Hypoglycemia		TI-Gen2	IAsp	Treatment Difference Asymptotic 95% CI	Nominal p-value
Severe	Incidence Rate	32/174 (18.4%)	50/171 (29.2%)	-10.9% (-19.8%, -1.9%)	0.0225
	Event Rate	65/807.7 (0.08)	130/899.6 (0.14)	---	0.1022
All	Incidence Rate	167/174 (96.0%)	170/171 (99.4%)	-3.4% (-6.6%, -0.3%)	0.0672
	Event Rate	7919/807.7 (9.80)	12571/899.6 (13.97)	---	< 0.0001

Mild or Moderate	Incidence Rate	166/174 (95.4%)	170/171 (99.4%)	-4.0% (-7.3%, -0.7%)	0.0367
	Event Rate	7854/807.7 (9.72)	12441/899.6 (13.83)	---	< 0.0001

Incidence rate was calculated as number of patients with at least 1 event / total number of patients at risk.
Event rate was calculated as total number of events / total exposure time in subject-month.
P-value for incidence rate was based on Fisher's exact test.
P-value for event rate was obtained using a negative binomial regression analysis with terms for region, basal insulin type, treatment, and duration of treatment exposure (sponsor's analysis).
Note that Subject 2042 was randomized to the TI-MedTone group, but received insulin aspart throughout the trial; therefore the patient was included in the IAsp group in the safety population.

Insulin Dose (U). As depicted in Figures 12 and 13 below, during the 24-week treatment period, the average daily basal and prandial insulin doses used in the TI-Gen2 group were consistently higher than those used in the IAsp group. Note that the original dosage units for prandial TI and IAsp were U and IU, respectively. In order to compare the dose levels between the 2 treatment groups, a rough conversion of 10 U of TI-Gen2 to 4 IU of IAsp (i.e., 2.5 U of TI-Gen2 ≈ 1 IU of IAsp, as implied in the sponsor's clinical study report page 46 conversion table) was applied in Figure 13.

Figure 12

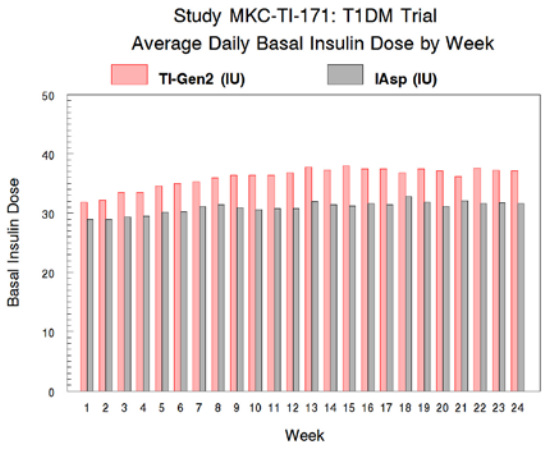
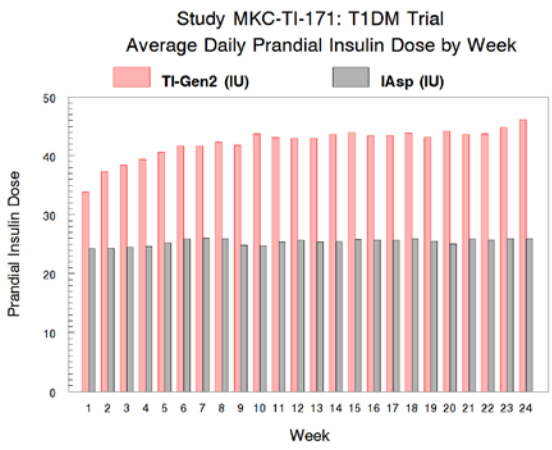


Figure 13



3.5.2 Type 2 Diabetes Mellitus (T2DM) – Study 175

The mean duration of exposure in years were similar between the TI-Gen2 and placebo groups (0.42 and 0.39 years [5.0 and 4.7 months]).

Hypoglycemic Episodes. For any definition of hypoglycemic episodes (e.g., severe, mild/moderate, and all), numerically higher incidence rate (proportion of patients with at least 1 specific episode) and event rate per subject-month were consistently seen in the TI-Gen2 group when compared with the placebo group (Table 10).

Table 10 – Study 175 (T2DM): Hypoglycemic Episodes

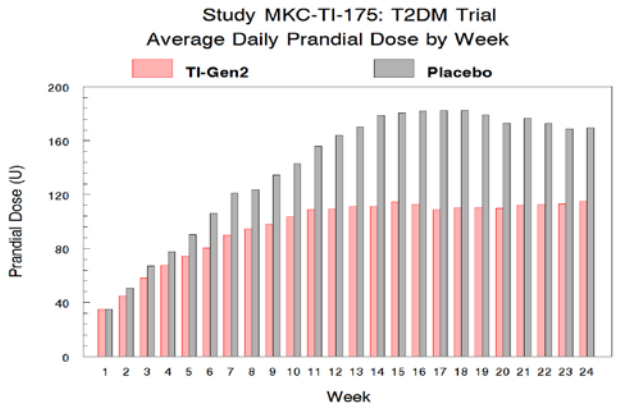
Safety Population Type of Hypoglycemia		TI-Gen2	Placebo	Treatment Difference Asymptotic 95% CI	Nominal p-value
Severe	Incidence Rate	9/177 (5.1%)	3/176 (1.7%)	3.4% (-0.4%, 7.1%)	0.1391
	Event Rate	21/885.1 (0.024)	5/834.1 (0.006)	---	0.2024
All	Incidence Rate	120/177 (67.8%)	54/176 (30.7%)	37.1% (27.4%, 46.8%)	< 0.0001
	Event Rate	1030/885.1 (1.16)	417/834.1 (0.50)	---	< 0.0001
Mild or Moderate	Incidence Rate	119/177 (67.2%)	53/176 (30.1%)	37.1% (27.4%, 46.8%)	< 0.0001
	Event Rate	1009/885.1 (1.14)	412/834.1 (0.49)	---	< 0.0001

Incidence rate was calculated as number of patients with at least 1 event / total number of patients at risk.
Event rate was calculated as total number of events / total exposure time in subject-month.
P-value for incidence rate was based on Fisher's exact test.
P-value for event rate was obtained using a negative binomial regression analysis with terms for region, OAD type, treatment, and duration of treatment exposure (sponsor's analysis).
Data collected after initiation of rescue therapy were excluded from the analysis.

Similar findings for severe, all, and mild/moderate hypoglycemic episodes were observed when data after initiation of rescue therapy were included in the analyses.

Insulin Dose (U). During the 24-week treatment period, the average daily prandial doses used in the TI-Gen2 group were consistently lower than those used in the placebo group (Figure 14). Since the study was conducted in insulin naïve patients, a sharp increase in dose in both treatment arms during the 12-week prandial titration period was expected.

Figure 14



4. CONCLUSIONS

The primary analysis from the T1DM trial (Study 171) met the criterion that TI (prandial insulin), delivered via a Gen2 inhaler, was non-inferior to insulin aspart in lowering HbA1c after 24 weeks of treatment in subjects whose disease were suboptimally controlled with their current basal insulin regimens (insulin glargine, insulin detemir, or NPH insulin). However, the comparative efficacy shown here was not compelling since the upper bound (0.37%) of the 95% CI of the treatment difference (TI-Gen2 minus insulin aspart) in change from baseline in HbA1c at Week 24 was almost right at the boundary of the pre-specified margin (0.4%), and the mean reduction in the TI-Gen2-treated patients was actually statistically significantly worse (by an estimate of 0.22%) when compared with that in the insulin aspart-treated patients. There were 25% and 11% dropouts in the TI-Gen2 and insulin aspart treatment arms which could have potentially impacted the primary non-inferiority analysis. Among the sensitivity analyses conducted by the sponsor, all showed similar findings to the primary analysis except for the multiple imputation under the non-inferiority null method where 0.4% was added to every discontinued patient in the TI-Gen2 group. That analysis showed a treatment difference of 0.3% (TI-Gen2 minus insulin aspart) with 95% CI = (0.15%, 0.48%), failing to satisfy the non-inferiority criterion. The 95% confidence intervals for the primary and sensitivity analyses were all above zero, demonstrating that TI-Gen2 was inferior to insulin aspart in the HbA1c change from baseline to Week 24. There were approximately 55% and 73% of the TI-Gen2 and insulin aspart treated patients, respectively, having an improved HbA1c level (i.e., change < 0) after 24 weeks of treatment. At Week 24, the TI-Gen2 treated patients had a mean decrease in body weight from baseline (-0.5 kg), while the insulin aspart treated patients showed a mean increase (+0.9 kg). For any definition of hypoglycemic episodes (e.g., severe, mild/moderate, and all), the proportion of patients experiencing at least 1 specific event was lower in the TI-Gen2 group than in the insulin aspart group. Both the mean daily prandial and basal insulin doses used in this T1DM open-label trial were consistently higher in the TI-Gen2 group than in the insulin aspart group.

Data from the T2DM trial (Study 175) have demonstrated that TI, delivered via a Gen2 inhaler, was statistically superior to placebo in lowering HbA1c after 24 weeks of treatment in subjects whose disease were suboptimally controlled on optimal/maximally tolerated doses of metformin only or 2 or more OAD agents. However, the treatment difference (TI-Gen2 minus placebo) in change from baseline in HbA1c at Week 24 was modest (-0.4%). There were 21% and 30% dropouts in the TI-Gen2 and placebo treatment arms (15% and 21%, respectively, if rescued and completed patients were discounted) which could have potentially impacted the primary superiority analysis. However, among the sensitivity analyses conducted, all showed similar findings to the primary analysis. There were approximately 86% and 72% of the TI-Gen2 and placebo treated patients, respectively,

having an improved HbA1c level (i.e., change < 0) after 24 weeks of treatment. Unlike the case in the T1DM trial, at Week 24, a mean increase in body weight from baseline was observed in the TI-Gen2 treated patients (+0.5 kg) while a mean decrease was seen in the placebo treated patients (-1.2 kg). As expected, for any definition of hypoglycemic episodes (e.g., severe, mild/moderate, and all), the proportion of patients experiencing at least 1 specific event was higher in the TI-Gen2 group than in the placebo group. The mean daily prandial doses used in this T2DM double-blind trial were consistently lower in the TI-Gen2 group than in the placebo group.

In conclusion, treatment with TI using Gen2 inhaler was shown to be effective in lowering HbA1c when compared with placebo in the T2DM trial. Based on the protocol-defined non-inferiority margin (0.4%), treatment with TI using Gen2 inhaler was also non-inferior to insulin aspart in lowering HbA1c in the T1DM trial based on the primary analysis. However, because of missing data, the robustness of this analysis is an issue. Since there was only one confirmatory study submitted for the indication of type 1 diabetes mellitus, this makes drawing a solid conclusion regarding efficacy for this type of diabetes mellitus problematic. The final conclusions for approval of the drug/device should also take the comparability of TI and insulin aspart doses as well as safety factors such as hypoglycemia and lung function into consideration.

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS SUMMARY

Date:	March 11, 2014
To:	Lisa Yanoff, M.D., Medical Officer, DMEP Ali Mohamadi, M.D., Acting Medical Team Leader, DMEP Jean-Marc Guettier, M.D., Acting Division Director, DMEP
From:	Miya Paterniti, M.D., Medical Officer, DPARP
Through:	Banu Karimi-Shah, M.D., Medical Team Leader, DPARP Sally Seymour, M.D., Deputy Director for Safety, DPARP
Subject:	Pulmonary Safety of Afrezza (insulin monomer human [rDNA origin] Inhalation Powder)

General Information

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

I. Introduction

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

The inhaled route of administration for Afrezza and potential for chronic administration raise pulmonary safety concerns. There has been one previously approved inhaled insulin marketed for the treatment of Type 1 and Type 2 DM, Exubera Inhalation Powder. Review of the clinical development program for Exubera demonstrated respiratory related adverse events, a small decline in FEV1 (forced expiratory volume in 1 second) over time, and risk of bronchospasm in patients with asthma or COPD (chronic obstructive lung disease). Lung cancer was also a concern based upon long-term safety data with Exubera. The pulmonary safety findings from the Exubera program will be summarized briefly in this review, as they are relevant to the current application.

With regards to the pulmonary safety of Afrezza, one of the main issues is the significant change in device during the development program. In the original submission, TI was delivered via the MedTone Inhaler. Subsequently, the Applicant proposed a new device, the Gen2 Inhaler. In general, for locally-acting pulmonary drug products, a substantial change in device (e.g. MedTone →Gen2 inhaler) constitutes a new drug/device combination, requiring a full clinical development program to support both efficacy and safety. The reason for the new clinical development program is that changing the device can significantly modify the drug delivery characteristics (particle size, distribution in the respiratory tract, etc.), which can impact the efficacy and safety of a locally-acting pulmonary drug. Afrezza, however, is for systemic therapy, so the systemic efficacy and safety may be easier to assess with device changes. However, the pulmonary safety effects are local effects and with a substantial change in the device, the local delivery may be significantly different and thus, the pulmonary safety may be different.

For the original new drug application (NDA), the Applicant collected 2 years of pulmonary safety data with the MedTone inhaler, as well as shorter-term data in patients with asthma and COPD. When the Applicant changed the device to the Gen2 inhaler, FDA had to consider what pulmonary safety data would be sufficient with the new Gen2 inhaler. As two additional trials were proposed to support the efficacy of Afrezza, FDA requested that the Applicant also collect pulmonary safety data with the new Gen2 inhaler, comparing it to the MedTone inhaler, with the intention to "bridge" the pulmonary safety data from the MedTone inhaler to the Gen2 inhaler. Whether this approach and the pulmonary safety data with the Gen2 inhaler are sufficient to support the pulmonary safety of Afrezza is a question we ask you to consider.

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

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

1. Decline in FEV1

A greater decline in FEV1 with Afrezza therapy versus comparator was noted during the first 3 months of therapy. The treatment differences were small (on average about 40-60 mL) and the results from 2-year studies show that the early difference persisted, but did not appear to progress over the 2-year period. As noted above, the 2-year pulmonary function data were obtained with the MedTone inhaler and 6-month pulmonary function data are available with the Gen2 inhaler; however, the decline in FEV1 (mean treatment difference) at 6 months was similar between the two devices. Controlled pulmonary safety data beyond 2 years of treatment are not available.

2. Bronchospasm in Patients with Underlying Lung Disease

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

In one study in asthmatic patients, mean FEV1 declined approximately 400 mL from baseline when measured 15 minutes after inhaling Afrezza. This decline recovered towards baseline (to within 20 mL) at 2 hours. Asthma symptoms and SAEs of bronchospasm were also noted. In another study, patients with COPD had a smaller mean decline (200 mL) and a slower recovery over 8 hours towards baseline.

3. Cough

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

The following review covers the regulatory history of Afrezza by summarizing prior reviews completed by DPARP regarding the pulmonary safety data of TI delivered via the MedTone inhaler, as well as new data submitted by the Applicant, with respect to pulmonary safety of TI delivered via the Gen2 inhaler. Of note, a discussion of lung malignancy has not been included in our review, but is included in Dr. Yanoff's review. Following a presentation of the data, which is largely in agreement with the Applicant's analyses, labeling concepts with respect to pulmonary safety are outlined for the committee's consideration.

