CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022472Orig1s000

<u>SUMMARY REVIEW</u>

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Summary Review
NDA/BLA # Supplement #	22472
Applicant Name	MannKind Corporation
Date of Submission	October 15th 2013
PDUFA Goal Date	July 15th 2014
Proprietary Name / Established (USAN) Name	Afrezza/Insulin Human
Dosage Forms / Strength	Inhalation Powder
Proposed Indication(s)	1. To improve glycemic control in adult patients with diabetes mellitus.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Lisa Yanoff, MD, Lee Pai-Scherf MD, Miya Paterniti MD, Banu Karimi-Shah MD,
Statistical Review	Cynthia Liu, PhD, Mark Rothman PhD
Pharmacology Toxicology Review	Miyun Tsai-Turton, PhD
CMC Review/OBP Review	Edwin Jao, PhD, Muthukumar Ramaswamy PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Sang Chung PhD, Lokesh Jain PhD
DDMAC	Kalola Ankur
DSI	Cynthia Kleppinger MD
CDTL Review	N/A
OSE/DMEPA	Sarah Vee
OSE/DEPI	Patricia Bright, MSPH, PhD
OSE/DRISK	Joyce Weaver, PharmD
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management

CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

On October 15, 2013 MannKind corporation submitted a Class 2 resubmission of the new drug application for Afrezza under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act. The resubmission is a complete response to the Complete Response Letter issued by the Agency on January 18th 2011.

The applicant is seeking to indicate Afrezza to improve glycemic control in adults with diabetes mellitus. Afrezza is a drug-device combination product consisting of a dry powder formulation of recombinant insulin packaged in pre-metered unit dose cartridges and an inhaler device. Afrezza dose is to be individualized and administered by oral inhalation before each meal.

No inhaled insulin products are currently marketed in the United States. The other approved inhaled insulin, Exubera, was voluntarily withdrawn from the market by Pfizer in 2008 due to poor sales. Currently approved and marketed outpatient insulin therapies are administered via the subcutaneous route (SC), often as multiple daily injections per day or through subcutaneous infusion using an insulin pump device.

Afrezza insulin was developed as a "mealtime" insulin. Currently, so called "regular" and "short or rapid acting" insulins are approved and used for this purpose. Mealtime insulins cover the blood glucose changes that result from absorption of macronutrients. The glucose lowering effect of a "mealtime" insulin would ideally peak relatively early (e.g., 1-2 hours), diminish over time and disappear altogether to coincide with blood glucose changes associated with absorptive processes[1]. Because the action of Afrezza does not last beyond more than a few hours, Afrezza cannot be used to replace background or "basal" insulin needs (i.e., insulin needed to maintain glucose homeostasis during fasting).

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[1] *"The magnitude and time of the peak plasma glucose concentration depend on a variety of factors, including the timing, quantity, and composition of the meal. In nondiabetic individuals, plasma glucose concentrations peak; 60 min after the start of a meal, rarely exceed 140 mg/dl, and return to preprandial levels within 2–3 h. Even though glucose concentrations have returned to preprandial levels by 3 h, absorption of the ingested carbohydrate continues for at least 5–6 h after a meal."* DIABETES CARE, VOLUME 24, NUMBER 4, APRIL 2001

Maintenance of good glycemic control in patients with type 1 diabetes necessitates use of insulin injections multiple times daily. The most commonly used regimen involves using one injection per day of "basal" insulin and three injections per day of "mealtime" insulin (sometimes referred to as a basal/bolus or basal/prandial regimen). In this scenario, inhalation of Afrezza could replace three of four daily subcutaneous insulin injections.

In patients with type-2 diabetes "mealtime" insulin is generally reserved as an option of last resort for patients who fail to achieve good glycemic control on therapies with less invasive routes of administration, less inherent hypoglycemic risks and simpler dosing regimen/schedules (i.e., oral agents, fixed-dose injectable agents and basal insulin).

2. Background

This application has had a complex regulatory history and the full history is summarized in Drs. Parks, Joffe and Yanoff's previous memoranda and reviews. In this section, I will briefly summarize salient regulatory and scientific issues.

On March 16th, 2009 MannKind Corporation submitted a new drug application (NDA) for Afrezza. A first Complete Response Letter was issued on March 12, 2010. A major deficiency highlighted in the letter concerned device-related issues. During product development, the applicant had altered the delivery device considerably but had failed to adequately characterize the impact of device related changes on efficacy and safety. Although the applicant had submitted a bioequivalence study as a means to link the device studied in pivotal trials (Model C inhaler) to the device intended for commercialization (Model D inhaler), inspection of the study and analytical sites by the Division of Scientific Investigations revealed multiple deficiencies related to study conduct and the data derived from these sites were deemed unreliable.

Besides device related issues the other deficiency was scientific in nature and concerned benefit-risk determination. While data from proof of concept trials showed that Afrezza could lower glucose in the short term, results from Phase 3 trials raised significant questions about the usefulness of Afrezza as a mealtime insulin replacement for the chronic treatment of diabetes (specific findings are summarized in the paragraph that follows). In Phase 3 trials, patients randomized to Afrezza were less able to maintain glycemic control compared to patients randomized to a standard of care mealtime insulin comparator. Maintenance of glycemic control is essential for prevention of acute (e.g., symptomatic relief, diabetic ketoacidosis) and long term microvascular complications[2] (e.g., retinal, kidney and nerve

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[2] NEW ENGLAND JOURNAL OF MEDICINE 1993; 329:977-986.

damage) associated with diabetes. While it was recognized that Afrezza offered a convenient way to administer small doses of mealtime insulin, it was not immediately clear that this benefit outweighed the observed lower efficacy and novel risks associated with this unique route of administration (i.e., bronchospasm, lung function decline, increased immunogenicity and potential increase in lung cancer risk). In the Complete Response Letter, the applicant was asked to interpret the observed benefit-risk of Afrezza in the context of contemporary therapeutic goals and was notified that external input from advisors would be sought to address the complex benefit-risk questions raised by the application in future review cycles.

In the original application four active-controlled trials were pivotal in supporting an efficacy determination. Comparators included a once a day oral agent (Study 103), a twice daily pre-mixed insulin regimen (Study 102), and a standard of care mealtime insulin (i.e., Studies 009 and 014). Three out of four pivotal trials (i.e., Studies; 009, 014 and 103) failed to meet their intended primary efficacy objectives (i.e., refer to Dr. Parks' 3/12/2010 memorandum for details). In studies 009 and 014 benefit was captured by contrasting the glucose lowering effect of Afrezza to a standard of care mealtime insulin (i.e., insulin aspart) each added to background basal insulin. In these two trials, the regimen relying on Afrezza for meal coverage provided statistically significantly worse glucose control than the regimen relying on aspart for meal coverage. Moreover, the intended primary objective of excluding a between group effect size difference larger than an agreed-upon non-inferiority margin was not met in either of these trials (i.e., preservation of an agreed upon minimum amount of the comparator's effect could not be guaranteed). Finally, interpretability and reliability of the estimated difference in efficacy between interventions in the Phase 3 program was confounded by findings suggestive of differential titration aggressiveness between arms and missing data. Specific issues included an observed differential use of basal insulin between arms (i.e., higher mean doses of basal insulin were used in subjects randomized to Afrezza), differential dose titration of the intervention insulins (i.e., more prandial insulin was used in subjects randomized to Afrezza), and significant and differential amount of discontinuation due to poor tolerability and lack of efficacy at trial end (i.e., 25-30% data missing at endpoint in the Afrezza arm).

MannKind resubmitted the application in June 2010 seeking to market a third device (Gen-2 inhaler). The applicant provided in vitro and clinical pharmacology comparability data for the MedTone C and Gen-2 inhalers. These data were insufficient to ensure efficacy and safety data collected using the MedTone C inhaler could be relied upon to inform efficacy and safety of the new to-be marketed inhaler (i.e., Gen-2). The applicant was asked to carry out two new phase 3 trials to evaluate the impact of changes to the device (e.g., usability, performance, delivery characteristics etc…) on safety and address issues confounding

interpretability of the efficacy results in the previous Phase 3 trials. The applicant was also asked to submit updated analyses of lung cancer cases in the Afrezza program. For details refer to Complete Response Letter issued on 1/18/2010.

3. CMC/Device

Afrezza is a kit consisting of an inhaler device (see figure 1) and plastic cartridges containing a dry powder formulation of regular human insulin. Users must remove the cartridge from the packaging, insert the cartridge into the inhaler and inhale deeply once to administer the dry powder contained in the cartridge. Users may have to repeat these steps multiple times to administer their full mealtime dose of insulin. The composition of the dry powder for the two dose strengths is shown below.

