

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

OBSERVATIONAL STUDIES

NDA/Serial Number: NDA 22472

Drug Name: Afrezza (Technosphere insulin inhalation system)

Indication(s): Diabetes mellitus

Safety Outcome: Lung cancer

Applicant: MannKind Corporation

Consult Date: February 26, 2014

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Keywords: Lung cancer, insulin inhalation system, registry study, single-arm observational study

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1 EXECUTIVE SUMMARY

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 sponsor is seeking the indication of improving glycemic control in adults with type 1 and type 2 diabetes mellitus. On October 15, 2013, the sponsor submitted the new drug application for the third time. The previous two submissions both resulted in issuance of Complete Response Letters due to multiple identified deficiencies in the application.

In the Afrezza development program, four cases of lung malignancy were reported among subjects exposed to Afrezza. No lung malignancy cases were reported among comparator-exposed subjects. Hence, the potential safety issue of lung cancer was raised for Afrezza. In October 2013, the sponsor submitted a study protocol synopsis of “A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus”. In preparation for the Advisory Committee Meeting on April 1, 2014, the Division of Epidemiology I consulted the Division of Biometrics VII to evaluate the statistical aspects of the protocol synopsis and explore other study designs to investigate the association between Afrezza and lung cancer.

This review comments on three potential study designs---the sponsor’s one-arm observational study, a registry study and a randomized clinical trial. The comments were conveyed to the Office of Surveillance and Epidemiology (OSE) and were presented by OSE at the Advisory Committee meeting on April 1, 2014. If a post-marketing requirement is imposed at the approval of Afrezza, DB7 will be available to review the full protocol and analysis plan for the proposed study to investigate the association between Afrezza use and lung cancer.

2 INTRODUCTION

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 sponsor is seeking the indication of improving glycemic control in adults with type 1 and type 2 diabetes mellitus. On October 15, 2013, the sponsor submitted the new drug application for the third time. The previous two submissions both resulted in issuance of Complete Response Letters due to multiple identified deficiencies in the application.

The potential safety issue of lung cancer was raised for Afrezza, because four cases of lung malignancy were reported among subjects exposed to Afrezza, and no lung malignancy cases

were reported among comparator-exposed subjects. In October 2013, the sponsor submitted a study protocol synopsis of “A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus”. In preparation for the Advisory Committee Meeting on April 1, 2014, the Division of Epidemiology I consulted the Division of Biometrics VII to evaluate the statistical aspects of the protocol synopsis and explore other study designs to investigate the association between Afrezza and lung cancer.

This review summarizes and comments on the statistical methods of sponsor’s postmarketing study, and explores different study designed proposed by the Division of Epidemiology I. It should be noted that the scope of this review was limited to the information provided in sponsor’s protocol synopsis, and FDA briefing document for Afrezza.

Material Reviewed

- Sponsor’s Protocol Synopsis “A Postmarketing Observational Cohort Study to Evaluate the Long-term Safety of Afrezza in the Treatment of Patients with Diabetes Mellitus”.
- Afrezza FDA Briefing Document (page 230—232).

3 STATISTICAL REVIEW

The Sponsor’s Study

The sponsor proposed a single arm, observational cohort study of patients who have been treated with Afrezza. The study will enroll 1800 patients over two years, and continue for five years from the date of the last patient enrolled. The primary objective is to determine the incidence of pulmonary malignancies in long-term users of Afrezza. The significant increase in the risk of pulmonary malignancies among Afrezza users will be demonstrated if the 95% confidence interval is above 64.6/100000 person years, which is the incidence rate of pulmonary malignancies in SEER data. The sponsor calculated the person years to be 8000 assuming the loss of follow up rate to be 10%. Consequently, the study will have 90% power to detect a three-fold increase in the rate of pulmonary malignancies with a two-sided significance level of 0.05.

Comment:

The follow-up period of five years seems reasonable.

We recommend that the sponsor specify a minimum exposure to Afrezza, and include only patients who had been exposed to Afrezza more than the minimum exposure. Without this

minimum exposure criterion, the risk of pulmonary malignancy might be diluted by patients with various length of drug use.

The assumption of 10% loss of follow-up rate is optimistic. We calculated the person years with the following assumptions:

- *The loss of follow-up rate is 10%, 15%, and 20%;*
- *Enrollment of 1800 subjects is uniformly distributed over two years;*
- *Follow up continues for five years from the end of enrollment year two.*

Table 1 shows the total person years at the end of the follow-up period and the minimum number of events so that the observed lower 95% confidence bound is above 64.6/100000.

Table 1. Person years assuming different loss of follow-up rates.

Loss of Follow-Up Rate	Total Person Year	Min. No. of Event	Incidence Rate (/100000)	95% CI (/100000)	
10%	8012	11	137.3	72.2	253.7
15%	6914	10	144.6	73.5	275.4
20%	5977	9	150.6	73.5	296.9

The study is conducted among diabetic patients, which is very different from a normal population. Therefore, the incidence rate of pulmonary malignancies in SEER data, which is population based, may not reflect the incidence rate among diabetic patients. Dr. Patricia Bright in the Office of Surveillance and Epidemiology provided some incidence rates that are more relevant to the study population. We calculated the power for the study to detect a three-fold risk increase in pulmonary malignancies with the following assumptions:

- *The person years are 8012, 6914, and 5977.*
- *The background incidence rate is 64.6/100000, 80/100000 and 130/100000 person-years.*
- *The two-sided significance level is 0.05.*
- *Exact test is used to compare the incidence rate in the study to the background incidence rate.*

Table 2 shows that the study will have sufficient power to detect a three-fold increase in the risk of pulmonary malignancy with the background rate of 64.6/100000, 80/100000 and 130/100000 person-years.

Table 2. Power to detect a three-fold increase in the risk of pulmonary malignancy.

Background Incidence Rate (/100000)	Total Person-Years	Power
64.6	8012	0.905
64.6	6914	0.859
64.6	5977	0.816
80	8012	0.945
80	6914	0.9
80	5977	0.906
130	8012	0.996
130	6914	0.991
130	5977	0.973

Registry study

The OSE suggested an alternative single, arm, observational cohort study of diabetic patients who are prescribed Afrezza. The incidence of lung cancer, lung cancer mortality, and all-cause mortality at three, five, and ten years will be compared between patients with the lowest quartile of exposure duration and patients with the upper two quartiles of exposure duration, adjusted for smoking. The alternative study was suggested so as to reduce detection bias of the safety outcome.

Comment:

We agree that the alternative study may reduce detection bias. However, we do not recommend the study length to be more than five years. In ten years, the study result is possibly not relevant given alternative treatments, trend in the incidence rate of the outcome and the baseline covariates.

Randomized study

The OSE considered a large randomized study to assess the long-term risk of pulmonary malignancy of Afrezza. The study will randomize diabetic patients to two treatment groups: Afrezza and an active control.

Comment:

The randomized study seems more appropriate to address any confounding that may occur between Afrezza use and lung cancer. However, the study will need a large sample size due to the rarity of lung cancer. We calculated the sample size with the following assumptions:

- *The baseline incidence rate of lung cancer in diabetic population is 80 to 130 per 100,000 person-years,*
- *The study power is 0.8,*
- *Subjects are equally allocated in two treatment groups,*
- *Fisher's exact test is used to detect a relative risk of 3, with a two-sided significance level of 0.05.*

The sample size is 20868 total (10434 per group) if the baseline incidence rate is 80/100000 person-years, and 12832 total (6416 per group) if the baseline incidence rate is 130/100000 person-years. The sample size might be smaller if time to event analysis is used instead of Fisher's exact test.

4 CONCLUSION

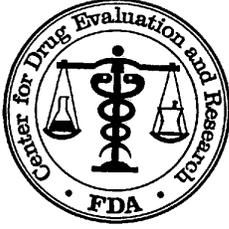
Our comments on the study designs were incorporated in the presentation by the Office of Surveillance and Epidemiology on the AC meeting on April 1, 2014. If a post-marketing requirement is imposed at the approval of Afrezza, DB7 will be available to review the full protocol and analysis plan for the proposed study to investigate the association between Afrezza use and lung cancer.

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04/15/2014

MARK S LEVENSON
04/15/2014



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

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

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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Keywords: NDA review, clinical studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

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.

Labeling Comments: In Section 14 of the proposed labeling, the sponsor included the results from Study 171 (T1DM), Study 175 (T2DM), (b) (4)

(b) (4)
Therefore, I think (b) (4)

should not be included in the efficacy section of the labeling.

Advisory Committee Meeting: An Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting is scheduled on April 1st, 2014 for Afrezza to discuss clinical pharmacology, efficacy, and safety issues and to vote on whether the applicant has demonstrated that Afrezza is safe and effective for the treatment of adults patients with T1DM and T2DM to justify approval.

1.2 Brief Overview of Clinical Studies

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 CR letter issued on 01/18/2011 to conduct two 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 where the Gen2 inhaler was used (Study MKC-TI-171 and MKC-TI-175, see Text Table 1 for study highlights, the prefix before numbers in each study name is omitted).

Text Table 1 – Study Design Summary

Study	Target Population	Treatment Duration	Design	Treatment Group	Background Medication	Stratifying Factor
171	Subjects with T1DM	24 weeks	Randomized, open-label, parallel-group, active-controlled, multicenter, multinational	TI-Gen2 (174) TI-MedTone (174) Insulin aspart (170)	Basal insulin	Region and basal insulin
175	Subjects with T2DM	24 weeks	Randomized, double-blind, parallel-group, placebo-controlled, multicenter, multinational	TI-Gen2 (177) Placebo (176)	OADs	Region and OADs
Region strata consisted of North America, Latin America, and Eastern Europe. Basal insulin strata consisted of insulin glargine, insulin detemir, and NPH insulin. OADs strata consisted of metformin only, metformin + SU, metformin + DPP-4, metformin + 1 or more OADs not specified above, and 2 or more OADs not including metformin						

The primary objective of Study 171 was to demonstrate that TI Inhalation Powder administered using the Gen2 inhaler in combination with a basal insulin was non-inferior to insulin aspart (IAsp) 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 IAsp groups. Comparison of the changes from baseline to the final treatment visit in FEV₁ between the TI-Gen2 and TI-MedTone groups was the main safety objective but is not a focus of this review.

The primary objective of Study 175 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.

For Study 171, 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 insulin aspart group (11%).

For Study 175, a total of 353 subjects were randomized. Overall, about 18% of the randomized subjects discontinued from the study regardless of rescue status. The placebo group had a higher dropout rate (21%) than the TI-Gen2 group (15%).

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.

1.3 Statistical Issues and Findings

Since the study design (rescue therapy used in T2DM, but not in T1DM), population, comparator, background medication, etc., were different between the two confirmatory safety and efficacy trials, the data were not combined to obtain overall treatment estimate. The collective evidence is summarized here for each study.

Type 1 Diabetes Mellitus

In Study 171, 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 Text Table 2. 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

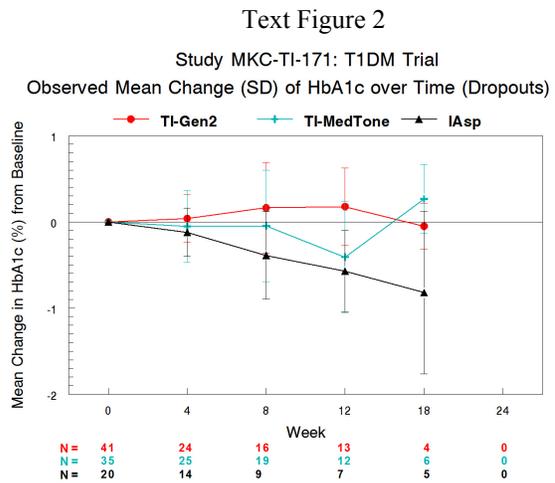
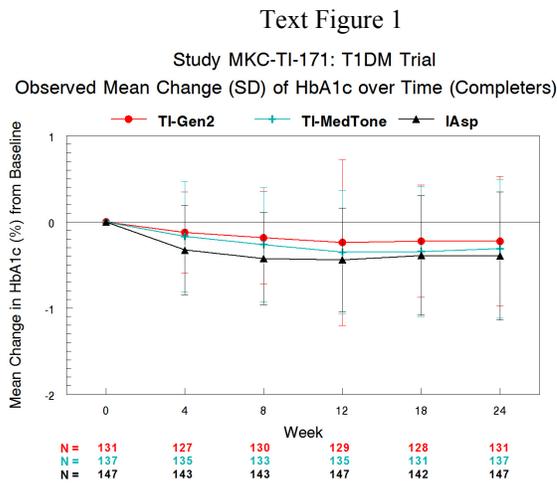
24 weeks. Additionally, the dropout rate was higher in the TI-Gen2 arm (25%) than in the IAsp arm (11%) in this open-label inhalation vs. subcutaneous injection study. Therefore, several sensitivity analyses were performed to evaluate the impact of missing data on the results of the primary analysis.

Text Table 2 – 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 (Text Figure 1) 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 (Text Figure 2), 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.



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 (see Appendix I for details).

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.

Text Table 3 – 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

As shown in Text Table 3 above, 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.

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 $\leq 7.0\%$ at Week 24 when compared with the IAsp group (27%).

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 ($\leq 8.0\%$ 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 Text Table 2, 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 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).

The mean reduction in FPG after 24 weeks of treatment 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). At Week 24, the mean change from baseline in body weight was -0.5 kg in the TI-Gen2 group and +0.9 kg in the IAsp group.

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 (Text Table 4).

Text Table 4 – Study 171 (T1DM): Hypoglycemic Episodes

Safety Population				Treatment Difference	Nominal
Type of Hypoglycemia		TI-Gen2	IAsp	Asymptotic 95% CI	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.

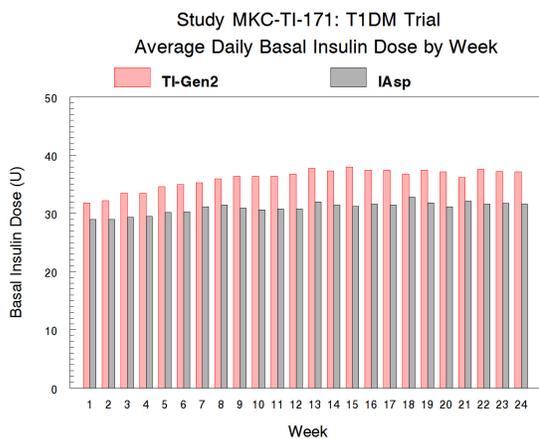
P-value for incidence rate was based on Fisher’s Exact test.

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).

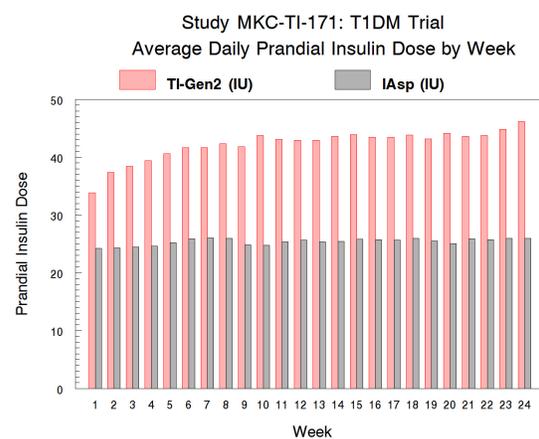
Note that Subject 2042 was randomized to the TI-MedTone group, but received insulin aspart throughout the trial; therefore the patient was included in the IAsp group in the safety population.

In this T1DM trial, 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 (Text Figures 3 and 4).

Text Figure 3



Text Figure 4



Type 2 Diabetes Mellitus

In Study 175, 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 Text Table 5. 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.

Text Table 5 – Study 175 (T2DM): Summary of Statistical Results

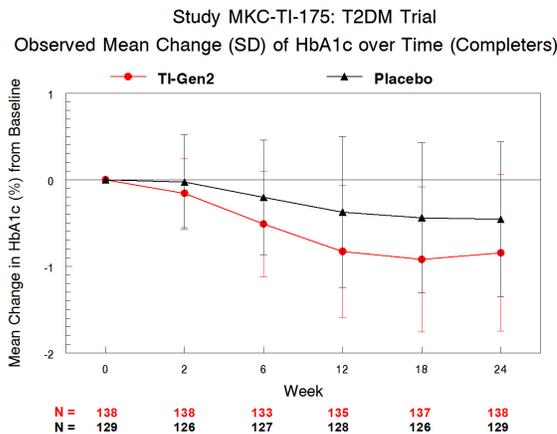
FAS Population	LS Mean Change from baseline ± SE (N)		Treatment Difference	95% CI
	TI-Gen2	Placebo		
Change in HbA1c (%)	-0.84 ± 0.07 (138)	-0.41 ± 0.07 (129)	-0.42 ± 0.08	(-0.58, -0.27)

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

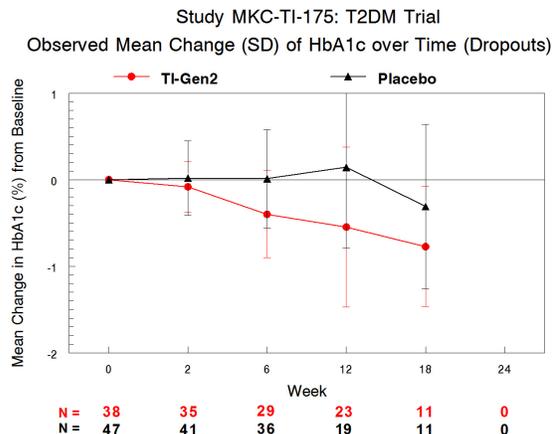
Data collected after initiation of rescue therapy were excluded from the analysis.

My analysis using the completers cohort (Text Figure 5) 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 (Text Figure 6). 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 -0.4% shown in the primary analysis.

Text Figure 5



Text Figure 6



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 (see Appendix I for details) and both of them consistently demonstrated superiority of TI-Gen2 over placebo in HbA1c lowering (Text Table 6).

- 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)

Text Table 6 – 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%).

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).

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)). 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).

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 (Text Table 7).

Text Table 7 – Study 175 (T2DM): Hypoglycemic Episodes

Safety Population				Treatment Difference	Nominal
Type of Hypoglycemia		TI-Gen2	Placebo	Asymptotic 95% CI	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.

In this T2DM trial, 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 18 above). 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.

2. INTRODUCTION

2.1 Overview

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 and MKC-TI-175) 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.

2.2 Data Sources

The clinical study reports and electronic data files are located in the sub-folders of EDR [\\CDSESUB1\EVSPROD\NDA022472\0074](#). The subsequent submission in response to my request on 01/17/2014 regarding missing data handling was in [\\CDSESUB1\EVSPROD\NDA022472\0077](#). In general, the quality of the electronic data sets and integrity of the study reports were satisfactory.

3. STATISTICAL EVALUATION

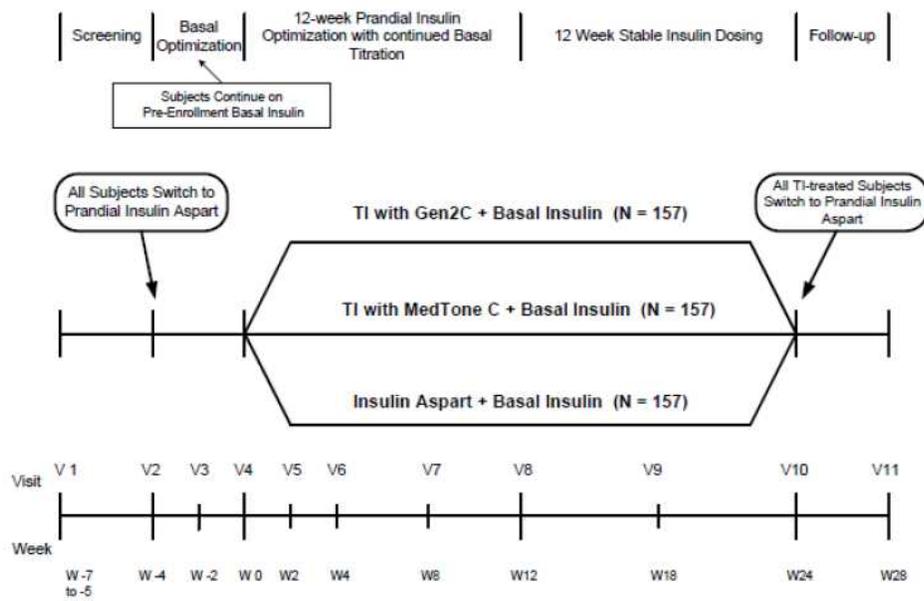
3.1 Evaluation of Efficacy

3.1.1 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 – Study schema for Study 171 (sponsor’s figure)



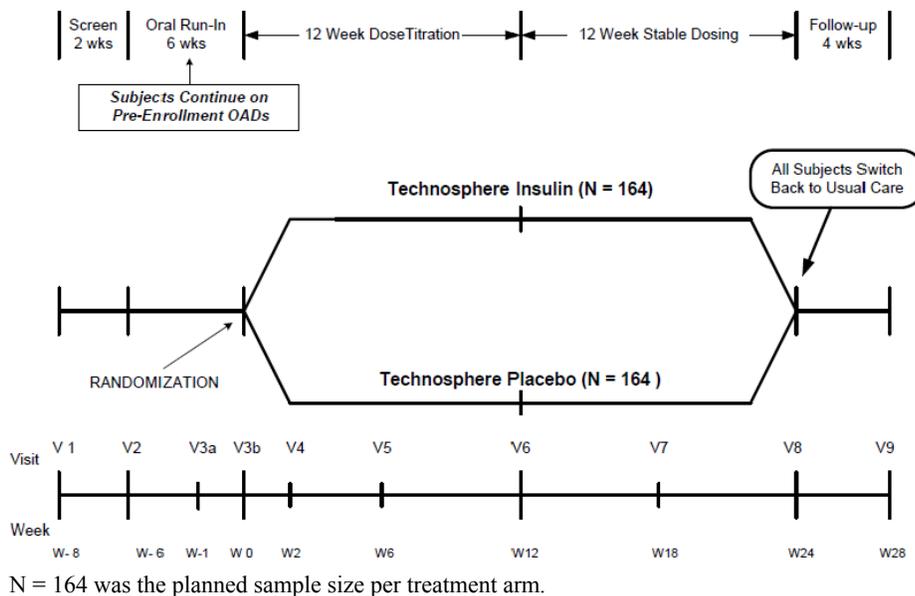
N = 157 was the planned sample size per treatment arm.

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 FEV₁ 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 $\geq 7.5\%$ and $\leq 10.0\%$.

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 – Study schema for Study 175 (sponsor’s figure)



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 \leq 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.

3.1.2 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 \leq 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 TI-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 Wilcoxon rank-sum test and Fisher's exact test.

3.1.3 Subject Disposition

For Study 171 (T1DM), a total of 518 subjects were randomized: 174, 174, and 170 in the TI-Gen2, TI-MedTone, and IAsp groups, respectively. 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. According to the sponsor, the most frequently provided explanations for "Withdrawal by Subjects" were related to subjects' personal circumstances (work/family conflict/relocation) or unwillingness to comply with study requirements. 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.

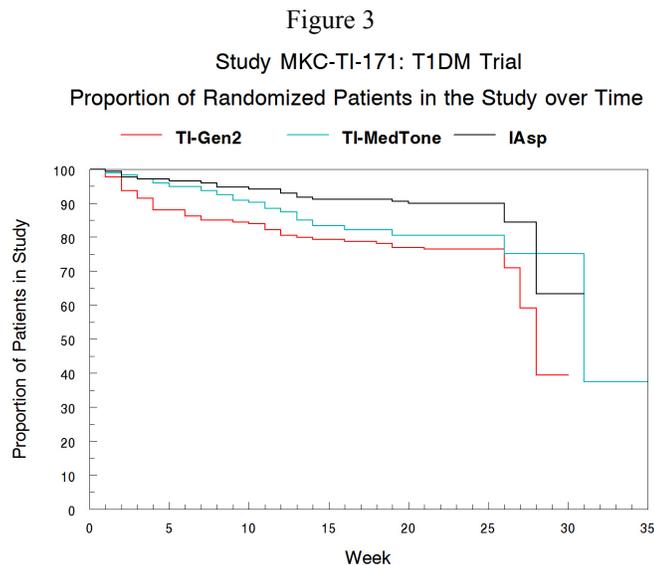


Table 1 – Study 171 (T1DM): Subject Disposition (extracted from sponsor’s table)

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: 177 and 176 in the TI-Gen2 and placebo groups, respectively. 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.