II. Background and Regulatory History

A. Afrezza

The NDA for Afrezza was originally submitted on March 16, 2009. In the original submission, Afrezza consisted of TI Inhalation Powder pre-metered into unit dose cartridges to be delivered via the MedTone Inhaler. The MedTone inhaler (Figure 1) was proposed to be breath-powered and re-usable for 12 months. A Complete Response (CR) action was taken on March 12, 2010, in which several deficiencies were cited including: 1) unproven clinical utility resulting from a

failure to demonstrate adequate glycemic control versus comparators, 2) unreliability of pivotal bioequivalence study results, 3) unproven usability of the MedTone device, and 4) lack of data to support proposed 1-year in-use life of the MedTone device.

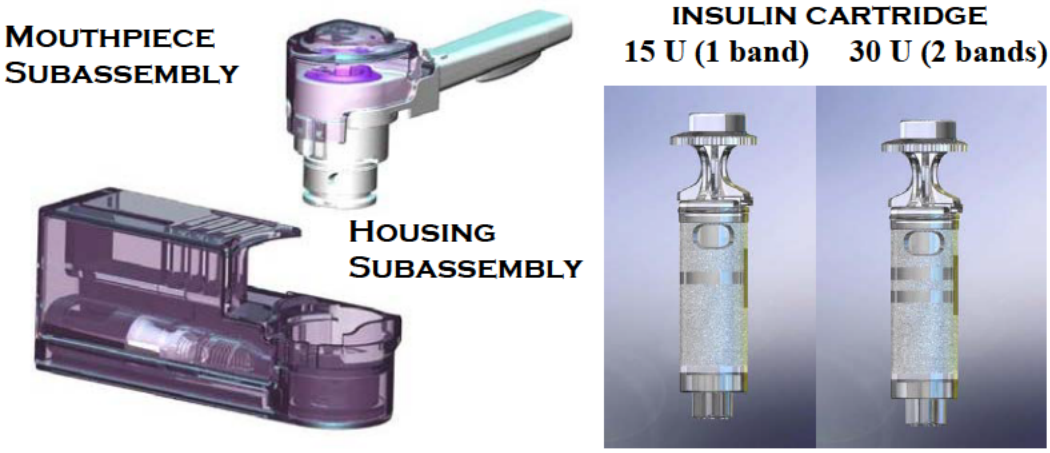


Figure 1. MedTone Inhaler Schematic

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

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

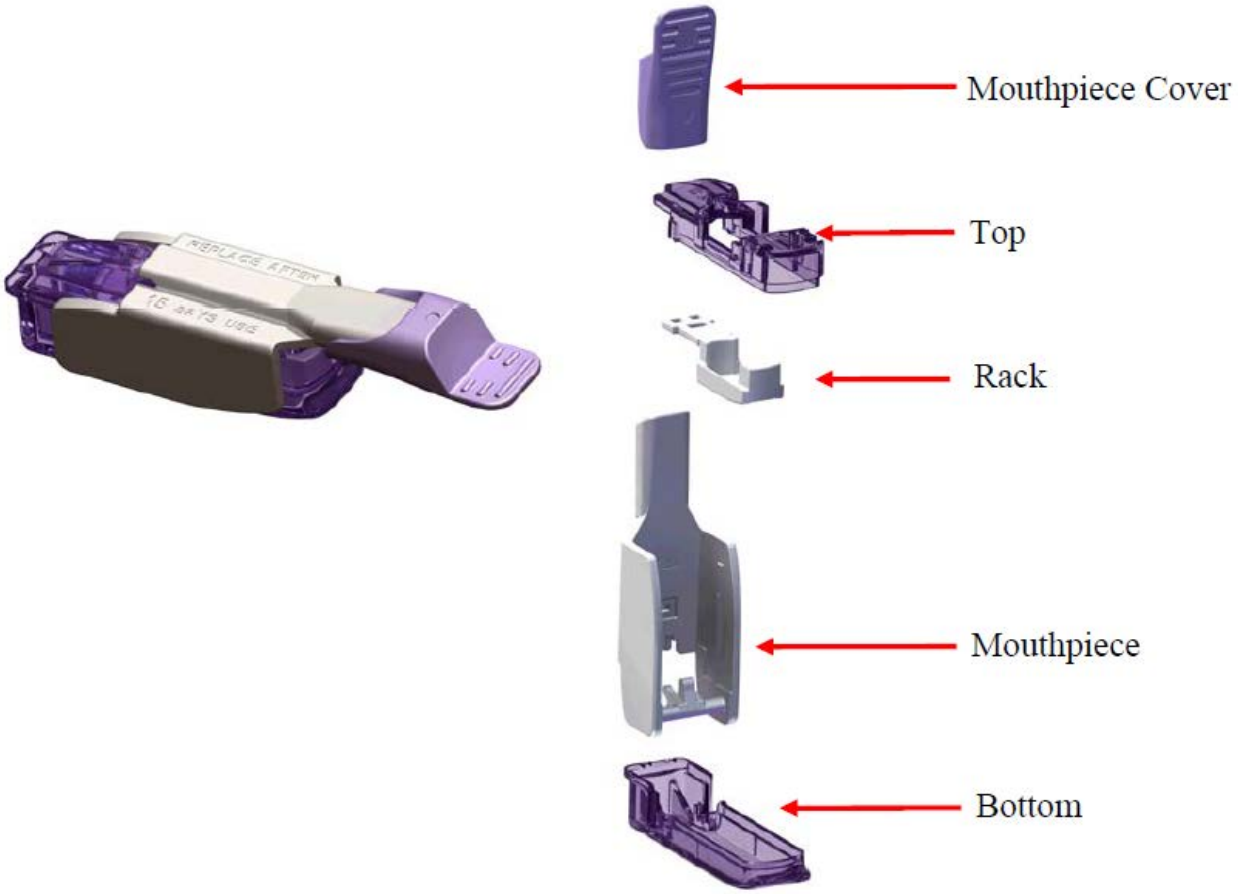


Figure 2. Gen 2 Inhaler with Exploded Schematic

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

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

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

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

B. Exubera

The pulmonary safety findings with Exubera are included here as relevant background for the committee's discussion.

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

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

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

patient were to start or resume smoking, that Exubera should be discontinued immediately due to the increased risk of hypoglycemia.

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

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

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

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

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

III. Review of Pulmonary Safety of Afrezza

A. Original Submission – March 2009

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

Table 1. Clinical Studies Used in the Evaluation of Pulmonary Safety (Original NDA Submission): TI delivered via the MedTone Inhaler				
Study	**Design**	**Study Duration**	**Treatment Arms**	**N***
Type 1 DM				
MKC-TI-101	R, OL	12 weeks	TI Comparator	54 56
MKC-TI-009	R, C, OL	1 year	TI Comparator	301 288
Type 2 DM				
MKC-TI-005	MC, R, DB, PC	11 weeks	TI Comparator	181 46
PDS-INS-0008	R, DB, PC, PG	12 weeks	TI Comparator	61 62
MKC-TI-026	R, C, OL	12 weeks	TI Comparator	75 15
MKC-TI-014	R, OL	24 weeks	TI Comparator	151 158
MKC-TI-103	R,C, OL	24 weeks	TI Comparator	358 170
MKC-TI-102	R, C, OL	1 year	TI Comparator	334 343
Type 1 and Type 2 DM				
MKC-TI-030	MC, R, OL	2 years	Type 1	
			TI Comparator	267 271
			Type 2	
			TI Comparator	656 678

*Number randomized; R: randomized; OL: open label; C: controlled; MC: multicenter; DB: double blind, PC: placebo controlled, PG: parallel group, TI: Technosphere Insulin, Afrezza (delivered via MedTone inhaler)
Source: DPARP Review 2009, Table 4, p. 38.

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

Table 2. Total Subjects for Pooled Analysis in Original Submission, by Treatment Arm and Disease Type

	TI MedTone	Comparator	TP MedTone
Type 1	614	599	
Type 2	1795	1345	114
Totals	**2409**	**1944**	**114**

TI: Technosphere Insulin, Afrezza; TP: Technosphere particles (excipient only)
Source: Module 5.3.5.3, ISS 2009, Table 9, p 60; Table 10, p 61

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

In the original review of the pulmonary safety data, >600 patients with Type 1 DM and >1700 patients with Type 2 DM, without underlying lung disease, were exposed to Afrezza via the MedTone inhaler. In addition, exposure data of up to 2 years was reviewed for 538 patients with Type 1 DM and 1334 patients with Type 2 DM.

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

1. Pulmonary Function in Diabetic Patients without Underlying Lung Disease

a) FEV1 Decline Over Time

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

Patients with Type 1 or Type 2 DM treated with TI via the MedTone inhaler had a greater decline in FEV1 over time than patients treated with non-inhaled comparators. The decline was noted during the first 3 months of therapy. The treatment differences were small (on average about 40-60 mL), as depicted in Table 3 (Type 1 DM) and Table 4 (Type 2 DM). The nature and magnitude of the change in FEV1 was consistent with what was observed in the Exubera clinical development program.

Table 3. Change in FEV1 from Baseline in Type 1 DM with TI via the MedTone Inhaler (Safety Population, Original Submission)

Timepoint	FEV1 (L)		
	TI MedTone Mean (SD)	**Comparator** Mean (SD)	**Treatment Difference** TI – Comparator (95% CI)
6 months	**Applicants 2009 Pooled Type 1 (MMRM)**		
	-0.09 (0.01) N=370	-0.05 (0.01) N=437	**-0.04** (95% CI: -0.7, -0.1)
1 year	**MKC-TI-009 (Agency-LOCF)**		
	-0.07 (0.22) N=235	-0.04 (0.17) N=244	**-0.04** (95% CI: -0.08, -0.05)
2 years	**MKC-TI-030 (Agency-LOCF)**		
	-0.13 (0.22) N=200	-0.10 (0.19) N=246	**-0.04** (95% CI: -0.08, -0.001)

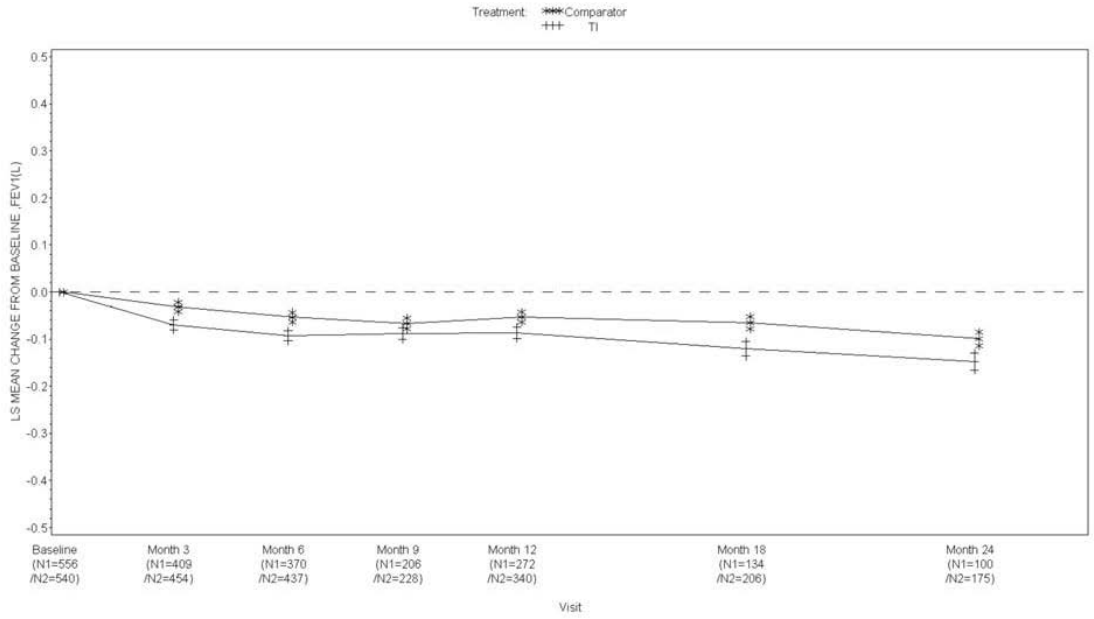
TI: Technosphere Insulin, Afrezza
Source: DPARP NDA 2009 Review, Table 23, p. 69; Table 25, p. 71; Table 27, p. 76.

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

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

The results from the long-term studies showed that the early difference persisted and that the results were statistically different when compared to an active control. As can be seen in the Applicant's analysis, in both Type 1 DM (Figure 3) and Type 2 DM (Figure 4), after the initial separation between groups, the difference did not appear to be progressive; however controlled pulmonary safety data beyond 2 years of treatment is not available. The Applicant's analysis represents pooled data from both 1 and 2 year trials (Studies 009, 102, and 030). The Agency's analysis, which examined Study MKC-TI-030 (2 year data) in Type 1 DM and Type 2 DM showed similar results. There was insufficient data to draw definitive conclusions regarding reversal of the FEV1 effects due to few patients (<25% of randomized patients) providing follow-up data after withdrawal of treatment.

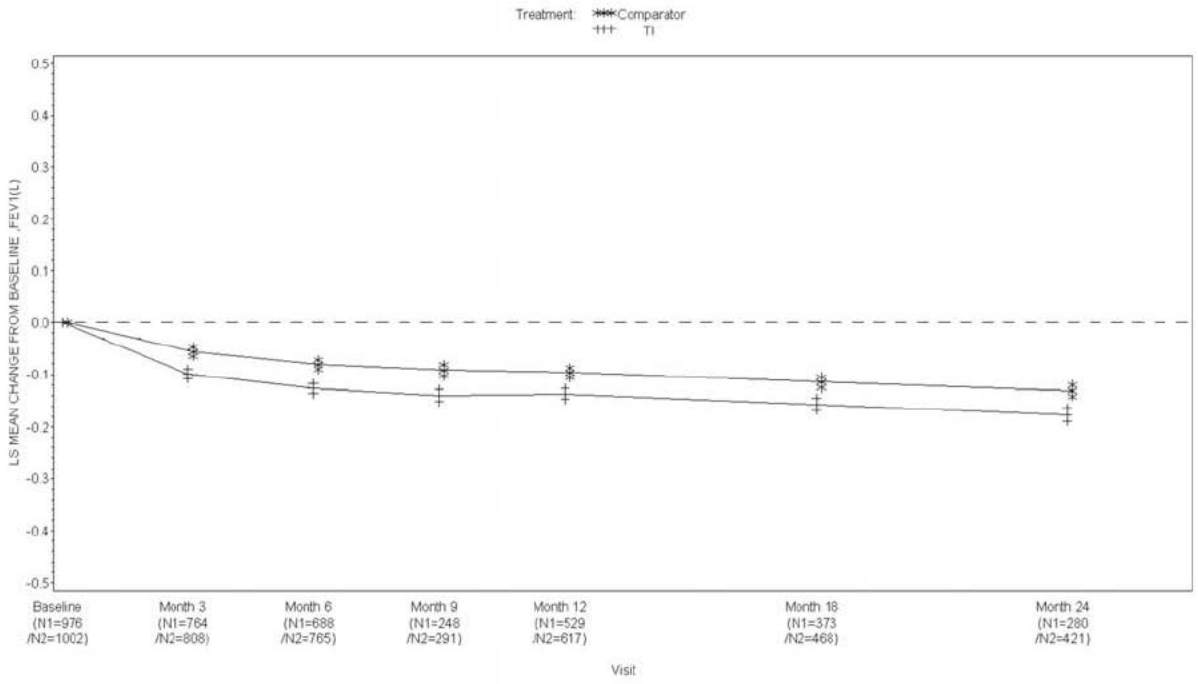
Figure 3. LS Mean (SE) of Change from Baseline in FEV1 (L) by Visit to 2 years (MMRM Model, Type 1 DM, Applicant's Analysis)



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

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

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



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

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

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

Table 5. Proportion of Subjects with a Decline in FEV ≥ 15% (Original Submission, Safety Population)

Timepoint	% of Subjects	
	TI MedTone	Comparator
	Type 1	
1 year [1]	2.5	1.2
2 year [2, 3]	5.5	0.8
	Type 2	
1 year [2, 4]	9.0	2.8
2 year [3]	5.9	4.3

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

b) Decline in FEV1 Post-Inhalation

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

2. Bronchospasm in Patients with Underlying Lung Disease

The Applicant conducted five studies in patients with underlying lung disease, as listed in Table 6.