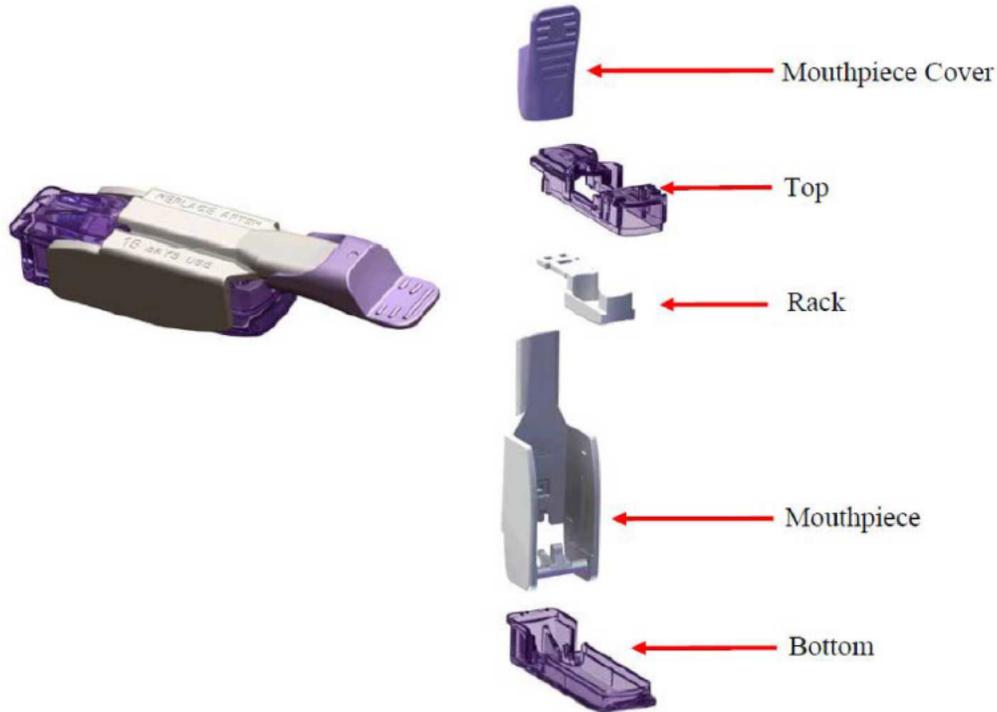| Component | 10 U cartridge strength | 20 U cartridge strength |
	3.3 mg nominal fill	6.7 mg nominal fill
	Quantity per cartridge	Quantity per cartridge
Insulin	10 U	20 U
FDKP		
Polysorbate 80[a]		

b(4)

The powder is composed predominantly of fumaryl diketopiperazine (FDKP) a novel excipient and part of the inhalable fraction. Cartridges come in two insulin dosage strengths, 10 USP insulin units (0.35 mg) and 20 USP insulin units (0.7 mg) which, based on bioavailability studies, are pharmacologically equivalent to approximately 4 and 8 units of subcutaneously delivered insulin respectively. Cartridge strengths will be labeled according to their pharmacologically equivalent dose strengths and not their USP dose strengths because of prescribers' inherent familiarity with subcutaneous dosing for insulin and to facilitate conversion between the subcutaneous and inhaled route. See CMC reviews by Drs. Muthukumar Ramaswamy and Edwin Jao and device review by Dr. Melanie Choe for full details.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Drug product stability testing supports an expiry of 24-months

for storage at 2-8°C or 10 days of storage (in-use storage) at room temperature (i.e., 25°C). There are no outstanding issues.

Figure 1: Gen-2 Inhaler Device with Exploded Schematics (Source: Module 3.2.P.1)
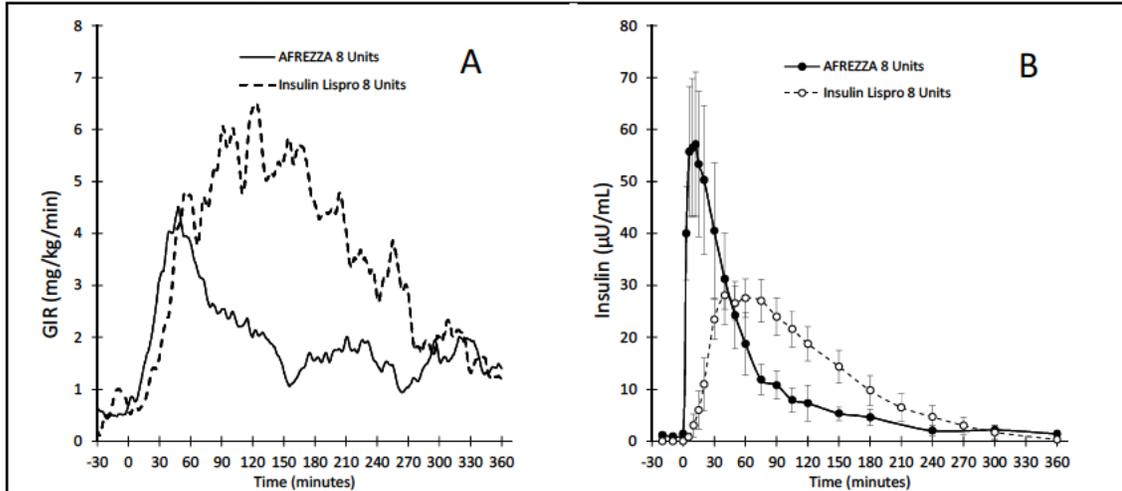

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The clinical pharmacology of Afrezza was reviewed previously. Afrezza is ~ 25-30% bioavailable compared to subcutaneous insulin and each unit of Afrezza is equivalent to approximately 2.5 units of subcutaneous insulin. The starting dose and conversion algorithm in the full prescribing information will be similar to the one that was used in the pivotal phase 3 trials.

Several issues related to clinical pharmacology were scrutinized in this cycle. A discrepancy (delay) between the time-concentration profile and time-action profile of Afrezza delivered via the Gen-2 device was noted (refer to figure 2 below taken from the full prescribing information).

Figure 2: Insulin Action (A) and Insulin Concentration (B) Time Curves for Afrezza/Gen-2 and Insulin Lispro

Although peak insulin concentration was observed between 12-15 minutes after dosing (panel B), peak insulin action did not occur until 60 minutes after dosing (panel A). This and the fact that the higher insulin concentration achieved with Afrezza/Gen-2 did not translate into greater insulin action could suggest that circulating insulin is cleared before it has time to reach insulin sensitive tissues and exert its effect. Although the applicant touted the rapid absorption as an advantage, the unique pharmacokinetic did not translate into better glucose control in clinical trials (refer to Study 171 below). Another clinical pharmacology issue which was discussed at the April 1st EMDAC meeting involves the apparent plateauing of the dose response curve above a 60 unit dose (equivalent to 24 units of subcutaneous insulin) in study MKC-TI-176. This finding was scrutinized because nonlinearity may impact dosing recommendations (i.e., switching to an alternative route once a maximally effective inhaled dose is reached) and because in a previously reviewed phase 2 trials, a fixed dose of 28 units delivered using the MedTone C was observed to provide similar placebo-adjusted HbA1c reduction than fixed doses of 42 and 56 units (refer to Study 005 in previous memoranda). From the data in the application it is unclear whether the shape of the dose response curve for inhaled insulin differs from the shape of the dose response curve for subcutaneously delivered insulin. The applicant will be asked to address this question in the post-marketing phase.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

This section summarizes efficacy data submitted with the resubmission, refer to reviews by Drs. Liu and Yanoff for full reviews. For a detailed discussion of efficacy findings for trials performed using the first generation inhaler (MedTone C), refer to past reviews by Drs. Liu and Yanoff.

To support the indication of improved glycemic control, the long term glucose lowering effect of Afrezza delivered using the Gen-2 device was evaluated in two pivotal Phase 3 clinical trials. One trial evaluated the efficacy of Afrezza in patients with type-1 diabetes (Study 171) and the other trial evaluated the efficacy of Afrezza in patients with type-2 diabetes (Study 175).

Study 171-Type 1 Diabetes Mellitus:

Study 171 compared the glucose lowering effect of mealtime Afrezza to mealtime aspart both dose-titrated to optimize mealtime glucose control. In this study, Afrezza and aspart were used in combination with a basal insulin dose-titrated to optimize fasting glucose control.

Design

The study was a multi-center, open-label, randomized, active-controlled trial carried out at sites in Brazil, Ukraine, Russia and the United States[3]. The population studied were adults with type 1 diabetes not optimally controlled (i.e., HbA1c 7.5-10%) on a pre-trial insulin regimen consisting of a basal and mealtime insulin or a pre-mixed insulin. Subjects with underlying pulmonary disease (i.e., asthma, COPD, underlying pulmonary fibrosis, abnormalities on CXR) and smokers were excluded.