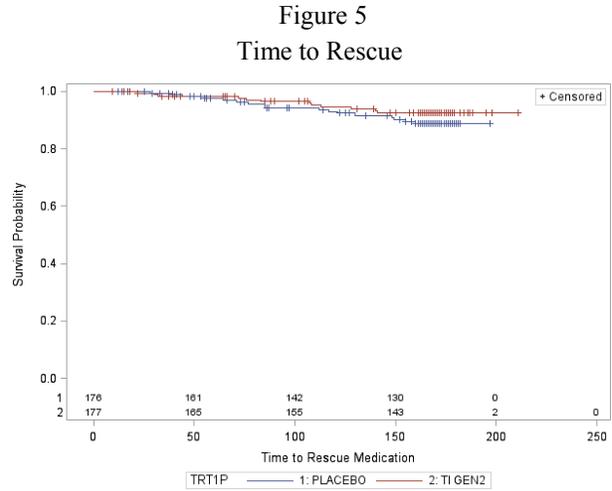
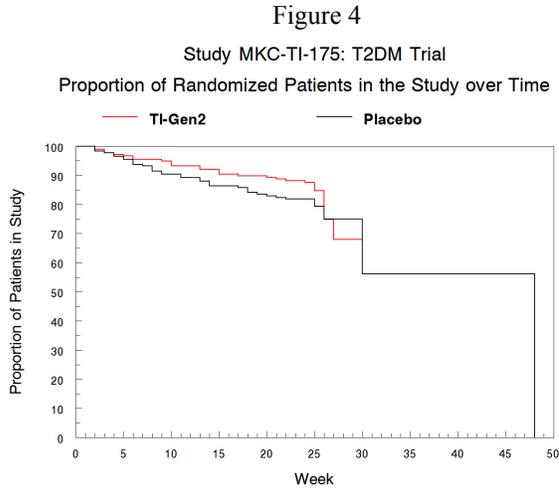


Table 2 – Study 175 (T2DM): Subject Disposition (extracted from sponsor's table)

Disposition	Subjects, n (%)		
	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

3.1.4 Demographic and Baseline Characteristics

For Study 171 (T1DM), the 3 treatment groups were similar with respect to demographic and baseline characteristics such as age, gender, race, ethnic, country, region, basal insulin type, duration of the disease (T1DM), baseline BMI, baseline HbA1c, and baseline FPG for the FAS population (Table 3). In this trial, approximately 95% of the randomized subjects were < 65 years old at entry and most of them were in their middle age (mean age = 39 years). Slightly more than half of the randomized subjects were females (55%). About 40% of the subjects were from the US sites. White constituted 96% of the randomized population. Mean BMI at entry was around 26 kg/m². Approximately 70% of the subjects in each group used insulin glargine as their basal insulin medication. The baseline HbA1c (at Week 0) ranged from 5.8% to 10.6% with mean around 8.0% in each group.

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

For Study 175 (T2DM), the 2 treatment groups were similar with respect to demographic and baseline characteristics such as age, gender, race, ethnic, country, region, OAD type, duration of the disease (T2DM), baseline BMI, baseline HbA1c, and baseline FPG for the FAS population regardless of rescue status (Table 4). In this trial, approximately 80% of the randomized subjects were < 65 years old at entry and most of them were in the 50 – 64 age range (mean age = 57 years). Slightly more than half of the randomized subjects were

females (56%). About 50% of the subjects were from the US sites. White constituted 87% of the randomized population, then Black/African American (11%). Mean BMI at entry was around 32 kg/m². Approximately 65% of the subjects in each group used metformin + sulfonylurea as their OAD therapy at entry and 23% of the subjects in each group took metformin only. The baseline HbA1c (at Week 0) ranged from 5.1% to 10.9% with mean around 8.0% in each group.

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

Demographic Characteristics	Category/Statistics	T1 Gen2		All (N=177)	Placebo		
		Not Rescued (N=165)	Rescued (N=12)		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	159	17	176
	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

3.1.5 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.

TYPE 1 DIABETES MELLITUS (T1DM) – Study 171

HbA1c (%). After 24 weeks of treatment, both TI-Gen2 and IAsp groups showed a mean reduction in HbA1c from baseline (-0.20% and -0.42%, respectively). The reduction in the TI-Gen2 group was clinically non-inferior to that in the IAsp group since the upper bound of the 95% CI of the treatment difference (TI-Gen2 minus IAsp) was +0.37%, less than +0.4% the pre-specified non-inferiority margin. However, the reduction in the TI-Gen2 group was inferior to that in the IAsp group since the lower bound of the 95% CI of the treatment difference (TI-Gen2 minus IAsp) was above 0%. In fact, the estimated mean reduction in the TI-Gen2 group was worse by 0.2% when compared with that in the IAsp group (Table 5).

Table 5 – Study 171 (T1DM): Efficacy Results for HbA1c (%)

Treatment Group (FAS Population)	Baseline Mean ± SD (N)	Week 24 Mean ± SD (N)	Change From Baseline		
			Mean ± SD (N)	LS Mean ± SE (N) ¹	
TI-Gen2	8.0 ± 0.8 (172)	7.8 ± 0.9 (131)	-0.23 ± 0.8 (131)	-0.20 ± 0.06 (131)	
TI-MedTone	8.0 ± 0.7 (172)	7.6 ± 0.8 (138)	-0.31 ± 0.8 (137)	-0.28 ± 0.06 (137)	
IAsp	7.9 ± 0.8 (167)	7.5 ± 0.9 (150)	-0.39 ± 0.7 (147)	-0.42 ± 0.06 (147)	
			Treatment Difference		
Treatment Comparison		LS Mean ± SE	95% CI	NI	SUP
TI-Gen2 vs. IAsp ¹		0.22 ± 0.07	(0.08, 0.37)	Yes	No
TI-Gen2 vs. IAsp ²		0.19 ± 0.09	(0.02, 0.36)	Yes	No

¹ Reviewer’s analysis using change from baseline in HbA1c as the dependent variable.
² Sponsor’s analysis using HbA1c as the dependent variable.
 Similar findings were observed when only TI-Gen2 and IAsp data were fit in the model.

Figure 6 below shows the mean HbA1c profile over time based on the observed data. In all 3 treatment groups, the mean HbA1c was slightly decreased from baseline to Week 12 during the prandial and basal insulin titration period, and then was sustained for the rest of the trial.

As seen in Figure 7, based on the available data at Week 24, approximately 55%, 67%, and 73% of the TI-Gen2, TI-MedTone, and IAsp treated patients, respectively, showed an improved HbA1c level (i.e., change < 0) after 24-week of treatment. In most part of the curves, the TI-Gen2 group consistently showed a smaller percentage of patients reaching any level of the change data when compared with the IAsp group.

Specifically, there was a significantly smaller percentage of responders defined as patients with Week 24 HbA1c value ≤ 7.0% in the TI-Gen2 group (13.8%) than in the IAsp group

(27.1%). In fact, all other responder criteria defined in Table 6 below showed a numerically smaller rate in the TI-Gen2 group than in the IAsp group.

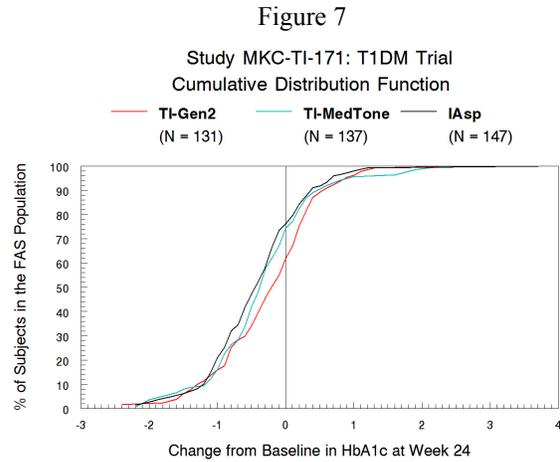
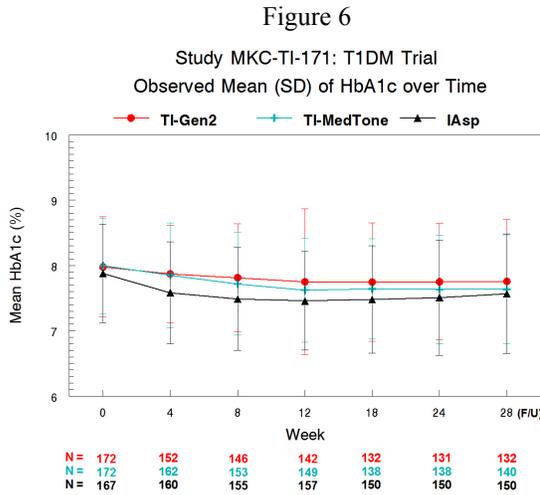
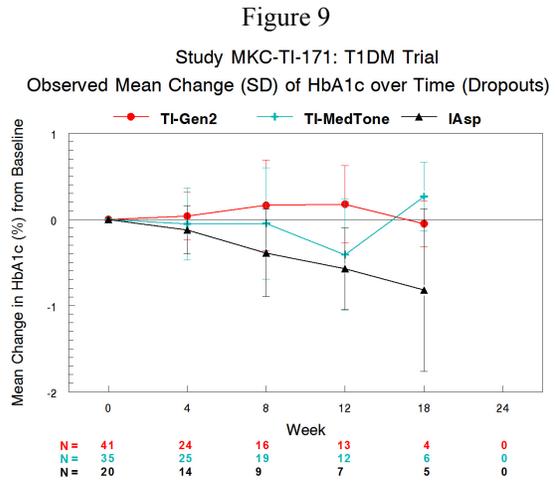
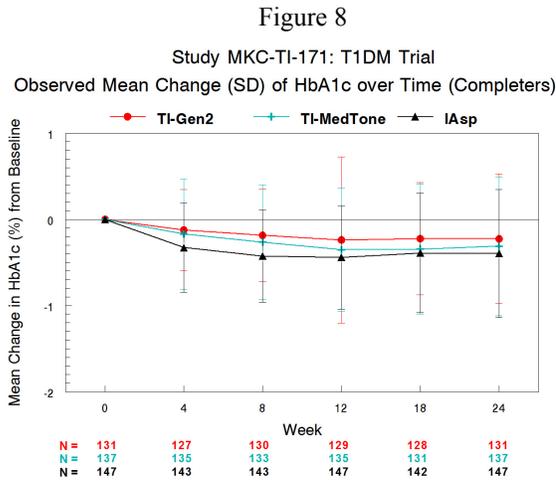


Table 6 – Study 171 (T1DM): Responder Rate for HbA1c at Week 24

FAS Population	TI-Gen2	Insulin Aspart	Difference in Proportion	Asymptotic 95% CI
HbA1c ≤ 6.5% at Week 24	10/174 (5.7%)	19/170 (11.2%)	-5.4%	(-11.3%, 0.4%)
HbA1c ≤ 7.0% at Week 24	24/174 (13.8%)	46/170 (27.1%)	-13.3%	(-21.7%, -4.9%)
HbA1c ≤ 7.0% at Week 24 w/o severe hypoglycemia	19/174 (10.9%)	33/170 (19.4%)	-8.5%	(-16.0%, -1.0%)
HbA1c ≤ 7.0% at Week 24 w/o severe hypoglycemia in last 12 weeks	20/174 (11.5%)	38/170 (22.4%)	-10.9%	(-18.7%, -3.0%)
Subjects with missing data at Week 24 were treated as non-responders.				

Sensitivity Analysis. My analysis using the completers cohort (Figure 8) had similar 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 9), 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.



In response to our request, the sponsor conducted the following 4 multiple imputation (MI) analyses (see Appendix I for details).

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 7, Analysis 2 – 4 had similar non-inferiority findings to the primary analysis results, while Analysis 1 showed an inferiority of TI-Gen2 to IAsp in lowering HbA1c since the upper bound of the 95% CI of the treatment difference was 0.48%, > 0.4% the pre-specific non-inferiority margin. This was foreseeable since the primary analysis result was already at the borderline of the margin and this imputation method (treating all missingness not at random) was a conservative scenario.

Table 7 – 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

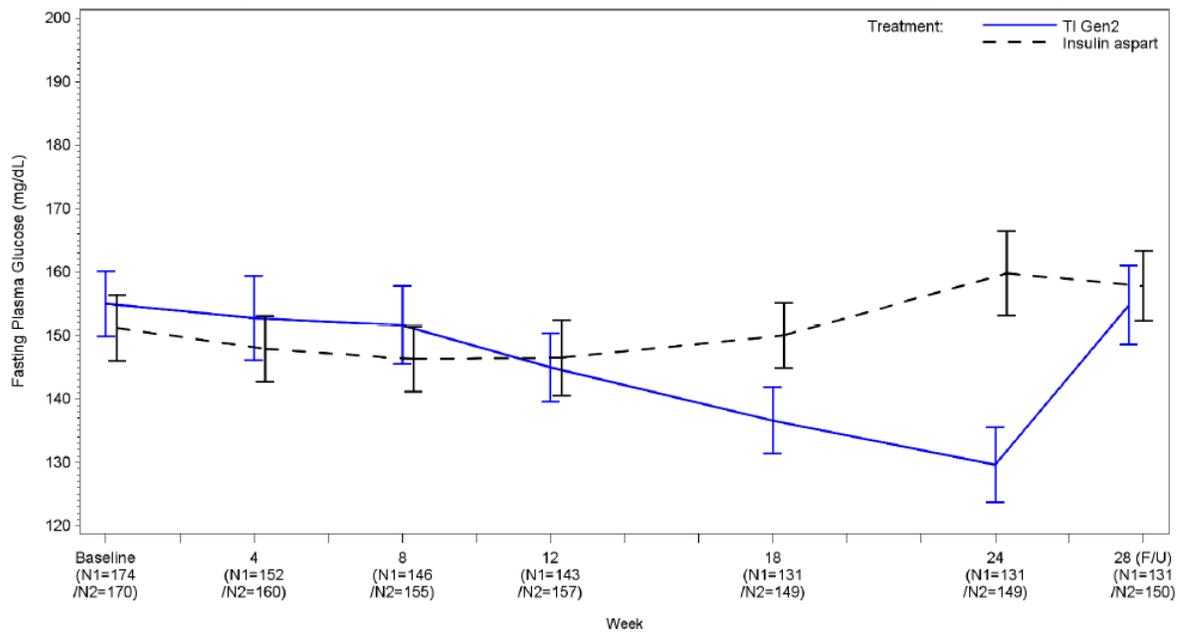
FPG (mg/dL). As Figure 10 shows, during the 12-week titration period, there was little change in FPG in both TI-Gen2 and IAsp groups. However, after Week 12, the mean FPG was gradually decreased through Week 24 in the TI-Gen2 group, while it was gradually increased in the IAsp group. The mean reduction 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, Table 8).

Table 8 – Study 171 (T1DM): Statistical Results for FPG (mg/dL)

FAS Population	LS Mean Change from baseline ± SE (N)		Treatment Difference	95% CI
	TI-Gen2	IAsp		
Reviewer’s analysis ¹	-19.2 ± 6.4 (131)	12.6 ± 6.1 (149)	-31.7 ± 8.4	(-48.1, -15.3)
Sponsor’s analysis ²	-25.3 ± 7.6 (131)	10.2 ± 7.4 (149)	-35.4 ± 10.6	(-56.3, -14.6)

¹ Reviewer’s analysis using change from baseline in FPG as the dependent variable.
² Sponsor’s analysis using FPG as the dependent variable.

Figure 10 – Study 171 (T1DM): Observed Mean (SE) of FPG over Time (sponsor’s figure)



N1=TI Gen2, N2=insulin aspart; FAS = full analysis set

Body Weight (kg). As shown in Table 9, 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.

Table 9 – Study 171 (T1DM): Statistical Results for Body Weight (kg)

FAS Population	LS Mean Change from baseline ± SE (N)		Treatment Difference	95% CI
	TI-Gen2	IAsp		
Reviewer’s analysis ¹	-0.46 ± 0.43 (132)	0.94 ± 0.42 (153)	-1.40 ± 0.50	(-2.38, -0.43)
Sponsor’s analysis ²	-0.39 ± 0.44 (132)	0.93 ± 0.44 (153)	-1.32 ± 0.51	(-2.33, -0.31)

¹ Reviewer’s analysis using ANCOVA with terms for baseline weight, treatment, region, and basal insulin type.

² Sponsor’s analysis using ANCOVA with terms for baseline weight, treatment, region, basal insulin type, and change from baseline in HbA1c at Week 24.

TYPE 2 DIABETES MELLITUS (T2DM) – Study 175

HbA1c. After 24 weeks of treatment, both TI-Gen2 and placebo groups showed a mean reduction in HbA1c from baseline (-0.84% and -0.41%, respectively). The reduction in the TI-Gen2 group was clinically superior to that in the placebo group since the upper bound of the 95% CI of the treatment difference (TI-Gen2 minus placebo) was below 0%. The

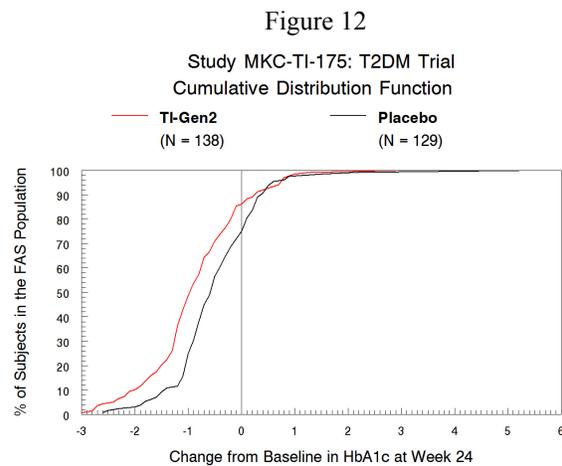
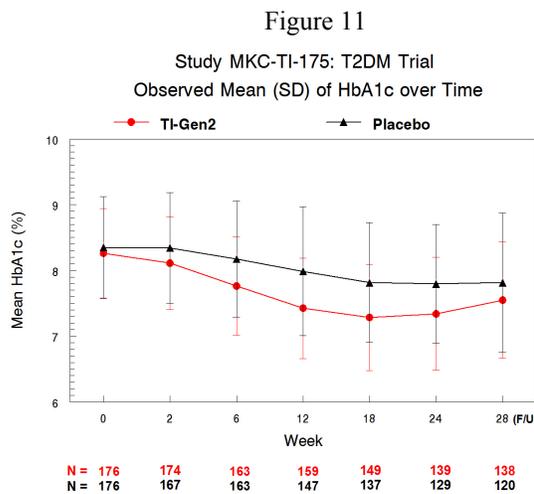
estimated mean reduction in the TI-Gen2 group was statistically significantly greater than that in the placebo group by 0.4% (Table 10).

Table 10 – Study 175 (T2DM): Efficacy Results for HbA1c (%)

Treatment Group (FAS Population)	Baseline Mean ± SD (N)	Week 24 Mean ± SD (N)	Change From Baseline	
			Mean ± SD (N)	LS Mean ± SE (N) ¹
TI-Gen2	8.3 ± 0.7 (176)	7.3 ± 0.9 (139)	-0.84 ± 0.9 (138)	-0.84 ± 0.07 (138)
Placebo	8.3 ± 0.8 (176)	7.8 ± 0.9 (129)	-0.46 ± 0.9 (129)	-0.41 ± 0.07 (129)
Treatment Comparison	Treatment Difference			
	LS Mean ± SE	95% CI	p-value	SUP
TI-Gen2 vs. Placebo ¹	-0.42 ± 0.08	(-0.58, -0.27)	< 0.0001	Yes
TI-Gen2 vs. Placebo ²	-0.40 ± 0.09	(-0.57, -0.23)	< 0.0001	Yes

¹ Reviewer’s analysis using change from baseline in HbA1c as the dependent variable.
² Sponsor’s analysis using HbA1c as the dependent variable.
 Data collected after initiation of rescue therapy were excluded from the analysis.

Figure 11 below shows the mean HbA1c profile over time based on the observed non-rescued data. In both treatment groups, the mean HbA1c was decreased noticeably (especially for the TI-Gen2 group) from baseline to Week 12 during the prandial titration period, and then was sustained for the rest of the trial.



As seen in Figure 12 above, based on the available non-rescued data at Week 24, approximately 86% and 72% of the TI-Gen2 and placebo treated patients, respectively, showed an improved HbA1c level (i.e., change < 0) after 24-week of treatment. In most part of the curves, the TI-Gen2 group consistently showed a greater percentage of patients reaching any level of the change data when compared with the placebo group.

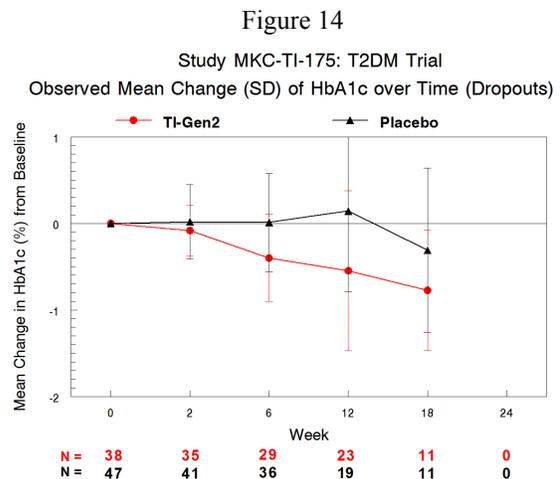
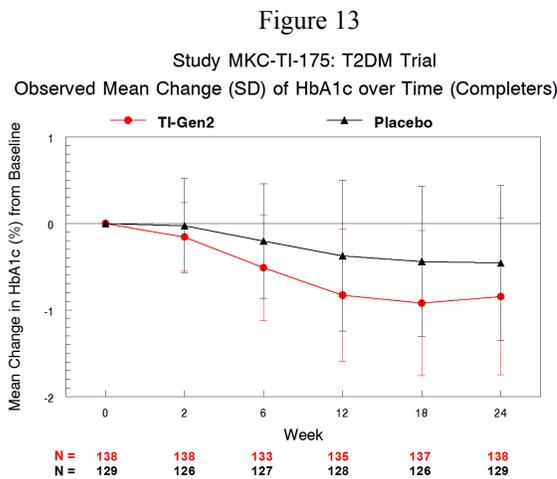
Specifically, significantly greater percentages of responders defined as patients with Week 24 HbA1c value $\leq 6.5\%$ or $\leq 7.0\%$ were seen in the TI-Gen2 group than in the placebo group, as shown in Table 11 below.

Table 11 – Study 175 (T2DM): Responder Rate for HbA1c at Week 24

FAS Population	TI-Gen2	Placebo	Difference in Proportion	Asymptotic 95% CI
HbA1c $\leq 6.5\%$ at Week 24	24/177 (13.6%)	6/176 (3.4%)	10.2%	(4.4%, 15.9%)
HbA1c $\leq 7.0\%$ at Week 24	57/177 (32.2%)	27/176 (15.3%)	16.9%	(8.2%, 25.6%)

Non-rescued patients with missing data at Week 24 and rescued patients were treated as non-responders.

Sensitivity Analysis w/o Rescued Data Included. My analysis using the completers cohort (Figure 13) had similar 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 14). 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 -0.4% shown in the primary analysis.



Sensitivity Analysis with Rescued Data Included. 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 analyzed the data using the primary analysis model, similar results to the primary analysis were observed (treatment difference = -0.41%, 95% CI = (-0.56%, -0.25%)).

In response to our request, the sponsor conducted multiple imputation (MI) analyses on the following two sets of data (see Appendix I for details). As shown in Table 12, both analyses had similar superiority findings to the primary analysis results.

- 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 12 – 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

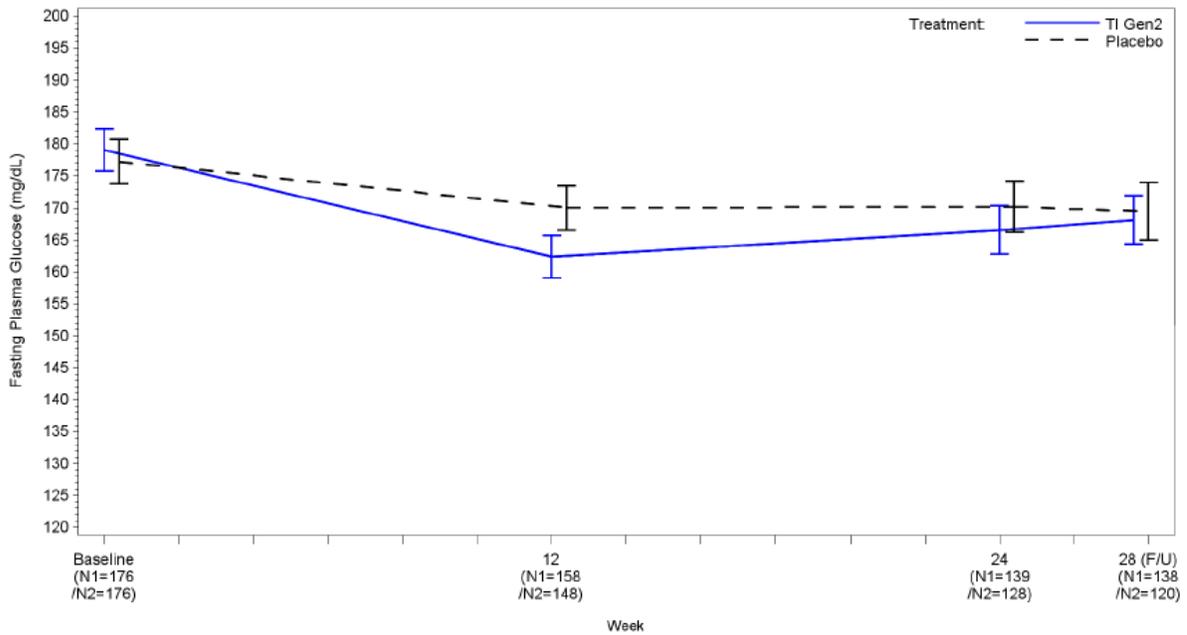
FPG (mg/dL). As Figure 15 shows, during the 12-week titration period, there was more decrease in FPG in the TI-Gen2 group than in the placebo group. After Week 12, the mean FPG was slightly increased in the TI-Gen2 group, while it was sustained in the placebo group. Nevertheless, there was a numerically 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), Table 13).