Table 6. Clinical Studies in Patients with Underlying Lung Disease with TI via MedTone Inhaler (Original Submission)

Study *Status*	Design	Study Duration	Population			N
			Diabetes	Asthma	COPD	
MKC-TI-027 *Completed*	OL, SD	-	x	x FEV1 > 60%		5 Asthma 15 non
MKC-TI-113 *Completed*	OL	-		x FEV1 ≥ 70%		17 Asthma 13 non
MKC-TI-015 *Completed*	OL	-		x FEV1 ≥ 50%	x	18[1] COPD 20[1] non
MKC-TI-134 *Ongoing*	R, OL	1 year	x	x	x	255 Asthma 255 COPD
MKC-TI-105 *Terminated due to poor enrollment*	R, OL	1 year	x	x		----

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

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

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

Study MKC-TI-015 studied the immediate effect of TI on pulmonary function in COPD and non-COPD subjects, measured as the change in FEV1 over 485 minutes (about 8 hours) post-TI administration. COPD subjects showed a small mean decline in FEV1 by 18 minutes (200 mL), which gradually recovered by 8 hours.

No specific study in patients with underlying lung disease with the Gen2 inhaler was provided in this resubmission, however an update on the enrollment status of study patients with asthma or COPD using TI via the MedTone inhaler (MKC-TI-134) was included. Study MKC-TI-134 was initiated in 2007. Out of a goal of 510 subjects, 84 have been screened, with the vast majority of subjects (77/84 (92%)) failing screening. The most common reason (n=29 (38%)) was HbA1c out of range. Only a small portion of subjects have failed screening due to pulmonary function criteria (n=8 (10%)).

3. Cough

Cough was the most common adverse event noted in the clinical program (approximately 30% incidence), and the most common reason for discontinuation due to an adverse event (approximately 3%). The frequency of coughing was similar to what was seen in the Exubera program, but more than what is typically observed for dry powder inhalers developed for the treatment of asthma/COPD. Cough usually occurred within 10 minutes, was generally mild, dry, intermittent or single-defined, and tended to decrease over time. Other common AEs that were reported in $\geq$ 1% of patients and more commonly than in the comparator group for the pooled safety population included: dyspnea, lung infiltration, pharyngolaryngeal pain, productive cough, throat irritation, bronchitis, nasopharyngitis, rhinitis, and pulmonary function test decreased (Table 7).

Table 7. Common Adverse Events Occurring at ≥ 1% and More Commonly with Active Treatment than Comparator (Safety Population, Original Submission, Pooled Analysis)			
System Organ Class/PT	**TI MedTone N = 2409**	**TP MedTone N = 114**	**Comparator N = 1944**
Subjects with Respiratory AE	1088 (45.2)	44 (38.6)	606 (31.2)
RESPIRATORY, THORACIC AND MEDIASTINAL	794 (33)	29 (25.4)	192 (9.9)
Cough	642 (26.7)	21 (18.4)	109 (5.6)
Crackles Lung	1 (0)	2 (1.8)	0
Dyspnea	32 (1.3)	0	5 (0.3)
Lung Infiltration	1 (0)	2 (1.8)	0
Pharyngolaryngeal Pain	56 (2.3)	4 (3.5)	20 (1)
Productive Cough	56 (2.3)	3 (2.6)	16 (0.8)
Throat irritation	55 (2.3)	2 (1.8)	2 (0.1)
INFECTIONS AND INFESTATIONS	574 (23.8)	29 (25.4)	497 (25.6)
Bronchitis	45 (1.9)	2 (1.8)	24 (1.2)
Nasopharyngitis	184 (7.6)	16 (14)	155 (8)
Rhinitis	26 (1.1)	1 (0.9)	19 (1)
INVESTIGATIONS	51 (2.1)	1 (0.9)	24 (1.2)
Pulmonary function test decreased	44 (1.8)	0	22 (1.1)
TI: Technosphere Insulin, Afrezza; TP: Technosphere powder, excipient only Source: Module 5, Pulmonary CIR, Table 12, p. 53-57; DPARP Review, Table 18, p 57			

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

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

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

In the second resubmission, the Applicant submitted two phase 3 studies which provided pulmonary safety data for up to 24 weeks with the new drug/device combination (TI delivered via the Gen2 inhaler), as well as a comparison to the pulmonary safety data obtained with the TI/MedTone inhaler drug/device combination. Table 8 outlines the two new studies. The purpose of including the MedTone inhaler in Study MKC-TI-171 was to compare the pulmonary safety data with the MedTone inhaler to the Gen2 inhaler, as the majority of the clinical safety data had been obtained with the TI/MedTone inhaler, as previously discussed.

Table 8. Clinical Studies Used in the Evaluation of Pulmonary Safety (Current Submission)

Study	Design	Study Duration (weeks)	Treatment Arms[1]	N	Population	Objective
MKC-TI-171	OL, R, C, FT, MC	24	TI in Gen2 Inhaler[2] TI in MedTone Inhaler Insulin Aspart	174 174 170	Adults:Type 1 DM suboptimally controlled with current insulin regimen	Non-inferiority to insulin aspart in HbA1c levels
MKC-TI-175	PC, DB, R	24	TI in Gen2 Inhaler[2] TP in Gen2 Inhaler[2]	177 176	Adults: Type 2 DM suboptimally controlled on metformin or ≥ 2 OAD	Superiority to placebo (excipient powder)

MC = multi-center, R = randomized, OL = open-label, FT = forced titration, C = controlled, DB = double-blind, PC = placebo controlled, OAD = oral antidiabetic agent, TI = Technosphere Insulin (Afrezza), TP = Technosphere particles (excipient only), DM = diabetes mellitus
[1] All Type 1 patients had Basal insulin = insulin glargine, insulin detemir, and NPH insulin
[2]Gen2 inhaler version C which is proposed for marketing.

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

In the following section, the pulmonary safety data from the new clinical studies with TI delivered via the Gen2 inhaler (MKC-TI-171 and -175) will be reviewed and compared to the data from the original clinical development program in which TI was delivered via the MedTone

inhaler. It is important to note, that while we have reviewed these studies for pulmonary safety, the primary objective of these studies was to provide further evidence to support the efficacy of Afrezza. Pulmonary safety assessments were added to these studies in order to obtain pulmonary safety data with the new Gen2 device, as the majority of the pulmonary safety data was derived from TI delivered via the MedTone inhaler. Whether the bridging of two devices in terms of pulmonary safety is adequate will warrant discussion by the committee.

Studies MKC-TI-171 and MKC-TI-175 are reviewed in detail in Appendix 1 and 2, respectively.

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

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

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

Pulmonary Safety Review

Exposure

Exposure for the pooled studies in the original submission and the current submission, up to the safety cut-off of July 31, 2013, are detailed for patients with Type 1 DM and Type 2 DM in Table 9 and Table 10, respectively.

Table 9. Duration of Exposure for Type 1 DM – Original Submission Phase 2/3 Clinical Trials and Current Submission (up to safety data cut-off July 31, 2013)

Exposure Duration (days)	TI Gen2 N = 174	TI MedTone N = 852	Comparator N = 599
Mean	141	270	340
SD	56	213	222
Median	169	173	362
Range	5-206	1-743	0-800

TI: Technosphere Insulin, Afrezza
Source: Summary of clinical safety, Table 3, p.. 14.

Table 10. Duration of Exposure for Type 2 DM – Original Submission Phase 2/3 Clinical Trials and Current Submission (up to safety data cut-off July 31, 2013)

Exposure Duration (days)	TI Gen2 N = 177[1]	TI MedTone N=1795	TP Gen2 N=176	TP MedTone N=114	Comparator N = 1363
Mean	158	259	152	81	369
SD	39	238	44	27	252
Median	169	127	169	91	364
Range	9-211	1-764	12-205	2-128	0-810

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

As can be seen in Table 9 and Table 10, the majority of the safety data is derived from TI delivered via the MedTone inhaler. The two clinical studies provided in the current submission (MKC-TI-171 and -175) intend to bridge the pulmonary safety of the MedTone inhaler to the Gen2 inhaler. As was discussed previously, the bridging of pulmonary safety data between two different devices is a novel approach. Whether the Applicant has provided adequate information to bridge the local pulmonary safety of the two devices will warrant the committee's discussion.

Deaths

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

Nonfatal Serious Pulmonary Adverse Events

The overall incidence of respiratory serious adverse events in the pooled, controlled phase 2/3 clinical studies was low and comparable between the treatment groups. No respiratory serious adverse events were noted in the Gen2 clinical studies (MKC-TI-171 and MKC-TI-175).

Dropouts and/or Discontinuations

Respiratory adverse events leading to discontinuation were more common in the TI Inhalation Powder group, both with the Gen2 inhaler and the MedTone inhaler, than the comparator group, as detailed in Table 11 and Table 12.

Table 11. Respiratory AE Leading to Discontinuation by Preferred Term in Type 1 DM (Safety Population; >1 Subject in Any Arm)

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

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

Table 12. Respiratory AE Leading to Discontinuation by Preferred Term in Type 2 DM (Safety Population; >1 Subject in Any Arm)

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

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

The most common respiratory adverse event leading to discontinuation was cough, as detailed below. Respiratory adverse events that led to discontinuation of study treatment were more common in the TI Gen2 group compared to the TI MedTone group in patients with Type 1 DM, but similar between groups for patients with Type 2 DM.

1. **FEV1**

The 2 new clinical studies in this resubmission included assessment of pulmonary function (FEV1 and FVC). FVC will not be discussed here, as it generally followed the same trend as FEV1. There was no significant difference in the mean change from baseline in FEV1 between the TI Gen2 and TI MedTone groups at Week 24 (TIGen2 - TI MedTone = 0.01L, 95% CI [-0.02, 0.04]) as displayed in Table 13. Although no analysis was done to compare the active arms in Study MKC-TI-171 to the active comparator, the numerical differences of -0.04 L for Gen2 and -0.05 L for MedTone are similar to the original submission.

Table 13. Change in FEV1 (L) from Baseline in Type 1 DM at 6 months in Studies MKC-TI-171 and MKC-TI-175 Compared to Original Submission (Safety population)

TI Gen 2 Mean (SE)	**TI MedTone** Mean (SE)	**Comparator** Mean (SE)	**Treatment Difference** Mean (SE)
MKC-TI-171			
-0.07 (0.01) N=127	-0.08 (0.01) N=133	-0.04 (0.01) N=146	TI Gen2 – TI MedTone **0.01** (95% CI: -0.02, 0.04)
			TI Gen2 – Comparator **-0.03**[1]
			TI MedTone – Comparator **-0.04**[1]
Original Submission[2]			
	-0.09 (0.01) N=370	-0.05 (0.01) N=437	TI MedTone – Comparator **-0.04** (95% CI: -0.7, -0.1)

[1] No analysis was done to determine statistical significance; [2] Applicants 2009 Pooled Type 1 (MMRM)
Source: Study MKC-TI-171 CSR, Table 52, p 168; Summary of clinical safety 2013, Table 29, p. 67; DPARP 2009 Review, Table 27, p. 76.

In patients with Type 2 DM, TI was compared to TP (excipient only), both delivered via the Gen2 inhaler. The change in FEV1 from baseline was similar to the changes seen in the original submission using the MedTone device, as shown in Table 14. The slight numerical difference is due to the comparator arm (Gen2 device with Technosphere particles without insulin), showing a smaller change in FEV1 from baseline than in the original submission.

Table 14. Change in FEV1 (L) from Baseline in Type 2 DM at 6 months in Current Submission Compared to Original Submission (Safety Population)	
MKC-TI-175	
TI Gen2 Mean (SE)	**TP Gen2** Mean (SE)
-0.13 (0.01) N=177	-0.04 (0.01) N=176
-0.09 (95% CI: -0.12, -0.05)	
Original Submission*	
TI MedTone Mean (SD)	**Comparator** Mean (SD)
-0.13 (0.01) N=688	-0.08 (0.01) N=765
-0.05 (95% CI: -0.07, -0.03)	

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

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

2. Cough

Cough was the most common adverse event (excluding hypoglycemia), with similar incident rates, discontinuation rates, and characteristics compared to the original submission (Table 15).

Table 15. Cough events in Current Submission Compared to Original Submission (Safety Population)

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

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

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

Other common respiratory adverse events that occurred more often in the treatment arms compared to the active comparator were dyspnea, bronchitis, throat irritation, oropharyngeal pain, dry throat, upper respiratory tract infection, nasopharyngitis, rhinitis, and pharyngitis for Study MKC-TI-171 (Type 1 DM), as seen in Table 20. Other common respiratory adverse events seen in Study MKC-TI-175 (Type 2 DM) occurring more often in the active arm as compared to the excipient only arm were oropharyngeal pain, throat irritation, dysphonia, nasopharyngitis, upper respiratory tract infection, and rhinitis (Table 25).

D. Labeling Considerations

If Afrezza is to be approved, the product label will need to address the pulmonary safety findings in the clinical program. Given that there are a number of pulmonary safety concerns, the pulmonary safety labeling concepts may be of interest to the Advisory Committee. As the findings in this program were consistent with the Exubera program, the labeling concepts with regards to pulmonary safety would be similar. The following is an outline of labeling concepts under consideration by the Agency divided by topic.

1. Acute bronchospasm in patients with asthma or COPD

The pivotal clinical trials to evaluate efficacy of Afrezza excluded patients with asthma or COPD or other underlying lung disease. The clinical trial in patients with asthma showed a clinically significant decline in FEV1 and reports of bronchospasm with Afrezza. The trial in patients with COPD also showed a decline in FEV1 with Afrezza. Proposed labeling concepts to address the concerns in patients with underlying lung disease are:

- **Contraindication** of Afrezza in patients with asthma, COPD, or other chronic lung disease
- **Warning and Precaution** regarding use in patients with underlying lung disease; Prior to initiating Afrezza, all patients should have history, physical exam, and spirometry to identify potential underlying lung disease. Patients who experience wheezing, bronchospasm, breathing difficulties, or persistent or recurring cough, should be carefully evaluated, including spirometry to determine if continuation of Afrezza is appropriate for such patients.

2. Decline in pulmonary function over time

The clinical program showed a decline in FEV1 over time with Afrezza. Proposed labeling concepts to address this safety issue are:

- **Warnings/Precautions** to include a description of findings; recommendation for baseline spirometry and periodic assessment – 6 months, then annually; recommend consideration to d/c Afrezza if FEV1 decline > 20%.
- **Adverse Reactions** with description of trial findings and figure showing FEV1 decline
- **Dosage and Administration** with recommendation for pulmonary function assessment at baseline and periodically.

3. <u>Smoking</u>

Patients who smoke were excluded from the Afrezza clinical trials, therefore no efficacy or safety information is available in this population. In addition, patients who smoke may be at risk for concomitant underlying lung disease. Proposed labeling concepts to address safety information with respect smokers:

- **Contraindication** of Afrezza in patients who smoke.