Following the screening visit, eligible participants remained on their pre-trial basal insulin and were switched to insulin aspart if they were not on aspart pre-trial. Subjects then entered a

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[3] 8, 23, 29 and 40% of the randomized population were recruited from Brazil, Ukraine, Russia and the United States respectively. Source: Table 22 Study 171 CSR.

4-week run-in phase aimed at optimizing basal insulin dose prior to randomization. Following the 4-week basal insulin optimization phase, subjects with a fasting plasma glucose of ≤ 180 mg/dL were randomized 1:1:1 to Afrezza delivered using the Gen-2 inhaler, Afrezza delivered using the old Medtone C inhaler or aspart delivered subcutaneously. The Afrezza/MedTone C arm was included for safety analyses only. Refer to Dr. Yanoff's review for the conversion algorithm used to establish the Afrezza starting dose.

The 24-week intervention phase was divided into two distinct periods: a 12-week prandial insulin dose optimization phase where continued basal titration was allowed and a 12-week stable insulin dose phase. The protocol instructed subjects to carry out seven-point self-monitoring of blood glucose (i.e., 7-point SMBG) at least three days each week. Prandial insulin dose was to be titrated based on 7-point SMBG data in accordance with protocol specified algorithms that targeted goal pre or post prandial glucose levels. Basal insulin dose was titrated in a similar fashion to target fasting or pre-dinner goal glucose levels. Refer to Dr. Yanoff's review for specifics.

Efficacy was to be assessed in the intent to treat population after 24-weeks of therapy or up to the time of discontinuation from study.   The variable used in the primary efficacy assessment was the difference in the change in hemoglobin A1c (i.e., HbA1c) from baseline to trial end between subjects randomized to Afrezza/Gen-2 and aspart. The trial was a non-inferiority trial and the primary objective of the trial was to exclude the possibility that the reduction in HbA1c from baseline afforded by Afrezza/Gen2 used in combination with basal insulin was smaller than the reduction in HbA1c from baseline afforded by aspart used in combination with basal insulin by a margin of 0.4% or greater (i.e., the pre-specified non-inferiority margin).

The general design features, primary endpoint and timing of the efficacy assessment conform with the Guidance for Industry entitled "*Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*" and are reasonable.

Trial Conduct and Efficacy in Type 1 DM

A total of 518 subjects were randomized to Afrezza/Gen 2 (n=174), Affreza/MedTone (n=174) and aspart (n=171). Demographic, anthropomorphic and baseline disease characteristics were balanced at baseline. Baseline HbA1c was 8.0% across the three groups.

Subjects randomized to Afrezza insulin dropped out at a significantly higher rate than subjects randomized to aspart (i.e., 25%, 21%, and 11% for Afrezza/Gen-2, Afrezza/MedTone

and aspart respectively). A greater than 20% dropout rate in the Afrezza arm is unusually high for a six-month, active-controlled, type 1 diabetes trial where retention rate has traditionally been above 90%. This dropout rate was consistent with the high dropout rates observed in previous trials performed using the MedTone C device (see Dr. Joffe's first cycle CDTL memorandum).

More subjects on Afrezza withdrew due to adverse events (9.2%, 5.2% and 0% in for Afrezza/Gen-2, Afrezza/MedTone and aspart). The most frequently reported adverse events resulting in study discontinuation suggested poor product tolerability (i.e., cough and dyspnea). 'Withdrawal by Subject', was the most frequently cited reason listed for discontinuation (12%, 9% and 5% for Afrezza/Gen-2, Afrezza/MedTone and aspart). Dr. Yanoff reviewed line listings for reasons given by patients or physicians for withdrawal. The most frequent reasons cited were personal conflict or lack of willingness to comply with protocol demands (n=14, n=17, and n=8 patients for Afrezza/Gen-2, Afrezza/MedTone and aspart) followed by hyperglycemia/poor efficacy (n=5, n=2, and n=0 patients for Afrezza/Gen-2, Afrezza/MedTone and aspart). These findings were similar to what had been previously observed with trials performed using the MedToneC device and suggest poor tolerability and efficacy issues had a role to play in the imbalanced discontinuation rates. The FDA asked the applicant to perform several sensitivity analyses to explore the potential impact of missing data and informative censoring on the reliability of the efficacy estimate.

At trial end, subjects randomized to Afrezza/Gen-2 as add-on to basal insulin each titrated to target had a reduction in HbA1c of 0.20% while subjects randomized to aspart as add-on to basal insulin each titrated to target had a larger decrease in HbA1c from baseline (i.e., 0.42%). The point estimate of the difference in HbA1c reduction between Afrezza/Gen-2 and aspart was 0.22% and the upper bound of the 95% interval around the difference was below the pre-specified non-inferiority margin of 0.4% (i.e., the primary objective of demonstrating non-inferiority was met). The lower bound of the 95% confidence interval around the difference was above zero, demonstrating Afrezza/Gen-2 provides statistically worse glucose control than aspart. These results are qualitatively similar to what had been previously observed with the MedTone C inhaler (refer to Dr. Parks' memorandum).

Table 1: Primary Efficacy Results Type 1 DM Trial-Study 171

Treatment Arm	n*	Baseline HbA1c [% (±SD)]	Adjusted Mean Change From Baseline HbA1c [% (±SEM)]	Adjusted Between Group[†] Difference in HbA1c Change from Baseline [% (95% CI)]
Afrezza/Gen2[†]	131	8.0 (0.8)	-0.20 (0.06)	**+0.22 (0.08, 0.37)**
Aspart[†]	147	7.9 (0.8)	-0.42 (0.06)	
Afrezza/MedToneC	137	8.0 (0.7)	-0.28 (0.06)	
Source: Table 5 in Dr. Liu's Review. *Subjects with complete data to 24-weeks †Primary comparison on the full analysis set population with data up to time of discontinuation used. Estimates are based on a Mixed Model Repeated Measures approach with treatment, visit, region, basal insulin, and treatment by visit interaction as fixed factor and change from baseline in HbA1c as covariate.			

A completer analysis was consistent with the intent to treat analysis (refer to Figure 8 in Dr. Liu's review). Dr. Liu compared the change in HbA1c observed for dropouts across the three randomized groups (refer to Figure 9 in her review). Subjects who dropped out from the aspart arm had reduction in HbA1c across visits while subjects randomized to Gen-2/Afrezza had an increase in HbA1c from baseline. The contrast in HbA1c response observed for dropouts across the two arms suggests that the difference in effect size between aspart and Afrezza/Gen2C could have been larger than 0.22% had subjects not discontinued prematurely.

Four sensitivity analyses were performed to evaluate the impact of missing data on the efficacy assessment (refer to Table 7 in Dr. Liu's review). The finding of non-inferiority to aspart was not met on the analysis which assumed that all patients who discontinued Gen-2 were missing not at random (i.e., subjects discontinued because of a treatment related issue) and where 0.4% was added to all individuals randomized to Afrezza/Gen-2 [Adjusted between group difference (95% CI); 0.3% (0.15%, 0.48%)]. Three other less conservative analyses were consistent with the findings from the primary analysis. Across all four sensitivity analyses, the lower bound of the 95% CI were above zero, a finding in keeping with the fact that glucose control was statistically worse in Afrezza treated subjects.

Conclusions reached based on responder analyses (i.e., proportion of individuals reaching glycemic goal) were also consistent with analyses based on HbA1c as a continuous measure (refer to Table 6 in Dr. Liu's review). A smaller proportion of individuals randomized to Afrezza compared to aspart reached the American Diabetes Association target glycemic goals of an HbA1c of ≤ 7% at trial end (10% versus 21% for Afrezza/Gen-2 versus aspart).

Although the applicant made a point to highlight the fact that fasting plasma glucose (FPG) was numerically better in subjects randomized to Afrezza the argument is misleading. Single time point glucose measures, such as FPG, are not as reliable as integrated glucose measures (HbA1c). An improvement in a short term measure, if durable, should in theory translate to an improvement in glycemic control captured on a chronic measure (i.e., it is known that FPG is correlated to HbA1c[4]). Moreover, FPG mostly reflects basal insulin effect (i.e., glargine, detemir, NPH) rather than mealtime insulin (i.e., Afrezza) whose effect is largely gone 2 hours after administration. If improvement in FPG are real for this time point they would be mostly attributable to basal insulin dosing and not Afrezza dosing.

The applicant also points to favorable weight and hypoglycemia secondary/tertiary outcome data. Weight gain and increased hypoglycemia risks are recognized sequela of intensive insulin therapy[5,6] and a less effective therapy is expected to result in less weight gain and less hypoglycemia. The results of these exploratory analyses are consistent with the fact that Afrezza was shown to have inferior efficacy.