Table 13 – Study 175 (T2DM): Statistical Results for FPG (mg/dL)

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

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

Figure 15 – Study 175 (T2DM): Observed Mean (SE) of FPG over Time (sponsor’s figure)



Note(s): N1 = TI Gen2, N2 = Placebo; Error bar denotes +/- standard errors
 Fasting Plasma Glucose collected after receiving rescue therapy are excluded.

Body Weight (kg). As shown in Table 14, 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.

Table 14 – Study 175 (T2DM): Statistical Results for Body Weight (kg)

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

¹ Reviewer’s analysis using ANCOVA with terms for baseline weight, treatment, region, and OAD type.

² Sponsor’s analysis using ANCOVA with terms for baseline weight, treatment, region, OAD type, and change from baseline in HbA1c at Week 24.

Data collected after initiation of rescue therapy were included in the analysis. Similar findings were observed when data collected after initiation of rescue therapy were excluded from the analysis.

3.2 Evaluation of Safety

My statistical analysis results of hypoglycemic episodes and insulin dose for each trial are summarized briefly in this section. See Dr. Lisa Yanoff’s medical review for a complete safety evaluation for this NDA submission.

TYPE 1 DIABETES MELLITUS (T1DM) – Study 171

Hypoglycemic Episodes. 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). The percentage of patients with at least 1 severe hypoglycemic episode during the randomized treatment period was statistically significantly lower in the TI-Gen2 group (18.4%) than in the IAsp group (29.2%). Although not statistically significant, the event rate per subject-month in the TI-Gen2 group (0.08) was numerically lower than that in the IAsp group (0.14). The number of severe events per subject and the event rate per year per subject were also significantly lower in the TI-Gen2 group than in the IAsp group ($p = 0.018$ and 0.024 , respectively, based on the Wilcoxon rank-sum test).

As shown in Table 15 below, regardless of the statistical significance, numerically lower incidence rate and event rate per subject-month for mild/moderate and all hypoglycemic episodes were all observed in the TI-Gen2 group when compared with the IAsp group.

Table 15 – Study 171 (T1DM): Hypoglycemic Episodes

Safety Population		Treatment Difference		Nominal	
Type of Hypoglycemia		TI-Gen2	IAsp	Asymptotic 95% CI	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.

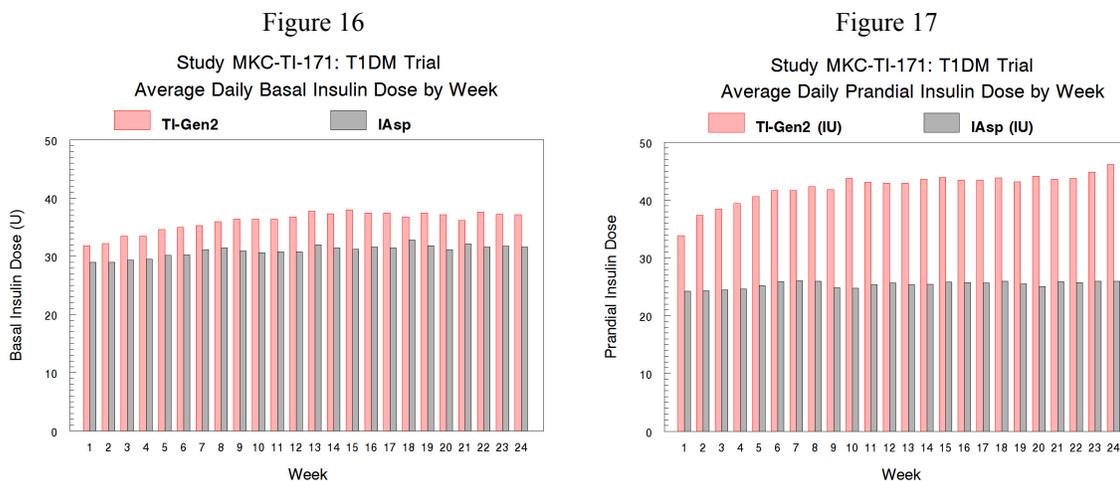
P-value for event rate was obtained using a negative binomial regression analysis with terms for region, basal insulin type, treatment, and duration of treatment exposure (sponsor's analysis).

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). The overall mean daily basal insulin doses for the TI-Gen2 and IAsp groups were 35.1 ± 17.9 (U) and 30.5 ± 19.5 (U), respectively. The overall mean daily prandial insulin doses for the TI-Gen2 and IAsp groups were 102.7 ± 51.8 (U) and 25.5 ± 12.6 (IU), respectively. 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 \approx 1 IU of IAsp) was applied (see the sponsor's CSR page 46 conversion table).

As depicted in Figures 16 and 17 below, both the basal and prandial mean daily insulin doses were consistently higher in the TI-Gen2 group than in the IAsp group during the 24 weeks of treatment.



TYPE 2 DIABETES MELLITUS (T2DM) – Study 175

Hypoglycemic Episodes. 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], respectively). The percentage of patients with at least 1 severe hypoglycemic episode during the randomized treatment period before rescue was numerically higher in the TI-Gen2 group (5.1%) than in the placebo group (1.7%), but the difference was not statistically significant. The event rate per subject-month in the TI-Gen2 group (0.024) was also not statistically significantly different from that in the placebo group (0.006). Similar findings were observed when the number of severe events per subject and the event rate per year per subject were analyzed ($p = 0.08$ for both analyses based on the Wilcoxon rank-sum test).

As shown in Table 16 below, the incidence rate and event rate per subject-month for mild/moderate and all hypoglycemic episodes were all statistically significantly higher in the TI-Gen2 group when compared with the placebo group.

Similar findings for severe, all, and mild/moderate hypoglycemic episodes were observed when data after initiation of rescue therapy were included in the analyses.

Table 16 – Study 175 (T2DM): Hypoglycemic Episodes

Safety Population				Treatment Difference	Nominal
Type of Hypoglycemia		TI-Gen2	Placebo	Asymptotic 95% CI	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.

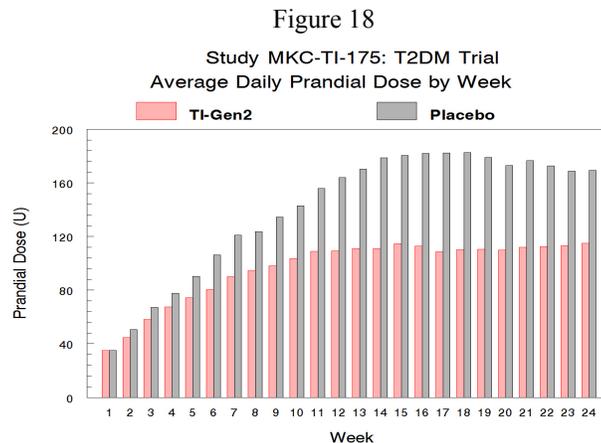
P-value for incidence rate was based on Fisher’s Exact test.

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.

Insulin Dose (U). The overall mean daily prandial doses before rescue for the TI-Gen2 and placebo groups were 92.3 ± 48.8 (U) and 128.0 ± 68.7 (U), respectively. Specifically, in the TI-Gen2 group, the mean daily dose was increased from 34.9 (U) at Week 1 to 115.0 (U) at Week 24; in the placebo group, the mean daily dose was increased from 35.1 (U) at Week 1 to 169.4 (U) at Week 24.

Figure 18 below shows that there was a sharp increase in prandial dose in both treatment groups during the 12-week titration period and then they were stable for the rest of the trial. The mean daily doses in the placebo group were all higher than those in the TI-Gen2 group.



4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

For Study 171 (T1DM), treatment effects on mean change from baseline in HbA1c at Week 24 between TI-Gen2 and IAsp were consistent across the subgroups defined by age (< 65 years or \geq 65 years) and race, but not gender since the treatment-by-sex interaction p-value was 0.01 based on the available data at Week 24. Therefore, the 2 sexes were evaluated separately. As shown in Table 17, 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.

Table 17 – Study 171 (T1DM): Efficacy Results for HbA1c (%) by Sex

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

For Study 175 (T2DM), treatment effects on mean change from baseline in HbA1c at Week 24 between TI-Gen2 and placebo were consistent across the subgroups defined by age (< 65 years or \geq 65 years), gender, and race, as no significant treatment-by-subgroup interactions were observed (all $p > 0.10$).

4.2 Other Special/Subgroup Populations

For Study 171 (T1DM), treatment effects on mean change from baseline in HbA1c at Week 24 between TI-Gen2 and IAsp were consistent across the subgroups defined by region, country, ethnic, basal insulin type, and baseline HbA1c (\leq 8.0% or $>$ 8.0% as defined by the sponsor), as no significant treatment-by-subgroup interactions were observed (all $p > 0.10$).

Since approximately 70% of the randomized patients in each group used insulin glargine as their basal insulin medication, Table 18 below summarizes the efficacy of TI-Gen2 vs. IAsp in this subgroup of T1DM patients. It was found that the results were similar to the primary analysis results based on the overall population.

Table 18 – Study 171 (T1DM): Efficacy Results for HbA1c (%) by Basal Insulin Type

FAS	Change from Baseline at Week 24 : LS Mean ± SE (N)		Treatment Difference	
	TI-Gen2	IAsp	LS Mean ± SE	95% CI
Basal Insulin				
Insulin Glargine	-0.18 ± 0.09 (87)	-0.35 ± 0.09 (107)	0.17 ± 0.11	(-0.04, 0.37)
Others	-0.20 ± 0.11 (44)	-0.52 ± 0.12 (40)	0.31 ± 0.14	(0.04, 0.59)

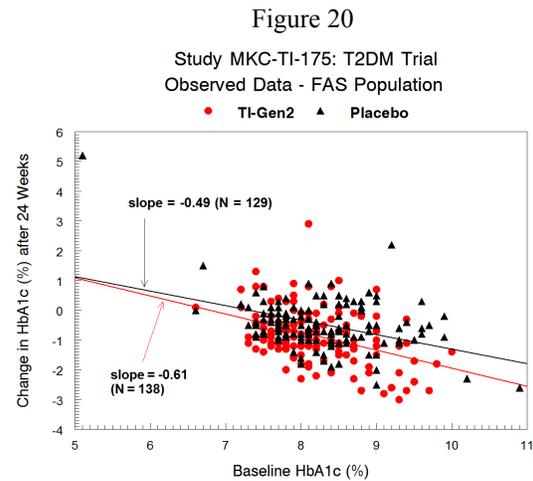
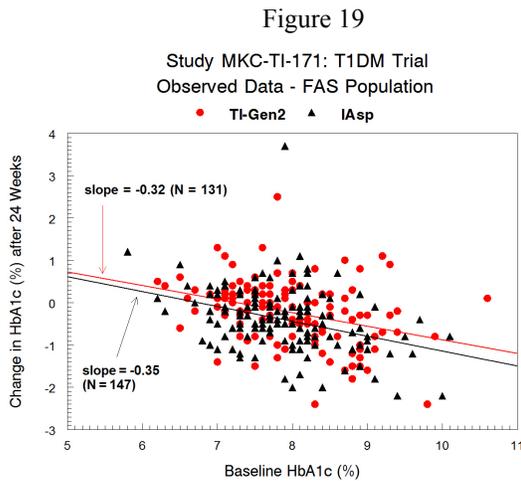
The results were obtained using ANCOVA on subjects who had a baseline and Week 24 HbA1c values. Similar findings were observed when MMRM approach was employed.

Subgroup analyses for baseline HbA1c ($\leq 8.0\%$ or $> 8.0\%$) were conducted by the sponsor. As Figure 19 depicts, the higher the baseline HbA1c, the greater the mean reduction from baseline to 24 weeks was observed in general. The phenomenon was consistently seen for each treatment group, as shown in Table 19 below. Also, the treatment difference within each subgroup was similar to that based on the overall population.

Table 19 – Study 171 (T1DM): Efficacy Results for HbA1c (%) by Baseline HbA1c Subgroup

FAS	Change from Baseline at Week 24 : LS Mean ± SE (N)		Treatment Difference	
	TI-Gen2	IAsp	LS Mean ± SE	95% CI
Baseline HbA1c				
$\leq 8.0\%$	-0.02 ± 0.10 (74)	-0.26 ± 0.10 (90)	0.24 ± 0.11	(0.02, 0.45)
$> 8.0\%$	-0.44 ± 0.12 (57)	-0.62 ± 0.13 (57)	0.18 ± 0.14	(-0.10, 0.45)

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.



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

Since approximately 65% of the randomized patients in each group used metformin + sulfonylurea as their OAD therapy at entry, Table 20 below summarizes the efficacy of TI-Gen2 vs. placebo in this subgroup of T2DM patients. It was found that the results were similar to the primary analysis results based on the overall population.

Table 20 – Study 175 (T2DM): Efficacy Results for HbA1c (%) by OAD type

FAS OADs	Change from Baseline at Week 24 : LS Mean ± SE (N)		Treatment Difference	
	TI-Gen2	Placebo	LS Mean ± SE	95% CI
Metformin + Sulfonylurea	-0.97 ± 0.10 (91)	-0.53 ± 0.10 (88)	-0.44 ± 0.13	(-0.70, -0.19)
Metformin only	-0.90 ± 0.19 (31)	-0.62 ± 0.21 (29)	-0.28 ± 0.20	(-0.69, 0.12)
Other	-0.90 ± 0.21 (16)	-0.36 ± 0.21 (12)	-0.55 ± 0.27	(-1.10, 0.01)

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

Subgroup analyses for baseline HbA1c ($\leq 8.0\%$ or $> 8.0\%$) were conducted by the sponsor. As Figure 20 depicts, the higher the baseline HbA1c, the greater the mean reduction from baseline to 24 weeks was observed in general. The phenomenon was consistently seen for each treatment group, as shown in Table 21 below. Also, the treatment difference within each subgroup was similar to that based on the overall population.

Table 21 – Study 175 (T2DM): Efficacy Results for HbA1c (%) by Baseline HbA1c Subgroup

FAS Baseline HbA1c	Change from Baseline at Week 24 : LS Mean ± SE (N)		Treatment Difference	
	TI-Gen2	Placebo	LS Mean ± SE	95% CI
$\leq 8.0\%$	-0.72 ± 0.12 (64)	-0.42 ± 0.11 (55)	-0.30 ± 0.12	(-0.54, -0.05)
$> 8.0\%$	-1.04 ± 0.13 (74)	-0.54 ± 0.14 (74)	-0.50 ± 0.15	(-0.79, -0.21)

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

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Since the study design (rescue therapy used in T2DM, but not in T1DM), population, comparator, background medication, etc., were different between the two confirmatory safety and efficacy trials, the data were not combined to obtain overall treatment estimate. The collective evidence is summarized here for each study.

Type 1 Diabetes Mellitus

In Study 171, 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 22. 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 22 – 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 (see Figure 8 above) 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 (see Figure 9 above), 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.

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 (see Appendix I for details).

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 7 above, 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.

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 \leq 7.0% at Week 24 when compared with the IAsp group (27%).

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 \geq 65 years), race, region, country, ethnic, basal insulin type, and baseline HbA1c (\leq 8.0% or > 8.0% as defined by the sponsor), as no significant treatment-by-subgroup interactions were observed (all $p > 0.10$). 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 22, 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 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).

The mean reduction in FPG after 24 weeks of treatment 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). At Week 24, the mean change from baseline in body weight was -0.5 kg in the TI-Gen2 group and +0.9 kg in the IAsp group.

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 (see Table 15 above).

In this T1DM trial, 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 16 and 17 above).

Type 2 Diabetes Mellitus

In Study 175, 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 23. 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 23 – 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 (see Figure 13 above) 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 (see Figure 14 above). 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 -0.4% shown in the primary analysis.

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 (see Appendix I for details) and both of them consistently demonstrated superiority of TI-Gen2 over placebo in HbA1c lowering (see Table 12 above).

- 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)

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 \leq 7.0% at Week 24 when compared with the placebo group (15%).

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 \geq 65 years), gender, race, region, country, ethnic, OAD type, and baseline HbA1c (\leq 8.0% or > 8.0% as defined by the sponsor), as no significant treatment-by-subgroup interactions were observed (all $p > 0.10$).

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)). 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).

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 (see Table 16 above).

In this T2DM trial, 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 18 above). 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.

5.2 Conclusions and Recommendations

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.

5.3 Labeling Comments

In Section 14 of the proposed labeling, the sponsor included the results from Study 171 (T1DM), Study 175 (T2DM),

(b) (4)

(b) (4). Therefore, I think (b) (4) should not be included in the efficacy section of the labeling.

6. APPENDIX I

Sponsor's multiple imputation analyses methods are copied below per how they appear in the sponsor's submission.

Study MKC-TI-171

- Only TI Gen2 and Insulin aspart subjects were included in this analysis. TI Medtone subjects, which were not included in MKC-TI-171 for efficacy evaluation, were excluded from this MI analysis. This applies to all the analyses presented in this response for MKC-TI-171.
- For subjects who discontinued before the first scheduled post-baseline visit at week 4, their last on treatment post-baseline measurements were utilized as week 4 measurements. This applies to all the analyses discussed in this response for MKC-TI-171.

Analysis 1: Multiple imputation under null hypothesis with NI margin adjustment

- In SAS PROC MI, the MCMC method was used to impute the missing data by treatment arms and by basal insulin stratum (please see further discussion in section 2.1.1.1). The missing data were imputed in the order of study scheduled visits, which are baseline, week 4, week 8, week 12, week 18 and week 24. A total of 100 imputation data sets were produced with the seed number 171.
- After imputation was obtained as described above, 0.4% was added to the week 24 imputed HbA1c values for subjects randomized to TI Gen2 treatment arm only. This is based on the null hypothesis that TI Gen2 is inferior to Insulin aspart by 0.4% in HbA1c reduction at week 24 and the assumption that all subjects discontinued from TI Gen2 arm are MNAR in terms of the primary efficacy variable.

Once all missing values are filled, the complete data at week 24 from each of the 100 imputed data sets were used to estimate the treatment differences in change from baseline via standard ANCOVA method with predictor variables of baseline HbA1c value, treatment, basal insulin strata and region. The SAS PROC MIANALYZE was then applied to combine these results to generate the LSMeans, standard error and 95% CI of the estimated treatment difference at week 24 as well as the LSMeans and standard errors in change from baseline for each treatment arm.

Analysis 2: Pattern imputation based on reasons of discontinuation with NI margin adjustment

In this method, we adjudicated the detailed reasons of discontinuation and AE profiles for every subject who discontinued early from TI Gen2 arm. Discontinued subjects were divided into two groups: subjects who discontinued due to efficacy concern or due to AE(s) that are related to efficacy were adjudicated as MNAR; the rest of discontinued subjects were

adjudicated to be MAR.

Similar multiple imputation described in section 2.1.1 was conducted. Instead of adding 0.4% HbA1c on every discontinued subject in TI Gen2 arm, the non-inferiority margin was only added to those subjects who were adjudicated with MNAR discontinuation in TI Gen2.

Analysis 3: Multiple imputation using regression method

In this method, the average post-meal glucose during the four weeks before each visit or discontinuation were calculated and used as one of the regression predictors to impute the missing values. Post-meal glucose is considered the measurement that directly reflects glucose control performed by prandial insulin, which are the treatments being evaluated in this document. There is also a demonstrated strong correlation between post-meal glucose and HbA1c with Pearson correlation coefficient of 0.431 ($p < 0.0001$).

The missing data was first partially imputed with MCMC method and impute=monotone option by treatment arms and basal insulin strata. This step is to fill up the intermediate missing values of average post-meal glucose and HbA1c in the order of at baseline, Week 4, Week 8, Week 12, Week 18 and Week 24. The missing data in both treatment arms were then imputed step by step using Markov Chain fashion in the order of study scheduled visit via regression model. The imputation regression model includes predictor variables of treatment arm, basal insulin strata, average 4-weeks post-meal glucose, baseline HbA1c values and HbA1c values from the immediate previous visit.

Once all missing values were filled, the standard ANCOVA analysis and SAS PROC MIANALYZE were applied to obtain the statistical inferences for the primary efficacy variable.

Analysis 4: Multiple imputation with missing at random assumption

Similar multiple imputation described in section 2.1.1 and 2.1.2 was conducted. However, all discontinuations were considered MAR and non-inferiority margin was not added to any TI Gen2 subject.

MKC-TI-175

The imputation was performed under the null hypothesis that there is no difference between TI Gen2 and Placebo. The MCMC method was applied to impute the missing data for both arms combined by randomization stratification factors of region and oral medication (OAD) groups. The missing HbA1c data were imputed in the order of study scheduled visits, which are baseline, week 2, week 6, week 12, week 18 and week 24. The seed of 175 was used and 100 imputation data sets were produced.

After imputation, the complete data at week 24 from each of the 100 imputed data sets were used to carry out the statistical inference for the treatment differences in change from baseline via standard ANCOVA method with predictor variables of baseline HbA1c, treatment, OAD groups and region. The SAS PROC MIANALYZE was then used to combine these results to generate the LSMean, standard error, 95% CI and p-value of the estimated treatment difference at week 24 as well as the LSMeans and standard errors in change from baseline for each treatment arm.

The above described method was applied to two sets of data: (1) all HbA1c measurements collected before initiation of rescue therapy, with post-rescue measurements set to missing; (2) all HbA1c measurements including those collected after initiation of rescue therapy. For the analysis (2), rescue status (Yes, No) was added as an additional covariate to the ANCOVA analysis to indicate if subject received rescue therapy or not during the study.

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/s/

CYNTHIA Y LIU
03/18/2014

MARK D ROTHMANN
03/18/2014
I concur

THOMAS J PERMUTT
03/19/2014
I concur



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-472
Drug Name: Technosphere Insulin (Afrezza) inhalation Powder
Indication(s): Type 1 and type 2 diabetes
Applicant: Mannkind Corp
Date(s): Complete response submitted June 29, 2010
Review Priority: Standard (6-month review cycle)

Biometrics Division: Division of Biometrics 2 (HFD-715)
Statistical Reviewer: J. Todd Sahlroot, Ph.D., Team Leader and Deputy Director

Medical Division: Division of Metabolic and Endocrine Products (HFD-510)
Clinical Team: Lisa Yanoff, M.D., primary reviewer
Hylton Joffe, M.D., Diabetes clinical lead
Project Manager: Rachel Hartford

Keywords: NDA submission, clinical studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Study 117 achieved its primary goal of demonstrating the non-inferiority (NI) of Afrezza to the active control, Humalog, on the primary efficacy endpoint, HbA1c change from baseline, in patients receiving Lantus as basal insulin (Table 1). The mean treatment difference was -0.04% with a 95% confidence interval of (-0.25%, +0.18%) satisfying the prospectively-defined NI margin of +0.4%. Afrezza was also NI to Humalog in several sensitivity analyses.

Despite the apparent strong statistical results, there were a number of shortcomings in the design and execution that, in my opinion, render the results as less than conclusive. Study design issues of concern were the short duration of the trial (16 weeks) and the low baseline HbA1c (mean 7.7%). The latter in particular may have limited the ability of the trial to show changes in HbA1c from baseline and, therefore, differences between treatment groups. Regarding execution, the trial was stopped early at half the planned sample size ostensibly to allow development of the new Gen2 inhaler. The sponsor's analysis constituted an unplanned, interim analysis of data from an open-label trial. In general, results from unplanned analyses of interim data, even when the data seem compelling, should be considered with utmost caution.

In summary, the sponsor has presented interim data from an unplanned analysis of an open-label active-control trial, with design limitations, *that was stopped early*. As such, these data may not be of sufficient quality to remedy the inadequate statistical results in type 1 patients in the original submission. Please see Section 1.3 (Statistical Issues and Findings) for further details.

Table 1. Study 117¹ HbA1c change from baseline to Week 16 (ITT- LOCF)

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

1 Medtone inhaler device was used

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

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

1.2 Brief Overview of Clinical Studies

Study 117 was a randomized, multi-center, international, open-label 16-week trial of Technosphere Insulin (Afrezza) inhalation Powder versus Insulin Lispro (Humalog) SC injection in the treatment of patients with type 1 diabetes. The sponsor, Mannkind Corporation, submitted the study in a Complete Response (CR) to the FDA CR letter dated March 12, 2010. Cynthia Liu, Division of Biometrics 2, reviewed the studies in the original submission. Her

review stated “Since there was only 1 confirmatory study submitted for the indication of type 1 diabetes mellitus, making a solid conclusion regarding efficacy for this type of diabetes mellitus is problematic.” Study 117 used the Medtone inhaler device which was subsequently replaced in the sponsor’s development program by the Gen2 inhaler. The primary analysis was conducted on 126 patients, about 50% of the protocol-specified sample size of 260. According to the sponsor, the trial was ended early because the sponsor stopped development of the Medtone inhaler in favor of the new Gen2 inhaler. Study enrollment was stopped in September 2009. All enrolled subjects were allowed the opportunity to complete the trial.

1.3 Statistical Issues and Findings

Study 117 on its face achieved the primary goal of demonstrating the NI of Afrezza to the active control, Humalog, on the primary efficacy endpoint, HbA1c change from baseline, in patients receiving Lantus as basal insulin (LOCF results in Table 1). Afrezza was also NI to Humalog in two sensitivity analyses, e.g., in completers and in a conservative analysis that imputed a null mean result for the group of 130 patients who were planned but not randomized (See Section 3.1: Evaluation of Efficacy).