E. Post-marketing recommendations

At the time of the first complete response (March 12, 2010), DPARP recommended that in the face of approval, the Applicant should conduct a large controlled study designed to further assess the long-term safety of Afrezza. In the absence of a safety signal, the most appropriate duration and size of the study were uncertain, but a minimum of 5,000 patients in each treatment arm for a duration of at least 5 years, was suggested. Ideally, it was recommended that the study should include an assessment of FEV1. Further, DPARP recommended that the safety and efficacy of Afrezza should be evaluated in patients with underlying lung disease, such as asthma and COPD.

The committee's consideration of the adequacy of the pulmonary safety data, and what further data is required, whether it be pre- or post-approval will be an important topic of discussion.

IV. Summary and Discussion

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

Immediate post-inhalation changes in FEV1 were small (90-138mL) and not expected to cause symptoms in a patient with normal baseline FEV1. The FEV1 treatment difference over time between Afrezza and the comparator was noted during the first 3 months of therapy and was also

small (40-60 mL). Long-term studies showed that the early difference persisted and that the results were statistically different when compared against an active control. Per the Agency's review, there was insufficient data to draw definitive conclusions regarding reversal of the FEV1 effects due to few patients (<25% of randomized patients) contributing follow-up data after withdrawal of treatment.

Cough was the most common adverse event, but was generally mild, dry, intermittent or single-defined, and tended to decrease over time. Cough was also the most common reason for early discontinuation.

In patients with asthma, post-inhalation FEV1 declined approximately 400 mL, recovered within 2 hours, and was associated with asthma symptoms such as wheezing. A smaller decline was seen in COPD patients (200 mL) with recovery over 8 hours.

The applicant proposed a new device, the Gen2 inhaler, to address issues identified during review of the original NDA; however, the new device lacked pulmonary safety data. In response, the Applicant submitted 2 new phase 3 studies (MKC-TI-171 and MKC-TI-175).

Study MKC-TI-171 compared the to-be-marketed device (Gen2 inhaler) to the previously studied device (MedTone inhaler) by providing a head-to-head comparison in patients with Type 1 DM. Additional clinical data were provided in Study MKC-TI-175, which compared the Gen2 inhaler with and without active drug in patients with Type 2 DM. The populations for both studies were similar to the studies included in the original submission. After reviewing these new studies, the pulmonary safety profile for TI delivered via the Gen2 inhaler appears to be similar to TI delivered through the MedTone inhaler.

A key issue in the Afrezza clinical development program is the significant change in device, from the MedTone to the Gen2 inhaler. In general, for locally-acting pulmonary drug products, a substantial change in device (e.g. MedTone →Gen2 inhaler) constitutes a new drug/device combination, requiring a full clinical development program to support both efficacy and safety. The reason for the new clinical development program is that changing the device can significantly modify the drug delivery characteristics (particle size, distribution in the respiratory tract, etc.), which can impact the efficacy and safety of a locally-acting pulmonary drug. Afrezza, however, is for systemic therapy, so the systemic efficacy and safety may be easier to assess with device changes. However, the pulmonary safety effects are local effects and with a substantial change in the device, the local delivery may be significantly different and thus, the pulmonary safety may be different.

It is important to consider the limitations of the shorter duration (6 months vs. 2 years) and the small number of subjects (about 15% of subjects treated with TI were treated with the Gen2 inhaler), when evaluating the data submitted. Whether this approach and the pulmonary safety data with the Gen2inhaler are sufficient to support the pulmonary safety of Afrezza is a question we ask you to consider.

V. Appendices

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

Study Design Overview

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

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

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

Pulmonary Endpoints

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

PFT parameters

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

Study treatments

TI in Gen2 Inhaler

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

into unit (U) dose cartridges. It is administered by the Gen2 inhaler. Pre-metered single-dose cartridges are filled with 3.3 mg or 6.7 mg of Technosphere Insulin Inhalation Powder containing 10 U or 20 U of insulin, respectively. Details of the Gen2 inhaler are provided in Table 16.

Table 16. Description of Gen2 Inhaler

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

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

TI in MedTone Inhaler

Pre-metered single-dose cartridges are filled with 5 mg or 10 mg of Technosphere Insulin Inhalation Powder containing 15 U or 30 U of insulin, respectively. Details of the MedTone Inhaler are provided in Table 17.

Table 17. Description of MedTone Inhaler

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

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

Insulin aspart

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

Results

Population

Disposition: A total of 518 patients were randomized. Patient disposition is summarized in Table 18.

Table 18. Study MKC-TI-171 Subject Disposition (ITT population)

	TI Gen2	TI MedTone	Insulin Aspart
ITT Analysis Set	174	174	170
Safety Analysis Set	174	173	171
PP Analysis Set	130 (74.7%)	136 (78.2%)	147 (86.5%)
Randomized treatment phase completers	130 (74.7%)	138 (79.3%)	151 (88.8%)
Completed study	130 (74.7%)	135 (77.6%)	151 (88.8%)
Prematurely Discontinued	44 (25.3%)	36 (20.7%)	19 (11.2%)
Reason for Discontinuation			
Non-Safety			
Protocol violation	2 (1.1%)	2 (1.1%)	2 (1.2%)
Physician decision*	3 (1.7%)	1 (0.6%)	0
Withdrawal by subject*	21 (12.1%)	16 (9.2%)	8 (4.7%)
Non compliance	1 (0.6%)	2 (1.1%)	0
Lost to follow-up	1 (0.6%)	2 (1.1%)	4 (2.4%)
Safety			
AE	16 (9.2%)	9 (5.2%)	0
Death	0	0	1 (0.6%)

*One subject discontinued due to cough in Gen2 arm
Source: Module 5.3.5.1, Trial MKD-TI-171 CSR, Table 19, p. 96.

Demographics: Subject age (mean 37 years) was similar between the two treatment groups. The majority of subjects was Caucasian (94-98%) and divided approximately evenly by sex. Weight, height, BMI, and baseline FEV1 were similar between treatment groups, as seen in Table 19.

Table 19: Study MKC-TI-171 Demographic Characteristics of Safety Population						
Characteristic	**TI Gen2 N = 174**		**TI MedTone N = 173**		**Insulin Aspart N = 171**	
Subjects with at least one post-baseline PFT	148 (85)		157 (91)		159 (93)	
Gender						
Male	62 (42)		72 (46)		69 (43)	
Race						
Caucasian	164 (94)		166 (96)		167 (98)	
African American	8 (5)		5 (3)		3 (2)	
Other	2 (1)		2 (1)		1 (1)	
Age						
N	148		157		159	
Mean	37		41		40	
SD	12		13		13	
Range	18,71		18,76		18,76	
Age Group						
18-30	46 (31)		40 (26)		43 (27)	
31-49	81 (55)		75 (48)		80 (50)	
50 - 64	14 (10)		33 (21)		28 (18)	
≥65+	7 (5)		9 (6)		8 (5)	
Weight (Kg)						
N	148		157		159	
Mean	77		76		73	
SD	16		14		15	
Range	42, 129		48, 116		47, 120	
Height (cm)						
N	148		157		158	
Mean	170		171		169	
SD	9		9		10	
Range	150, 200		151, 194		149, 196	
BMI (kg/m^2)						
N	148		157		158	
Mean	26		26		25	
SD	5		4		4	
Range	17, 39		18, 36		17, 37	
FEV1 (L)	Observed	% Predicted	Observed	% Predicted	Observed	% Predicted
N	173	173	168	168	168	168
Mean	3.5	97	3.4	97	3.4	96
SD	0.8	12	0.8	11	0.8	12
Range	1.5, 6.6	72, 129	1.8, 5.3	71, 134	1.9, 6.1	63, 133

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

Efficacy

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

Safety

Exposure

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

Pulmonary safety:

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

Respiratory Adverse Events
No respiratory SAEs or deaths were noted. The most common respiratory adverse events are shown in Table 20.

Table 20. Study MKC-TI-171 Respiratory Adverse Events by Preferred Term in > 1 subject in Any Arm (Safety Population)

Preferred Term	Subject, n (%)		
	TI Gen2 N=174	TI MedTone N=173	Insulin aspart N=171
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough	55 (31.6)	39 (22.5)	4 (2.3)
Dyspnea	7 (4.0)	0	0
Throat irritation	5 (2.9)	3 (1.7)	1 (0.6)
Oropharyngeal pain	3 (1.7)	6 (3.5)	3 (1.8)
Sinus headache	1 (0.6)	0	2 (1.2)
Dry throat	0	2 (1.2)	0
INFECTIONS AND INFESTATIONS			
Upper Respiratory Tract Infection	14 (8.0)	16 (9.2)	12 (7.0)
Nasopharyngitis	5 (2.9)	13 (7.5)	12 (7.0)
Bronchitis	6 (3.4)	1 (0.6)	4 (2.3)
Respiratory Tract Infection Viral	3 (1.7)	1 (0.6)	3 (1.8)
Sinusitis	2 (1.1)	2 (1.2)	3 (1.8)
Rhinitis	2 (1.1)	0	1 (0.6)
Tracheitis	1 (0.6)	0	1 (0.6)
Pharyngitis	0	2 (1.2)	1 (0.6)

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

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

No subjects in the insulin aspart group discontinued due to respiratory AEs. Subjects did discontinue due to cough as shown in the table below. More subjects in the TI inhaled powder groups discontinued because of cough (5.7% in TI Gen2 and 2.9% in TI MedTone) compared to none in the insulin aspart group. More subjects also discontinued due to cough, dyspnea, bronchial hyperreactivity, and exertional dyspnea for Gen2 compared to MedTone and insulin aspart (Table 21).

Table 21. Study MKC-TI-171 Respiratory AE by Preferred Term Leading to Discontinuation (Safety Population)

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

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

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

FEV1

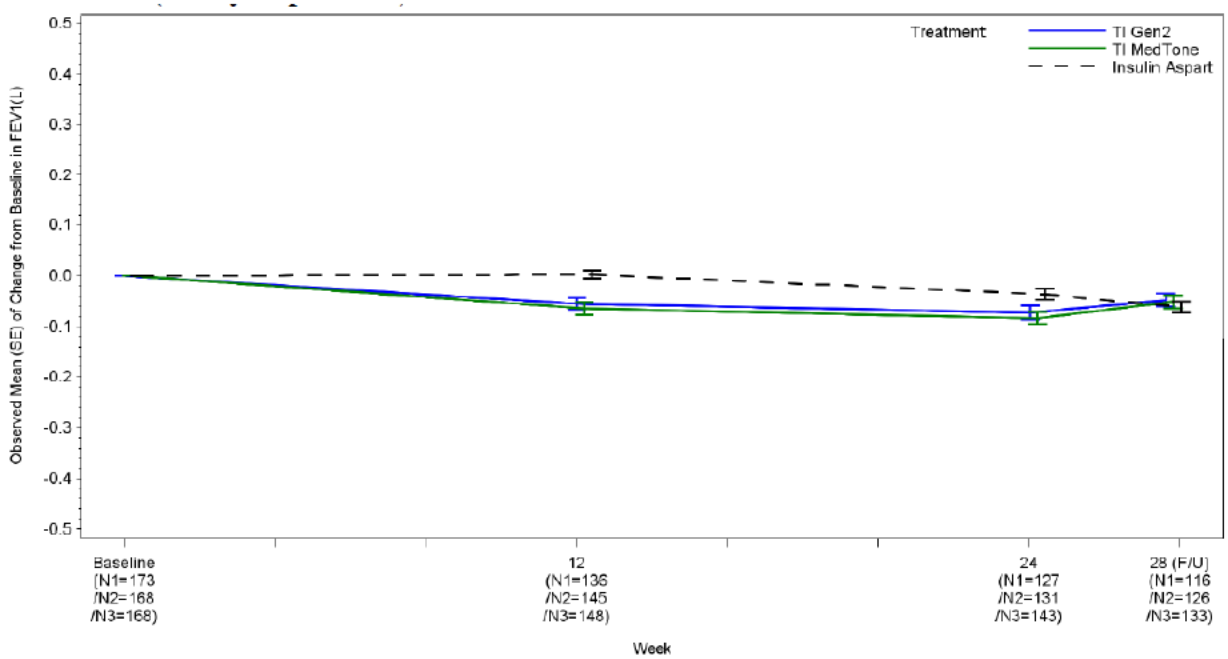
Baseline FEV1 was normal and comparable between the TI Gen2 and TI MedTone groups. Mean change from baseline in FEV1 at Week 24 was similar for TI delivered via the Gen2 inhaler and the MedTone inhaler (-0.01, 95% CI: -0.02, 0.04) (Table 22). The decline in the TI

MedTone group of about 40 mL compared to the active comparator arm was numerically similar to the original submission.

Table 22. Study MKC-TI-171 Adjusted Mean Change in FEV1 from Baseline to Week 24 Over Time Based on MMRM Analysis (Safety Population)				
	Statistics	**TI Gen2 N=174**	**TI MedTone N=173**	**Insulin Aspart N=173**
Baseline	N (%)	173 (99%)	168 (97%)	168 (98%)
	Adjusted Mean (SE)	3.43 (0.03)	3.43 (0.03)	3.43 (0.03)
Week 24	N (%)	127	133	146
	Adjusted Mean (SE)	3.35 (0.03)	3.35 (0.03)	3.39 (0.03)
	Adjusted Mean Change (SE)	-0.07 (0.01)	-0.08 (0.010	-0.04 (0.01)
	Treatment Difference (TI Gen2 – MedTone) Adjusted Mean Change (SE)	-0.01 (0.02) 95% CI: -0.02, 0.04		
Source: Module 5.3.5.1, Trial MKC-TI-171 CSR, Table 52, p 167				

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

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



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

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

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

FEV1 Summary

Mean change from baseline in FEV1 at Week 24 was similar for TI delivered via the Gen2 inhaler and the MedTone inhaler (-0.01, 95% CI: -0.02, 0.04). Numerically, both the treatment arms showed a similar mean change from baseline in FEV1 compared to placebo, as was seen in the original submission (about 40 mL). Mean changes in PFT parameters were not driven by a small number of subjects with large PFT changes. After 4 weeks off treatment (Week 28), the mean FEV1 value in the TI Gen2 group and TI MedTone groups returned to a level similar to that of insulin aspart. No noteworthy or consistent patterns were observed in the change from baseline in FEV1 across subject characteristics, including gender, age, race/ethnicity, average daily dose of TI, and cough status.

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

Study Design Overview

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

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

Study treatments:

TI in Gen2 Inhaler

Detailed in Study MKC-TI-171.

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

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

Results

Disposition: A total of 353 subjects were enrolled in this study. Subject disposition is summarized in Table 23.

Table 23. Study MKC-TI-175 Subject Disposition (ITT population)

	TI Gen2	TP Gen2
ITT Analysis Set	177	176
Safety Analysis Set	177 (100%)	176 (100%)
PP Analysis Set	144 (81.4%)	131 (74.4%)
Completed randomized treatment phase	150 (84.7%)	139 (79.0%)
Completed study	149 (84.2%)	138 (78.4%)
Prematurely Discontinued	27 (15.3%)	37 (21.0%)
Reason for Discontinuation		
Non-Safety		
Protocol violation	1 (0.6%)	2 (1.1%)
Physician decision*	1 (0.6%)	1 (0.6%)
Withdrawal by subject*	10 (5.6%)	14 (8.0%)
Non compliance	1 (0.6%)	3 (1.7%)
Lost to follow-up	6 (3.4%)	4 (2.3%)
Safety		
AE	7 (4.0%)	9 (5.1%)
Death	0	0

*None of these subjects withdrew for pulmonary reasons
TI: Technosphere Inhalation Powder (active), TP: Technosphere particles (excipient only)
Source: Module 5.3.5.1, Trial MKC-TI-175 CSR, Table 14, p 83

Demographics: Subject age (mean 57 years) was similar between the two treatment groups. The majority of subjects was Caucasian (85-88%) and divided approximately evenly by sex. Weight, height, BMI, and baseline FEV1 were similar between treatment groups, as seen in Table 24.