Insulin Dose Changes

The changes in insulin dose over time were reviewed to: assess adequacy of dose titration[7], explore the potential for bias in this open-label trial and determine whether use of the control within the trial was reasonably reflective of historical use (i.e., glucose lowering performance of the control in the trial was consistent with past observations). On this last point, in a non-inferiority trial efficacy of the control is assumed (i.e., constancy assumption), if the control in the trial is not effective or is only minimally effective one runs the risk of declaring the new agent effective when in actuality it is not.

Figures 1 and 2 below show that on average subjects randomized to Afrezza/Gen-2 had significant increases in their basal (Figure 1) and prandial (Figure 2) insulin doses from baseline whereas subjects randomized to aspart had little change in basal dose and almost no change in aspart dose over the duration of the trial. Figure 16 and 17 in Dr. Liu's review show that subjects randomized to Afrezza/Gen-2 were receiving on average ~ 20 extra units of insulin per day (i.e., 5 units extra of basal + 15 units extra of prandial). This differential use of insulin between groups is concerning for the reasons mentioned above (i.e., inadequate control titration and bias). It was also unexpected because the applicant had already

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[4] DIABETES CARE, VOLUME 24, NUMBER 4, APRIL 2001
[5] NEW ENGLAND JOURNAL OF MEDICINE 1993; 329:977-986
[6] NEW ENGLAND JOURNAL OF MEDICINE 2007; 357:1716-1730
[7] This had been called into question in the review of previous trials, refer to Drs. Yanoff and Joffe's first cycle review for details.

accounted for differences in bioavailability (i.e., bioavailability of inhaled insulin is ~30% that of SQ) in the conversion algorithm used to establish the starting Afrezza/Gen-2 dose (i.e., the starting inhaled dose was ~2.5 times above pre-randomization SQ dose).

The sponsor was asked to perform several exploratory analyses to address potential reasons to explain differences between arms. Optimal prandial dosing in the control arm did not account for differences as more subjects on Afrezza/Gen-2 had reached protocol titration targets for lunch, dinner and breakfast at Week 12 compared to aspart (refer to slide 20 in Dr. Yanoff's EMDAC presentation).

Ultimately retrospective analyses cannot fully allay concerns of bias or poor optimization of the comparator on the validity of the reported efficacy results. At the very least, the data support the overall efficacy conclusion that Afrezza/Gen-2 titrated relatively aggressively is less effective than a standard of care SQ regimen (i.e., more insulin is needed to achieve worse control). Notwithstanding issues which confound interpretability of the results, the fact that Afrezza was shown to have a glucose lowering effect beyond that of placebo at the end of Week 24 (absent confounding by a basal insulin) in the type 2 DM trial (see below), in my mind provides compelling supportive evidence that Afrezza did retain at least some efficacy in this trial. The issues of interpretability were presented and considered by advisors at the April 1st 2014 EMDAC.

Figure 3: **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**
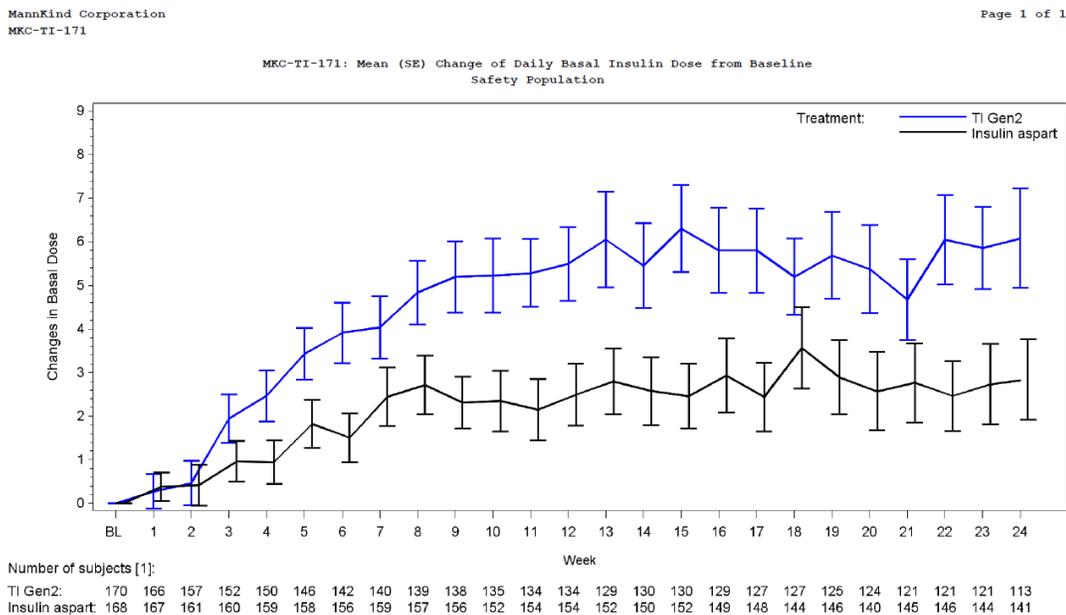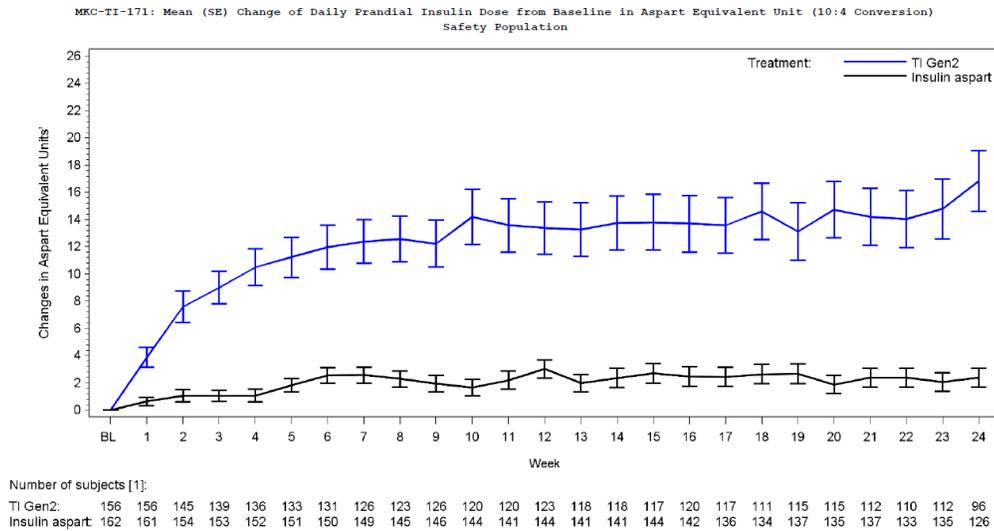
Figure 4: Study 171 – Mean (SE) Daily "Prandial" Insulin Dose Change from Baseline (IU/day) over time (Safety Population) in Aspart and Afrezza TI Gen 2 Arms[8]

Study 175-Type 2 Diabetes Mellitus:

Study 175 compared the glucose lowering effect of mealtime Afrezza titrated to optimize mealtime glucose control to a placebo[9] in insulin naïve subjects with type-2 diabetes. In this study, Afrezza and placebo were used as add-on therapy to metformin alone (≥ 1500 mg per day) or any two of the following oral anti-diabetics used at maximally effective doses: metformin (≥1500 mg); sulfonylurea (50% of maximum dose); DPP-4 (maximum dose), meglitinide (maximum dose) and alpha-glucosidase inhibitor (maximum dose).

<u>Note:</u> *Initiation of three times daily SQ mealtime insulin is not the most widely used or recommended therapeutic approach for the majority of insulin naïve patients with type 2 diabetes failing two oral drugs. The majority of prescribers would intensify treatment either with a third oral drug (low inherent hypoglycemic risk, once daily dosing), a single injection of a non-insulin injectable (low inherent hypoglycemic risk and once daily/weekly injection) or a basal insulin (once daily injection). In light of this fact this design was viewed as valuable because it does away with having to establish efficacy relative to a known active drug and*

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[8] Note that for this figure interventions are compared using equivalent units (i.e., differences in bioavailability between routes are taken into account using a conversion factor established from PK/PD characterization and recommended by the applicant).

[9] PBO consisted of the insulin carrier particle which contains fumaryl diketopiperazine (FDKP), polysorbate 80, acetic acid and water.

with having to deal with a confounder which was present in other Phase 2/3 placebo and active controlled trials (i.e., titratable background basal insulin).

Design

The study was a multi-center, double-blind, randomized, placebo-controlled trial carried out at sites in Brazil, Ukraine, Russia and the United States[10]. The population studied were insulin naïve adults with type-2 diabetes not optimally controlled (i.e., HbA1c 7.5-10%) on a pre-trial anti-diabetic regimen consisting of maximally effective dose of metformin alone, or a combination of two of the following oral anti-diabetic drugs (OAD): metformin, sulfonylurea, meglitinide, DPP-4 inhibitors, and alpha-glucosidase inhibitors. Subjects who had used GLP-1 agonists, PPAR-gamma agonists, or weight lowering drugs within 3 months of screening were excluded. Subjects with underlying pulmonary disease (i.e., asthma, COPD, underlying pulmonary fibrosis, abnormalities on CXR) and smokers were excluded.