There were a number of shortcomings in the design and execution of the trial that, in my opinion, render these apparently strong statistical results as less than conclusive. The design elements of concern were the short duration of the trial (16 weeks) and baseline HbA1c values which were low compared to historical diabetes trials (mean 7.7%). The low baseline HbA1c values in particular may have limited the ability of the trial to show changes in HbA1c from baseline and, therefore, differences between treatment groups.

There were no planned interim analyses. The trial was stopped early at half the planned sample size to allow, according to the sponsor, development of the new Gen2 inhaler. The sponsor calculated post-hoc (“observed”) power for the study ostensibly to show that the study was adequately powered even for the reduced sample size:

“The Sponsor then evaluated the data in a blinded fashion to determine if the sample size was adequate to analyze study” (Study Report, p. 47).

“Because the study was stopped early, the overall variability was assessed in a blinded manner on all available data as of 19 Mar 2010 [Reviewer note: this date is one week following the issuance of the FDA CR letter]. The standard deviation for the change from Baseline in HbA1c was 0.635%, approximately half the expected standard deviation. Based on this variability, the observed power of the study to achieve noninferiority with a 0.4% noninferiority margin was estimated at 90%.” (Study Report, p. 48)

By showing that the stopped trial was adequately powered, the sponsor seems to be implying that the observed result is not a “mistake”. But post-hoc power is not meaningful once a trial is stopped or completed. At that point, a trial either meets or fails to meet its primary objective. I view the statements above as rationalizations and nothing more.

The scope of Study 117 is very similar to phase-2 Study 101 in the original submission. That trial randomized 111 type 1 patients (also taking Lantus) to Afrezza or Insulin Aspart. Similar to Study 117, Study 101 was a substitution study. HbA1c was not the primary endpoint though it is

not clear why that would negatively impact the assessment of HbA1c in the trial. HbA1c was also evaluated over 16 weeks. (Note: The Screening HbA1c value (Week -4) in Study 101 was used as the baseline value so that HbA1c change from baseline to Week 12, the primary timepoint, represented a 16-week assessment). Study 101 was a phase 2 study. The statistical reviewer for the original submission considered Study 101 to be a secondary source of evidence concerning the efficacy of Afrezza due to limitations of study design. The same could be said of Study 117.

2. INTRODUCTION

2.1 Overview

The primary objective of Study 117 was to demonstrate that Afrezza inhalation powder in combination with Lantus was non-inferior to Humalog in combination with Lantus in effects on HbA1c. The NI margin for HbA1c was set at 0.4 percentage units (%), by protocol amendment. (The original margin was 0.5%). A margin of 0.4% is used consistently by the Division in diabetes trials with insulin controls and so is considered satisfactory for Trial 117. The study hypotheses were (let μ = true mean treatment difference in HbA1c change from baseline):

$$\begin{array}{l} \text{Null hypothesis: } \mu > 0.4\% \\ \text{versus} \\ \text{Alternative hypothesis: } \mu \leq 0.4\% \end{array}$$

All patients received Lantus (insulin glargine) as basal insulin during the trial. A 3-week run-in period was used to optimize Lantus titration. Doses were adjusted to achieve fasting blood glucose (FBG) levels ≤ 120 mg/dL. The Lantus dose could be adjusted beyond the run-in phase if necessary. Treatment goals for both groups were pre-prandial and bedtime blood glucose (BG) levels < 120 mg/dL, 2-hour PPG levels < 140 mg/dL and HbA1c $< 7.0\%$ or 6.5% . All patients used a fast- or intermediate-acting insulin before the trial and during the run-in. Forced treat-to-target algorithms were not employed. According to the sponsor, only suggestions for dose adjustments were recommended.

HbA1c was measured every 4 weeks. 130 patients per group gave the study greater than 95% power to rule out a 0.5% NI margin (original protocol) in HbA1c change from baseline assuming a SD of 1.2%.

The primary analysis population consisted of randomized patients who were treated and had HbA1c data following randomization. Treatment groups were compared statistically using contrasts from an ANCOVA with treatment and country as factors and baseline HbA1c as covariate. Statistical testing was performed at the 1-sided 2.5% significance level.

2.2 Data Sources

The final report and raw data were located in, respectively,

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\\cdsesub1\EVSPROD\NDA022472\0045\m5\datasets\mkc-ti-117\analysis\datasets\analysis_adev.xpt

3. STATISTICAL EVALUATION

3.1 Study 117 --- Evaluation of Efficacy

One hundred thirty (130) subjects were randomized in equal numbers to Afrezza and Humalog (Table 2). 126 of 130 randomized patients (97%) were included in the ITT-LOCF analysis. 112 patients (86%) completed the study. The dropout rate was higher in the Afrezza arm compared to Humalog (20% vs 8%). Patients taking Afrezza who dropped did so for reasons related mostly to adverse events and withdrawn consent.

Table 2. Patient disposition

	Afrezza	Humalog	Total
Pts randomized	65 (100%)	65 (100%)	130 (100%)
Exposed	65 (100%)	65 (100%)	130 (100%)
ITT population	61 (94%)	65 (100%)	126 (97%)
Completed	52 (80%)	60 (92%)	112 (86%)

Most patients were Caucasian (89%) and male (56%). The mean age was 39 years. The mean duration of diabetes was 17 years in this type 1 population.

Table 3 shows that test drug exposure was comparable between groups.

Table 3. Test drug exposure

Endpoint	Measure	Afrezza	Humalog
Exposure time (wks)	N	65	65
	Mean (SD)	15.0 (4.3)	17.2 (2.6)
	Median	16.1	16.3
	Min, max	1.0, 20.4	7.1, 22.6
Category (wks)	0-4	4 (6%)	0
	>4-8	2 (3%)	1 (1%)
	>8-12	3 (5%)	0
	>12-16	56 (86%)	64 (99%)

Lantus doses were consistently as high or higher in the Afrezza group compared to Humalog (Sponsor's study report, Table 6.2) ranging from ~0-15% higher (mean 2.1 IU or 7% higher) on

a weekly basis. Lantus doses in both groups were relatively stable over time. The Lantus dose at Week 16 was an average of 2.5 IU higher than the Week 1 dose.

Table 4 shows the primary analysis results for Study 117. Afrezza was, on its face, NI to Humalog on the primary endpoint, HbA1c change from baseline. The non-inferiority objective was achieved despite a relatively small sample size, about 50% of the planned sample size. Both groups showed little or no mean change from baseline in HbA1c over the 16-week treatment period. Mean baseline HbA1c values were low by historical standards (mean 7.7%). The latter may have limited the ability of the trial to show changes in HbA1c from baseline and, therefore, differences between treatment groups. The observed SD in the trial was half what was planned for in the sample size calculations.

Table 4. HbA1c change from baseline ^{1,2}

HbA1c (% units)	Treatment group	
	Afrezza	Humalog
<u>ITT (LOCF)</u>	N=61	N=65
Baseline mean (SD)	7.75 (0.55)	7.62 (0.60)
LS mean change at 16 wks	-0.09	-0.05
Mean treatment difference	-0.04	
95% CI	(-0.25, +0.18)	
p-value for non-inferiority	p<.001	
Completers		
	N=52	N=60
Baseline mean (SD)	7.81 (0.56)	7.59 (0.62)
LS mean change at 16 wks	-0.10	-0.03
Mean treatment difference	-0.07	
95% CI	(-0.31, +0.16)	
p-value for non-inferiority	p<.001	

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

2 Pre-specified non-inferiority margin (by protocol amendment) was 0.4%

Afrezza was NI to Humalog in a sensitivity analysis that imputed a null mean result (treatment difference equal to +0.4%) for the group of 130 patients who were planned but not randomized. Assuming a SD of 0.6%, the same as the observed SD, the overall treatment difference for the 260 planned patients was +0.18% with 95% CI = (0.04%, 0.32%) satisfying the non-inferiority criterion.

Figure 1 shows individual patient HbA1c changes from baseline and fitted regression lines by treatment group.

Figure 1
Individual patient HbA1c change from baseline to week 16 (LOCF)
Afrezza n=61; Humalog n=65

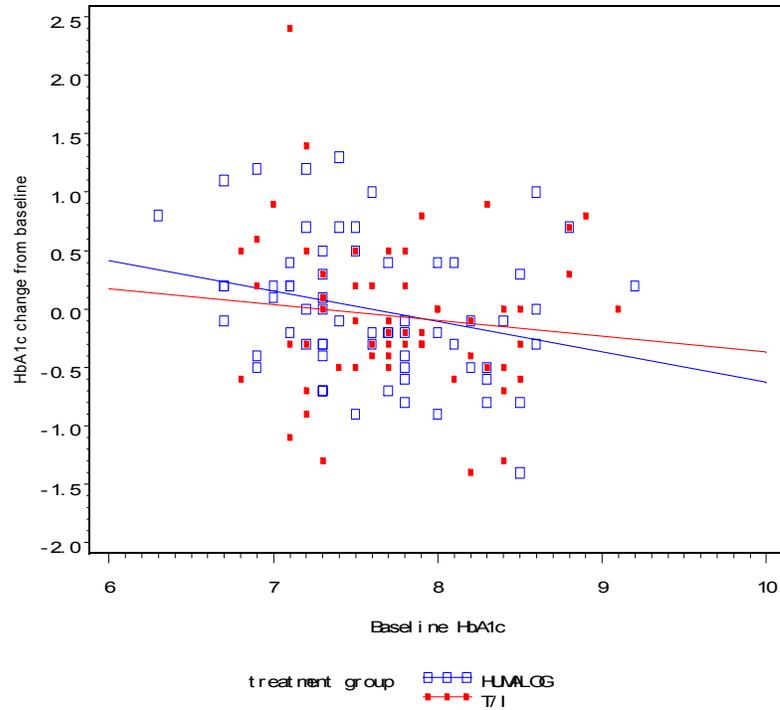


Figure 2 shows mean HbA1c changes over time by 4 dropout cohorts. Dropout cohorts were defined by the time point of the last on-treatment HbA1c value (Week 5, 8, 12 or 16). Afrezza completers experienced initial poor control with respect to HbA1c followed by better control over time. This trend coincides with increased Afrezza dosing over time. Humalog completers experienced good initial control of HbA1c followed by subsequent higher HbA1c values. Afrezza dropouts (20% of randomized patients) had generally poorer HbA1c control than Humalog dropouts (8% of randomized patients)

Figure 2
 Mean HbA1c change from baseline by dropout cohorts
 defined by last study week with HbA1c data
 (Afrezza n=61; Humalog n=65)

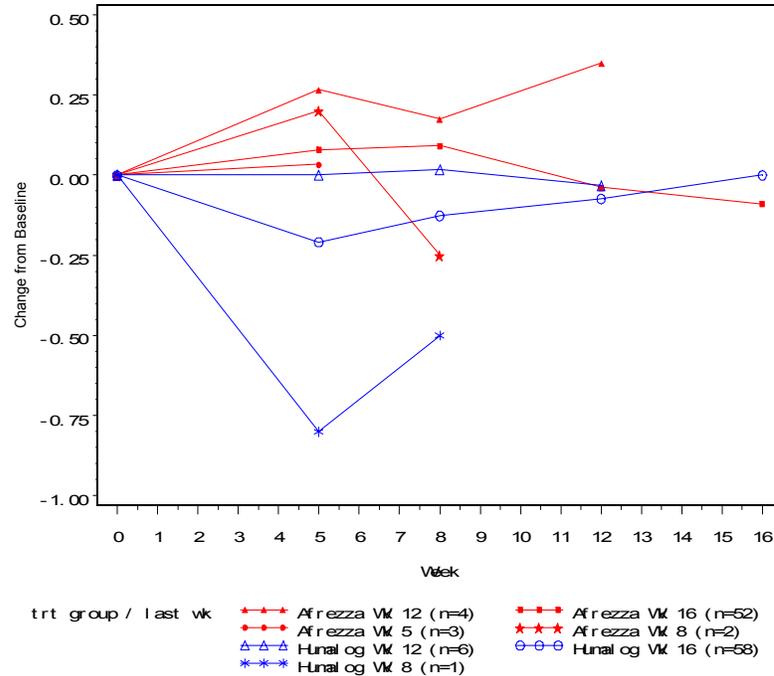


Table 5 shows HbA1c results by country (US, Brazil). Treatment differences favored Afrezza in Brazil (delta=-0.23%) and Humalog in the US (delta=+0.05%). The numerical differences between the two countries were not statistically significant (interaction p=0.13).

Table 5. HbA1c change from baseline by country¹

HbA1c (% units)	Treatment group	
	Afrezza	Humalog
USA	N=40	N=41
Baseline mean (SD)	7.71 (0.60)	7.51 (0.63)
LS mean change at 16 wks (LOCF)	+0.08	+0.03
Mean treatment difference	+0.05	
95% CI	(-0.16, 0.27)	
Brazil	N=21	N=24
Baseline mean (SD)	7.85 (0.46)	7.79 (0.53)
LS mean change at 16 wks (LOCF)	-0.32	-0.09
Mean treatment difference	-0.23	
95% CI	(-0.66, 0.21)	

¹ Least squares (LS) mean and confidence interval based on ANCOVA with treatment group as factor and baseline HbA1c as a covariate.

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/s/

JON T SAHLROOT
12/12/2010



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

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 22-472/N-000

Drug Name: AFREZZA[®] (insulin monomer human [rDNA origin])
Inhalation Powder and AFREZZA[®] Inhaler

Indication(s): Treatment of Diabetes Mellitus in Adults

Applicant: MannKind Corporation

Date(s): Received 03/16/09; user fee (10 months) 01/16/10

Review Priority: Standard

Biometrics Division: Division of Biometrics II (HFD-715)

Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer(s): Todd Sahlroot, Ph.D., Statistical Team Leader and Deputy
Director of Biometrics II

Medical Division: Division of Metabolic and Endocrine Products (HFD-510)

Clinical Team: Lisa Yanoff, M.D., Medical Reviewer
Hylton Joffe, M.D., Medical Team Leader

Project Manager: Rachel Hartford

Keywords: NDA review, clinical studies

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1. EXECUTIVE SUMMARY

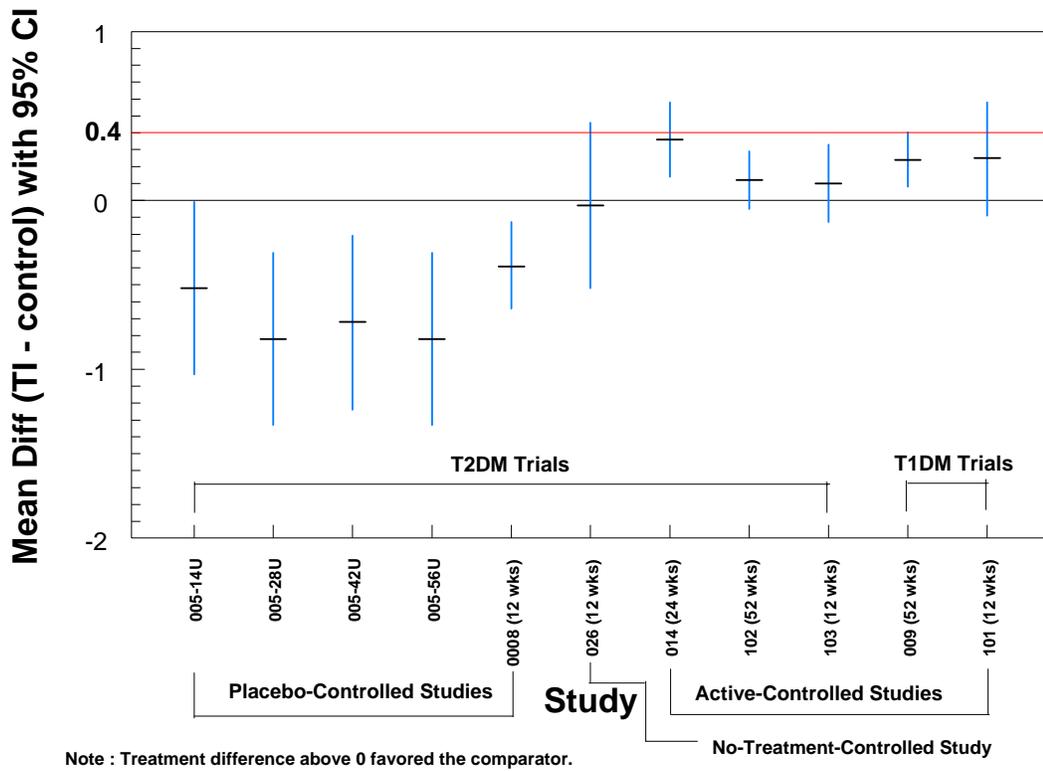
1.1 Conclusions and Recommendations

In this Technosphere[®] Insulin (TI) Inhalation Powder development program, data have demonstrated that TI, when combined with either insulin glargine (Lantus[®]) or OAD(s), was effective in lowering HbA1c when compared with placebo for type 2 diabetic patients.

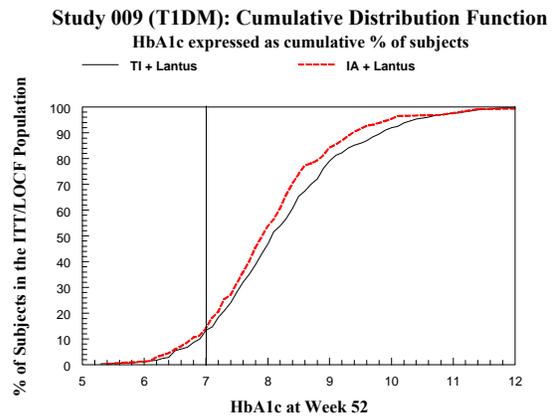
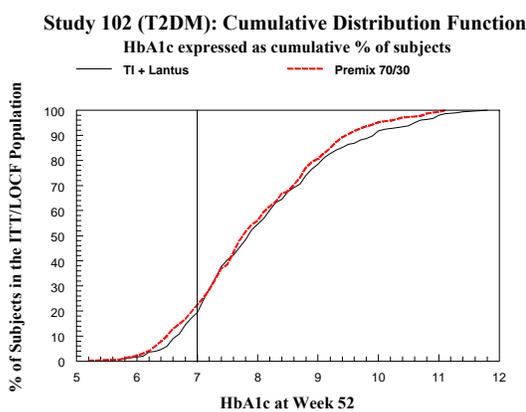
In the type 2 and type 1 diabetes mellitus (T2DM and T1DM) active-controlled trials, the mean reductions in HbA1c from baseline to endpoint were all numerically less in the TI arm than in the comparator arm. Assessment of non-inferiority with respect to active controls produced varying results. Specifically, in Study 103, treatment with TI + metformin was found to be non-inferior to metformin + secretagogue in lowering HbA1c for type 2 diabetic patients, since the upper bound of the 95% confidence interval (CI) of the treatment difference was 0.33%, smaller than the 0.4% non-inferiority margin. Treatment with TI + Lantus was also found to be non-inferior to Premixed 70/30 insulin analog in reducing HbA1c in Study 102 for type 2 diabetic patients, but was **not** non-inferior to treatment with insulin aspart + Lantus in Study 014 for type 2 diabetic patients and in Study 009 for type 1 diabetic patients. The upper bounds of the 95% CI of the treatment differences were 0.58% and 0.404% (0.45% for completers), respectively, and the mean HbA1c reductions were statistically significantly different between the 2 study groups, favoring the insulin aspart + Lantus treatment in both studies. Treatment with TI + Lantus was also shown to be not non-inferior to insulin aspart + Lantus in Study 101 for type 1 diabetic patients. However, this was not a confirmatory study and HbA1c was not the primary efficacy variable. In other words, the study may not have enough power to make a sound conclusion for HbA1c.

The figure below clearly depicts the statistical results across all trials.

HbA1c Reduction (ITT/LOCF Population) Treatment Difference in LS Mean Change from Baseline



The 2 figures below compare responder rates in the long-term trial (52-week) of each type of diabetes mellitus. The TI + Lantus group consistently showed a similar % of subjects reaching any level of HbA1c at endpoint when compared with the Premixed 70/30 analog group (Study 102), but a smaller % of subjects reaching any level of HbA1c at endpoint was observed when compared with the insulin aspart + Lantus group (Study 009).



In summary, treatment with TI was effective in lowering HbA1c when compared with placebo. Based on the statistical criteria, non-inferiority of TI + metformin or TI + insulin glargine (Lantus[®]) to OAD(s) or Premixed 70/30 insulin analog, respectively, in the reduction of HbA1c was established in adult patients with type 2 diabetes mellitus. However, when TI + Lantus was compared with insulin aspart + Lantus, data were not sufficient to support the non-inferiority claim in adult patients with either type 2 or type 1 diabetes mellitus. Since there was only 1 confirmatory study submitted for the indication of type 1 diabetes mellitus, making a solid conclusion regarding efficacy for this type of diabetes mellitus is problematic.

Nevertheless, the final conclusions for approval of the drug/device should also take the comparability of insulin and non-insulin doses as well as safety factors such as hypoglycemia and lung function into consideration.

Labeling Comments: The following bullets summarize this reviewer's comments for the sponsor's proposed labeling.

- [Redacted]
 - [Redacted]
 - [Redacted]
 - [Redacted]
 - [Redacted]
- (b) (4)

1.2 Brief Overview of Clinical Studies

MannKind Corporation is developing an ultra rapid acting prandial insulin, called AFREZZA™, for the treatment of hyperglycemia associated with type 1 and type 2 diabetes mellitus 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 MedTone® inhaler. TI is intended for use as a prandial insulin and is dosed at each meal.

The sponsor's TI development program consists of at least 8 efficacy and safety diabetic studies, 3 pulmonary studies, and 1 QT study. The main focus of this report is to review the efficacy of TI versus other insulins and non-insulin therapies. The statistical safety aspects of the drug-device product such as hypoglycemia and pulmonary function are evaluated by another FDA statistician, Joy Mele, M.S.

The 8 Phase 2/3 efficacy and safety diabetic trials of interest in this review report were MKC-TI-005, PDC-INS-0008, MKC-TI-026, MKC-TI-014, MKC-TI-102, MKC-TI-103, MKC-TI-009, and MKC-TI-101. They are grouped by type of diabetes mellitus and type of control group in the following table (the prefix before numbers in each study name is omitted). The sponsor considered PDC-INS-0008, MKC-TI-102, MKC-TI-009, and MKC-TI-101 as the pivotal efficacy and safety trials for the TI program.

Efficacy	Placebo-Controlled	No-Treatment-Controlled	Active-Controlled (Insulin)	Active-Controlled (OAD)	Other
Type 2	005 (11 weeks), 0008 (12 weeks)	026 (12 weeks)	014 (24 weeks), 102 (52 weeks)	103 (12 weeks)	030 (2 years)
Type 1			101 (12 weeks), 009 (52 weeks)		
<ul style="list-style-type: none"> ❖ Except Study 030, there was only 1 long-term (52 weeks) study for each type of diabetes mellitus. ❖ HbA1c was the primary efficacy variable, except for Study 101 and Study 030. 					

Note that Study 030 was designed to evaluate changes in pulmonary function outcomes over a 2-year period and was conducted in both type 1 and type 2 diabetic patients (randomized cohort) as well as subjects without abnormalities in glucose control (non-randomized cohort). For subjects with diabetes, TI was compared with usual anti-diabetic care (UC) and both groups of patients could also have concomitant anti-diabetic medication freely based on

investigators' discretion. Efficacy results may be confounded due to the study design. Therefore, the study is not evaluated in this review report.

In the placebo-controlled trials, Technosphere Inhalation Powder (T; no insulin in it) was used as the placebo. In the active-controlled trials, insulin aspart (NovoLog[®], NovoRapid[®], or Premixed 70/30 insulin analog) was used as the sc prandial insulin comparator and metformin + secretagogue (sulfonylurea [SU] or meglitinide) was used as the OAD(s) comparator. Insulin glargine (Lantus[®]) was used in all treatment groups requiring basal insulin for long acting insulin. The following table presents the differences in study designs of the trials.

Study	Treatment Group	Phase	Site	Country	TI Dosage	Rand pts.
T2DM						
005 (06/04 – 08/05)	TI (4 fixed dose levels) + Lantus vs. T (placebo) + Lantus	2	30	Multi-national	14, 28, 42, 56 U	227 (181:46 for all TI vs. T)
0008 (12/03 – 11/04)	TI vs. T (placebo)	2b	21	USA	6 to 48 U	123 (61:62)
026 (08/04 – 01/05)	TI vs. No Treatment (control)	2b	10	Russia	15 to 60 U	90 (75:15)
014 (12/04 – 07/06)	TI + Lantus vs. Insulin aspart + Lantus	3	25	Russia	15 to 60 U	309 (151:158)
102 (02/06 – 09/08)	TI + Lantus vs. Premixed 70/30 analog (NovoLog Mix 70/30)	3	124	Multi-national	15 to 90 U	677 (334:343)
103 (05/06 – 03/08)	TI alone vs. Metformin + Secretagogue vs. TI + Metformin	3	108	Multi-national	15 to 90 U	528 (183:170:175)
T1DM						
009 (02/06 – 05/08)	TI + Lantus vs. Insulin aspart + Lantus	3a	106	Multi-national	45 to 90 U	589 (301:288)
101 (03/05 – 12/05)	TI + Lantus vs. Insulin aspart + Lantus	2	17	Russia	Not specified	111 (55:56)

All the 8 efficacy studies reviewed here were randomized, multicenter trials. Except for the 2 double-blind placebo-controlled trials, all others were open-label trials. Also, except Study 005 which was a forced titration trial (14, 28, 42, and 56 U for TI), all the other studies were free titration trials allowing investigators to titrate TI Inhalation Powder at their clinical discretion with upper limits specified for preprandial and postprandial blood glucose.