Table 24: Study MKC-TI-175 Demographic Characteristics of Safety Population				
Characteristic	**TI Gen2 N = 177, n (%)**		**TP Gen2 N = 176, n (%)**	
Subjects with at least one post-baseline PFT	163 (92)		155 (88)	
Gender				
Male	75 (46)		64 (41)	
Race				
Caucasian	151 (85)		155 (88)	
African American	21 (12)		17 (10)	
Other	5 (3)		4 (2)	
Age				
N	163		155	
Mean	57		57	
SD	9		8	
Range	27, 75		36, 79	
Age Group				
25-39	7 (4)		2 (1)	
40-65	133 (82)		130 (84)	
>65	23 (14)		23 (15)	
Weight (Kg)				
N	163		155	
Mean	90		91	
SD	17		18	
Range	54, 142		58, 137	
Height (cm)				
N	163		155	
Mean	168		167	
SD	10		10	
Range	146, 188		143, 197	
BMI (kg/m^2)				
N	163		155	
Mean	32		33	
SD	5		5	
Range	22, 44		21, 44	
FEV1 (L)	Observed	% Predicted	Observed	% Predicted
N	173	173	166	166
Mean	2.9	98	2.8	98
SD	0.7	13	0.7	12
Range	1.7, 4.9	68, 150	1.6, 4.6	71, 125

TI=Technosphere Insulin (active); TP = Technosphere particles (excipient only)
Source: MKC-TI-171 CSR, Table 41, p 140-1; Table 42, p 142; MKC-TI-171, Table 14.1.2.1, p. 587.

Efficacy

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

Safety

Exposure

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

Pulmonary Safety

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

Respiratory adverse events

No respiratory SAEs or deaths were noted. The most common adverse event in both treatment groups was cough (TI Gen2: 24%; TP Gen2: 20%). Additional respiratory adverse events are listed in Table 25.

Table 25. Study MKC-TI-175 Respiratory Adverse Events by Preferred Term Occurring in > 1 Subject in Any Arm (Safety Population)

Preferred Term	Subject, n (%)	
	TI Gen2 N=177	TP Gen2 N=176
RESPIRATORY, THORACIC, MEDIASTINAL DISORDERS		
Cough	42 (24%)	35 (20%)
Oropharyngeal pain	8 (5%)	4 (2%)
Throat irritation	3 (2%)	2 (1%)
Dysphonia	2 (1%)	0
Dyspnea	1 (1%)	2 (1%)
INFECTIONS AND INFESTATIONS		
Nasopharyngitis	15 (9%)	8 (5%)
Upper Respiratory Tract Infection	9 (5%)	5 (3%)
Bronchitis	5 (3%)	7 (4%)
Rhinitis	3 (2%)	0
Respiratory Tract Infection*	4 (2%)	5 (3%)
Sinusitis	2 (1%)	2 (1%)

*Combined respiratory tract infection viral and respiratory tract infection
Source: Module 5.3.5.1, Trial MKC-TI-175 CSR, Table 34, p 128

Cough was the most common reason for discontinuation. More subjects who received the excipient powder discontinued due to cough (3%) than subjects who received TI (1%), as summarized in Table 26. Other respiratory adverse events causing discontinuation were uncommon.

Table 26. Study MKC-TI-175 Respiratory AEs Leading to Discontinuation (Safety population)

Preferred Term	Subject, n (%)	
	TI Gen2 N=177	TPGen2 N=176
Cough	2 (1%)	6 (3%)
Dyspnea	1 (1%)	0
Oropharyngeal pain	1 (1%)	0
Nasal congestion	0	1 (1%)
Wheezing	0	1 (1%)

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

FEV1

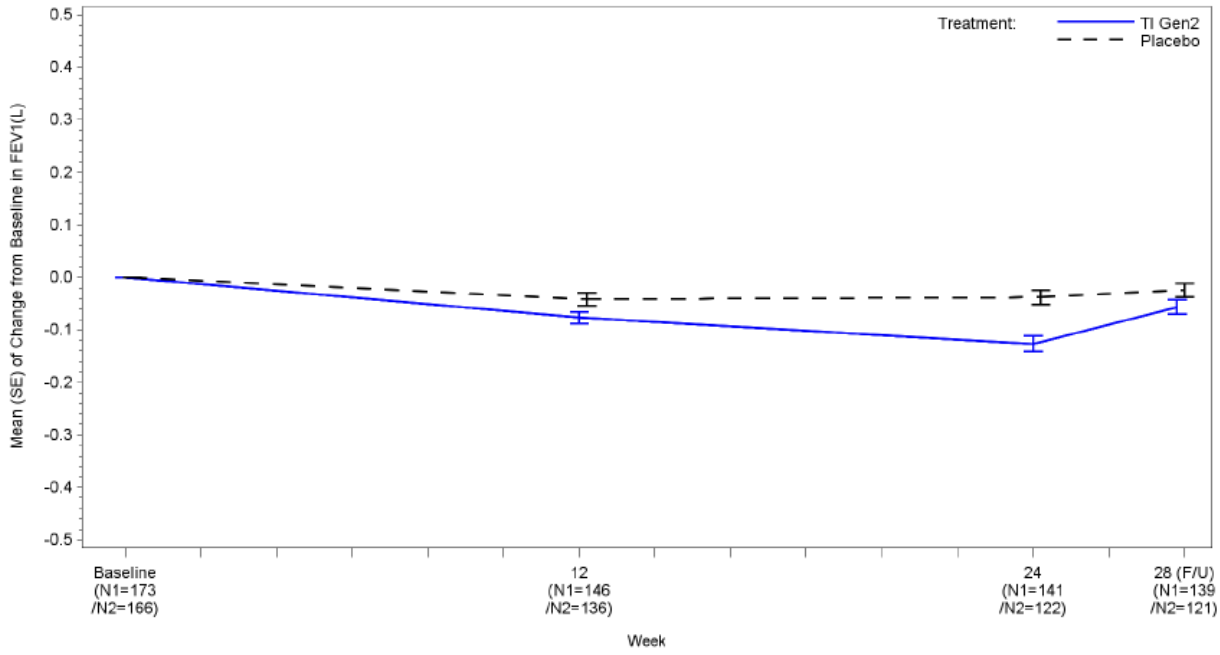
Baseline FEV1 was normal and comparable between TI Gen2 and the TP Gen2 groups. The TI Gen2 group showed greater decline from baseline in FEV1 at Week 24 compared to the TP Gen2 group (Table 27). This was numerically similar to the original submission with the TI MedTone inhaler. After 4 weeks after stopping treatment (Week 28) the mean FEV1 value in the TI Gen2 group returned to a level similar to that of the TP Gen2 group (placebo), as seen in Figure 6.

Table 27. Study MKC-TI-175 Adjusted Mean Change in FEV1 from Baseline to Week 24 (Safety Population; MMRM Analysis)

	Statistics	TI Gen2 N=177	TP Gen2 N=176
Baseline	N (%)	173 (98)	166 (94)
	Adjusted Mean (SE)	2.83 (0.02)	2.83 (0.03)
Week 24	N (%)	144 (81)	128 (73)
	Adjusted Mean (SE)	2.70 (0.03)	2.79 (0.03)
	Adjusted Mean Change (SE)	-0.13 (0.01)	-0.04 (0.01)
	Treatment Difference (TI Gen2 – TP Gen2) Adjusted Mean Change (SE)	-0.09 (0.02) 95% CI: -0.12, -0.05	

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

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



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

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

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

FEV1 Summary

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

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Summary: Review of Study Protocol

Date:	February 28, 2014
Reviewer(s):	Patricia L. Bright, M.S.P.H., Ph.D., Epidemiologist, Division of Epidemiology 1 (DEPI 1), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Team Leader:	Diane K. Wysowski, M.P.H., Ph.D., DEPI 1, OPE, OSE
Division Director:	Cunlin Wang, M.D., Ph.D., DEPI 1, OPE, OSE
Subject:	Review of the Sponsor's proposed postmarketing study for Afrezza entitled "A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus" (October 2013 resubmission to the FDA)
Drug Name(s):	Afrezza (Technosphere Insulin Inhalation System)
Application Type/Number:	NDA 022472
Applicant/sponsor:	MannKind
OSE RCM #:	2014-304
TSI #:	Not Applicable

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Afrezza (insulin, human [rDNA] inhalation powder) is an ultra-rapid acting inhaled insulin indicated for improving glycemic control in adults with type 1 and type 2 diabetes.

Following the second Complete Response (CR) of the new drug application in January 2011, the sponsor responded to the FDA's concerns and resubmitted the application to the FDA on October 15, 2013. On October 22, 2013, the Division of Metabolism and Endocrinology Products (DMEP) requested the Division of Epidemiology 1 (DEPI 1) to evaluate the sponsor's proposed postmarketing study for Afrezza entitled "A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus."

The sponsor submission did not include a fully developed postmarketing study protocol, but included a four-page proposal for an observational study. The proposal was for a non-interventional, multicenter, non-comparative, postmarketing study to evaluate the long-term safety profile of Afrezza when prescribed in usual clinical practice for the treatment of diabetes. The main study objective was to determine the incidence of primary pulmonary malignancies in patients taking Afrezza. Secondary objectives were to determine the incidence of the following outcomes: all other malignancies (except non-melanoma skin cancers), serious pulmonary events (besides malignancies), serious allergic events, and hypoglycemic events requiring medical intervention. All treatment decisions would be made at the discretion of the patient's healthcare provider and would not be mandated by the study design or protocol. The study would be conducted in the U.S. with other countries added (contingent upon national approval of Afrezza and the study protocol).

Although the method for site selection was not described, the proposal stated that 200 sites that care for type 1 and type 2 diabetes patients would be identified for study participation (including a heterogeneous sample of family practice, internal medicine, diabetes, and endocrinology practices). The anticipated sample size would be 1,800 participants recruited over approximately two years and followed for at least five years from date of the last patient enrollment. Data collection would take place at usual care visits (with a minimum of every 6 months) and follow-up would take place even if Afrezza is discontinued.

The proposal indicates that the incidence of pulmonary malignancies from the study would be compared to the background rate in the general population based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data with 90% power to detect a 3-fold increase in the rate of pulmonary malignancy.

DEPI staff concluded that the registry proposal had insufficient detail. Also, given that pulmonary malignancy risk is heavily confounded by smoking and that Afrezza users may have more thorough or frequent pulmonary assessments than the proposed comparator, the proposed postmarketing approach would be inadequate to evaluate risk of pulmonary malignancies with Afrezza use. In addition, the age-adjusted U.S. incidence rate of lung cancer is a crude comparator. Rather lung cancer incidence rates

adjusted by frequency, duration, and pack-years of cigarette smoking might be a more appropriate comparator. Since frequency and duration of cigarette smoking is the most important risk factor for lung cancer incidence, collection of frequency, duration, and number of pack-years of cigarette smoking would be critical for evaluation of the role of Afrezza in lung cancer incidence and mortality.

DEPI I staff have recommended two alternative post-marketing approaches that might better assess pulmonary malignancy risk with Afrezza use. These approaches are listed at the end of section 4 (Discussion).

Additional recommendations for the sponsor are listed in Section 6 of this review.

1 INTRODUCTION

In March 2010 and January 2011, the FDA issued Complete Responses (CR) for a new drug application (NDA) submission for Afrezza. On October 15, 2013, the sponsor resubmitted the application to the FDA, responding to the FDA's concerns. On October 22, 2013, the Division of Metabolism and Endocrinology Products (DMEP) requested the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Epidemiology1 (OSE/OPE/DEPI1) evaluate a sponsor's proposed postmarketing study for Afrezza entitled "A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus."

1.1 BACKGROUND

Brief Drug Description

Afrezza (insulin, human [rDNA] inhalation powder) is an ultra-rapid acting inhaled insulin seeking approval for improving glycemic control in adults with type 1 and type 2 diabetes. The dry powder is administered at the beginning of a meal by a Gen2 inhaler with cartridges containing 10 units or 20 units of drug product.

The sponsor has proposed in the Afrezza labeling that Afrezza be contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD) or other chronic lung disease. The sponsor also has proposed labeling under Warnings and Precautions that Afrezza not be recommended for current smokers and those who have smoked in the last 6 months and that prior to initiating therapy with Afrezza, all patients should be clinically evaluated with a detailed medical history, physical examination and spirometry (FEV1) to identify any potential underlying disease.

Safety Concerns

- Lung Cancer

  Exubera

  The FDA approved Exubera, another inhaled insulin, in January 2006, but Exubera was later withdrawn by the sponsor due to lower than expected sales. Prior to official withdrawal, however, the FDA required changes to the Exubera product labeling due to postmarketing pulmonary malignancies. The labeling noted that there were too few cases to determine whether the events were related to Exubera and that all

patients who were diagnosed with lung cancer had a prior history of cigarette smoking.

Since that time, study results from an observational follow-up study of patients previously enrolled in Exubera (FUSE) controlled clinical trials found the following:

- Primary lung cancer mortality--Six cases were reported in 12,605.9 person years in the Exubera group and 2 cases in 11,802.5 person years in the comparator group. The incidence density ratio (IDR) was 2.81 (95% CI: 0.50 - 28.46).
- Primary lung cancer incidence--Twelve cases were reported in 11,180.7 person years in the Exubera group and 3 cases in 10,467.9 person years in the comparator group. The IDR was 3.75 (95% CI: 1.01 - 20.68).

Pulmonary malignancies remain adverse events of special interest for inhaled insulins [1].

Afrezza

During the clinical development program for Afrezza in which Afrezza use was compared primarily with other insulin use[1], two cases of pulmonary malignancies were identified in Afrezza-exposed patients: One was identified after 120 days of treatment in a 62-year-old male subject with a prior history of smoking. The other involved a non-small cell bronchogenic carcinoma in an Afrezza-exposed patient in an uncontrolled trial. The patient was "a 67-year-old male subject with a history of heavy smoking and a family history of lung cancer" [2].

Two additional lung cancers were spontaneously reported at 2.5 and 3.5 years, respectively, after clinical trial discontinuation in a 59-year-old male non-smoker and in a 73-year-old female non-smoker who had been prescribed a high dose of Afrezza [3].

No lung cancer cases were reported in comparator-exposed patients.

- Non-Malignant Pulmonary Adverse Events: Bronchospasms and Pulmonary Function Decline

  The FDA review of pulmonary safety from the original NDA submission found that cough was the most common adverse event, with occasional bronchospasm. This was exacerbated for patients with underlying disease, such as asthma. Although cough rates were similar to those in the Exubera development program, they exceeded frequencies typically found in patients with asthma/chronic obstructive pulmonary disease (COPD) treated with dry powder inhalers [4].

  Patients with type 1 or type 2 diabetes treated with Afrezza also had a non-clinically significant decline in FEV1 (average of 40-50 ml) with a decline of 90-138 ml immediately post inhalation. Declines started during the first three months of treatment and persisted over time. Data were insufficient to evaluate reversal after

[1] The comparators in the trials were generally insulin aspart or insulin lispro with a background basal insulin (typically insulin glargine) as compared to Afrezza with a background basal insulin. Other trials used placebo as a comparator in combination with metformin or two or more oral anti-diabetic agents.