Following the screening visit, eligible participants remained on their pre-trial OADs and entered a 6-week run-in where they received counseling regarding diet and physical activity as well as training on issues related to self-monitoring of blood glucose. Following the 6-week run-in period, subjects with a fasting plasma glucose of ≤ 270 mg/dL and an HbA1c ≥ 7.5% were randomized 1:1 Afrezza delivered using the Gen-2 inhaler or placebo. The starting dose was 10 units of Afrezza or placebo for each of the three daily meals.

The 24-week intervention phase was divided into two distinct periods: a 12-week dose titration phase and a 12-week stable dose phase. The protocol instructed subjects to carry out seven-point self-monitoring of blood glucose (i.e., 7-point SMBG) at least three days each week. Prandial insulin dose was to be titrated based on 7-point SMBG data in accordance with protocol specified algorithms which targeted a 90-min post prandial glucose range. Optimal dosing based on the algorithm was defined as the dose needed to achieve a 90-min post prandial glucose value of between ≥ 110 mg/dL and < 160 mg/dL. Rescue therapy with sulfonylurea or basal insulin was implemented in the protocol. Refer to Dr. Yanoff's review for specifics.

Efficacy was to be assessed in the intent to treat population after 24-weeks of therapy or up to the time of rescue or discontinuation from study. The variable used in the primary efficacy assessment was the difference in the change in hemoglobin A1c (i.e., HbA1c) from baseline to trial end between subjects randomized to Afrezza/Gen-2 and the carrier-particle

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[10] 8, 11, 32 and 50% of the randomized population were recruited from Brazil, Ukraine, Russia and the United States respectively. Source: Table 4 Dr. Liu's review.

placebo. The trial was a superiority trial and the primary objective of the trial was to show that the glucose lowering afforded by Afrezza/Gen-2 titrated to target was superior to that afforded by the carrier particle placebo.

The general design features, primary endpoint and timing of the efficacy assessment conform with the Guidance for Industry entitled "*Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention"* and are reasonable.

Trial Conduct and Efficacy in Type 2 DM

A total of 353 subjects were randomized to Afrezza/Gen 2 (n=177) or carrier-particle placebo (n=176). Demographic, anthropomorphic and baseline disease characteristics were balanced at baseline. The mean age was 57 years, the majority of participants were female (58%) and white (88%). Sixty-five percent of subjects were on metformin and a sulfonylurea and 22% were on metformin alone. The baseline HbA1c was 8.4%.

Fewer subjects randomized to Afrezza/Gen-2 withdrew from the study [i.e., 15% (n=27) versus 21% (n=37) for Afrezza/Gen-2 versus placebo respectively] and required rescue therapy [i.e., 6% (n=11) versus 9% (n=16) for Afrezza/Gen-2 versus placebo respectively]. 'Withdrawal by Subject', was the most frequently cited reason listed for discontinuation (6% and 8% for Afrezza/Gen-2, and carrier- placebo). Dr. Yanoff reviewed line listings for reasons given by patients or physicians for withdrawal. The most frequent reasons cited were personal (i.e., relocating) or lack of willingness to comply with protocol demands. In the trial, 4% (n=7) and 5% (n=9) withdrew due to adverse events and the most commonly cited adverse events leading to discontinuation suggested product relatedness (i.e., 'cough', 'wheezing', 'dyspnea', 'oropharyngeal pain'). A greater number of subjects (i.e., 2 versus 6) randomized to the inhaled carrier-particle placebo withdrew due to 'cough' and it is possible that the larger dose titration in this group accounts for the difference. These results suggest the irritant properties of the product reside in the carrier-particle.

At trial end, subjects randomized to Afrezza/Gen-2 titrated to target as add-on to background oral medication(s) had a reduction in HbA1c of 0.84% while subjects randomized to carrier-particle placebo as add-on to background oral medications had a decrease in HbA1c from baseline of 0.41%. The placebo-adjusted difference in HbA1c reduction (95% CI) between Afrezza/Gen-2 and placebo was -0.42% (-0.58, -0.27).   The upper bound of the 95% confidence interval around the difference is below zero, demonstrating Afrezza/Gen-2 provides statistically better glucose control than placebo.   A reduction in HbA1c from baseline in the placebo arm is not an unusual observation in placebo-control add-on to OAD

trials in subjects with type 2 DM and is likely attributable to optimization of background medication, greater compliance with background medication, changes in behavior with greater adherence to dietary and exercise recommendations or any of the above.

Table 2: Primary Efficacy Results Type 2 DM Trial-Study 175

Treatment Arm	n*	Baseline HbA1c [% (±SD)]	Adjusted Mean Change From Baseline HbA1c [% (±SEM)]	Adjusted Between Group Difference in HbA1c Change from Baseline [% (95% CI)]
Afrezza/Gen2[†]	139	8.3 (0.7)	-0.84 (0.07)	**-0.42 (-0.58, -0.27)**
Carrier-Particle Placebo	129	8.3 (0.8)	-0.41 (0.07)	
Source: Table 5 in Dr. Liu's Review. *Subjects with complete data to 24-weeks Primary comparison on the full analysis set population with data up to time of discontinuation or rescue used. Estimates are based on a Mixed Model Repeated Measures approach with treatment, visit, region, basal insulin, and treatment by visit interaction as fixed factor and change from baseline in HbA1c as covariate.				

Conclusions reached based on responder analyses (i.e., proportion of individuals reaching glycemic goal) were consistent with analyses based on HbA1c (refer to Table 11 in Dr. Liu's review). Dr. Liu, also examined HbA1c results for dropouts across the two arms (i.e., figure 14) and in contrast to the type 1 DM trial, dropouts in this trial biased the results toward the null (i.e., the difference between arms would have likely been larger had dropouts continued in the study). Dr. Liu performed several sensitivity analyses to evaluate the impact of missing data on efficacy. These confirmed that the findings of the primary analyses were robust as even the most conservative sensitivity analyses were consistent with the conclusion that Afrezza/Gen-2 improves glycemic control to an extent greater than placebo at the end of 24 weeks.

Subjects randomized to Afrezza/Gen-2 gained more weight and had more hypoglycemic events than subjects randomized to placebo. These findings indirectly support efficacy analyses and the notion that risks of hypoglycemia and weight gain are directly attributable to the products effect on glucose lowering.

8. Safety

The safety of Afrezza delivered using the MedTone C device was reviewed during the first review cycle and the reader is referred to reviews by Drs. Yanoff, Karimi-Shah, Joffe, and Parks for details. Drs. Yanoff (general safety), Paterniti (comparative pulmonary safety data), Pai-Scherf and Bright (lung cancer risk evaluation) have reviewed updated safety information.

The reader is referred to their reviews for details. This summary will focus on updates to pulmonary safety, lung cancer cases, and general safety.

The safety dataset comprises all subjects who participated in phase 2/3 studies. In phase 2/3, 3017 subjects were exposed to Afrezza and the mean exposure time was ~ 9 months. The proportion of subjects exposed to Afrezza by defined exposure duration is shown below. The number of individuals exposed to product for ≥ 12 months is fewer than recommended by the guidance (i.e., n=1300-1500) and the number exposed for ≥ 18 months slightly greater (i.e., n=300-500). Few patients were exposed for long duration ≥ 24 months and conclusions related to risks associated with chronic exposure are limited.

Table 3: Number of Subjects Exposed to Afrezza by Defined Duration of Exposure and Diabetes Types across Phase 2/3 studies (MedTone C and Gen-2 inhaler combined)[11]

	Type 1 Diabetes	Type 2 Diabetes	Combined
≥ 0 months	1026	1991	3017
≥ 6 months	632	984	1616
≥ 12 months	355	638	993
≥ 18 months	135	379	514
≥ 24 months	112	316	428

Pulmonary Safety Concerns

Afrezza is administered via the inhaled route and is intended to be used chronically. This peculiarity raises specific concerns with regard to acute and long term side effects of the product on the respiratory tract. Specific pulmonary safety concerns identified in the review include tolerability related adverse reactions (i.e., cough, throat pain etc.), serious acute pulmonary adverse reactions (i.e., bronchospasm) and lung function decline. In addition, chronic administration of a known growth factor (i.e., insulin) to the lung where it may reach high local concentration raises the theoretical concern that Afrezza could promote respiratory tract tumors. Pulmonary safety concerns are described briefly below.