For Studies 0008 and 026, all subjects continued their usual oral anti-diabetic therapy that they were taking prior entry throughout the course of the trials. For Study 103, the primary efficacy comparison was TI + Metformin (Group 3) vs. Metformin + Secretagogue (Group

2). The Metformin + Secretagogue (Group 2) vs. TI alone (Group1) comparison was one of the secondary efficacy comparisons.

1.3 Statistical Issues and Findings

Since the study duration, comparator, type of disease, etc., were different among the 8 efficacy trials, this reviewer thinks that the data should not be combined for overall treatment estimate. The collective evidence is then summarized across the 8 efficacy trials by type of diabetes mellitus. Text Table 1 below shows the mean HbA1c at baseline and endpoint as well as the mean changes from baseline for all trials. Text Table 2 shows the statistical hypothesis testing results for HbA1c for all trials using the ITT population with LOCF.

Discussions of Type 2 Diabetic Trials

For the 2 placebo-controlled trials, the TI + Lantus (in Study 005) and TI + OAD(s) (in Study 0008) groups both showed a significant mean reduction in HbA1c from baseline at endpoint when compared with the placebo group. In the 005 forced-titration trial, the mean reductions were similar among the 28, 42, and 56 U dose groups, which implied that the dose levels might have reached a plateau or HbA1c levels might not have reached their steady states yet in this 11-week trial.

In Studies 0008 and 026, the patients in the TI group continued to take their previously (prior entry) described OAD(s), while in Study 103, the patients in the TI alone group were not allowed to take any other anti-glycemic therapies. All 3 studies were of 12 weeks of duration. The raw mean HbA1c changes for TI in Studies 0008 and 026 as shown in Text Table 1 were -0.71 ± 0.77 (n = 58) and -1.40 ± 1.15 (n = 75), respectively, while the raw mean change in Study 103 was $+0.23 \pm 1.19$ (n = 176).

Among all the active-controlled T2DM trials, TI + metformin was not superior (the sponsor's primary objective), but was non-inferior (this reviewer's analysis using the 0.4% NI margin), to metformin + secretagogue in lowering HbA1c in Study 103. The upper bound of the 95% CI of the treatment difference was 0.33% in this study (Text Table 2). TI + Lantus was non-inferior to Premixed 70/30 analog in reducing HbA1c in Study 102, but was **not** non-inferior to insulin aspart + Lantus in Study 014. The upper bounds of the 95% CI of the treatment differences were 0.29% and 0.58%, respectively, in these studies (Text Table 2). For all the active-controlled trials, the mean reductions in HbA1c from baseline to endpoint were numerically less in the TI arm than in the comparator arm. The treatment difference in Study 014 (+0.36%) showed statistical significance (p = 0.002), favoring the insulin aspart + Lantus treatment. Note that the sponsor's primary objective for Study 014 was an equivalence test defining as lower and upper bounds of the 95% CI of the treatment difference within $\pm 0.4\%$.

It is apparent that the study did not have sufficient evidence to support the primary claim of equivalence.

Studies 102 and 103 had high dropout rates in the TI arms (32% and 31%, respectively). Therefore, statistical analyses were also performed for the completer cohort. Results were similar to the ones based on the ITT/LOCF population, indicating that the dropouts in each study did not have any major impact on the reduction of HbA1c.

Discussions of Type 1 Diabetic Trials

Technically speaking, there was only 1 confirmatory study submitted for the type 1 diabetes indication (Study 009). In this active-controlled trial, the mean reduction in HbA1c from baseline to endpoint in the TI + Lantus group was relatively small (-0.14%), which was statistically significantly less than that in the insulin aspart + Lantus group (treatment difference = +0.24%, $p = 0.003$, Text Table 2). The non-inferiority of TI + Lantus to insulin aspart + Lantus could **not** be established because the upper bound of the 95% CI of the treatment difference was 0.404%, greater than the pre-specified NI margin (0.4%) for this study. Since the dropout rate was high in the TI arm (32%), the completer cohort was analyzed as well. The results also showed that TI + Lantus was not non-inferior to insulin aspart + Lantus in lowering HbA1c because the upper bound of the 95% CI of the treatment difference was 0.45% (see Table 19 in the main body of this report). In addition, similar results were observed when a mixed model repeated measures (MMRM) analysis with contrast at Week 52 was performed to take missing data into consideration; the upper bound of the 95% CI of the treatment difference at endpoint in this case was 0.44% (see Table 19 in the main body of this report).

In Study 101, the mean reduction in HbA1c from baseline to endpoint was numerically less in the TI + Lantus group than in the insulin aspart + Lantus group. Although the treatment difference was not statistically significant, the upper bound of the 95% CI of the treatment difference was 0.58%, greater than the 0.4% non-inferiority margin (no pre-defined NI margin given by the sponsor). Note that HbA1c was not the primary efficacy variable in this study and the sample size was small.

Text Table 1 – Summary Statistics for HbA1c across Trials

Study (Duration)	Treatment Group (ITT with LOCF)	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change From Baseline	
					Raw Mean (SD)	LS Mean (SE)
Type 2 Diabetes Mellitus						
005 (11-week)	T (placebo)	41	8.70 (1.30)	8.94 (1.30)	0.24 (0.91)	0.23 (0.15)
	TI 14 U	43	8.91 (1.38)	8.55 (1.30)	-0.35 (1.15)	-0.29 (0.14)
	TI 28 U	43	8.59 (1.36)	8.05 (1.16)	-0.54 (1.15)	-0.59 (0.14)
	TI 42 U	41	8.68 (1.16)	8.21 (1.20)	-0.47 (0.91)	-0.49 (0.15)
	TI 56 U	42	8.82 (1.16)	8.20 (1.25)	-0.62 (1.11)	-0.59 (0.15)
Type 2 Diabetes Mellitus						
0008 (12-week)	TI	58	7.87 (1.15)	7.16 (1.09)	-0.71 (0.77)	-0.70 (0.09)
	T (placebo)	61	7.78 (1.11)	7.48 (1.12)	-0.30 (0.72)	-0.31 (0.09)
Type 2 Diabetes Mellitus						
026 (12-week)	TI	75	9.58 (1.39)	8.18 (1.12)	-1.40 (1.15)	-1.38 (0.10)
	No Treatment Control	15	9.33 (1.50)	8.09 (1.06)	-1.24 (0.93)	-1.35 (0.23)
Type 2 Diabetes Mellitus						
014 (24-week)	TI + Lantus	150	8.85 (1.10)	7.96 (1.34)	-0.89 (1.14)	-0.92 (0.08)
	Insulin aspart + Lantus	155	9.00 (1.31)	7.69 (1.09)	-1.31 (1.08)	-1.28 (0.08)
Type 2 Diabetes Mellitus						
102 (52-week)	TI + Lantus	302	8.69 (1.12)	8.11 (1.26)	-0.58 (1.22)	-0.59 (0.06)
	Premixed 70/30 analog	316	8.68 (1.08)	7.98 (1.16)	-0.70 (1.16)	-0.71 (0.06)
Type 2 Diabetes Mellitus						
103 (12-week)	TI alone	176	8.92 (0.95)	9.15 (1.27)	0.23 (1.19)	0.21 (0.07)
	Metformin + Secretagogue	162	8.90 (0.94)	8.15 (1.04)	-0.75 (0.90)	-0.78 (0.08)
	TI + Metformin	169	8.95 (0.97)	8.25 (1.09)	-0.70 (1.01)	-0.67 (0.07)
Type 1 Diabetes Mellitus						
009 (52-week)	TI + Lantus	277	8.41 (0.92)	8.28 (1.19)	-0.14 (1.03)	-0.13 (0.06)
	Insulin aspart + Lantus	262	8.48 (0.97)	8.09 (1.13)	-0.39 (0.93)	-0.37 (0.06)
Type 1 Diabetes Mellitus						
101 (12-week)	TI + Lantus	51	9.01 (1.22)	8.19 (1.10)	-0.81 (1.10)	-0.78 (0.12)
	Insulin aspart + Lantus	56	8.88 (1.18)	7.89 (0.95)	-0.99 (1.07)	-1.02 (0.12)

Text Table 2 – Efficacy Results for HbA1c across Trials Using the ITT/LOCF population

Study (Phase)	Duration	Treatment Group (ITT no.)	Primary Hypothesis Test	Treatment Difference (TI – control)			Reviewer’s Conclusion
				LS Mean (SE)	95% CI	p-value	
Type 2 Diabetes Mellitus							
005 (2)	11-week	<ul style="list-style-type: none"> • TI 14, 28, 42, 56 U + Lantus (43, 43, 41, and 42, respectively) • T (placebo) + Lantus (41) 	Superiority	14: -0.52 (0.21)	(-1.03, -0.01)	0.0439	➤ All doses (especially 28, 42, and 56 U) significantly better than placebo
				28: -0.82 (0.21)	(-1.33, -0.31)	0.0004	
				42: -0.72 (0.21)	(-1.24, -0.21)	0.0026	
				56: -0.82 (0.21)	(-1.33, -0.31)	0.0004	
0008 (2b)	12-week	<ul style="list-style-type: none"> • TI (58) • T (placebo) (61) 	Superiority	-0.39 (0.13)	(-0.64, -0.13)	0.003	➤ Significantly better than placebo
026 (2b)	12-week	<ul style="list-style-type: none"> • TI (75) • No Treatment (control) (15) 	Not specified	-0.03 (0.25)	(-0.52, 0.46)	0.90	<ul style="list-style-type: none"> ➤ Significant change from baseline ➤ No difference from no-treatment group
014 (3)	24-week	<ul style="list-style-type: none"> • TI + Lantus (150) • Insulin aspart + Lantus (155) 	Equivalence	+0.36 (0.11)	(0.14, 0.58)	0.002 a	<ul style="list-style-type: none"> ➤ Not NI (NI margin not pre-defined) ➤ Statistically worse
102 (3)	52-week	<ul style="list-style-type: none"> • TI + Lantus (302) • Premixed 70/30 analog (316) 	NI	+0.12 (0.09)	(-0.05, 0.29)	0.16 a	➤ NI
103 (3)	12-week	<ul style="list-style-type: none"> • TI alone (176) • Met. + Secretagogue (162) • TI + Metformin (169) 	Superiority	TI+M vs. M+S (primary test): +0.10 (0.10)	(-0.13, 0.33)	0.51 a	<ul style="list-style-type: none"> ➤ Not Superior (TI + M vs. M + S) ➤ NI (NI margin not pre-defined)
Type 1 Diabetes Mellitus							
009 (3a)	52-week	<ul style="list-style-type: none"> • TI + Lantus (277) • Insulin aspart + Lantus (262) 	NI	+0.24 (0.08)	(0.08, 0.404)	0.003 a	<ul style="list-style-type: none"> ➤ Not NI ➤ Statistically worse
101 (2)	12-week	<ul style="list-style-type: none"> • TI + Lantus (51) • Insulin aspart + Lantus (56) 	Not specified	+0.25 (0.17)	(-0.09, 0.58)	0.15 a	➤ Not NI (NI margin not pre-defined)
a Regardless of statistical significance, the TI group showed a numerically less reduction in HbA1c when compared with the comparator.							

The proportions of subjects achieving HbA1c level $\leq 7.0\%$ at endpoint for Studies 014, 102, 103, 009, and 101 are presented in Text Table 3. It is shown that across the 5 comparative trials, regardless of type of diabetes mellitus, no more than 25% of the ITT subjects in the TI arm had reached 7% or less of HbA1c at endpoint. This phenomenon may be attributed to the high mean HbA1c at baseline ($\geq 8.5\%$ in general, see Table 8 in the main body of this report) with less than 1% of mean change at endpoint (Text Table 1) across the trials.

Text Table 3 – Summary of Responder Rate for HbA1c $\leq 7.0\%$ (ITT Population with LOCF)

Study	End of Treatment	TI	Comparator	Difference in Proportion	Asymptotic 95% CI
014 (T2DM)	Week 24	36/150 (24.0%)	51/155 (32.9%)	-8.9%	(-19.0%, 1.2%)
102 (T2DM)	Week 52	59/302 (19.5%)	71/316 (22.5%)	-2.9%	(-9.4%, 3.5%)
103 (T2DM)	Week 12	24/169 (14.2%)	20/162 (12.3%)	+1.9%	(-5.5%, 9.2%)
009 (T1DM)	Week 52	37/277 (13.4%)	37/262 (14.1%)	-0.8%	(-6.6%, 5.1%)
101 (T1DM)	Week 12	5/51 (9.8%)	10/56 (17.9%)	-8.1%	(-21.0%, 4.9%)

Treatment effects on mean change from baseline in HbA1c at endpoint were consistent across the subgroups defined by age (< 65 years or ≥ 65 years), gender, and race for all the T2DM and T1DM comparative trials, except that treatment effect on gender was significant in Study 009 (treatment-by-sex interaction $p = 0.0139$). As shown in Text Table 4, the mean reduction from baseline in HbA1c at Week 52 for the male subjects with T1DM was almost 0% in the TI + Lantus group, compared with a 0.47% reduction in the insulin aspart + Lantus group. For the female subjects with T1DM, the mean reductions in HbA1c after 52 weeks of treatment were 0.19% and 0.26% for the TI + Lantus and insulin aspart + Lantus groups, respectively. The difference in treatment effect on HbA1c between the 2 subgroups was quantitative, not qualitative.

Text Table 4 – Study 009 – Efficacy Results for HbA1c by Sex

ITT LOCF	Change from Baseline at Week 52 : LS Mean \pm SE (N)		Treatment Difference		
	TI + Lantus	Insulin aspart + Lantus	LS Mean (SE)	95% CI	p-value
ITT Population with LOCF					
Male	-0.00 \pm 0.09 (146)	-0.47 \pm 0.08 (136)	0.47 (0.12)	(0.23, 0.70)	0.0001
Female	-0.19 \pm 0.09 (131)	-0.26 \pm 0.09 (126)	0.07 (0.12)	(-0.17, 0.30)	0.58
Completers					
Male	-0.06 \pm 0.11 (106)	-0.49 \pm 0.10 (117)	0.43 (0.14)	(0.15, 0.71)	0.0027
Female	-0.29 \pm 0.11 (92)	-0.35 \pm 0.10 (103)	0.06 (0.15)	(-0.23, 0.34)	0.69

The 2-hour postprandial glucose (PPG) after a standardized liquid meal (12 ounces Boost Plus[®], Novartis) was evaluated by the sponsor as one of the secondary efficacy endpoints. Change from Time 0 after the meal challenge in PPG at 2 hours was analyzed for Studies 102 (T2DM) and 009 (T1DM) using an ANCOVA model with treatment and pooled site as class variables and Time 0 plasma glucose as the covariate. The sponsor’s results for Week 52 are summarized below.

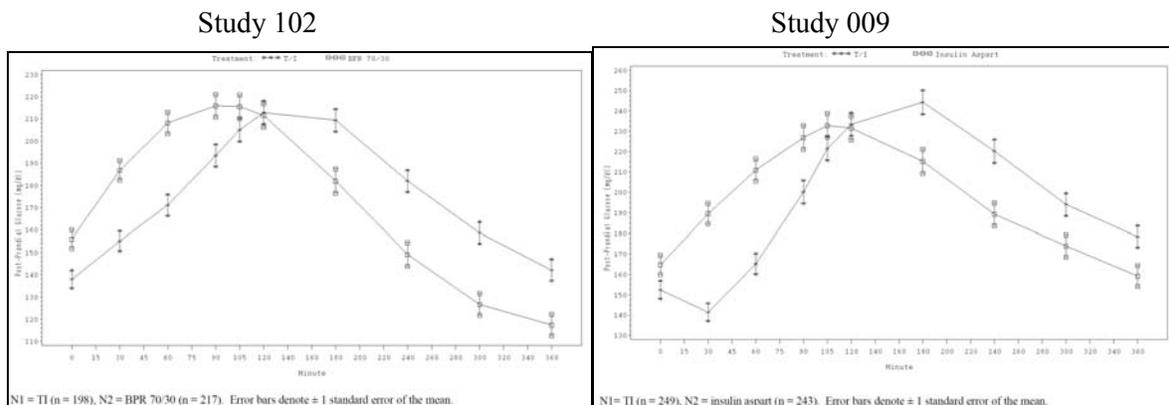
Text Table 5 – 2-Hour PPG (mg/dL) after a Meal Challenge (ITT Population)

Study (Week)	Change from Time 0 in PPG at 2 hours LS Mean ± SE (N)		Treatment Difference		
	TI	Comparator	LS Mean (SE)	95% CI	p-value
102 (Week 52)	75.8 ± 4.4 (193)	56.4 ± 4.0 (213)	19.4 (5.7)	(8.2, 30.6)	0.0007
009 (Week 52)	74.6 ± 6.1 (170)	57.3 ± 5.8 (180)	17.3 (8.1)	(1.4, 33.2)	0.0332

The ANCOVA model included treatment and pooled site as fixed factors and Time 0 glucose as the covariate.

For both studies, at Week 52, the Time 0-corrected 2-hour PPG was significantly better in the comparator arm than in the TI arm, which was probably due to the higher Time 0 glucose value in the comparator arm (thus yielding a smaller change), as there was no marked difference in the 2-hour PPG value between the 2 treatment arms (see Text Figure 1 below for Studies 102 and 009). The % of subjects reaching 140 mg/dL or less in the 2-hour PPG at Week 52 was 15.6% and 18.7% for the TI and Premixed 70/30 analog arms, respectively, for Study 102, and 16.8% and 19.1% for the TI and insulin aspart arms, respectively, for Study 009.

Text Figure 1 – PPG (mg/dL) after a Meal Challenge at Week 52 (ITT)



2. INTRODUCTION

2.1 Overview

MannKind Corporation is developing an ultra rapid acting prandial insulin, called AFREZZA™, for the treatment of hyperglycemia associated with type 1 and type 2 diabetes mellitus 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 MedTone® inhaler. TI is intended for use as a prandial insulin and is dosed at each meal.

The sponsor's TI development program consists of at least 8 efficacy and safety diabetic studies, 3 pulmonary studies, and 1 QT study. The main focus of this report is to review the efficacy of TI versus other insulins and non-insulin therapies. The statistical safety aspects of the drug-device product such as hypoglycemia and pulmonary function are evaluated by another FDA statistician, Joy Mele, M.S.

The 8 Phase 2/3 efficacy and safety diabetic trials reviewed here were MKC-TI-005, PDC-INS-0008, MKC-TI-026, MKC-TI-014, MKC-TI-102, MKC-TI-103, MKC-TI-009, and MKC-TI-101 (see study highlights below). The MKC-TI-009 and MKC-TI-101 trials were conducted to seek approval for type 1 diabetes mellitus (T1DM) in adults; the rest for approval in type 2 diabetes mellitus (T2DM) in adults. The sponsor considered PDC-INS-0008, MKC-TI-102, MKC-TI-009, and MKC-TI-101 as the pivotal efficacy and safety trials for the TI program.

Throughout this report, the prefix before numbers in each study name will be omitted for the ease of discussions. For example, Study MKC-TI-005 will be referred as Study 005.

Study Identifier/ Study Status	Objective(s) of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	No. of Subjects Enrolled	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
MKC-TI-005 Completed Full	To evaluate safety and glycemic response of TI dosed prandially, in addition to basal administration of Lantus®	Multicenter, randomized, prospective, double-blind, placebo-controlled, stepwise titration study	<u>Test Product:</u> TI <u>Dosage:</u> Variable; 14, 28, 42, or 56 U TI per meal <u>Route:</u> Inhaled	227	Suboptimally treated type 2 diabetes mellitus	Short (11 wk)
PDC-INS-0008 Completed Full	To evaluate the efficacy and safety of inhaled TI compared to Technosphere®/ following diabetes education	Prospective, double-blind, randomized, placebo-controlled, parallel-group study, as an add-on to oral therapy, dose-finding	<u>Test Product:</u> TI <u>Dosage:</u> Variable; 6 to 48 U TI per meal or prandial TIP <u>Route:</u> Inhaled	126	Suboptimally treated type 2 diabetes mellitus	Short, 12 wk
MKC-TI-026 Completed Full	To evaluate the safety and tolerability of 12 wk of treatment with inhaled TI in subjects with suboptimally treated type 2 diabetes	Prospective, controlled, OL, randomized, 12-week safety and efficacy study	<u>Test Product:</u> TI <u>Dosage:</u> 15 to 60 U TI per meal <u>Route:</u> Inhaled	90	Suboptimally treated type 2 diabetes mellitus	Short, 12 weeks
MKC-TI-101 Completed: Full	To evaluate use of prandial inhaled TI in combination with basal sc Lantus® as basal insulin versus prandial sc NovoRapid® insulin in combination with basal sc Lantus® insulin	Randomized, open-label, multisite substitution study	<u>Test Product:</u> TI <u>Dosage:</u> Specific doses not selected, each subject's established dose of prandial sc insulin replaced with a corresponding dose of prandial TI <u>Route:</u> Inhaled	120	Subjects receiving basal prandial insulin therapy for type 1 diabetes mellitus	Medium, 12 wk
MKC-TI-014 Completed Full	To compare the efficacy of prandial TI + basal insulin vs prandial rapid acting sc insulin + basal insulin in subjects with type 2 diabetes receiving Lantus® as basal insulin with a 22-wk posttreatment follow-up on conventional therapy	Randomized, OL, comparative study	<u>Test Product:</u> TI <u>Dosage:</u> Variable; 15, 30, 45, or 60 U TI per meal <u>Route:</u> Inhaled	309	Type 2 diabetes mellitus receiving Lantus® as basal insulin	Medium, 24 wk, with option of continuing for 22 wk on conventional therapy
MKC-TI-103 Completed Full	To evaluate the efficacy and safety of prandial inhalation of TI in combination with metformin or TI alone vs 2 oral antidiabetic agents (metformin and a secretagogue) in subjects with suboptimally controlled type 2 diabetes	24-wk OL, randomized, controlled study	<u>Test Product:</u> TI <u>Dosage:</u> Variable; 15 to 90 U TI <u>Route:</u> Inhaled	528	Suboptimally controlled type 2 diabetes mellitus	Medium, 6 months
MKC-TI-009 Completed Full	To evaluate the efficacy and safety of TI in subjects with type 1 diabetes receiving sc basal insulin + prandial TI vs prandial sc insulin treatment + basal insulin treatment over 12 months	Prospective, OL, randomized, controlled study	<u>Test Product:</u> TI <u>Dosage:</u> Variable; 45 U TI, with maximum of 90 U <u>Route:</u> Inhaled	589	Type 1 diabetes mellitus	Long (52 wk of treatment + 4 weeks of follow-up)
MKC-TI-102 Completed Full	To evaluate the efficacy and safety over 12 mos in subjects with suboptimally controlled type 2 diabetes administered prandial inhalation of TI in combination with basal insulin therapy vs a prandial premix of intermediate- and rapid-acting insulin in subjects treated with sc insulin ± oral antihyperglycemic agents	Prospective, OL, randomized, controlled study	<u>Test Product:</u> TI <u>Dosage:</u> Variable; 15 to 90 U TI <u>Route:</u> Inhaled	677	Type 2 diabetes mellitus	Long (59 wk: 52 wk of treatment + 4 wk of follow-up)

2.2 Data Sources

The original clinical study reports and electronic data files are located in the sub-folders of EDR [\CDSESUB1\EVSPROD\NDA022472\0000](#). The subsequent submissions in response to this reviewer's questions and requests were via e-mail on 08/28/2009, 09/03/2009, 10/23/2009, 10/27/2009, 11/10/2009, and 11/16/2009.

In general, the quality of the electronic data sets and integrity of the study reports were not satisfactory. For example, data formats such as variable names and LOCF flagging system for HbA1c were not consistent across the 8 trials. For Study 005, baseline data in hba005.xpt were actually the Visit 1 (screening) values, not the Visit 5 (baseline) values. Similar errors were also found in hba026.xpt for Study 026. Time adjusted Lantus exposure data were derived incorrectly for Study 005 and were not submitted for Study 014. No LOCF indicator was given for Study 0008 and names and descriptions of data files were not easy to understand (ilabs.xpt and implabs.xpt were both described as "imputed laboratory data" and the differences between the 2 data files were not clear at all). There were at least 18 subjects who were randomized but early terminated with a baseline and post-baseline HbA1c values recorded for Study 103. However, the early termination values were not flagged for the primary efficacy analysis in the ITT/LOCF population. The sponsor has corrected the issues noted for data problems.