Afrezza discontinuation. In asthmatic patients, FEV1 declined 400 ml at 15 minutes post-inhalation, but recovered over a two-hour period [4].

- Serious Allergic Events and Hypoglycemia
  The 2010 FDA clinical review found that the incidence of hypoglycemia in trial 117 (a randomized open-label study in patients with Type 1 diabetes) was lower for Afrezza than for Humalog, but the difference was not statistically significant. The risk of hypoglycemia was directly proportional to dose [1].

To further assess these safety concerns, the sponsor proposed a non-interventional, post-marketing study to evaluate the long-term safety profile of Afrezza when prescribed in usual clinical practice for the treatment of diabetes. The proposal states that "The study will provide additional quantification and characterization of potential adverse events with low incidence or long latency after exposure to Afrezza. In addition, the study will help identify adverse events that may occur outside of the controlled clinical trial setting." The proposed postmarketing proposal is the basis for this review.

1.2 REGULATORY HISTORY (ABBREVIATED):

- December 22, 2000: IND 061729 submitted to the FDA.
- March 16, 2009: NDA 022472 submitted to the FDA.
- March 12, 2010: The FDA issued a Complete Response letter.
- June 29, 2010: The sponsor sent a class 2 resubmission for NDA 022472.
- January 18, 2011: The FDA issued another Complete Response letter.
- October 15, 2013: The sponsor sent a class 2 resubmission for NDA 022472.
- October 22, 2013: DMEP consulted DEPI1 on the sponsor's submission. The sponsor's proposed postmarketing study is the basis for this review.

1.3 PRODUCT LABELING

Afrezza has not yet been approved and product labeling has not been finalized. However, Mannkind has proposed in the Afrezza labeling that Afrezza be contraindicated in patients with a current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD) or other chronic lung disease. The sponsor also has proposed labeling under Warnings and Precautions that Afrezza not be recommended for current smokers and those who have smoked in the last 6 months and that prior to initiating therapy with Afrezza, all patients should be clinically evaluated with a detailed medical history, physical examination and spirometry (FEV1) to identify any potential underlying disease.

2 REVIEW METHODS AND MATERIALS

Following the second FDA Complete Response for NDA 022472, the FDA received a third submission for the product on October 15, 2013. On October 22, 2013, DMEP requested that DEPI 1 evaluate the sponsor's proposed postmarketing study for Afrezza entitled "A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus." DEPI staff reviewed this proposal using as a reference "Registries for Evaluating Patient Outcomes: A User's Guide" [5].

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

The sponsor submission did not include a fully developed postmarketing study protocol, but included a four-page proposal for an observational study. This proposal was for a non-interventional, multicenter, non-comparative, postmarketing study to evaluate the long-term safety profile of Afrezza when prescribed in usual clinical practice for the treatment of diabetes. All treatment decisions would be made at the discretion of the patient's healthcare provider and would not be mandated by the study design or protocol. The study would be conducted in the U.S. with other countries added (contingent upon national approval of Afrezza and the study protocol).

Although the method for site selection was not described, the proposal stated that 200 sites that care for type 1 and type 2 diabetes patients would be identified for study participation (including a heterogeneous sample of family practice, internal medicine, diabetes, and endocrinology practices). The anticipated sample size would be 1,800 participants recruited over approximately two years and followed for at least five years from date of the last patient enrollment. Data collection would take place at usual care visits (with a minimum of every 6 months) and follow-up would take place even if Afrezza is discontinued. Study outcomes are listed under the objectives below.

The proposal stated that the investigators will compare the incidence of pulmonary malignancies to the background rate in the general population based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data (see the statistical analysis section 3.3.5 below)

3.2 STUDY OBJECTIVES

The primary study objective would be to determine the incidence of primary pulmonary malignancies in patients taking Afrezza. The secondary objectives would be to determine the incidences of:

- All other malignancies (except non-melanoma skin cancers)
- Serious pulmonary events
- Serious allergic events
- Hypoglycemic events requiring medical intervention

3.3 STUDY METHODS

3.3.1 Design & Setting

3.3.1.1 Study Type

The study would be a prospective, observational, follow-up product exposure registry without an internal study comparison group. The study will compare the observed lung cancer incidence rate in the Afrezza registry with the age-adjusted incidence rate of lung cancer in the U.S. population.

3.3.1.2 Time Period

The study population would be recruited over two years until a target of 1,800 patients is reached. Participants would be followed for at least five years from last patient enrollment with the duration of individual patient participation ranging from 5-7 years.

3.3.1.3 Population -- Selection, Inclusion and Exclusion Criteria

Selection:
The proposal stated that 200 sites that care for type 1 and type 2 diabetes patients would be identified for study participation (including a heterogeneous sample of family practice, internal medicine, diabetes, and endocrinology practices). Methods and criteria for site and health care provider selection to participate were not addressed.

Inclusion Criteria:
- Adult patients (age $\geq$ 18 years) who are initiating treatment with Afrezza. The decision to prescribe Afrezza would need to be made prior to study enrollment.
- Patients would need to be able to understand the requirements of the study, and provide written informed consent.

Exclusion Criteria:
- Patients previously enrolled in other studies evaluating inhaled insulin products.
- Patients receiving an investigational agent (any drug or biologic agent that has not received marketing authorization in the Unites States).

3.3.2 Outcome & Exposure

Exposure:
Although Afrezza use is the exposure of interest, the proposal did not address how Afrezza exposure would be determined.

Outcome:
Outcomes of interest in the follow-up study were new (incident) primary pulmonary malignancies, all malignancies (except non-melanoma skin cancers), and serious pulmonary, serious allergic, and hypoglycemic events requiring medical intervention. The proposal did not contain any details on how these outcomes would be defined or validated.

3.3.3 Covariates

Baseline:
The following covariate information would be collected at baseline: age, gender, race/ethnicity, smoking history, height and weight, diabetes treatment (diagnosis, treatment history, complications, history of hypoglycemia), pulmonary history, cancer history, history of allergic conditions, and concomitant medications.

Follow-up:
The following covariate information would be collected at follow-up: weight, current diabetes treatment regimen, changes in concomitant medications, and serious adverse events.

3.3.4 Sample Size/Power

The investigators suggested a sample size of 1,800 participants (calculated using a background rate of 64.6 pulmonary malignancies per 100,000 person-years). The proposal stated that this rate was determined from the SEER database, but the associated years for the rates were not provided. As of Jan 3, 2014, the SEER website reported that the number of new cases of lung and bronchus cancer was 61.4 per 100,000 men and women per year, age-adjusted, based on 2006-2010 cases.

The proposal estimated that if 1,800 patients were enrolled in the study over a two-year period and followed for at least five years after the end of enrollment and assuming a study discontinuation rate of 10%, approximately 8,000 person-years of follow-up would accumulate. The proposal stated that the 8,000 person-years of follow-up would provide 90% power to detect a 3-fold increase in rate of pulmonary malignancy with a two-sided alpha of 0.05.

The calculation appears to rely on the assumption that Afrezza use would have no more than a 10% discontinuation rate throughout the entire study period.

No sample size estimation was provided for estimated ranges of losses to follow-up and for discontinuation rates exceeding 10%.

3.3.5 Statistical Analyses

The proposal stated that "The primary endpoint is the incidence of pulmonary malignancies, with a background rate assumed to be 64.6 events per 100,000 person-years of surveillance. If the lower limit of the 95% confidence interval is above 64.6, then exposure to Afrezza will be deemed to have demonstrated a significant risk for pulmonary malignancies." The proposal further stated that for binomial endpoints, the number of person-years of follow-up and incidence per 100,000 person-years would be calculated with 95% confidence intervals. Exploratory analyses would also be conducted using logistic regression comparing those who experienced the safety outcomes to those who did not. An exploratory analysis would also evaluate Afrezza dose and duration.

4 DISCUSSION

Study Objectives

The objectives appear appropriate, but may need to be revised if the FDA identifies additional safety outcomes of interest through the FDA review process. Such requirements would be specified if the drug receives FDA approval and if a Post-marketing Requirement (PMR) for a safety study is issued to the sponsor.

Study Design

The sponsor proposed a prospective, observational, follow-up product exposure registry without an internal comparator group. Rather, they plan to compare the observed lung cancer incidence rates with the expected rate in the U.S. population. However, since smoking is the major risk factor for lung cancer, lung cancers in Afrezza exposed and comparator groups should be adjusted for, or stratified by, frequency, duration, and pack-years of cigarette smoking to compare risk in the two groups.

Cough is a common side effect in Afrezza exposed patients, and the previous inhaled insulin, Exubera, underwent a labeling change to include information on pulmonary malignancies. Therefore, exposed patients may have more thorough or frequent pulmonary assessments than the general population leading to higher detection rates for pulmonary malignancies (detection bias).

Time Period
The sponsor proposed that the study continue for five years after the last patient enrollment. However, the FDA typically requires observational studies of malignancy to continue for 10 years to allow for sufficient length of follow up given the unknown latency period and to obtain a large enough sample size to evaluate malignancy development and detection.

Selection
The proposal did not clarify how sites will be identified for study participation. If a PMR is issued, we would expect a revised protocol containing greater detail on the methodology for how sites and physicians would be identified and invited to participate.

Inclusions and Exclusions
The proposal stated that inclusion criteria were broad and exclusion criteria were limited so as to include a representative population of patients taking the product in usual clinical practice. We agree with the proposed inclusion and exclusion criteria.

Exposure
The proposal does not address procedures to document Afrezza exposure or adherence beyond collecting data on "current diabetes treatment regimen" at follow-up visits. The proposal should indicate how prescribing information for Afrezza would be documented at enrollment, and how changes in Afrezza exposure would be documented over time (including stopping, starting, changes in dose, and periods of non-adherence). The clinicians should ask and record changes in actual use at each patient visit.

Outcomes
The proposal did not provide details on how the outcomes would be defined and validated (pulmonary malignancies, all malignancies excluding non-melanoma skin cancers, serious pulmonary, serious allergic, and hypoglycemic events requiring medical attention). For malignancies, the protocol should include (as appropriate) plans for documentation of histopathology, stage, invasiveness, tumor size, extension, and lymph node involvement.

We also recommend that the study evaluate the frequency of pulmonary function tests performed at baseline (before Afrezza initiation), lung cancer mortality and all-cause mortality (with cause of death) in study participants as secondary outcomes.

Covariate Data
A detailed smoking history (number of cigarettes smoked per day and duration of smoking) should be collected on all study participants at baseline. In addition to the covariate information mentioned in the proposal, data collection at baseline and as appropriate at each participant visit should include current smoking status and intensity, other tobacco use, personal history of cancer, body mass index (BMI), other

comorbidities, asbestos exposure, radiation exposure, immunosuppressive therapy, family history of cancer, and history of alcohol consumption. Follow-up data collection should address changes in smoking status, tobacco use (and document intensity if applicable), and other variables that may have changed since the previous patient visit.

Follow-up

The proposal did not provide details on procedures to contact and trace participants, but did project 90% participant retention. We encourage the inclusion of more detailed plans to maintain patients' follow-up during the study and a search of the National Death Index (NDI) in the U.S. (and similar databases in other countries) for participants lost to follow-up to ascertain death and causes of death.

Sample Size

The sample size calculated for this study was based on the U.S. age-adjusted incidence rates of pulmonary malignancies per 100,000 person-years (data years not specified). However, since most cases of lung cancer with inhaled insulin have been in previous smokers, we recommend estimating the sample size that would be needed to detect a two-fold increase in the incidence of pulmonary malignancies (with 80% power and 95% confidence) for former smokers in addition to using the U.S. population rates that include both smokers and non-smokers.

Sample size calculations did not account for varying rates of Afrezza loss to follow-up. We suggest that the revised protocol calculate the estimated sample size based on various rates of loss to follow-up and Afrezza discontinuation that exceed 10%.

Analysis

The revised protocol should include a detailed analysis plan and describe how missing data would be addressed.

The investigators should also plan to report registry enrollment to the FDA annually by country.

Alternative study designs:

We suggest two potential postmarketing study approaches to evaluate the relationship between pulmonary malignancies and Afrezza use in addition to the sponsor's proposed study:

- **A registry with methodology to reduce detection bias**
  A study of diabetic patients who are prescribed Afrezza to evaluate the incidence of lung cancer, lung cancer mortality, and all-cause mortality at 3, 5, and 10 years by Afrezza use (lowest quartile for exposure duration as compared to upper two quartiles of exposure duration) adjusting for pack-years of smoking. The study would collect detailed information on smoking history (number of cigarettes smoked per day and duration of smoking) and on other potential risk factors (current smoking status and intensity, other tobacco use, age, gender, race, BMI, diabetes severity, family history of lung cancer, history of cancer and other comorbidities, asbestos exposure, radiation exposure, immunosuppressive therapy, concomitant medications, etc.). After agreement on a targeted sample size with the FDA, the study would continue for 10 years from the date of last patient's enrollment.

By limiting the study to Afrezza users, detection bias could be minimized that might result from Afrezza users undergoing more thorough or frequent pulmonary assessments that might arise due to clinician familiarity with the pulmonary malignancy data associated with Exubera use. Detection bias due to coughing may remain an issue when comparing current users of Afrezza to those who have discontinued.

The total number of events needed to detect the associated hazard ratios (HRs) were calculated by Dr. Mark Levenson of DBVII, and are listed in Table 1 (90% power and a two-sided alpha of 0.05).

Table 1: Numbers of events needed to detect the corresponding HR

Hazard Ratio (HR)	Total Events (lower exposer plus higher exposure)
2	87
3	35
4	22

The secondary outcomes proposed by the sponsor (other malignancies, serious pulmonary events, serious allergic events and hypoglycemic events requiring medical intervention), also could be assessed in this registry.

Or

- **A Large Randomized Controlled Study**
  The FDA may request a large randomized controlled study designed to further assess the long-term pulmonary safety of Afrezza. We recommend that lung cancer, lung cancer mortality, and all-cause mortality be study outcomes. In addition, we recommend that participants also undergo further observational follow-up for lung cancer, lung cancer mortality, and all-cause mortality after trial discontinuation.

  The study would need to collect detailed information on smoking history (number of cigarettes smoked per day, duration of smoking, and pack-years) and on other potential risk factors for pulmonary malignancies (age, gender, race, current smoking status and intensity, other tobacco use, BMI, diabetes severity, personal history of cancer, alcohol use, other comorbidities, asbestos exposure, radiation exposure, immunosuppressive therapy, concomitant medications, etc.). The other outcomes proposed by the sponsor (all malignancies except non-melanoma skin cancers, and serious pulmonary, serious allergic, and hypoglycemic events requiring medical intervention) could also be assessed with this study approach.

5 CONCLUSION

If Afrezza receives FDA approval and if a postmarketing study is required, the sponsor will be obligated to submit to the FDA a formal well-developed study protocol to

evaluate the outcomes identified in the postmarketing requirement. The currently proposed registry has inadequate detail.

Also, given that pulmonary malignancy risk is heavily confounded by smoking and that Afrezza users may have more thorough or frequent pulmonary assessments than a comparator, resulting in possible detection bias, the proposed postmarketing approach would be inadequate to evaluate pulmonary malignancy risk with Afrezza use.

DEPI I staff have recommended two alternative postmarketing approaches that include collecting detailed information on cigarette smoking history and status that might better assess pulmonary malignancy risk with Afrezza use. These approaches are listed above at the end of section 4 (the Discussion).

Additional recommendations for the sponsor concerning this proposal are listed in Section 6 of this review (below).