Respiratory Adverse Reactions in Patients without Underlying Lung Disease

Cough was the most common adverse event term reported in the MedTone C clinical program (i.e., 27% versus 6% for Afrezza/MedTone C versus comparators) and the most common adverse event leading to early trial withdrawal. The incidence of cough in the trials evaluating the new device was similar to the incidence observed with the old device (i.e., 32%

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[11] Source ISS: Table G.3.4.3

versus 2% for Afrezza/Gen-2 versus aspart respectively). Other respiratory adverse advents occurring more frequently in patients randomized to Afrezza included: pharyngolaryngeal pain (2.3% versus 1%), productive cough (2.3% versus 0.8%), throat irritation (2.3% versus 0.1%) and dyspnea ~ 1%. These tolerability issues could impact efficacy and safety indirectly in individual patient (e.g., not taking the full dose because of significant symptoms associated with dosing, taking the dose but expelling some of the active agent through coughing, or miscalculating the dose needed because the previous dose was not fully delivered).

Serious Acute Pulmonary Adverse Reactions in Patients with Underlying Lung Disease (i.e., Acute Bronchospasm)

The impact of Afrezza use on airway reactivity was evaluated in 5 small studies comparing subjects with underlying pulmonary disease to subjects without lung disease (refer to Table 8 in Dr. Paterniti's review). Across all studies, 29 subjects diagnosed with asthma and 26 subjects diagnosed with chronic obstructive pulmonary disease (COPD) were exposed to at least one dose of Afrezza.

In the largest study enrolling patients with asthma (MKC-TI-113), 29% of patients with asthma and 0% of patients without asthma exposed to Afrezza experienced adverse events of wheezing and bronchospasm. Two episodes of Afrezza-induced bronchospasm were associated with significant decline in pulmonary function (45 and 33% reduction in FEV_1) and were qualified as serious. In both cases, treatment with a short-acting β_2-adrenergic receptor agonist was needed. In study MKC-TI-113, inhalation of Afrezza induced a clinically significant mean acute reduction in FEV_1 of ~ 400 mL fifteen minutes post dose. Lung function captured using FEV_1 returned gradually toward baseline by 120 minutes. In patients with COPD (MKC-TI-015) a single dose of Afrezza reduced FEV_1 by a mean of 200 mL eighteen minutes post dose. Lung function captured using FEV_1 returned to baseline over 8 hours.

In the two new clinical trials which specifically excluded patients with underlying chronic lung disease (using history and spirometry) serious bronchospasm events were rarely observed. Dr. Yanoff in her review notes one serious adverse event of potential 'bronchial hyperreactivity' requiring hospitalization and observed in a 58 year old man with type 1 DM relatively early in the course of treatment (day 20) and enrolled in Study 171. Two other potential pulmonary related serious adverse events coded to the term 'Chest tightness' and 'CMV with exertional dyspnea' are insufficiently detailed to determine causality. Rare occurrence of serious bronchospasm events in population without underlying lung disease suggest that this serious event can be mitigated with appropriate patient selection.

At the April 1st advisory committee meeting, the advisors with pulmonary expertise voiced concerns regarding the serious consequence associated with development of acute bronchospasm triggered by Afrezza in patients with undiagnosed underlying lung disease. There was general agreement that an attempt to screen patients for undiagnosed lung disease should be made prior to initiating the product. The merits of various strategies aimed at identifying patients with undiagnosed underlying lung disease were discussed. These included identifying patients based on history and physical exam, baseline spirometry, administration of the first dose under medical supervision and provocative testing. No consensus on best approach was reached.

In patients with chronic underlying lung disease the risk of serious bronchospasm outweighs any potential benefits of Afrezza and in these patients the drug will be contraindicated. It is clear that the serious risk of acute bronchospasm can be prevented by appropriate patient selection. A Boxed Warning will be used to: describe the serious risk, the population for whom the drug is contraindicated and measures that prescribers should follow to prevent occurrence of this serious risk (i.e., appropriate patient selection). A risk evaluation and mitigation strategy which includes a communication plan to inform prescribers about this risk will be implemented.

Lung Function Decline in Patients without underlying lung disease.

In the Phase 2/3 program patients with underlying lung disease were excluded. In these trials, subjects randomized to Afrezza were observed to have a small but greater and statistically significant decline in lung function (as measured by FEV_1) compared to control-treated patients in both diabetes types. Use of Afrezza was associated with an average (95% CI) FEV_1 loss of 40 mL (-80, -1) above that of control. The difference in lung function decline occurred early (month 3) and the rate of lung function decline did not appear to differ between groups once the new baseline was established. Information regarding the long term effect of Afrezza on lung function is available for exposure duration of up to two years but these data are limited due to loss of information (missing data) over time. Too few patients were followed post-treatment discontinuation to allow a meaningful assessment of reversibility. Dr. Paterniti compared FEV_1 changes at 6 months between the MedTone C inhaler and the Gen-2 inhaler and notes no difference between the two inhalers with regard to this risk.

At the April 1st advisory committee meeting, the advisors with pulmonary expertise voiced concerns regarding the impact of Afrezza on lung function over time in general and specifically in patients with undiagnosed chronic lung disease. They recommended

evaluating pulmonary function prior to use and periodically thereafter to establish baseline lung function and monitor lung function deterioration over time. The advisors also pointed to the lack of data beyond two years as concerning and recommended a longer term assessment of the impact of Afrezza on pulmonary function post-marketing.

The serious potential risk of significant pulmonary function decline will be described in the Warning and Precautions section of the label. To mitigate the risk, Afrezza will be contraindicated in patients with established chronic lung disease. In patients with no known diagnosis of lung disease, prescribers will be asked to perform a history and physical to evaluate unrecognized chronic lung disease, to establish baseline lung function and to monitor the impact of Afrezza on pulmonary function over time using spirometry. Discontinuation of Afrezza for patients who have a significant decline in FEV1 (i.e., ≥ 20%) will be recommended.

Lung Cancer Risk Evaluation

Drs. Pai-Scherf, Yanoff and Bright have reviewed this topic in detail. No specific genotoxic or carcinogenic concerns for Afrezza were identified in the non-clinical evaluation (Refer to Dr. Tsai-Turton's memo for details). Residual uncertainties remain with regard to how well these studies inform human risk (i.e., route of delivery differs somewhat). It is unclear whether in these studies lung tissue was chronically exposed to high concentration of Afrezza and whether these studies would be suited to detect a promotional effect of the product on human tumors.

In clinical trials, two cases of lung cancer (small cell and bronchogenic carcinoma) were observed in participants exposed to Afrezza while no cases of lung cancer were observed in comparator treated subjects. In both cases, a prior history of heavy tobacco exposure was identified as a confounder for lung cancer in the causality assessment. Two additional cases of lung cancer (squamous cell) were spontaneously reported by investigators after clinical trial completion in patients exposed to Afrezza for 3.5 years and 1 year, respectively. These two cases are unusual in that they occurred in patients with no reported smoking history. Three out of the four identified lung cancer cases occurred outside the controlled intervention phase. The clinical data in the application is of limited value to inform potential lung cancer risk associated with Afrezza use due to small numbers, limited exposure, potential role of detection bias in contributing to the imbalance (i.e., open-label, pulmonary symptoms) and absence of a concomitant control group with which to compare the risk. I agree with Dr. Pai-Scherf's assessment that the available limited evidence does not allow a meaningful analysis of the lung cancer risk in patients exposed to Afrezza.

Dr. Bright has reviewed the post-market lung cancer risk evaluation for the other inhaled insulin product (i.e., Exubera) and the reader is referred to her review for specifics. In the post-market assessment an imbalance in lung cancer mortality [2.81 (0.5-28.5)][12] and lung cancer incidence [3.75 (1.01-20.7)][13] was detected in a follow-on observational cohort study of patients previously enrolled in Exubera controlled clinical trials program (i.e., Follow-up Study of Exubera or FUSE study). Pfizer, the developer of Exubera, in a public presentation[14] stated that these results were indicative but not conclusive of a potential risk of lung cancer with Exubera. Detection bias or promotional effects among smokers were invoked as potential reasons to explain the increased risk observed.

The data in the Afrezza program are insufficient to draw clear conclusions with regard to lung cancer risk associated with the product. This topic was discussed at the April 1st 2014 advisory committee meeting and conclusions reached by DMEP are similar to the conclusions reached by committee members with oncology expertise. In light of the limited data and residual concerns raised by, the two spontaneous reports of lung cancer in non-smokers, the results of the FUSE trial, and existence of a plausible biological mechanism (i.e., exposure to high concentration of a growth factor) the applicant will be asked to demonstrate conclusively that Afrezza does not increase the risk of lung cancer post-marketing in a five-year randomized controlled trial. The applicant had proposed has small voluntary product based registry. The proposal was inadequate on multiple levels but particularly because it was voluntary (selection bias), it was not randomized (i.e., could not handle measured and unmeasured confounders), it lacked a comparable concomitant control and was underpowered. A five year randomized controlled trial was selected because it was assessed as being most likely to answer the question in a timely fashion, feasible with an enrichment strategy and addressed many of the shortcomings of risk assessment based on spontaneous reports, voluntary product registry and observational data (e.g., confounding, detection bias, lack of reliable control data etc..).