This reviewer has also found several mistakes in the sponsor's individual study reports as well as ISE. For example, in Study 005, the sponsor presented summary statistics using the Visit 1 (screening) values as baselines in some tables, but the Visit 5 (baseline) values in others. In Study 0008, the sponsor stated that the results were based on the ITT population with LOCF, but they were actually from the ITT population with observed data. In Study 103, the sponsor claimed that the TI alone group and the other 2 groups showed comparable mean reductions in HbA1c at Week 12, but the TI alone group was actually significantly different from the other 2 groups. Moreover, in Study 009, the sponsor also claimed that the TI group and insulin aspart group were comparable, but the TI group actually showed a significantly less reduction in HbA1c at Week 52 when compared with the insulin aspart group.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

All the 8 efficacy trials reviewed here were randomized, multicenter trials. Of these, 2 placebo-controlled trials were double-blind, 1 no-treatment-controlled trial was open-label, and 5 active-controlled trials were also open-label. Study 0008 was conducted in USA and Studies 026, 014, and 101 in Russia. All other studies were multi-national trials. Also,

Study 005 was a forced titration trial (14, 28, 42, and 56 U for TI) and all others were free titration trials allowing investigators to titrate TI Inhalation Powder at their clinical discretion with upper limits specified for preprandial and postprandial blood glucose. The TI dosage was 6 to 48 U for Study 0008, 15 to 60 U for Studies 026 and 014, 15 to 90 U for Studies 102 and 103, and 45 to 90 U for Study 009. The inclusion criterion for HbA1c at entry was somewhere in the range of 7% to 12% for all trials, except for Study 0008 where it was between 6.6% and 10.5%.

The treatment groups, study duration, HbA1c collection time points, primary efficacy endpoint are tabulated in Tables 1 and 2 for the type 2 diabetes mellitus (T2DM) and type 1 diabetes mellitus (T1DM) trials, respectively. The schematic diagram for each study design is shown in Appendix I.

Table 1 – Study Design for Type 2 Diabetes Mellitus Trials

Study	Treatment Group	Phase	Duration	Rand pts.	HbA1c Collection Time Points	Primary Endpoint
005 (06/04 – 08/05)	TI (4 fixed dose levels: 14, 28, 42, and 56 U) + Lantus vs. T (placebo) + Lantus	2	11 weeks	227 (181:46 for all TI vs. T)	Weeks 1 (Screening), 6 (Baseline), and 17	Change from baseline (Week 6) in HbA1c at Week 17
0008 (12/03 – 11/04)	TI vs. T (placebo)	2b	12 weeks	123 (61:62)	Weeks 1 (Screening), 3 (Baseline), 7, 11, and 15	Change from baseline (Week 3) in HbA1c at Week 15
026 (08/04 – 01/05)	TI vs. No Treatment (control)	2b	12 weeks	90 (75:15 for 5:1 ratio as designed)	Weeks 0, 2 (Baseline), 6, 8, 10, 12, and 14	Change from baseline (Week 2) in HbA1c at Week 14
014 (12/04 – 07/06)	TI + Lantus vs. Insulin aspart + Lantus	3	24 weeks	309 (151:158)	Weeks -4 (Screening), 0 (Baseline), 2, 4, 8, 12, 16, 20, and 24	Change from baseline (Week 0) in HbA1c at Week 24
102 (02/06 – 09/08)	TI + Lantus vs. Premixed 70/30 analog (NovoLog Mix 70/30)	3	52 weeks	677 (334:343)	Weeks -3 (Screening), 0 (Baseline), 14, 26, 38, and 52	Change from baseline (Week 0) in HbA1c at Week 52
103 (05/06 – 03/08)	TI alone vs. Metformin + Secretagogue (sulfonylureas or meglitinides) vs. TI + Metformin	3	12 weeks	528 (183:170: 175)	Weeks -2 (Screening), 0 (Baseline), 4, and 11/12	Change from baseline (Week 0) in HbA1c at Week 11/12
TI inhalation power was given 3 to 4 times per day immediately before meals or a snack.						

The sc insulin aspart was NovoRapid[®] given 3 to 4 times per day immediately before meals or a snack.
 The sc basal insulin was Lantus[®] (insulin glargine) given once per day, at bedtime.
 The sc Premixed 70/30 analog (BPR 70/30) was NovoLog[®] Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart) given twice per day, once before breakfast and once before main evening meal.

For Study 005, change from Visit 5 (baseline, Week 6) in mean postprandial glucose excursions (AUC_{glucose}) during 0-300 minutes at the time of a standardized meal challenge at Visit 12 (Week 17) was also a primary efficacy endpoint in this study. However, it is not evaluated in this report. For Studies 0008 and 026, all subjects continued their usual oral anti-diabetic therapy that they were taking prior entry throughout the course of the trials (add-on studies). For Studies 014, 102, and 103, subjects were followed for an additional 22 (optional conventional therapy), 4, and 12 (observational period) weeks after the primary end time point, respectively. Note that for Study 103, the last time point HbA1c collected prior to the observational period was planned at Week 11 (pre-Visit 5), but some subjects had it collected at Week 12 (Visit 5). In addition, the primary efficacy comparison for Study 103 was TI + Metformin (Group 3) vs. Metformin + Secretagogue (Group 2). The Metformin + Secretagogue (Group 2) vs. TI alone (Group1) comparison was one of the secondary efficacy comparisons.

Table 2 – Study Design for Type 1 Diabetes Mellitus Trials

Study	Treatment Group	Phase	Duration	Rand pts.	HbA1c Collection Time Points	Primary Endpoint
009 (02/06 – 05/08)	TI + Lantus vs. Insulin aspart + Lantus	3a	52 weeks	589 (301:288)	Weeks -3 (Screening), 0 (Baseline), 14, 26, 38, and 52	Change from baseline in HbA1c at Week 52
101 (03/05 – 12/05)	TI + Lantus vs. Insulin aspart + Lantus	2	12 weeks	111 (55:56)	Weeks -4 (Screening and Baseline), 0, and 12	Not HbA1c

TI inhalation power was given 3 to 4 times per day immediately before meals or a snack.
 The sc insulin aspart was NovoLog[®]/NovoRapid[®] for Study 009 and NovoRapid[®] for Study 101, given 3 to 4 times per day immediately before meals or a snack.
 The sc basal insulin was Lantus[®] (insulin glargine) given once per day, at bedtime.

For Study 009, subjects were followed for an additional 4 weeks after the primary end time point. For Study 101, 100% replacement of TI for the sc prandial insulin (NovoRapid[®]) in the TI group was done in a step-wise fashion during a 3-week substitution period. Therefore, the Visit 1 (screening, Week -4) value was used by the sponsor as the baseline for HbA1c because treatment changes occurred during the 3-week substitution period (Week -3 to Week

0). HbA1c was one of the secondary efficacy variables. The primary efficacy endpoint for this study was change in blood glucose following a standard meal expressed as AUC_{glucose} during 0-300 minutes which is not evaluated in this report.

3.1.2 Statistical Methods

Change from baseline in HbA1c at endpoint in each study was analyzed by the sponsor and this reviewer using the statistical methods as described in Table 3.

Table 3 – Statistical Methods of Treatment Groups Comparisons

Study	Primary Hypothesis Test	Sponsor's Primary Method	Reviewer's Primary Method
T2DM			
005	Superiority	2-sample t-test comparing the TI groups (starting with the highest TI dose and then step-down) with the T (placebo) group.	Basic ANCOVA model with Dunnett's t-test for group comparisons.
0008	Superiority	2-sample t-test.	Basic ANCOVA model.
026	Not specified	2-sample t-test.	Basic ANCOVA model.
014	Equivalence	ANCOVA model with treatment and site as fixed factors and baseline HbA1c as the covariate.	Basic ANCOVA model.
102	Non-inferiority	ANCOVA model with treatment and <u>pooled</u> site as fixed factors and baseline HbA1c as the covariate.	Same as the sponsor's ANCOVA model.
103	Superiority comparing TI + M vs. M + S	ANCOVA model with treatment and <u>pooled</u> site as fixed factors and baseline HbA1c as the covariate. Unadjusted t-test for group comparisons.	Same as the sponsor's ANCOVA model, but using Dunnett's t-test for group comparisons.
T1DM			
009	Non-inferiority	ANCOVA model with treatment and <u>pooled</u> site as fixed factors and baseline HbA1c as the covariate.	Same as the sponsor's ANCOVA model.
101	Not specified	2-sample t-test	Basic ANCOVA model.
Basic ANCOVA model included treatment as a fixed factor and baseline HbA1c as a covariate.			

For Study 014, the sponsor defined that equivalence of the 2 treatment groups would be established if the lower bound of the 95% CI of the treatment difference in mean change from baseline in HbA1c at Week 24 was greater than -0.4% and the upper bound of the 95% CI was less than +0.4%. In the sponsor's statistical model, site was included as a fixed factor. However, there were a lot of sites participating in this study and some consisted of

only a few patients. In order to avoid the problem of sparse data, this reviewer used a basic model including treatment and baseline HbA1c only for the statistical analysis.

For both Studies 102 and 009, the sponsor defined that non-inferiority (NI) of TI Inhalation Powder + Lantus over the comparator drug would be established if the upper bound of the 95% CI of the treatment difference in mean change from baseline in HbA1c at Week 52 was less than +0.4% (the pre-defined NI margin by the sponsor).

For Studies 014, 103, and 101, this reviewer also performed a non-inferiority test for TI versus comparator using a margin of 0.4%. This margin was chosen to be consistent with the pre-defined margin in Studies 102 and 009. Also, this margin has been used in other diabetes programs having studies with active controls.

For all trials, regardless which population was used as the main efficacy population in the sponsor's analyses (e.g., ITT/observed for Studies 005 and 0008, and PP for Study 014), the ITT population with LOCF technique for missing values was used in this reviewer's primary evaluation. In addition, results based on different populations such as completers were also evaluated as supportive evidence.

The sponsor had identified some disqualified sites due to issues related to data collection practices, trial operations, or GCP non-compliance. Although they were included in the sponsor's analyses, this reviewer has analyzed the data with and without the sites.

There were interim analyses conducted for Studies 0008, 014, and 101. The sponsor indicated that no type 1 error adjustments were made because these interim analyses were done after last patient last visit value was collected and they were mainly for the purpose of planning future studies.

3.1.3 Subject Disposition

Table 4 presents the subject disposition for the placebo and no-treatment control trials in T2DM and Table 5 for the comparative trials in both T2DM and T1DM. Except for Studies 102 (T2DM), 103 (T2DM), and 009 (T1DM), all the other trials had at least 80% of the randomized subjects completing their treatment periods.

Both Studies 102 and 009 were long-term trials (52 weeks) and subject withdrew consent was the most recorded reasons for withdrawal. Study 103 was a short-term trial (12 weeks), but a lot of dropouts were seen especially in the TI arms. The sponsor's clinical study report stated that some of the discontinued subjects identified in their CRFs as due to withdrawn consent, investigator decision, or other were actually discontinued due to inadequate

glycemic control (lack of efficacy/hyperglycemia) according to the adjudication (Table 6). The sponsor also indicated that the lack of efficacy was probably caused by the slow titration process (thus subjects not being fully titrated by Week 12) in the TI arms.

Table 6 – Study 103 – Discontinuation Reasons with Most Discrepancy Between CRF and Adjudication

Most Reason for Discontinuation During Treatment	CRF Reason for Early Termination			Adjudicated Reason for Early Termination		
	TI alone (n = 183)	M + S (n = 170)	TI + M (n = 175)	TI alone (n = 183)	M + S (n = 170)	TI + M (n = 175)
Withdrew Consent	20 (10.9)	6 (3.5)	19 (10.9)	12 (6.6)	6 (3.5)	11 (6.3)
Investigator Decision	13 (7.1)	2 (1.2)	10 (5.7)	2 (1.1)	0 (0)	7 (4.0)
Other	3 (1.6)	0 (0)	20 (11.4)	1 (0.5)	0 (0)	0 (0)
Lack of Efficacy	---	---	---	21 (11.5)	2 (1.2)	31 (17.7)

Subjects who were randomized but did not receive any study drug were excluded from this table. See Table 5 for the complete categories of reasons for withdrawal.

3.1.4 Demographic and Baseline Characteristics

Table 7 presents the demographic and baseline characteristics for the placebo and no-treatment control trials in T2DM and Table 8 for the comparative trials in both T2DM and T1DM. In general, within each study, the treatment groups were similar with respect to age, gender, race, country, BMI, and HbA1c at baseline for the ITT population. For all trials, the majority of patients consisted of either Caucasian alone or Caucasian and Hispanic combined. For the T2DM trials, the mean age at entry was above 50 years and the mean BMI was above 29 kg/m². For the T1DM trials, the mean age at entry was above 30 years and the mean BMI was above 23 kg/m². Specifically, 97% of the ITT population in Study 009 (T1DM) was < 65 years old and all the ITT subjects in Study 101 (T1DM) were between 18 and 59 years old (no geriatric population in this study). Except for Study 0008 (T2DM), all the T2DM and T1DM trials had a mean HbA1c \geq 8.5% at baseline.

Table 4 – Subject Disposition of the T2DM Placebo and No-Treatment Control Trials

Study	005 (11-week)					0008 (12-week)		026 (12-week)	
	T (placebo)	TI 14 U	TI 28 U	TI 42 U	TI 56 U	TI	T (placebo)	TI	No- Treatment
Randomized	46	45	46	45	45	61	62	75	15
Safety	46 (100)	45 (100)	46 (100)	45 (100)	45 (100)	61 (100)	62 (100)	75 (100)	15 (100)
ITT	41 (89.1)	44 (97.8)	44 (95.7)	41 (91.1)	42 (93.3)	58 (95.1)	61 (98.4)	75 (100)	15 (100)
Completed	40 (87.0)	42 (93.3)	41 (89.1)	41 (91.1)	41 (91.1)	54 (88.5)	53 (85.5)	69 (92.0)	14 (93.3)
Withdrawn Prior Receiving Drug	5 (10.9) ^a	1 (2.2) ^a	1 (2.2) ^a	3 (6.7) ^a	2 (4.4) ^a	0 (0)	0 (0)	0 (0)	0 (0)
Withdrawn During Treatment	1 (2.2)	2 (4.4)	4 (8.7)	1 (2.2)	2 (4.4)	7 (11.5)	9 (14.5)	6 (8.0)	1 (6.7)
Adverse Event	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.3)	1 (1.6)	2 (2.7)	1 (6.7)
Protocol Violation	1 (2.2)	0 (0)	2 (4.3)	0 (0)	0 (0)	0 (0)	1 (1.6)	3 (4.0)	0 (0)
Withdrew Consent	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (2.2)	0 (0)	5 (8.1)	1 (1.3)	0 (0)
Subject Died	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Investigator Decision	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.6)	0 (0)	0 (0)	0 (0)
Lost to Follow-up	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	2 (4.4)	1 (2.2)	0 (0)	1 (2.2)	4 (6.6)	2 (3.2)	0 (0)	0 (0)

^a Those subjects received single-blind T (placebo) beginning at Visit 3 (Week 4), but were withdrawn before double-blind treatment began at Visit 5 (Week 6).

Table 5 – Subject Disposition of the T2DM and T1DM Comparative Trials

Study	Type 2 Diabetes Mellitus (T2DM)							Type 1 Diabetes Mellitus (T1DM)			
	014 (24-week)		102 (52-week)		103 (12-week)			009 (52-week)		101 (12-week)	
Group	TI + L	IA + L	TI + L	Premix	TI alone	M + S	TI + M	TI + L	IA + L	TI + L	IA + L
Randomized	151	158	334	343	183	170	175	301	288	55	56
Safety	151 (100)	158 (100)	323 (96.7)	331 (96.5)	181 (98.9)	166 (97.6)	174 (99.4)	293 (97.3)	272 (94.4)	54 (98.2)	56 (100)
ITT	150 (99.3)	155 (98.1)	302 (90.4)	316 (92.1)	177 (96.7)	162 (95.3)	169 (96.6)	277 (92.0)	262 (91.0)	51 (92.7)	56 (100)
Completed	123 (81.5)	153 (96.8)	216 (64.7)	246 (71.7)	133 (72.7)	152 (89.4)	119 (68.0)	198 (65.8)	220 (76.4)	49 (89.1)	56 (100)
Withdrawn Prior Receiving Drug	0 (0)	0 (0)	11 (3.3)	12 (3.5)	2 (1.1) ²	4 (2.4) ²	1 (0.6) ²	8 (2.7)	16 (5.6)	1 (1.8)	0 (0)
Withdrawn During Treatment	28 (18.5) ¹	5 (3.2)	107 (32.0)	85 (24.8)	48 (26.2)	14 (8.2)	55 (31.4)	95 (31.6) ³	52 (18.1)	5 (9.1)	0 (0)
Adverse Event	14 (9.3)	0 (0)	29 (8.7)	12 (3.5)	8 (4.4)	2 (1.2)	6 (3.4)	17 (5.6)	2 (0.7)	1 (1.8)	0 (0)
Protocol Violation	1 (0.7)	4 (2.5)	6 (1.8)	3 (0.9)	3 (1.6)	1 (0.6)	0 (0)	4 (1.3) ³	14 (4.9)	1 (1.8)	0 (0)
Withdrew Consent	9 (6.0)	0 (0)	50 (15.0)	32 (9.3)	20 (10.9)	6 (3.5)	19 (10.9)	47 (15.6)	19 (6.6)	3 (5.5)	0 (0)
Subject Died	0 (0)	1 (0.6)	4 (1.2)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Investigator Decision	3 (2.0)	0 (0)	5 (1.5)	8 (2.3)	13 (7.1)	2 (1.2)	10 (5.7)	15 (5.0)	7 (2.4)	0 (0)	0 (0)
Lost to Follow-up	1 (0.7)	0 (0)	6 (1.8)	22 (6.4)	1 (0.5)	3 (1.8)	0 (0)	5 (1.7)	5 (1.7)	0 (0)	0 (0)
Other	0 (0)	0 (0)	7 (2.1)	7 (2.0)	3 (1.6)	0 (0)	20 (11.4)	7 (2.3)	5 (1.7)	0 (0)	0 (0)

¹ Study 014: The sponsor reported 30 TI-treated subjects prematurely discontinued which included 2 subjects who completed the treatment, but 1 did not complete the follow-up visit and 1 discontinued later due to an adverse event.

² Study 103: The sponsor grouped those subjects in the discontinuation *during treatment* categories.

³ Study 009: Including 1 subject (no. 5007) who was not a completer, but did not have any discontinuation reason recorded in the electronic data file submitted.

Table 7 – Demographic and Baseline Characteristics of the T2DM Placebo and No-Treatment Control Trials

Study	005 (11-week)					0008 (12-week)		026 (12-week)	
Group	T (Placebo)	TI 14 U	TI 28 U	TI 42 U	TI 56 U	TI	T (placebo)	TI	No- Treatment
ITT	(n = 41)	(n = 44)	(n = 44)	(n = 41)	(n = 42)	(n = 58)	(n = 61)	(n = 75)	(n = 15)
Gender:									
Male	19 (46.3)	22 (50.0)	27 (61.4)	24 (58.5)	25 (59.5)	37 (63.8)	43 (70.5)	19 (25.3)	3 (20.0)
Female	22 (53.7)	22 (50.0)	17 (38.6)	17 (41.5)	17 (40.5)	21 (36.2)	18 (29.5)	56 (74.7)	12 (80.0)
Race:									
Caucasian	41 (100)	44 (100)	44 (100)	41 (100)	41 (97.6)	39 (67.2)	38 (62.3)	75 (100)	15 (100)
Black	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (10.3)	3 (4.9)	0 (0)	0 (0)
Hispanic	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	11 (19.0)	14 (23.0)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.7)	5 (8.2)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)	1 (1.7)	1 (1.6)	0 (0)	0 (0)
Country:									
USA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	58 (100)	61 (100)	0 (0)	0 (0)
Non-USA	41 (100)	44 (100)	44 (100)	41 (100)	42 (100)	0 (0)	0 (0)	75 (100)	15 (100)
Age (years)	58.4 ± 8.8	58.5 ± 8.9	57.8 ± 7.8	59.4 ± 9.0	55.5 ± 8.0	56.0 ± 8.7	53.8 ± 10.0	53.9 ± 4.8	53.1 ± 3.7
BMI (kg/m ²)	29.8 ± 3.5	30.1 ± 5.1	30.5 ± 4.2	29.3 ± 3.4	29.8 ± 4.3	29.8 ± 3.3	31.3 ± 4.1	30.8 ± 4.1	32.9 ± 3.5
HbA1c (%)	9.1 ± 1.3	9.3 ± 1.5	8.8 ± 1.4	8.7 ± 1.3	9.2 ± 1.4	7.9 ± 1.2	7.8 ± 1.1	9.6 ± 1.4	9.3 ± 1.5

Table 8 – Demographic and Baseline Characteristics of the T2DM and T1DM Comparative Trials

Study	Type 2 Diabetes Mellitus (T2DM)						Type 1 Diabetes Mellitus (T1DM)				
	014 (24-week)		102 (52-week)		103 (12-week)		009 (52-week)		101 (12-week)		
Group ITT	TI + L (n = 150)	IA + L (n = 155)	TI + L (n = 302)	Premix (n = 316)	TI alone (n = 177)	M + S (n = 162)	TI + M (n = 169)	TI + L (n = 277)	IA + L (n = 262)	TI + L (n = 51)	IA + L (n = 56)
Gender:											
Male	40 (26.7)	31 (20.0)	153 (50.7)	137 (43.4)	84 (47.5)	74 (45.7)	68 (40.2)	146 (52.7)	136 (51.9)	13 (25.5)	28 (50.0)
Female	110 (73.3)	124 (80.0)	149 (49.3)	179 (56.6)	93 (52.5)	88 (54.3)	101 (59.8)	131 (47.3)	126 (48.1)	38 (74.5)	28 (50.0)
Race:											
Caucasian	149 (99.3)	155 (100)	202 (66.9)	215 (68.0)	133 (75.1)	114 (70.4)	129 (76.3)	237 (85.6)	227 (86.6)	51 (100)	56 (100)
Black	0 (0)	0 (0)	25 (8.3)	27 (8.5)	9 (5.1)	8 (4.9)	12 (7.1)	18 (6.5)	14 (5.3)	0 (0)	0 (0)
Hispanic	0 (0)	0 (0)	61 (20.2)	64 (20.3)	26 (14.7)	25 (15.4)	23 (13.6)	13 (4.7)	17 (6.5)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	8 (2.6)	4 (1.3)	4 (2.3)	5 (3.1)	2 (1.2)	5 (1.8)	1 (0.4)	0 (0)	0 (0)
Other	1 (0.7)	0 (0)	6 (2.0)	6 (1.9)	5 (2.8)	10 (6.2)	3 (1.8)	4 (1.4)	3 (1.1)	0 (0)	0 (0)
Country:											
USA	0 (0)	0 (0)	140 (46.4)	138 (43.7)	34 (19.2)	29 (17.9)	29 (17.2)	141 (50.9)	128 (48.9)	0 (0)	0 (0)
Non-USA	150 (100)	155 (100)	162 (53.6)	178 (56.3)	143 (80.8)	133 (82.1)	140 (82.8)	136 (49.1)	134 (51.1)	51 (100)	56 (100)
Age (years)	58.7 ± 8.6	58.3 ± 8.2	55.9 ± 10.6	55.9 ± 10.0	57.3 ± 8.5	57.6 ± 9.1	56.8 ± 8.3	37.9 ± 13	38.2 ± 13	32.9 ± 11	35.6 ± 12
BMI (kg/m ²)	31.2 ± 4.9	30.4 ± 4.5	31.6 ± 4.8 (n = 290)	31.1 ± 4.9 (n = 311)	31.2 ± 4.3	30.7 ± 4.6	30.8 ± 4.4	26.1 ± 4.0	26.2 ± 3.6	24.9 ± 4.0	23.8 ± 2.9
HbA1c (%)	8.9 ± 1.1	9.0 ± 1.3	8.7 ± 1.1	8.7 ± 1.1	8.9 ± 0.9	8.9 ± 0.9	9.0 ± 1.0	8.4 ± 0.9	8.5 ± 1.0	9.0 ± 1.2	8.9 ± 1.2

3.1.5 Efficacy Results and Discussion

Unless otherwise noted, the following discussions were based on the ITT population with LOCF for missing data. Also, unless otherwise noted, the presented results were based on this reviewer’s analyses.

TYPE 2 DIABETES MELLITUS (T2DM)

Study 005 (a placebo-controlled trial)

As shown in Table 9, for all the TI dose groups (14, 28, 42, and 56 U), the mean HbA1c values were decreased from baseline after 11 weeks of treatment, while the T (placebo) group exhibited a mean increase. Except the 14 U dose group, all the other TI dose groups showed a highly significant mean reduction in HbA1c when compared with the T (placebo) group. However, the reductions were not strictly monotonic across the dose groups based on either raw or adjusted means. In fact, the reductions were numerically similar among the 28, 42, and 56 U dose groups. This reviewer did a regression analysis with change from baseline as the dependent variable and dose (14, 28, 42, and 56 U) and baseline HbA1c as the independent variables to assess dose-response. It was found that there was no statistically significant dose-response as the slope was -0.0058 with p-value = 0.22 (Figure 1).

Note that in this study, patients randomized to the 28, 42, and 56 U groups actually received the doses for only 10, 9, and 8 weeks, respectively, during the 11-week treatment period. Because of the study design, the true dose response to HbA1c may be confounded by the forced titration scheme.