6 RECOMMENDATIONS TO SPONSOR

If Afrezza receives FDA approval and if a postmarketing study is required, you will have to submit to the FDA a formal well-developed study protocol to evaluate the outcomes identified in the postmarketing requirement. The currently proposed registry includes inadequate detail.

Also, given that pulmonary malignancy risk is heavily confounded by smoking history and that Afrezza users may have more thorough or frequent pulmonary assessments than a comparator (detection bias), the proposed postmarketing approach would be inadequate to evaluate pulmonary malignancy risk with Afrezza use. We suggest that the sponsor discuss with the FDA alternative approaches that may better address the challenges posed in the postmarketing setting.

Our recommendations are listed below about your proposed study. However, the FDA may require an alternative study(ies).

1. The objectives appear appropriate, but you may need to revise them if the FDA identifies additional safety outcomes of interest. Such requirements would be specified if the drug receives FDA approval and if a safety Postmarketing Requirement (PMR) is issued.
2. Evaluate lung cancer mortality and all-cause mortality (with cause of death) in study participants as secondary outcomes.
3. Evaluate the frequency of pulmonary function tests performed at baseline (before Afrezza initiation).
4. Clarify how sites will be identified for study participation. If a PMR is issued, we would expect a revised protocol containing greater detail on the methodology for how sites and physicians will be identified and invited to participate.
5. Describe data collection including standardized forms or instructions to physicians for documenting all information including prescribing information for Afrezza at enrollment, and how changes in Afrezza exposure would be documented over time (including stopping, starting, changes in dose, and periods of non-adherence).

Provide details on how the outcomes will be defined and validated. For malignancies, the protocol should include (as appropriate) plans for documentation of histopathology, stage, invasiveness, tumor size, extension, and lymph node involvement.

6. Collect detailed smoking histories (number of cigarettes smoked per day, duration of smoking, and pack-years) at baseline. In addition to the covariate information mentioned in the proposal, collect current smoking status and intensity, other tobacco use, body mass index (BMI), personal history of cancer, other comorbidities, asbestos exposure, radiation exposure, immunosuppressive therapy, family history of cancer, and history of alcohol consumption. Follow-up data collection should address changes in smoking status or tobacco use (and document intensity) as well as other risk factors that change over time.
7. Analyze the data by age; sex; smoking frequency, duration, and pack years; Afrezza dose and duration; and controlling for covariates.
8. Include procedures to contact and trace participants. We encourage plans to search the National Death Index (NDI) in the U.S. for participants lost to follow-up to ascertain death and causes of death. Obtain vital statistics and cause of death data from countries in which the drug is approved and that participate in the Afrezza registry. Calculate the sample size that would be needed to detect a two-fold increase in the incidence of pulmonary malignancy (with 80% power and 95% confidence) separately for former smokers and for patients with no smoking history. Include sample size projections for differing rates of loss to follow-up and Afrezza discontinuation that exceed 10%.
9. Include a detailed analysis plan and describe how missing data would be addressed.
10. Report registry enrollment to the FDA annually by country.

7 REGULATORY RECOMMENDATIONS TO DMEP

If this drug is approved, DEPI suggests that a PMR obligation be issued to evaluate pulmonary malignancies. We provided recommendations on the proposal submitted by the sponsor. In addition, we also suggested two alternative postmarketing approaches described at the end of the Discussion in Section 4.

8 REFERENCES

[1] Review completed by Lisa Yanoff M.D., Division of Metabolism and Endocrinologic Products (DMEP) of the Office of New Drugs, FDA, dated December 9, 2010.
[2] A postmarketing observational cohort study to evaluate the long-term safety of Afrezza in the treatment of patients with diabetes mellitus. Mannkind, October 2013 resubmission.
[3] Pai-ScherfL. E-mail with additional information on spontaneously reported pulmonary malignancies, Feb 20, 2014.
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[5] Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcomes Sciences, Inc. d/b/a Outcome] under Contract No.

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Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Summary: Review of Sponsor Slides Based on FUSE Final Study Report

Date:	February 28, 2014
Reviewer(s):	Patricia L. Bright, M.S.P.H., Ph.D., Epidemiologist, Division of Epidemiology 1 (DEPI 1), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Team Leader:	Diane K. Wysowski, M.P.H., Ph.D., DEPI 1, OPE, OSE
Division Director:	Cunlin Wang, M.D., Ph.D., DEPI 1, OPE, OSE
Subject:	Summary of slides submitted by Pfizer from the observational follow-up study of patients previously enrolled in Exubera (FUSE) controlled clinical trials
Drug Name(s):	Exubera (Insulin human [rDNA origin] Inhalation Powder)
Application Type/Number:	NDA 021868/ IND 043313
Applicant/sponsor:	Pfizer
OSE RCM #:	2013-2395
TSI #:	Not Applicable

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EXECUTIVE SUMMARY

Exubera (Insulin Human [rDNA origin] Inhalation Powder) was approved by the FDA in January 2006 to improve glycemic control in adults with type 1 and type 2 diabetes. Exubera was later withdrawn by the sponsor (Pfizer) due to lower than expected sales.

At the time of the NDA filing in 2006, there was a known imbalance in lung cancers. As of 2008, this imbalance in new lung cancer cases among participants in the controlled trials had increased to 5 cases of incident lung cancer per 3,846 person-years (PYs) in Exubera-exposed patients to 1 case of incident lung cancer per 3,925 PYs in comparator patients, yielding a crude hazard ratio (HR) of 5.1 (95% CI: 0.71 - 121.4). Comparator patients included patients across 17 trials randomized to standard of care (ranging from no treatment to subcutaneous insulin). All of the patients who developed lung cancer had type 2 diabetes mellitus (DM), were over 55 years of age, and were previous smokers.

The sponsor suggested that this imbalance may have resulted, in part, from detection bias. Most of the 17 trials were open label (not blinded to exposure) since Exubera use required a novel route of administration, and cough was a common side effect – which could have led to more thorough or frequent pulmonary assessments in Exubera-exposed patients.

A follow-up study was undertaken of participants who had been exposed to Exubera and to comparators in pre-approval clinical trials to further assess their lung cancer risk.

On March 1, 2013, Pfizer submitted slides [1] to the FDA from an August 24, 2012, presentation summarizing results from an observational follow-up study of patients previously enrolled in Exubera (FUSE) controlled clinical trials. The Division of Epidemiology 1 was requested to summarize the results as communicated in the 2012 slides. Information included in this summary was copied and adapted from the 2012 Pfizer slides.

Study results included the following:

- Overall, 7,439 subjects contributed retrospective data to the study; however, only 2,536 (34%) of original participants completed the FUSE prospective portion.
- Primary lung cancer mortality – Six cases were reported in 12,605.9 PYs in the Exubera group and 2 cases in 11,802.5 PYs in the comparator group. The incidence density ratio (IDR) was 2.81 (95% CI: 0.50 - 28.46).
- Primary lung cancer incidence – Twelve cases were reported in 11,180.7 PYs in the Exubera group and 3 cases in 10,467.9 PYs in the comparator group. The IDR was 3.75 (95% CI: 1.01 - 20.68).
- All-cause mortality -- The estimated rate was 6.0 per 1,000 PYs (76 deaths in 12,605.9 PYs) in the Exubera group and 7.4 per 1000 PYs (87 deaths in 11,802.5 PYs) in the comparator group. The hazard ratio (HR) was 0.81 (95% CI: 0.60 - 1.10).

The findings in the Pfizer summary slide are largely consistent with the overall results of FUSE reported during their presentation at ICPE.

1 INTRODUCTION

Exubera Slides
On March 1, 2013, Pfizer submitted slides to the FDA from an August 24, 2012, presentation on Exubera (an inhaled insulin) given by Pfizer representatives to the International Conference on Pharmacoepidemiology (ICPE) in Barcelona, Spain. The slides summarized results from an observational Follow-Up Study of patients previously enrolled in Exubera (FUSE) controlled clinical trials. Information included in this summary was copied and adapted from the 2012 Pfizer slides [1].

Afrezza
The FDA is currently reviewing an NDA submission for another inhaled insulin, Afrezza, from a different sponsor (MannKind). The FDA has scheduled an Advisory Committee (AC) meeting to discuss issues related to approval of Afrezza. As part of the preparation for the AC meeting, the Division of Metabolism and Endocrinology Products (DMEP) requested the Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Division of Epidemiology1 (OSE/OPE/DEPI1) present results from the FUSE study as communicated in Pfizer's August 2012 slides of the Exubera follow-up study (in the public domain).

The content of the ICPE slides will be discussed in this document; however, FDA questions, comments, and correspondence with the sponsor regarding the content of the ICPE presentation will not be included since this information is covered under confidentiality agreements with the FDA.

1.1 BACKGROUND

Brief Description -- Exubera
Exubera (Insulin Human [rDNA origin] Inhalation Powder) was approved by the FDA in January 2006 to improve glycemic control in adults with type 1 and type 2 diabetes. The dry powder was administered in a unit dose blister. Each unit dose blister contained a 1 mg or 3 mg dose of insulin in a powder formulation. After an Exubera blister was inserted into the inhaler, the patient pumped the inhaler and pressed a button piercing the blister. The insulin was then dispersed into the chamber, allowing the patient to inhale the aerosolized powder [2].

Exubera was contraindicated in patients who smoked or who had discontinued smoking less than 6 months prior to starting Exubera therapy.

Although Exubera was approved by the FDA in January 2006, it was later withdrawn by the sponsor due to lower than expected sales. In October 2007, Pfizer publically announced that it would withdraw Exubera from the market [3]. The withdrawal was posted in the Federal Register on May 19, 2009 [4] and all Exubera use had discontinued by the second quarter of 2009 [5].

Primary Safety Concern – Lung Cancer

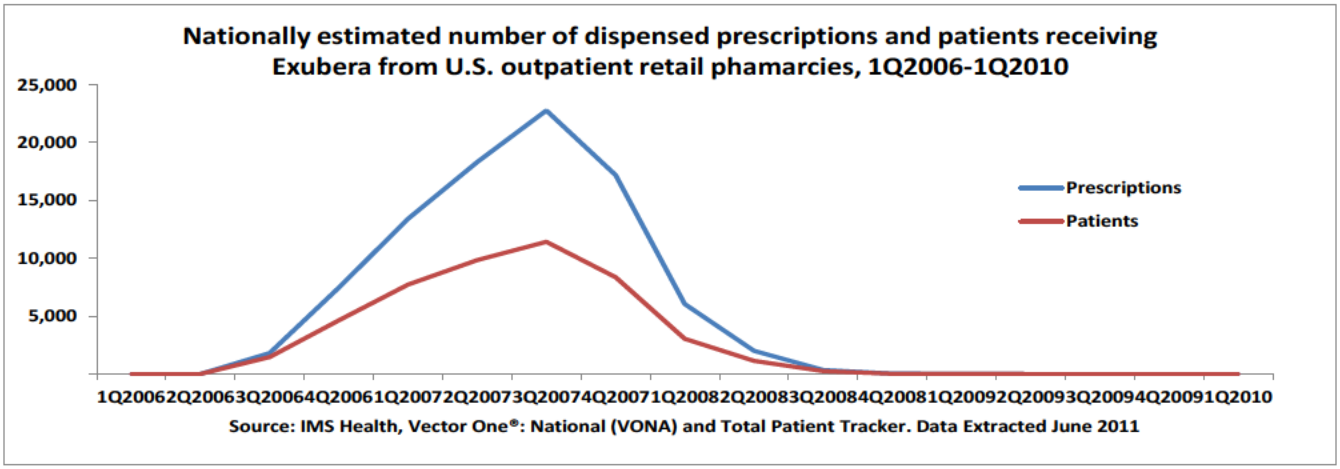
On September 29, 2008, the FDA changed the product labeling for Exubera[1] to include, under Warnings, information on lung cancer cases that occurred during the clinical trial and post-marketing. (The original labeling did not comment on pulmonary malignancy.) The added labeling noted, however, that there were too few cases to determine whether the emergence of these events was related to Exubera and that all patients who were diagnosed with lung cancer had a prior history of cigarette smoking.

The sponsor agreed to conduct a follow-up study of participants exposed to Exubera and to the comparator in the pre-approval clinical trials to further assess their lung cancer risk. This follow-up was a regulatory commitment made to both the European Medicines Agency (EMA) and the FDA.

Drug Utilization Data for Exubera

An FDA drug utilization assessment, based on data extracted on June 14, 2011, from IMS Health, Vector One®: National (VONA) and Total Patient Tracker (TPT) [5], found that the use of Exubera started in the second quarter of 2006, peaked in the third quarter of 2007, and declined rapidly in 2008 (prior to the labeling change and official market withdrawal). There were no prescriptions dispensed and patients receiving Exubera by the second quarter of 2009. From the beginning of marketing through the first quarter of 2010, an estimated 89,000 prescriptions were dispensed and 24,000 patients received a dispensed prescription for Exubera in the U.S. (Figure 1 and Tables 1, 2).

Figure 1: Nationally estimated number of dispensed prescriptions and patients receiving Exubera from U.S outpatient retail pharmacies, 1QTR06 – 1QTR10



[1] Added to Exubera Prescribing Information Under Warnings: "In clinical trials of Exubera, there have been 6 newly diagnosed cases of primary lung malignancies among Exubera treated patients, and 1 newly diagnosed case among comparator-treated patients. There has also been 1 postmarketing report of a primary lung malignancy in an Exubera-treated patient. In controlled clinical trials of Exubera, the incidence of new primary lung cancer per 100 patient-years of study drug exposure was 0.13 (5 cases over 3800 patient-years) for Exubera-treated patients and 0.03 (1 case over 3900 patient-years) for comparator-treated patients. There were too few cases to determine whether the emergence of these events is related to Exubera. All patients who were diagnosed with lung cancer had a prior history of cigarette smoking."

Table 1: Projected number of Exubera Prescriptions Dispensed from the U.S Outpatient Retail Pharmacy, 1QTR06 – 1QTR10

	1st QRT 2006 TRxs	2nd QRT 2006 TRxs	3rd QRT 2006 TRxs	4th QRT 2006 TRxs	1st QRT 2007 TRxs	2nd QRT 2007 TRxs	3rd QRT 2007 TRxs	4th QRT 2007 TRxs	1st QRT 2008 TRxs	2nd QRT 2008 TRxs	3rd QRT 2008 TRxs	4th QRT 2008 TRxs	1st QRT 2009 TRxs	2nd QRT 2009 TRxs	TOTAL 1/2006-03/2010 TRxs
Grand Total Exubera	--	--	1,809	7,476	13,412	18,335	22,782	17,191	6,052	2,004	329	25	11	--	89,425

Source: IMS Health, Vector One®: National (VONA), data extracted 6-14-11, File: VONA 2011-1196 exubera Trx Jan06-Mar10 6-14-11.xls
9 Products – Exubera (5), Exubera Chamber (1), Exubera Combination Pack (1) Exubera Kit (1), Exubera Release Unit (1)

Table 2: Projected Number of Patients Filling a Prescription for Exubera* at a U.S. Outpatient Retail Pharmacy, 1QTR06-1QTR10

	1st QRT 2006 PT Count	2nd QRT 2006 PT Count	3rd QRT 2006 PT Count	4th QRT 2006 PT Count	1st QRT 2007 PT Count	2nd QRT 2007 PT Count	3rd QRT 2007 PT Count	4th QRT 2007 PT Count	1st QRT 2008 PT Count	2nd QRT 2008 PT Count	3rd QRT 2008 PT Count	4th QRT 2008 PT Count	1st QRT 2009 PT Count	2nd QRT 2009 PT Count	TOTAL 1/2006-03/2010 PT Count
Grand Total Exubera	--	--	1,461	4,631	7,718	9,847	11,430	8,363	3,045	1,126	247	20	11	--	24,081

Source: IMS Health, Vector One®: Total Patient Tracker (TPT), data extracted 6-14-11, Files: TPT 2011-1196 exubera Trx Jan06-Mar10 agg 6-14-11.xls and TPT 2011-1196 exubera Trx Jan 06-Mar10 disp 6-14-11.xls
**({Product Brand} = EXUBERA CHAMBER, EXUBERA COMBINATION PACK, EXUBERA KIT, EXUBERA RELEASE UNIT)*
Subtotals may not sum exactly due to rounding. Because of patients aging during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts.