<u>CV-risk Evaluation</u>

Since issuance of the 2008 FDA Guidance for Industry entitled: *Diabetes Mellitus-Evaluating Cardiovascular (CV) Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes,* applicants that seek to market new drugs for the treatment of type-2 diabetes mellitus are asked to prospectively evaluate the ischemic cardiovascular disease risk associated with use of the

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[12] Incidence Density Ratio (95% CI)
[13] Incidence Density Ratio (95% CI)
[14] 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.

new drug. The Guidance explicitly recognizes that patients with diabetes have a higher prevalence of CV disease compared to the population without diabetes and requires product developers to definitively exclude an increase in CV-risk of 80% relative to comparators before approval and an increase in CV-risk of 30% relative to comparators after approval. Insulin products were not explicitly subject to the requirements in the guidance because insulin is the only life-saving treatment available for patients with type 1 diabetes and is the last-line treatment for patients with type 2 diabetes who have failed all other available therapies.   However, insulin products are not regarded as inherently "safer" from a CV-risk perspective compared to other antidiabetics. In fact, many adverse reactions specific to insulin suggest at least indirectly that insulin therapy could adversely impact the cardiovascular system (e.g., increase weight, edema and high inherent hypoglycemic risk[15]). Currently, applicants seeking to market a novel insulin formulation are asked at end of phase 2 to collect reliable cardiovascular outcomes data and define a prospective plan to analyze cardiovascular risk in Phase 3. Although the CV-risk assessment is expected to conform with guidance recommendation, applicants to date have not been asked to exclude a pre-defined threshold of risk pre-marketing. The robustness of the findings that result from the pre-marketing CV-risk assessment is evaluated on a case by case basis during product review.

The Afrezza Phase 3 clinical program was initiated prior to implementation of the guidance. As such, the applicant was not encouraged to enrich the population with individuals at risk for CV events or required to prospectively define, collect and blindly adjudicate cardiovascular outcomes of interest. In many ways, the collection of CV-safety information in this application reflects what had been the standard approach for most anti-diabetic drugs prior to issuance of the guidance. To analyze the inherent CV-risk associated with Affrezza use, the applicant performed an analysis of "CV" adverse events across all Phase 2/3 trials using a broad list of MedDRA preferred terms subsumed under multiple system organ classes (i.e., some key SOC that could signal CV-events were excluded ECG and laboratory abnormalities). With this strategy the applicant retrieved 216 "CV adverse events" (10.5 events per 100 patient year of exposure) in Afrezza exposed patients and 175 "CV adverse events" (8.1 events per 100 patient year of exposure) in comparator treated patients. The large number of identified events for a program this size is reflective of the poor specificity of most of these terms (i.e., most are not serious adverse events and most are not ischemic CV events). Adjudication of events of interest was not performed and for events that lack standardized definitions (e.g., 'worsening angina') and may be subject to interpretation this is problematic.   In general poor specificity will tend to bias the assessment towards no difference. Finally most trials were open-label and referral bias is always concern in such trials.

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[15] DIABETES CARE, VOLUME 34, SUPPLEMENT 2, MAY 2011

The large number of "CV adverse events" in the applicant's CV-risk analysis relying on pooling of MedDRA preferred terms contrasts to the small numbers of events meeting the regulatory definition of a serious event and coded to specific CV ischemic events (e.g., 6 and 4 serious 'myocardial infarction' events on Afrezza and comparator respectively). Dr. Yanoff has reviewed listings of individual serious adverse events preferred terms denoting potential CV ischemic events. Her qualitative assessment has not identified a specific concern. Although adverse event, laboratory and vital sign data do not point to an obvious CV-risk "signal" that would preclude approval, the CV-risk analyses in the Afrezza program are limited and minimally informative due to their retrospective nature, insufficient power and issues of specificity discussed above. The sponsor will be asked to better characterize the CV-risk profile of Afrezza in the post-market setting by collecting reliable prospective CV-outcomes data in the large outcomes trial designed to address the potential lung cancer risk.

Diabetic Ketoacidosis

Diabetic ketoacidosis was identified as a possible drug related adverse reaction in the previous review cycle. Diabetic ketoacidosis is a life threatening condition for patients with type 1 diabetes. This risk was identified based on an observed 13 to 3 imbalance not favoring Afrezza for events of diabetic ketoacidosis (DKA) across type 1 diabetes trial. Using exposure adjusted incidence rate, DKA occurred ~5 times more frequently in Afrezza-treated patients than in comparator treated patients (2.4 DKA events per 100 patient years versus 0.4 DKA events per 100 patient years). Review of narratives for DKA cases revealed presence of predisposing risk factors in some reports (i.e., missed insulin doses and infection). I agree with Dr. Yanoff that the striking imbalance in DKA events is concerning and in light of the observed lower efficacy of Afrezza that drug relatedness cannot be excluded (i.e., absolute or relative insulin deficiency is the physiological cause of DKA). It is somewhat reassuring that in the new trial no new cases of DKA were identified. To mitigate against this potential product-related serious risk, prescribers will be informed of the observed imbalance in Section 5 of the label and will be recommended to implement strategies to prevent the risk (e.g., appropriate patient selection, increased vigilance in patients with predisposing illness and choosing alternative routes of insulin administration in patients that may be at risk)

Hypoglycemia, Hypersensitivity Reactions, Immunogenicity, Vital, ECG and Laboratory data have been previously reviewed (refer to Drs. Yanoff and Joffe's cycle 1 reviews). Inclusion of data from the new trials would not change conclusions reached during the first cycle of reviews. The reader is referred to these past reviews for full details.

9. Advisory Committee Meeting

On April 1st 2014 an Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting was convened to discuss efficacy and safety of Afrezza in type 1 and type 2 diabetes. Salient discussions from the meeting surrounding safety concerns are presented by topic in Section 8 of this review.

With regard to efficacy issues in type 1 diabetes, the committee noted that residual uncertainty remains concerning the non-inferiority conclusion in the type 1 DM trial and that sensitivity analyses did not resolve these uncertainties. The committee also noted that Afrezza may not be useful and efficacious in all patients with type-1 diabetes and identified some subgroup of patients that could potentially derive a net benefit from Afrezza. The committee cited as examples, patients with needle phobias, patients who are noncompliant with available subcutaneous regimen, patients who need insulin between meals, patients with visual impairment or manual dexterity issues. However, the committee noted that there is no definitive data to conclude that patients would be more compliant with Afrezza than with injectable insulin. On the issue of compliance with injectable regimen, Dr. Thomas stated that over the last two decades reduction in needle gauge for devices used to deliver insulin subcutaneously had gone a long way towards reducing the discomfort associated with injection. To make the point that compliance may not be related to the need for injection, he pointed to his own clinical practice experience with another group of injectable anti-diabetic drugs (GLP-1 agonist) used in type 2 diabetes stating that he had not noted compliance issues with these products.

Dose response relationship issues and their potential relationship to DKA were brought up. Some committee members noted that the pharmacokinetic characteristics of Afrezza as compared to other insulin analogs may be advantageous in some patients and disadvantageous in others.

With regard to efficacy in patients with type 2 diabetes, the committee noted that there are likely circumstances where Afrezza would be an effective treatment for patients with type 2 diabetes. But as was stated for type 1 diabetes, the committee noted that this drug would not be used in all patients, and probably would not be used simply as a replacement for other forms of insulin. The committee discussed the subgroup of patients that may derive the most benefit from Afrezza, which include those discussed for type 1 diabetes and also include elderly patients that are receiving some degree of caregiver assistance outside of a nursing care facility. The committee expressed concern about the potential for the use of mealtime insulin without concomitant basal insulin coverage and the broader concern over who will be

instituting the treatment and their understanding of the typical management strategy of type 2 diabetes, i.e., initiating basal insulin before initiating prandial insulin.

Refer to the full transcript and meeting minutes for a summary of the discussion.

At the end of the meeting the advisors were asked to vote on the following questions (discussions of the vote excerpted from the official minutes follow):

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

<u>***Vote Results:***</u> **Yes =13, No=1, Abstain=0**

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

The committee recommended the following safety signals be evaluated in post-marketing studies: 1) long term effect on pulmonary function; 2) lung cancer, including prevalent and incident cases of cancer. One panel member was unable to stay for the entire meeting, accounting for one "No Vote". Please see the transcript for details of the committee discussion.