Table 9 – Study 005 – Efficacy Results for HbA1c

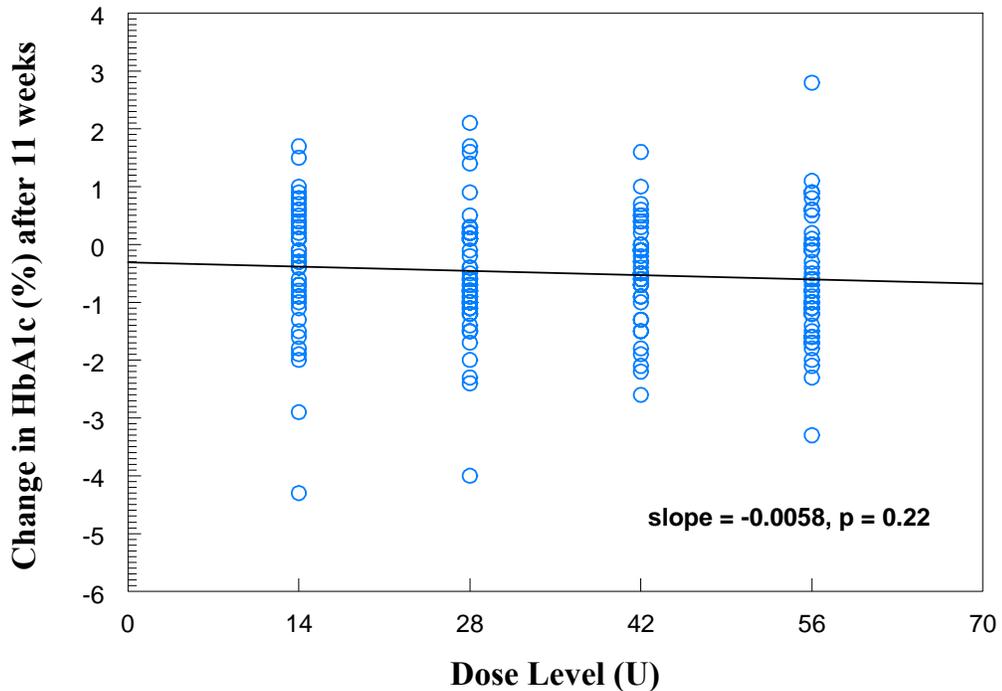
Trt Group ITT/LOCF	N	Chg from Baseline Raw Mean (SD)	Chg from Baseline LS Mean (SE)	Treatment Diff LS Mean (SE)	95% CI *	p-value *
T (placebo)	41	0.24 (0.91)	0.23 (0.15)	---	---	---
TI 14 U	43	-0.35 (1.15)	-0.29 (0.14)	-0.52 (0.21)	(-1.03, -0.01)	0.0439
TI 28 U	43	-0.54 (1.15)	-0.59 (0.14)	-0.82 (0.21)	(-1.33, -0.31)	0.0004
TI 42 U	41	-0.47 (0.91)	-0.49 (0.15)	-0.72 (0.21)	(-1.24, -0.21)	0.0026
TI 56 U	42	-0.62 (1.11)	-0.59 (0.15)	-0.82 (0.21)	(-1.33, -0.31)	0.0004

The ANCOVA model included treatment as a fixed factor and baseline HbA1c as a covariate.
 * Results were based on Dunnett’s t-test and similar to the sponsor’s unadjusted t-test (with site included in the statistical model).

Similar findings were also observed for completers or when time adjusted Lantus exposure (TALE) was included in the statistical model.

Figure 1

Study 005 (T2DM): HbA1c (%)
ITT Population with LOCF



Study 0008 (a placebo-controlled trial)

After 12 weeks of treatment, the mean HbA1c in the TI and T (placebo) groups were reduced by 0.7% and 0.3% from baseline, respectively (Table 10). The mean reduction was statistically significantly larger in the TI group than in the T (placebo) group regardless of analysis population (ITT with observed data, ITT with LOCF, or completers) and method (2-sample t-test or ANCOVA). The treatment difference between the TI and T (placebo) group was about -0.4%, with 95% CI = (-0.6%, -0.1%). Note that p = 0.0026 reported by the sponsor for comparing the 2 study groups was obtained by 1-sided 2-sample t-test on the ITT population with observed data.

The sponsor’s SAP also called for a subgroup analysis for baseline HbA1c (6.6 – 7.9% and 8.0 – 10.5%). The treatment-by-subgroup interaction p was 0.054 using the ITT population with LOCF. Therefore, the 2 subgroups were evaluated separately. For the subjects in the lower baseline HbA1c subgroup (6.6 – 7.9%), the mean reductions in HbA1c after 12 weeks of treatment were 0.44% and 0.23% for the TI and T (placebo) groups, respectively. For the

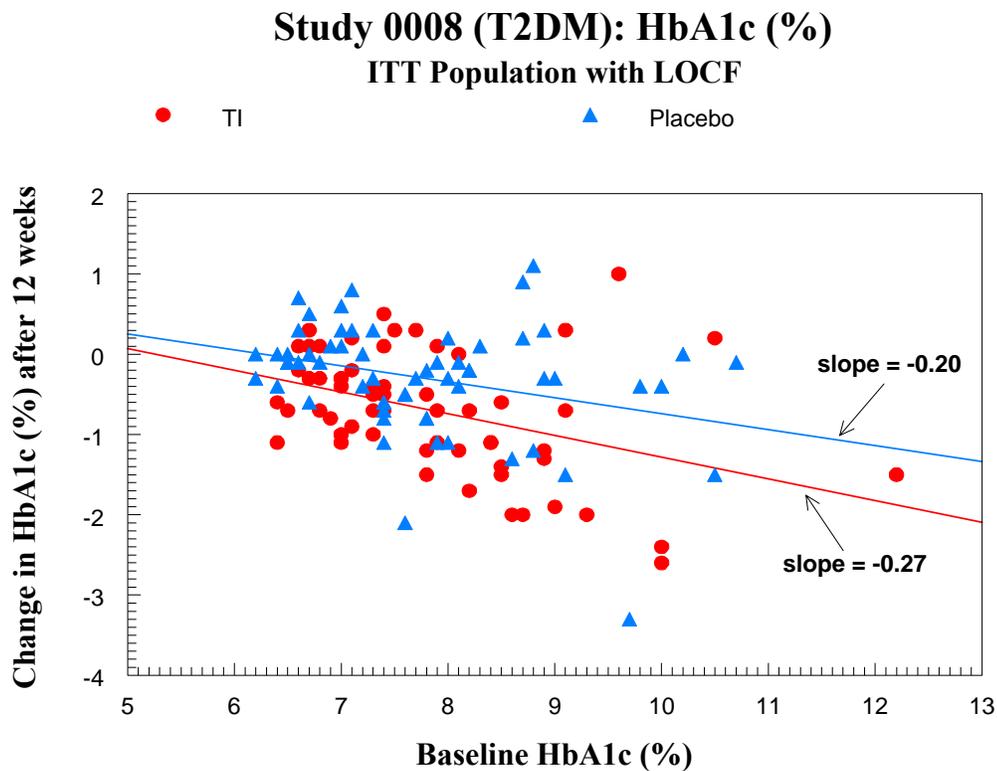
subjects in the higher baseline HbA1c subgroup (8.0 – 10.5%), the mean reductions in HbA1c after 12 weeks of treatment were 1.15% and 0.43% for the TI and T (placebo) groups, respectively. The difference in treatment effect on HbA1c between the 2 subgroups was quantitative, not qualitative. As Figure 2 depicts, the higher the baseline HbA1c was, the greater the reduction was observed in general.

Table 10 – Study 0008 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 3) Mean (SD)	Week 15 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI	58	7.87 (1.15)	7.16 (1.09)	-0.71 (0.77)	-0.70 (0.09)
T (placebo)	61	7.78 (1.11)	7.48 (1.12)	-0.30 (0.72)	-0.31 (0.09)
Treatment Comparison			Treatment Difference		
			LS Mean (SE)	95% CI	p-value
TI vs. T (placebo) (ITT w/ LOCF)			-0.39 (0.13)	(-0.64, -0.13)	0.0032
TI vs. T (placebo) (Completers)			-0.37 (0.13)	(-0.64, -0.11)	0.0065

The ANCOVA model included treatment as a fixed factor and baseline HbA1c as a covariate.

Figure 2



Study 026 (a no-treatment control trial)

After 12 weeks of treatment, the TI group showed a significant mean reduction in HbA1c from baseline (-1.40%, $p < 0.0001$, $n = 75$). However, the no-treatment control group also showed a significant mean reduction in HbA1c from baseline (-1.24%, $p = 0.0001$, $n = 15$). The difference between the 2 study groups was not statistically significant ($p = 0.90$, Table 11). Note that the patients in both study groups continued their previously (prior entry) described OAD(s) during the course of the study.

Table 11 – Study 026 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 2) Mean (SD)	Week 14 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI	75	9.58 (1.39)	8.18 (1.12)	-1.40 (1.15)	-1.38 (0.10)
No Treatment Control	15	9.33 (1.50)	8.09 (1.06)	-1.24 (0.93)	-1.35 (0.23)
Treatment Comparison			Treatment Difference		
			LS Mean (SE)	95% CI	p-value
TI vs. No Treatment Control (ITT w/ LOCF)			-0.03 (0.25)	(-0.52, 0.46)	0.90
The ANCOVA model included treatment as a fixed factor and baseline HbA1c as the covariate. Similar results were observed when the disqualified site (No. 518) was excluded from the analysis.					

Study 014 (an active-controlled trial)

After 24 weeks of treatment, both TI + Lantus and insulin aspart + Lantus groups showed a significant mean reduction in HbA1c from baseline ($p < 0.0001$). However, the HbA1c reduction in the TI + Lantus group was statistically significantly less than that in the insulin aspart + Lantus group (treatment difference = +0.36%, p -value = 0.002, Table 12) using the ITT population with LOCF. The 95% CI of the treatment difference was (0.14%, 0.58%). If the sponsor’s equivalence definition (95% CI within $\pm 0.4\%$, primary objective) was applied, the 2 study groups were not comparable. If the non-inferiority criterion (upper bound of 95% CI $< 0.4\%$) was applied, the TI + Lantus group was not non-inferior to the insulin aspart + Lantus group (reviewer’s analysis, no pre-defined NI margin given).

In the sponsor’s findings (Table 13), the TI + Lantus and insulin aspart + Lantus groups were comparable in reducing HbA1c from baseline after 24 weeks of treatment in the ITT (no LOCF) population, but not in the primary efficacy (i.e., PP) population, according to their equivalence definition (95% CI within $\pm 0.4\%$). This reviewer thinks that the sponsor’s comparable finding based on the ITT (no LOCF) population was biased because the results were conservative due to exclusion of missing data. When the ITT/LOCF population was

used, the sponsor’s results (with site in the statistical model) were similar to this reviewer’s results (without site in the statistical model).

Table 12 – Study 014 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 24 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	150	8.85 (1.10)	7.96 (1.34)	-0.89 (1.14)	-0.92 (0.08)
Insulin aspart + Lantus	155	9.00 (1.31)	7.69 (1.09)	-1.31 (1.08)	-1.28 (0.08)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF)			0.36 (0.11)	(0.14, 0.58)	0.002
TI + Lantus vs. Insulin aspart + Lantus (Completers)			0.23 (0.12)	(-0.00, 0.47)	0.052
The ANCOVA model included treatment as a fixed factor and baseline HbA1c as the covariate. Similar results were observed when the disqualified sites (Nos. 517 and 518) were excluded from the analysis.					

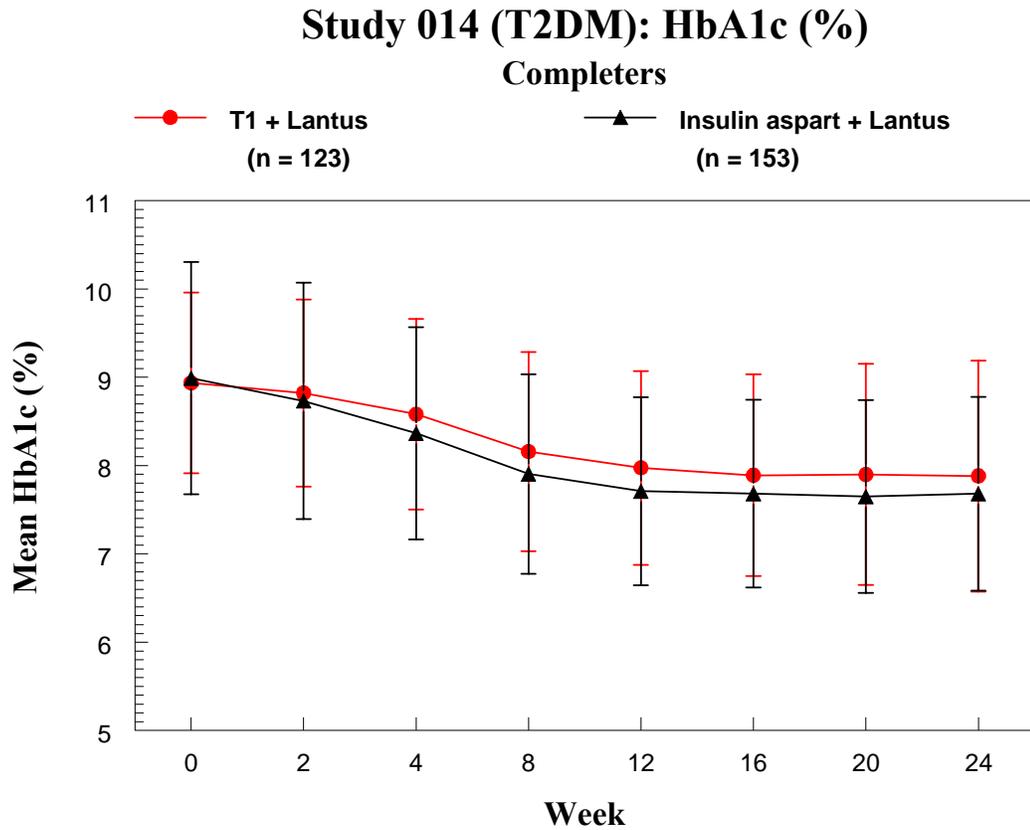
Table 13 – Study 014 – Comparison of HbA1c Efficacy Results with or without Site in Statistical Model

Including Site	Population	Treatment Diff.	95% CI	Equivalence ^a	p-value	Equivalence ^b
Yes (sponsor’s)	PP	0.21	(-0.03, 0.45)	No	0.082	Yes
	ITT (no LOCF)	0.15	(-0.09, 0.38)	Yes	0.224	Yes
	ITT (LOCF)	0.29	(0.07, 0.52)	No	0.011	No
No (reviewer’s)	PP	0.28	(0.04, 0.51)	No	0.021	No
	ITT (no LOCF)	0.24	(0.00, 0.47)	No	0.046	No
	ITT (LOCF)	0.36	(0.14, 0.58)	No	0.002	No
^a Conclusion based on the sponsor’s equivalence definition (95% CI of treatment difference within ±0.4%)						
^b Conclusion based on significance level at p ≤ 0.05						

Similar findings were observed when time adjusted Lantus exposure (TALE) was included or when pooled site factor was used in this reviewer’s model. The overall mean daily Lantus dose used in the TI and insulin aspart arms were 31.6 ± 10.6 and 31.2 ± 10.8 IU, respectively.

Figure 3 below shows the mean HbA1c profile over time for the completers. In both treatment groups, the mean HbA1c was decreasing gradually from baseline to Week 12 and then sustained throughout the rest of the trial, with the TI + Lantus group consistently showing less reduction than the insulin aspart + Lantus group at all time points.

Figure 3



Figures 4 and 5 below depict that at least 75% of the subjects in each group had their HbA1c lowered from baseline at endpoint, but % of subjects reaching 7% or lower in the final HbA1c was small in each group. The TI + Lantus group consistently showed a smaller reduction in HbA1c for any % of subjects and a smaller % of subjects reaching almost any level of HbA1c at endpoint when compared with the insulin aspart + Lantus group.

Figure 4

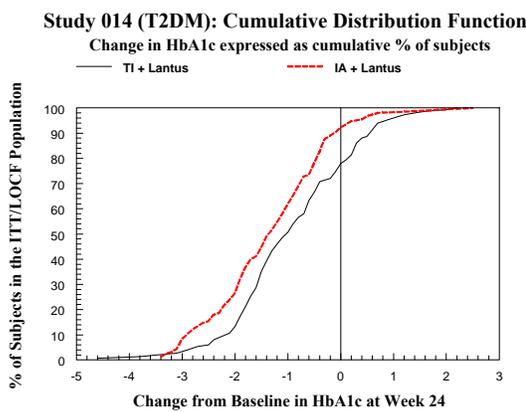
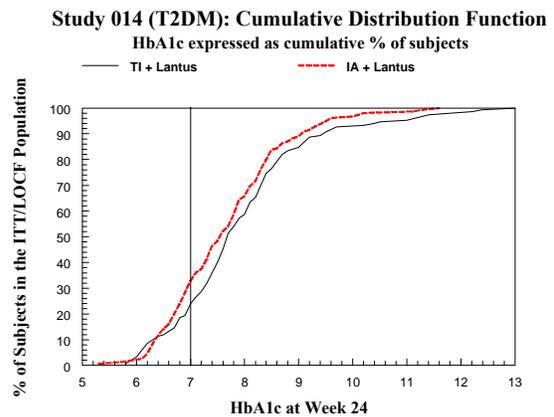


Figure 5



Specifically, the percentages of responders defined as patients with Week 24 HbA1c value $\leq 6.5\%$, $\leq 7.0\%$, or $\leq 8.0\%$ were all numerically smaller in the TI + Lantus group than in the insulin aspart + Lantus group, as shown in Table 14.

Table 14 – Study 014 – Responder Rates for HbA1c

ITT with LOCF	TI + Lantus (n = 150)	Insulin aspart + Lantus (n = 155)	Difference in Proportion	Asymptotic 95% CI
HbA1c $\leq 6.5\%$ at Week 24	18 (12.0%)	22 (14.2%)	-2.2%	(-9.8%, 5.4%)
HbA1c $\leq 7.0\%$ at Week 24	36 (24.0%)	51 (32.9%)	-8.9%	(-19.0%, 1.2%)
HbA1c $\leq 8.0\%$ at Week 24	88 (58.7%)	102 (65.8%)	-7.1%	(-18.0%, 3.7%)

Study 102 (an active-controlled trial)

After 52 weeks of treatment, both TI + Lantus and Premixed 70/30 analog groups showed a significant mean reduction in HbA1c from baseline ($p < 0.0001$). Although the HbA1c reductions from baseline to Week 52 were not statistically different between the 2 study groups (treatment difference = +0.12%, $p = 0.16$), it was numerically less in the TI + Lantus group than in the Premixed 70/30 group. The non-inferiority of TI + Lantus to Premixed 70/30 analog in patients with T2DM was established in this study since the upper bound of the 95% CI of the treatment difference was 0.29%, less than the pre-defined non-inferiority margin 0.4%. All other supportive analyses also showed similar results (Table 15).

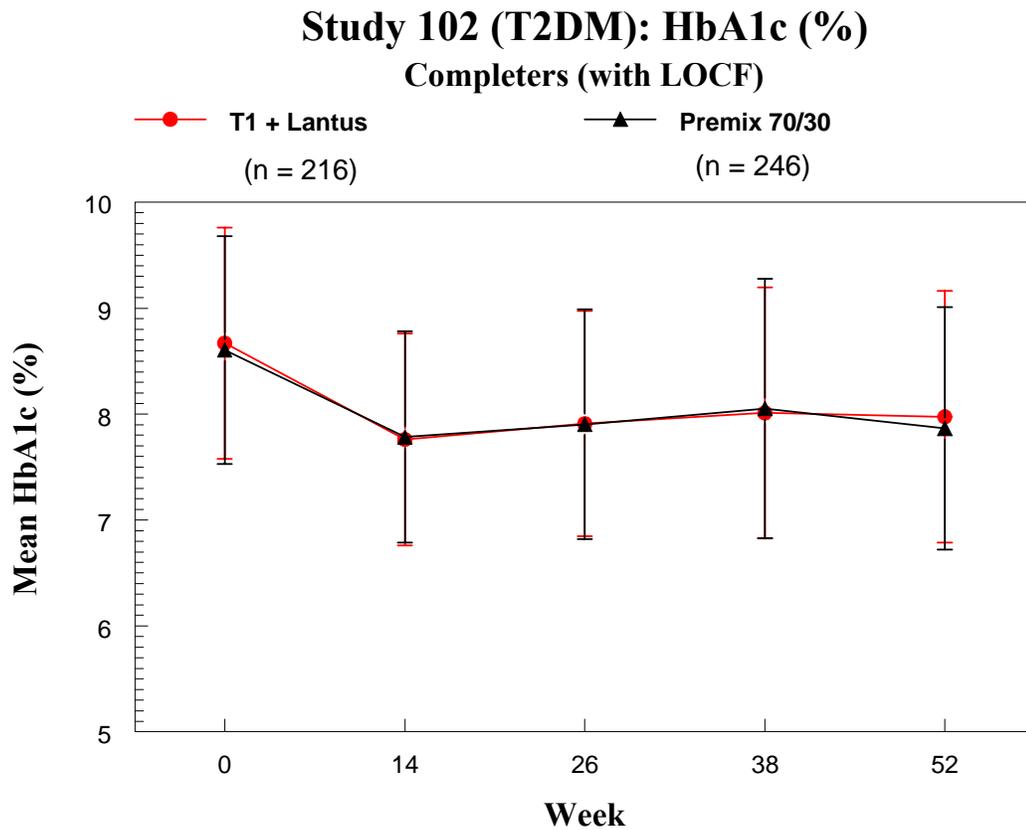
Table 15 – Study 102 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	302	8.69 (1.12)	8.11 (1.26)	-0.58 (1.22)	-0.59 (0.06)
Premixed 70/30 analog	316	8.68 (1.08)	7.98 (1.16)	-0.70 (1.16)	-0.71 (0.06)
Treatment Comparison	Treatment Difference				
	LS Mean (SE)	95% CI	p-value		
TI + Lantus vs. Premixed 70/30 analog (ITT w/ LOCF)	0.12 (0.09)	(-0.05, 0.29)	0.16		
TI + Lantus vs. Premixed 70/30 analog (Completers)	0.06 (0.10)	(-0.14, 0.26)	0.55		
TI + Lantus vs. Premixed 70/30 analog (Dropouts)	0.30 (0.19)	(-0.07, 0.68)	0.11		
TI + Lantus vs. Premixed 70/30 analog (ITT using MMRM with AR(1) for variance-covariance structure)	0.09 (0.09)	(-0.09, 0.27)	0.31		
The ANCOVA model included treatment and pooled site as fixed factors and baseline HbA1c as the covariate. Similar results were observed when pooled site factor was excluded from the model. In addition, similar results were observed when the disqualified sites (Nos. 286 and 325) were excluded from the analysis.					

In the dropout cohort, the TI + Lantus group showed a mean change of -0.30% (n = 86), while the Premixed 70/30 group showed -0.55% (n = 70), resulting in a raw mean treatment difference of +0.25%. Despite the magnitude, the treatment effect seen in the dropout cohort was consistent with what was observed in the ITT/LOCF population and completers.

Figure 6 below shows the mean HbA1c profile over time for the completers. In both treatment groups, the mean HbA1c was decreased from baseline to Week 14, then went up slightly at Week 26, and then was sustained for the rest of the trial.

Figure 6



Figures 7 and 8 below depict that at least 70% of the subjects in each group had their HbA1c lowered from baseline at endpoint, but % of subjects reaching 7% or lower in the final HbA1c was around 20% in each group. The TI + Lantus group consistently showed a similar change in HbA1c for any % of subjects and a similar % of subjects reaching any level of HbA1c at endpoint when compared with the Premixed 70/30 analog group.

Figure 7

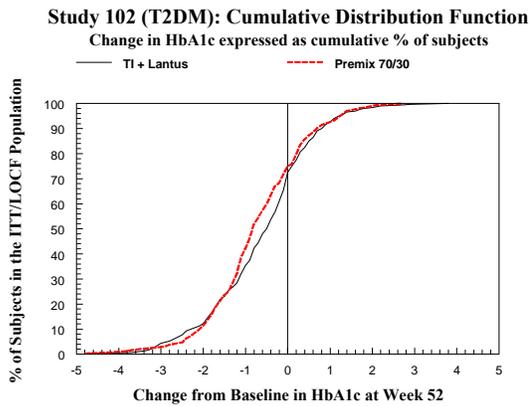
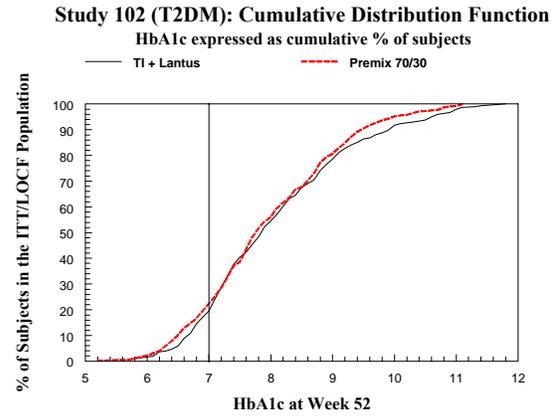


Figure 8



Specifically, the percentages of responders defined as patients with Week 52 HbA1c value $\leq 6.5\%$, $\leq 7.0\%$, or $\leq 8.0\%$ were similar between the 2 study groups, as shown in Table 16, although they were all numerically smaller in the TI + Lantus group than in the Premixed 70/30 analog group.