2 REVIEW METHODS AND MATERIALS

On March 1, 2013, Pfizer submitted slides to the FDA from an August 24, 2012, presentation on Exubera by Pfizer representatives at the annual ICPE meeting. The slides summarized results from an observational follow-up study of patients previously enrolled in Exubera (FUSE) controlled clinical trials. DMEP requested the Division of Epidemiology 1 to summarize results from the FUSE study as communicated in the Pfizer's August 2012 slides.

3 REVIEW MATERIALS

3.1 SLIDE PRESENTATION

Prior to the FUSE study

At the time of the NDA filing in 2006, there was a known imbalance in lung cancers in the controlled clinical trials submitted to the Agency. By 2008, this imbalance in newly diagnosed lung cancer cases among the controlled trials had increased to 5 cases of incident lung cancer per 3,846 person-years (PYs) of Exubera-exposed patients and 1 case of incident lung cancer per 3,925 PYs of comparator-exposed patients, yielding a crude hazard ratio of 5.1 (95% CI: 0.71-121.4). Comparator-exposed patients included the combined group of patients across 17 trials randomized to standard of care (including a range from no treatment to subcutaneous insulin). All of the patients who developed lung cancer had type 2 DM, were over 55 years of age, and had a history of smoking.

The sponsor suggested that this imbalance may have resulted, in part, from detection bias. Most of the 17 trials were open label (not blinded to the exposure) since Exubera use

required a novel route of insulin administration, and cough was a common side effect – all which could have led to more thorough or frequent pulmonary assessments in Exubera-exposed patients.

Because of this imbalance along with the concern that the pooled trials were not powered to rule out a chance imbalance in lung cancer risk, a follow-up study was undertaken of participants who had been exposed to Exubera and to comparators in pre-approval clinical trials to further assess their lung cancer risk.

Aim

The sponsor agreed to conduct an observational follow-up study with the aim of evaluating whether Exubera exposed patients experienced primary lung cancer mortality at a substantially higher rate than unexposed patients.

Design and Endpoints

The Follow-Up Study of Exubera (FUSE) was an international, multicenter, observational cohort study of patients previously enrolled in 17 Exubera controlled clinical trials that were active in 2003 or later. The first patient visit was August 27, 2008, and the last patient visit was January 6, 2012. Three hundred twenty-seven sites from 25 countries participated in FUSE and enrolled patients were followed an additional 2 years for incidence of lung cancer mortality.

Secondary endpoints were lung cancer mortality in former smokers, lung cancer incidence, and all-cause mortality. Lung cancer deaths and diagnoses were reported by investigators for patients who were enrolled in any of 17 previously conducted controlled clinical trials. These events occurred during the original trial, after the original trial, but before the start of FUSE, or after the start of FUSE prospective follow-up.

The study outcomes were identified from several sources:

- the original trial database (reported during or after the original trial);
- the screening FUSE questionnaire;
- baseline FUSE questionnaire administered to participants by investigators; and
- follow-up FUSE questionnaire administered to participants during scheduled telephone calls, from other treating physicians, and/or from hospital records.

Lung cancer cases and deaths were adjudicated by an expert committee blinded to the randomized exposure to determine if death was due to primary lung cancer and whether diagnosed lung cancer was incident (newly diagnosed) and primary. Cases classified as "highly likely" or "likely" during the adjudication were considered actual endpoints. Reported cases of primary lung cancer incidence that were classified by adjudicators as either 'unlikely' or having 'insufficient information' were not included as endpoints; however, sensitivity analyses was conducted to explore potential effects of misclassification or missing data on lung cancer diagnoses.

The follow-up period was comprised of a retrospective and a prospective component. All subjects from the 17 Exubera trials contributed to the retrospective component.

Those subjects at sites that agreed to participate in FUSE and who also agreed to be contacted for the yearly follow-up contributed to the prospective component. On a yearly basis (at Years 1 and 2), the investigator or a designated member of the clinical team

assessed and recorded the patient's vital status. Data collection included, at a minimum, current smoking status and reported lung cancer diagnosis (including date of diagnosis and histologic type). In the event that a patient had died, the investigator obtained a death certificate, hospital and medical records and charts, and other documents, as appropriate.

For most (but not all) subjects screened for FUSE, a lag period occurred between completion of the original trial and the FUSE screening date. If the study site agreed to participate in the FUSE study and provide prospective data, data was sought for the patients enrolled for the participating site for this interim period.

At the FUSE participating sites, data were collected during the interim period between the last trial visit, but before the start of FUSE prospective follow-up, for patients:

- who chose not to enroll in the prospective part of FUSE, or
- who chose to participate in the prospective part of FUSE.

Additional retrospective person-time could accrue on these patients from the last trial visit date until the date of death, or date last known to be alive.

Analysis

Intention to treat analysis was used in all primary analyses based on the group to which a patient was randomized in his/her original Exubera protocol. Cox proportional hazard models were utilized and unadjusted rate differences and their associated 95% CIs were estimated.

Results

Participation: For the overall patients at the 327 sites participating in this study, a total of 24,408 retrospective and prospective PYs of observation accumulated.

- 7,439 subjects contributed retrospective data. Of these:
  - 3,092 patients (41.6%) were from sites that did not participate in the prospective portion of FUSE;
  - 4,347 patients (58.4%) were from sites that participated in the prospective portion of FUSE, of which:
    - 2,631 patients (60.5%) consented to participate in the prospective FUSE (including 1,358 patients that were formerly randomized to Exubera and 1,273 patients formerly randomized to a comparator)
      - Of the 2,631 patients, 95 discontinued FUSE during the follow-up (20 were no longer willing to participate, 70 were lost to follow-up, 1 withdrew as the study was terminated, and 2 for other reasons).

Therefore, only 2,536 (34%) of the original trial patients completed FUSE.

Confounders

"All potential confounders (i.e., demographic and other baseline characteristics) were balanced at baseline in the original 17 trials across Exubera and comparator patients and remained balanced at start of the FUSE prospective follow-up for those patients who continued on into the prospective follow-up" [6]. In addition, potential confounders measured at the FUSE baseline visit (at the start of prospective data collection -- distinct

from the baseline visit in the original 17 trials) were balanced across the Exubera and comparator patients who participated in the prospective follow-up. This includes a balance in smoking history measured at the FUSE baseline visit who participated in the prospective follow-up.

Table 3: Smoking history at trial baseline -- prospective patients only

At Trial Baseline	Exubera (n = 1,356)	Comparator (n =1,271)
Smoking History (%)		
Never	56	57
Ever	44	43
Mean Pack-years	23	22
Median pack-years	14	15
Pack-years of Smoking (%)		
Never	56	57
Missing	3	3
Available	41	40
Q1 (0-5)	25	24
Q2 (>5-15)	26	24
Q3 (>15-32)	22	28
Q4 (>32-180)	27	23

Since there were only a small number of events and measured baseline covariates were balanced across exposure groups, the main analyses were not adjusted for covariates.

Endpoint Summary

A total of 8 participants were reported to have died from primary lung cancer (6 Exubera-exposed, 2 comparators). All 8 cases were adjudicated as 'highly likely' or 'likely', meeting the primary endpoint definition (Table 4). Of note: 7 primary lung cancer deaths were reported by investigators and 1 additional primary lung cancer death was identified during adjudication of an all-cause mortality case for a total of 8 cases.

Including the lung cancer deaths, a total of 19 participants (15 Exubera-exposed, 4 comparators) were reported to have developed primary lung cancer. Of the 15 cases of primary lung cancer in the Exubera-exposed, 12 were adjudicated as 'highly likely' or 'likely' primary lung cancer cases, 2 were adjudicated as 'unlikely' to be primary lung cancer cases, and one was adjudicated as having 'insufficient information' to determine if the case was primary lung cancer (Table 4).

Of the 4 potential cases of incident primary lung cancer in the comparator group, 3 were adjudicated as 'highly likely' and one was adjudicated as 'unlikely' to be incident primary lung cancers (Table 4).

Of the 163 (2.2%) all-cause deaths, 76 (2.0%) were among patients previously randomized to Exubera compared with 87 (2.4%) among patients previously randomized

to comparators. The all-cause mortality endpoint was based on reported cases (i.e., did not depend on adjudication).

Table 4: Summary of lung cancer and deaths

Endpoint	Randomized Group	Reported	Adjudicated as: "Highly likely" or "likely"	"Unlikely"	"Insufficient"
Primary Lung Cancer Mortality	Exubera	6	6	0	0
	Comparator	2	2	0	0
	Total	8	8	0	0
Primary Lung Cancer Incidence	Exubera	15	12	2	1
	Comparator	4	3	1	0
	Total	19	15	3	1
All-Cause Mortality	Exubera	76			
	Comparator	87		N/A	
	Total	163			

Of the cases adjudicated as "highly likely" or "likely," 7 of the 8 deaths and 14 of the 15 incident pulmonary malignancies were in former smokers (Table 5).

Table 5: Summary of adjudicated lung cancer and lung cancer deaths in former smokers

Endpoint	Randomized Group	Reported	"Highly likely" or "likely"	Adjudicated as: "Highly likely" or "likely" among former smokers
Primary Lung Cancer Mortality	Exubera	6	6	5
	Comparator	2	2	2
	Total	8	8	7
Primary Lung Cancer Incidence	Exubera	15	12	11
	Comparator	4	3	3
	Total	19	15	14
All-Cause Mortality	Exubera	76		
	Comparator	87		
	Total	163		N/A

Timing of lung cancer diagnoses and deaths

Twelve patients were adjudicated as 'highly likely' or 'likely' primary lung cancer cases in the Exubera group. Of these, 2 were diagnosed during the prospective FUSE follow-up and 7 were diagnosed after the end of the original trial but before the start of the

prospective FUSE follow-up. Four of the 7 were enrolled in the prospective FUSE follow-up and 2 of the 4 had lung cancer diagnosed at baseline.

Three patients were adjudicated as 'highly likely' or 'likely' incident primary lung cancers in comparators. Of these, one was diagnosed during the original clinical trial, one was diagnosed during the prospective FUSE follow-up, and the third was diagnosed after the end of the original trial but before the start of the prospective FUSE follow-up.

Primary Endpoint: Primary lung cancer mortality (Table 6)
In the analysis of the primary endpoint, there were 6 cases in 12,605.9 PYs in the Exubera group and 2 cases in 11,802.5 PYs in comparators. The incidence density ratio (IDR) using the exact method was 2.81 (95% CI: 0.50 - 28.46). These data did not change in the planned sensitivity analyses (in which cases adjudicated as 'insufficient information' or either 'insufficient information' or 'unlikely' were added to the endpoints in each analysis) since all reported cases were adjudicated as 'highly likely' or 'likely' (Table 6).

Table 6: Primary lung cancer mortality

	n	Person years (PYs) of follow-up	No. with event (%)	Rate per 1,000 PYs	Incidence density ratio (95% CI)
Exubera	3,875	12,606	6 (0.2%)	0.48	2.81
Comparator	3,564	11,803	2 (0.1%)	0.17	(0.50-28.46)

Secondary Endpoint: Primary lung cancer mortality in former smokers
One of the 6 primary lung cancer deaths was in a patient who never smoked. In the analysis of primary lung cancer mortality in former smokers, 5 lung cancer deaths were reported in 5,341.2 PYs among former smokers in the Exubera group and 2 lung cancer deaths in 4,885.6 PYs among former smokers in the comparator group. The IDR (exact method) was 2.29 (95% CI: 0.37 - 24.01).

Secondary Endpoint: Primary Lung Cancer Incidence (Table 7)
Twelve cases of primary lung cancer were reported in 11,180.7 PYs in the Exubera group and 3 cases in 10,467.9 PYs in the comparator group. The IDR (exact method) was 3.75 (95% CI: 1.01 - 20.68). The CI for this analysis was wide, but was borderline statistically significant.

Table 7: Primary lung cancer incidence

	n	Person years (PYs) of follow-up	No. with event (%)	Rate per 1,000 PYs	Incidence density ratio (95% CI)
Exubera	3,875	11,181	12 (0.3%)	1.07	3.75
Comparator	3,564	10,468	3 (0.1%)	0.29	(1.01-20.68)

Secondary Endpoint: All-cause mortality (Table 8)
The estimated rate of all-cause mortality was 6.0 per 1,000 PYs (76 deaths in 12,605.9 PYs in the Exubera group and 7.4 per 1,000 PYs (87 deaths in 11,802.5 PYs in the comparator group. The hazard ratio (HR) was 0.81 (95% CI: 0.60 - 1.10). No sensitivity analyses were planned for all-cause mortality since all reported cases were included as endpoints.

Table 8: All-cause mortality

	n	Person years (PYs) of follow-up	No. with event (%)	Rate per 1,000 PYs	Hazard ratio (95% CI)
Exubera	3,875	12, 606	76 (2.0%)	6.0	0.81
Comparator	3,564	11,803	87 (2.4%)	7.4	(0.60 - 1.10)

Study Strengths
The study has the following strengths:
- Largest source population, with baseline trial data available for all patients. Allowed comparison of baseline trial data:
  - Among participants and non-participants
  - Exubera and comparator prospective FUSE participants
- Geographically and ethnically diverse study population
- Balance in all measured potential confounders at baseline (start of clinical trials and start of FUSE follow-up)

Study Limitations
The study has the following study limitations:
- Low participation of sites and patients (only 34% of participants in the trials completed FUSE follow-up).
- Potential for detection and reporting biases for lung cancer incidence endpoint
- Potential for reporting bias in lung cancer mortality endpoint
- Possible changes over time in covariates
- Insufficient power to draw clear conclusions about primary lung cancer mortality for risk estimates less than ~4

Summary

The slides summarize the FUSE study results as follows:

- Data indicative of a potential increased lung cancer risk, but inconclusive
- Trend toward increased risk may be explained by:
  - Reporting/detection bias associated with preferential screening and reporting of cases for subjects exposed to Exubera in the original studies
  - Promotional effect among smokers
  - Combination of both
- No increased risk in all-cause mortality

4 CONCLUSION

The findings in the Pfizer summary slide are largely consistent with the overall results of FUSE reported during their presentation at ICPE.

5 REFERENCES

[1] Source: Gatto NM, Koralek DO, Bracken MB, Duggan WT, Lem J, Klioze SS, Jackson NC. Comparative lung cancer mortality with inhaled insulin or comparator: FUSE final results. ICPE, August 24, 2012.

[2] Approval labeling from January 27, 2006, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo, accessed February 7, 20014.

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[6] Pfizer. An observational follow-up study of patients previously enrolled in Exubera controlled clinical trials. Study Report dated: July 3, 2012.

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WhiteheadR/YanoffL/MohamadiA/BalakrishnanS/ColmanE/GuettierJM/DMEP
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