<u>***Vote Results:***</u> **Yes =14, No=0, Abstain=0**

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

Committee Discussion: *The committee unanimously agreed that based on data in both the briefing materials and presented at today's meeting, the applicant has demonstrated that Afrezza is safe and effective for the treatment of adult patients with type 2 diabetes mellitus to support approval. The committee noted that there is often a tremendous delay in getting type 2 diabetes patients to initiate insulin therapy, and because of its non-injectable route of administration this treatment option may help with the delay. The committee also commented that many patients with type 2 diabetes are older and overweight, so having an agent that does not promote weight gain and possibly even promotes weight loss would be an advantage for these patients.*

In addition to the safety signals noted in voting question #6, the committee recommended following safety signals be evaluated in post-marketing studies: 1) concomitant use with other medications and use in pregnant women; 2) data with the use of Afrezza in combination with basal and other agents as this drug product will likely be used as an add on to basal insulin; 3) a study that looks specifically at geriatrics for safety and efficacy

10.   Pediatrics

Please refer to Dr. Yanoff's review for relevant pediatric issues.

11.   Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12.   Labeling

Major issues with labeling have been discussed in relevant section of this review.

13.   Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend approval, pending agreement on final labeling.

- Risk Benefit Assessment

Benefit

The applicant has demonstrated in an adequate and well controlled trial (Study-175) that Afrezza titrated to goal and administered three times daily at each meal of the day using the Gen-2 device improves glycemic control compared to placebo in patients with type 2 diabetes inadequately controlled on one or two anti-diabetic agents. This Phase 3 trial confirms findings from a Phase 2 placebo-controlled trial in type-2 diabetes submitted in the

original application (Study 0008). Interpretability of the efficacy findings in these two trials is straightforward because, in contrast to other medium to longer term placebo-control trials in the program, basal insulin was not co-administered, eliminating the potential impact of this important confounder on the placebo-adjusted efficacy assessment. In addition in Study 175, the results of even the most conservative sensitivity analysis carried out to assess the impact of missing data on the primary analysis support the overall conclusion that Afrezza in its intended use reduces Hemoglobin A1c to a greater extent than placebo. The two trials in my mind provide the most robust evidence that regular insulin delivered to the lung at mealtime using the MedTone C or Gen-2 device result in glucose lowering over three to six months. I am also of the opinion that in light of the residual uncertainty concerning the non-inferiority conclusion in the type 1 diabetes trial, these two trials provide compelling indirect supportive evidence that Afrezza retained at least some glucose lowering effect against placebo in the type 1 trial.

It is worth noting that the effect size in the new Type 2 DM trial was again noted to be small (i.e., an HbA1c reduction of ~0.4% at the end of six months) particularly if one considers that the dose range of insulin is broad and flexible compared to the dose range of most non-insulin anti-diabetics. This peculiarity of insulin allows customized dose titration to meet an individual's need in order to achieve the desired therapeutic effect. I do not agree with the Dr. Yanoff's opinion that inadequate titration accounts for this low observed effect size since by all accounts Afrezza titration was aggressive for the first twelve weeks of therapy in both of the two new trials submitted in this application and should have been sufficient to robustly lower HbA1c.

The relatively small placebo-adjusted effect size is similar to effect sizes reported for other products approved for use in type-2 diabetes (e.g., glinides, bromocriptine, welchol, and alpha-glucosidase inhibitors). Several observations made in the review may be invoked as reasons for the small observed effect size including: the relatively short duration of action of the insulin (i.e., not contributing significantly to glucose lowering over 24 hours), plateauing of the dose response above a certain dose, and limited ability to dose-escalate due to tolerability issues (i.e., cough and hypoglycemia). With regard to the meaningfulness of the observed effect size, large randomized controlled trials have established that HbA1c reduction and microvascular disease risk reduction are strongly correlated[16] and it is estimated that every percentage point drop in HbA1c reduces the risk of microvascular complications (eye, kidney, and nerve diseases) by 40%[17]. The placebo-adjusted HbA1c

[16] DIABETES 57:995–1001, 2008
[17] UKPDS 35. BMJ 2000; 321: 405-12

reduction of 0.4% observed in the trial population would be expected to provide a meaningful benefit in terms of microvascular disease outcomes reduction to patients.

The data in the application has consistently shown that glucose lowering with Afrezza is numerically and statistically worse than glucose lowering achieved with a standard of care subcutaneous mealtime insulin. In the new type 1 diabetes trial (Study-171), the primary objective of non-inferiority was met. At face value the results suggest the applicant has demonstrated that the potential loss of efficacy associated with Afrezza relative to control does not exceed the pre-specified agreed-upon non-inferiority margin (assumed to represent ~ 50% of the comparator's placebo-adjusted effect at this time point and in this population).

As was stated in the review and by the Committee, issues related to missing data and possible bias favoring the intervention arm cast doubt around the robustness of the results based on the primary analysis. The possibility remains that the loss of efficacy with Afrezza relative to the control exceeds 0.4% and therefore does not preserve the agreed-upon amount of the comparator's effect. In light of the placebo-controlled data in type 2 diabetes, it is highly unlikely that in Study-171 Afrezza had absolutely no effect, allaying one of the concerns associated with efficacy assessment based non-inferiority (i.e., declaring an agent non-inferior to an ineffective control). Selection of a margin for a non-inferiority trial (i.e., in this case 0.4%) is complex and involves in part clinical judgment related to how much loss of effect relative to comparator one in willing to tradeoff for the benefits afforded by the new treatment (in this case benefits afforded by the new route of administration). This complex question was brought to the Advisory Committee. In spite of residual uncertainty around what the true difference in effect size is between Afrezza and comparator, the Committee did not believe that this uncertainty rose to such a level of concern as to preclude approval of Afrezza for the treatment of type 1 diabetes. The Committee pointed to specific examples of patients where having access to an inhalable form of insulin could be advantageous. In terms of benefits, the inhaled route of administration does offer convenience (small device that is relatively easy to carry and use) and is expected to reduce the discomfort associated with three daily mealtime insulin injections. Overall, I agree with the Committee's recommendation. I recognize that Afrezza, as used in the trial, is not an optimal mealtime insulin replacement for type 1 diabetes and I would not recommend its use in patients who are candidates for and seek to achieve the tightest possible level of glucose control. Nevertheless, diabetes management is burdensome on individuals and it is unlikely that all individuals with diabetes can adhere to what the medical community would consider optimal management. This is already well recognized and accepted. Physicians who treat diabetes tailor therapy to meet their individual patient's needs. An example of this would be the use of a relatively straightforward but inflexible subcutaneous insulin regimen in some patients

(e.g., 70/30 insulin). The Committee described numerous examples of patients whose needs are not currently met with available therapies and who may derive benefit from Afrezza being available.

Risks

The risks associated with the product and rationales behind strategies to mitigate these risks are detailed in Section 8 of this review. Insulin specific risks are discussed in Dr. Yanoff's review. As stated in my review none of the risks identified in the review rise to the level of precluding product approval. The most common adverse reaction associated with Afrezza use include hypoglycemia, cough and throat pain. Serious drug-related risks identified in the application include acute bronchospasm in patients with underlying lung disease, pulmonary function decline and diabetic ketoacidosis. The serious risks associated with product use will be mitigated through product labeling and in the case of acute bronchospasm in patients with underlying lung disease through use of a Black Box Warning and a Risk Evaluation and Mitigation Strategies (REMS) consisting of a communication plan to inform health care professionals about this serious risk. Lung cancer has been identified as a potential serious risk. It is important to emphasize that this risk is at this point theoretical and that the data in the Afrezza application are insufficient to draw clear conclusions with regard to lung cancer risk associated with use of the product. Physicians and patients should be aware of this potential risk and of the available clinical data available to date to make informed prescribing and use decisions.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Afrezza will be approved with a Risk Evaluation and Mitigation Strategies (REMS) comprising of a communication plan to mitigate the risk of acute bronchospasm associated with Afrezza use.

- Recommendation for other Postmarketing Requirements and Commitments

The following post-marketing studies were agreed upon and will be required under the Pediatric Research Equity Act (PREA) or Food and Drug Administration Amendments Act (FDAAA).

1. A clinical trial to evaluate dosing, efficacy, and safety in pediatric patients.

2. A 5-year, randomized, controlled trial in 8,000-10,000 patients with type-2 diabetes to assess the serious potential risk of pulmonary malignancy with Afrezza use. This trial will also assess cardiovascular risk based on prospectively defined, collected and

independently adjudicated major adverse cardiovascular event and include a substudy to evaluate the long-term effect of Afrezza use on pulmonary function.

3. A study to address the dose-response of Afrezza relative to subcutaneous insulin in type 1 diabetes to address the serious potential risk of DKA

4. A clinical pharmacology study to address the within-subject variability in PK and PD to address