Table 16 – Study 102 – Responder Rates for HbA1c

ITT with LOCF	TI + Lantus (n = 302)	Premixed 70/30 (n = 316)	Difference in Proportion	Asymptotic 95% CI
HbA1c $\leq 6.5\%$ at Week 52	18 (6.0%)	32 (10.1%)	-4.2%	(-8.4%, 0.1%)
HbA1c $\leq 7.0\%$ at Week 52	59 (19.5%)	71 (22.5%)	-2.9%	(-9.4%, 3.5%)
HbA1c $\leq 8.0\%$ at Week 52	165 (54.6%)	177 (56.0%)	-1.4%	(-9.2%, 6.5%)

Study 103 (an active-controlled trial)

After 12 weeks of treatment, both TI + Metformin and Metformin + Secretagogue groups showed a significant mean reduction in HbA1c from baseline ($p < 0.0001$). However, the TI alone group exhibited a mean **increase** in HbA1c from baseline at Week 12 (+0.23%, Table 17). The superiority of TI + Metformin over Metformin + Secretagogue treatment in improving HbA1c (primary objective) was not established since the 95% CI, (-0.13, 0.33), of the treatment difference contained zero (Table 17). However, TI + Metformin may be claimed to be non-inferior to Metformin + Secretagogue in reducing HbA1c after 12 weeks of treatment, since the upper bound of the 95% CI of the treatment difference was 0.33%, less than the 0.4% non-inferiority margin (reviewer’s analysis, no pre-defined NI margin given by the sponsor).

Similar findings were also observed when only the completers were analyzed, except that the mean HbA1c reduction was numerically smaller in the TI + Metformin group in the

ITT/LOCF population, but slightly larger in the completer cohort, when compared with the Metformin + Secretagogue group. This opposite finding in treatment difference between the ITT/LOCF population (+0.10%) and completers (-0.06%) may be due to the high dropout rate (31%) associated with less efficacy in the TI + Metformin group. In the dropout cohort, the TI + Metformin group showed a mean change of -0.17% (n = 50), while the Metformin + Secretagogue group showed -0.53% (n = 10), resulting in a raw mean treatment difference of +0.36%. Consequently, a compromised efficacy in the TI + Metformin group was shown in the ITT population when the last observations were carried forward for those dropouts.

The finding of an **increased** mean in HbA1c after 12 weeks of treatment in the TI alone group in the ITT/LOCF population (+0.23%, n = 176) was also observed in the completer (+0.12%, n = 133) and dropout (+0.57%, n = 43) cohorts. The mean change in the TI alone group was highly significantly different from that in the Metformin + Secretagogue group (Dunnett’s p < 0.0001), favoring treatment of metformin combined with secretagogue.

Table 17 – Study 103 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 12 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI alone	176	8.92 (0.95)	9.15 (1.27)	0.23 (1.19)	0.21 (0.07)
Metformin + Secretagogue	162	8.90 (0.94)	8.15 (1.04)	-0.75 (0.90)	-0.78 (0.08)
TI + Metformin	169	8.95 (0.97)	8.25 (1.09)	-0.70 (1.01)	-0.67 (0.07)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI *	p-value *
TI + Met. vs. Met. + Secretagogue (ITT w/ LOCF)			0.10 (0.10)	(-0.13, 0.33)	0.51
TI + Met. vs. Met + Secretagogue (Completers)			-0.06 (0.12)	(-0.33, 0.20)	0.81
TI + Met. vs. Met. + Secretagogue (Dropouts)			0.33 (0.26)	(-0.24, 0.90)	0.29
The ANCOVA model included treatment and pooled site as fixed factors and baseline HbA1c as the covariate. Similar results were observed when pooled site factor was excluded from the model. In addition, similar results were observed when the disqualified site (No. 286) was excluded from the analysis.					
* Results were based on Dunnett’s t-test and similar to the sponsor’s unadjusted t-test.					

Figures 9 and 10 below depict that at least 75% of the subjects in the TI + Metformin and Metformin + Secretagogue groups had their HbA1c lowered from baseline at endpoint, but % of subjects reaching 7% or lower in the final HbA1c was around 15% in each group. The TI + Metformin group consistently showed a similar change in HbA1c for any % of subjects, but a smaller % of subjects reaching almost any level of HbA1c at endpoint when compared with the Metformin + Secretagogue group.

Figure 9

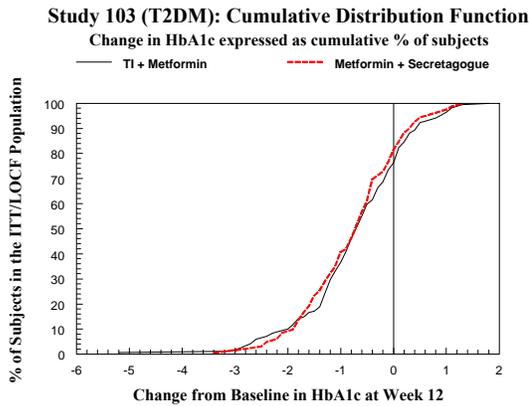
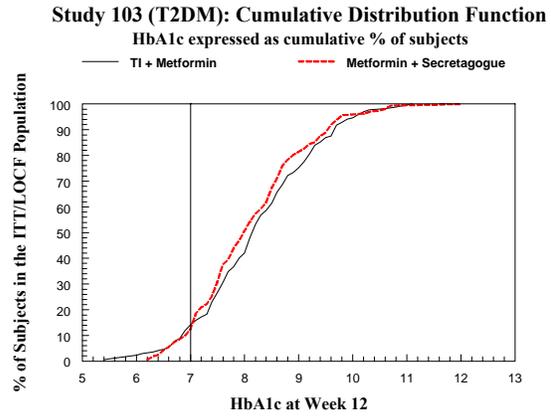


Figure 10



Specifically, the percentage of responders defined as patients with Week 12 HbA1c value $\leq 8.0\%$ was numerically smaller in the TI + Metformin group when compared with the Metformin + Secretagogue group, but was greater in the TI + Metformin group for the response categories of Week 12 HbA1c $\leq 6.5\%$ and $\leq 7.0\%$, as shown in Table 18.

Table 18 – Study 103 – Responder Rates for HbA1c

ITT with LOCF	TI + Metformin (n = 169)	Met. + Secretagogue (n = 162)	Difference in Proportion	Asymptotic 95% CI
HbA1c $\leq 6.5\%$ at Week 12	8 (4.7%)	7 (4.3%)	0.4%	(-4.1%, 4.9%)
HbA1c $\leq 7.0\%$ at Week 12	24 (14.2%)	20 (12.3%)	1.9%	(-5.5%, 9.2%)
HbA1c $\leq 8.0\%$ at Week 12	71 (42.0%)	82 (50.6%)	-8.6%	(-19.3%, 2.1%)

TYPE 1 DIABETES MELLITUS (T1DM)

Study 009 (an active-controlled trial)

After 52 weeks of treatment, both TI + Lantus and insulin aspart + Lantus groups showed a significant mean reduction in HbA1c from baseline ($p < 0.05$). However, the HbA1c reduction in the TI + Lantus group was statistically significantly less than that in the insulin aspart + Lantus group (treatment difference = +0.24%, p -value = 0.003, Table 19) using the ITT population with LOCF. (Note: the sponsor stated that the 2 treatment groups were *comparable*, but they were not in actuality.) The non-inferiority of TI + Lantus to insulin aspart + Lantus in patients with T1DM could **not** be firmly established in this study since the upper bound of the 95% CI of the treatment difference was 0.404%, right at the boundary of the pre-defined non-inferiority margin 0.4%.

The analysis for the completers also did not show non-inferiority of TI + Lantus to insulin aspart + Lantus in the reduction of HbA1c; the upper bound of the 95% CI of the treatment difference was 0.45% (> the NI margin 0.4%) for this cohort. In addition, there were 2 subjects (Nos. 1109 and 5029) listed as completers, but were excluded from the ITT/LOCF population by the sponsor since valid dosing/exposure data were not available on their trial dosing CRFs according to the sponsor. This reviewer re-analyzed the ITT/LOCF population by including the 2 patients' data and found no non-inferiority of TI + Lantus to insulin aspart + Lantus as well (upper bound of the 95% CI = 0.42%, > the NI margin 0.4%). Despite the magnitude, the treatment effect seen in the dropout cohort was consistent with what was observed in the ITT/LOCF population and completers.

Table 19 – Study 009 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	277	8.41 (0.92)	8.28 (1.19)	-0.14 (1.03)	-0.13 (0.06)
Insulin aspart + Lantus	262	8.48 (0.97)	8.09 (1.13)	-0.39 (0.93)	-0.37 (0.06)
Treatment Comparison	Treatment Difference			95% CI	p-value
	LS Mean (SE)				
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF)	0.24 (0.08)		(0.08, 0.404)	0.003	
TI + Lantus vs. Insulin aspart + Lantus (Completers)	0.26 (0.10)		(0.07, 0.45)	0.008	
TI + Lantus vs. Insulin aspart + Lantus (Dropouts)	0.06 (0.17)		(-0.28, 0.40)	0.731	
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF, but including Subjects 1109 and 5029)	0.25 (0.08)		(0.09, 0.42)	0.002	
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF, but excluding Sites 286 and 325)	0.26 (0.08)		(0.09, 0.42)	0.003	
TI + Lantus vs. Insulin aspart + Lantus (ITT using MMRM with AR(1) for variance-covariance structure)	0.27 (0.09)		(0.10, 0.44)	0.002	
The ANCOVA model included treatment and pooled site as fixed factors and baseline HbA1c as the covariate. Similar results were observed when pooled site factor was excluded from the model.					

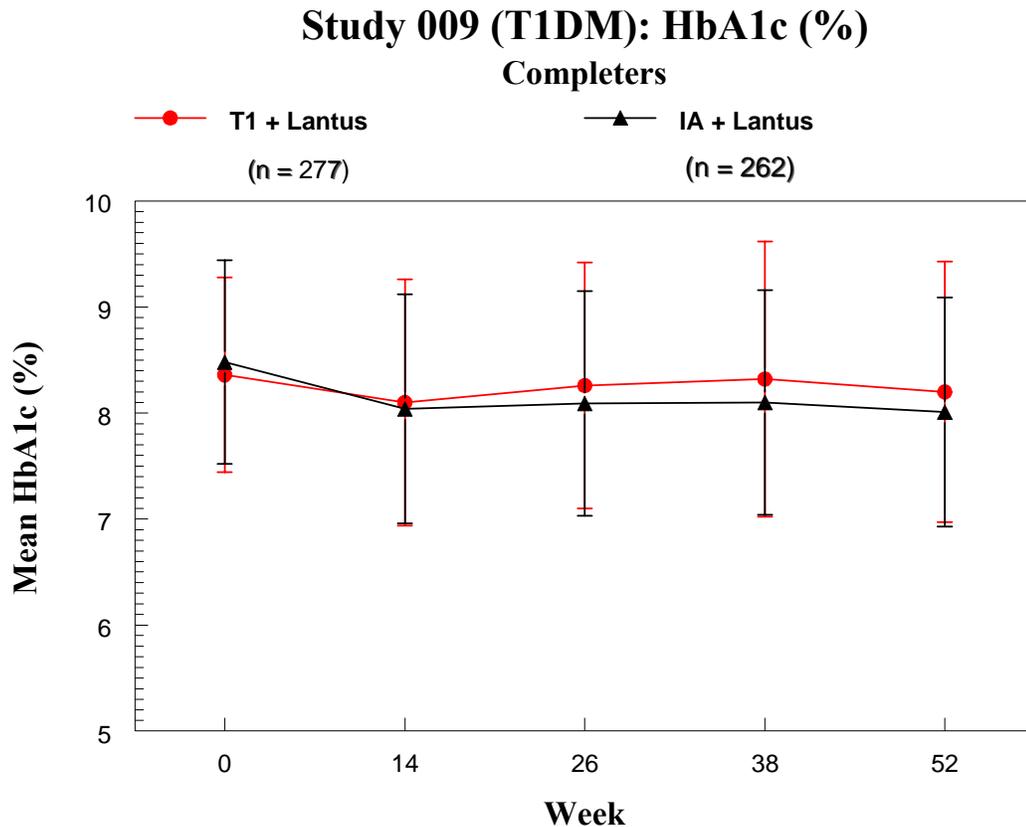
One of the sponsor's supportive analyses was mixed model repeated measures (MMRM) analysis which took the within-subject variation over time into consideration and did not require imputation for missing values. The sponsor's results from the MMRM analysis (with treatment and pooled site as fixed terms, visit as a repeated term, and baseline HbA1c as a covariate) showed a treatment difference of +0.25% with the associated 95% CI = (0.11, **0.38**), concluding that TI + Lantus treatment was non-inferior to insulin aspart + Lantus in lowering HbA1c since the upper bound of the 95% CI of the treatment difference was less than the NI margin 0.4%. However, the treatment-by-visit (time) interaction term was

omitted from the sponsor’s model. This reviewer thinks that this interaction term should be in the model in order to evaluate the contrast at Week 52. When this interaction term was included, the upper bound of the 95% CI of the treatment difference at Week 52 became 0.44% (> the NI margin 0.4%).

The overall mean daily Lantus dose used in the TI and insulin aspart arms were 32.4 ± 22.2 and 29.8 ± 12.8 IU, respectively. Similar finding was observed when the overall mean daily Lantus dose was included in the original statistical model.

Figure 11 below shows the mean HbA1c profile over time for the completers. In both treatment groups, the mean HbA1c was decreased from baseline to Week 14, then went up slightly at Week 26, and then was sustained for the rest of the trial.

Figure 11



Figures 12 and 13 below depict that at least 55% of the subjects in each group had their HbA1c lowered from baseline at endpoint, but % of subjects reaching 7% or lower in the final HbA1c was around 15% in each group. The TI + Lantus group consistently showed a

smaller reduction in HbA1c for any % of subjects and a smaller % of subjects reaching any level of HbA1c at endpoint when compared with the insulin aspart + Lantus group.

Figure 12

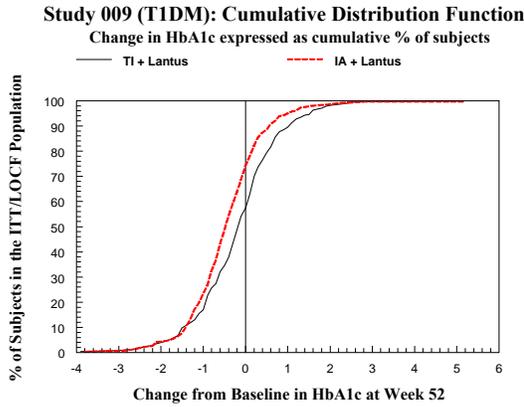
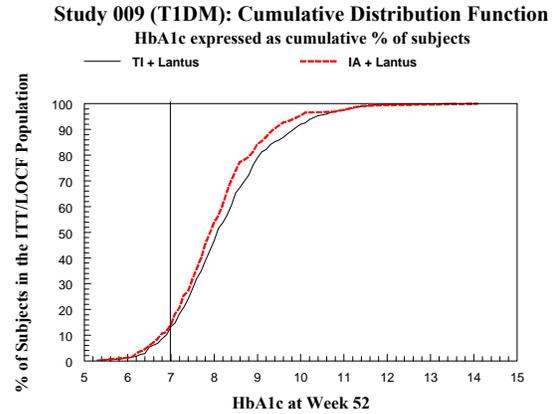


Figure 13



Specifically, the percentages of responders defined as patients with Week 52 HbA1c value $\leq 6.5\%$, $\leq 7.0\%$, or $\leq 8.0\%$ were all numerically smaller in the TI + Lantus group than in the insulin aspart + Lantus group, as shown in Table 20.

Table 20 – Study 009 – Responder Rates for HbA1c

ITT with LOCF	TI + Lantus (n = 277)	Insulin aspart + Lantus (n = 262)	Difference in Proportion	Asymptotic 95% CI
HbA1c $\leq 6.5\%$ at Week 52	15 (5.4%)	16 (6.1%)	-0.7%	(-4.6%, 3.3%)
HbA1c $\leq 7.0\%$ at Week 52	37 (13.4%)	37 (14.1%)	-0.8%	(-6.6%, 5.1%)
HbA1c $\leq 8.0\%$ at Week 52	130 (46.9%)	141 (53.8%)	-6.9%	(-15.3%, 1.5%)

Study 101 (an active-controlled trial)

In this substitution study, HbA1c was a secondary efficacy variable. Since TI was given during the 3-week (Week -3 to Week 0) substitution period to gradually replace sc prandial insulin in the TI + Lantus group (see Section 3.1.1), the Week -4 HbA1c (screening) value, not Week 0, was used as the baseline for HbA1c measures.

At the end of the 12-week treatment period, both TI + Lantus and insulin aspart + Lantus groups showed a significant mean reduction in HbA1c from baseline ($p < 0.0001$). Although the mean HbA1c reductions from Week -4 (baseline) to Week 12 were not statistically different between the 2 study groups (treatment difference = +0.25%, $p = 0.15$, Table 21), it was numerically less in the TI + Lantus group than in the insulin aspart + Lantus group. The 95% CI of the treatment difference was (-0.09%, 0.58%). If the non-inferiority criterion

(upper bound of 95% CI < 0.4%) was applied, the TI + Lantus group was not non-inferior to the insulin aspart + Lantus group (reviewer’s analysis, no pre-defined NI margin given by the sponsor). All other supportive analyses also showed similar results (Table 21).

Table 21 – Study 101 – Efficacy Results for HbA1c

Treatment Group (ITT with LOCF)	N	Baseline (Week -4) Mean (SD)	Week 12 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
TI + Lantus	51	9.01 (1.22)	8.19 (1.10)	-0.81 (1.10)	-0.78 (0.12)
Insulin aspart + Lantus	56	8.88 (1.18)	7.89 (0.95)	-0.99 (1.07)	-1.02 (0.12)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF)			0.25 (0.17)	(-0.09, 0.58)	0.15
TI + Lantus vs. Insulin aspart + Lantus (completers)			0.21 (0.17)	(-0.13, 0.54)	0.22
TI + Lantus vs. Insulin aspart + Lantus (ITT w/ LOCF, but including Subjects 162, 236, and 650)			0.24 (0.16)	(-0.08, 0.57)	0.14
The ANCOVA model included treatment as a fixed factor and baseline HbA1c as the covariate.					
Subjects 162, 236, and 650 were excluded from the sponsor’s ITT population because they did not have post-baseline measurement of primary efficacy endpoint which was post-prandial glucose excursions AUC _{0-300 minutes} .					

According to the sponsor, there were 10 TI-treated subjects who also received insulin aspart (NovoRapid®) sporadically during the 12-week treatment period. Similar results were also observed when they were excluded from the analysis.

Figures 14 and 15 below depict that at least 80% of the subjects in each group had their HbA1c lowered from baseline at endpoint, but % of subjects reaching 7% or lower in the final HbA1c was small in each group. The TI + Lantus group consistently showed a smaller % of subjects reaching any level of HbA1c at endpoint when compared with the insulin aspart + Lantus group.

Figure 14

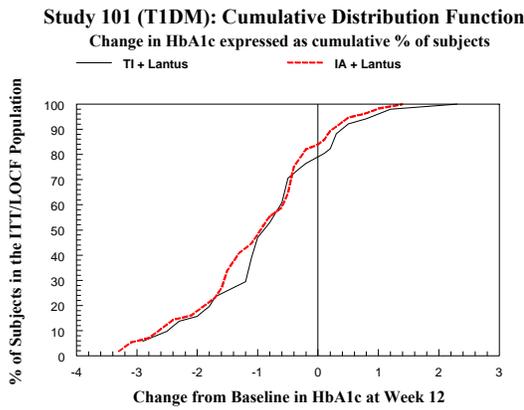
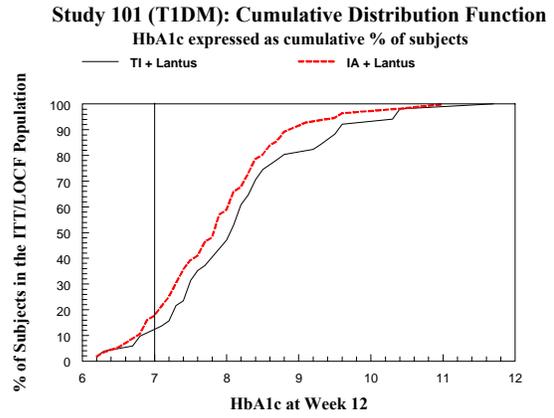


Figure 15



Specifically, the percentages of responders defined as patients with Week 12 HbA1c value $\leq 6.5\%$, $\leq 7.0\%$, or $\leq 8.0\%$ were all numerically smaller in the TI + Lantus group than in the insulin aspart + Lantus group, as shown in Table 22.

Table 22 – Study 101 – Responder Rates for HbA1c

ITT with LOCF	TI + Lantus (n = 51)	Insulin aspart + Lantus (n = 56)	Difference in Proportion	Asymptotic 95% CI
HbA1c $\leq 6.5\%$ at Week 12	2 (3.9%)	3 (5.4%)	-1.4%	(-9.4%, 6.5%)
HbA1c $\leq 7.0\%$ at Week 12	5 (9.8%)	10 (17.9%)	-8.1%	(-21.0%, 4.9%)
HbA1c $\leq 8.0\%$ at Week 12	24 (47.1%)	33 (58.9%)	-11.9%	(-30.7%, 6.9%)

3.2 Evaluation of Safety

See Dr. Lisa Yanoff (medical) and Joy Mele’s (statistical) reports for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Treatment effects on mean change from baseline in HbA1c at endpoint were consistent across the subgroups defined by age (< 65 years or ≥ 65 years), gender, and race for all the 3 T2DM comparative trials (Studies 014, 102 and 103) and Study 101 (T1DM), as no significant treatment-by-subgroup interactions were observed (all $p > 0.10$).

Treatment effects on mean change from baseline in HbA1c at endpoint for Study 009 (T1DM) were also consistent across the subgroups defined by age (< 65 years or ≥ 65 years) and race, but not gender since the treatment-by-sex interaction p-value was 0.0139 for the ITT/LOCF population. Therefore, the 2 sexes were evaluated separately. As shown in Table 23, the mean reduction from baseline in HbA1c at Week 52 for the male subjects with T1DM was almost 0% in the TI + Lantus group, compared with a 0.47% reduction in the insulin aspart + Lantus group. For the female subjects with T1DM, the mean reductions in HbA1c after 52 weeks of treatment were 0.19% and 0.26% for the TI + Lantus and insulin aspart + Lantus groups, respectively. The difference in treatment effect on HbA1c between the 2 subgroups was quantitative, not qualitative.

Table 23 – Study 009 – Efficacy Results for HbA1c by Sex

ITT LOCF	Change from Baseline at Week 52 : LS Mean ± SE (N)		Treatment Difference		
	TI + Lantus	Insulin aspart + Lantus	LS Mean (SE)	95% CI	p-value
ITT Population with LOCF					
Male	-0.00 ± 0.09 (146)	-0.47 ± 0.08 (136)	0.47 (0.12)	(0.23, 0.70)	0.0001
Female	-0.19 ± 0.09 (131)	-0.26 ± 0.09 (126)	0.07 (0.12)	(-0.17, 0.30)	0.58
Completers					
Male	-0.06 ± 0.11 (106)	-0.49 ± 0.10 (117)	0.43 (0.14)	(0.15, 0.71)	0.0027
Female	-0.29 ± 0.11 (92)	-0.35 ± 0.10 (103)	0.06 (0.15)	(-0.23, 0.34)	0.69

4.2 Other Special/Subgroup Populations

A subgroup analysis for baseline HbA1c (6.6 – 7.9% and 8.0 – 10.5%) was conducted for Study 0008 (specified in the sponsor's SAP); see discussions in Section 3.1.5 above. In response to the medical reviewer's request, subgroup analyses for baseline BMI (≤25, 25-30, >30 kg/m²) were conducted for Studies 014, 102, 103, 009, and 101; no significant treatment-by-BMI subgroup interactions were observed in these studies (all $p > 0.10$). There were no other special subgroups across all the T2DM and T1DM trials evaluated.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Since the study duration, comparator, type of disease, etc., were different among the 8 efficacy trials, this reviewer thinks that the data should not be combined for overall treatment estimate. The collective evidence is then summarized across the 8 efficacy trials by type of diabetes mellitus. Table 24 below shows the mean HbA1c at baseline and endpoint as well as the mean changes from baseline for all trials. Table 25 shows the statistical hypothesis testing results for HbA1c for all trials using the ITT population with LOCF.

Discussions of Type 2 Diabetic Trials

For the 2 placebo-controlled trials, the TI + Lantus (in Study 005) and TI + OAD(s) (in Study 0008) groups both showed a significant mean reduction in HbA1c from baseline at endpoint when compared with the placebo group. In the 005 forced-titration trial, the mean reductions were similar among the 28, 42, and 56 U dose groups, which implied that the dose levels might have reached a plateau or HbA1c levels might not have reached their steady states yet in this 11-week trial.

In Studies 0008 and 026, the patients in the TI group continued to take their previously (prior entry) described OAD(s), while in Study 103, the patients in the TI alone group were not allowed to take any other anti-glycemic therapies. All 3 studies were of 12 weeks of duration. The raw mean HbA1c changes for TI in Studies 0008 and 026 as shown in Table 24 were -0.71 ± 0.77 (n = 58) and -1.40 ± 1.15 (n = 75), respectively, while the raw mean change in Study 103 was $+0.23 \pm 1.19$ (n = 176).

Among all the active-controlled T2DM trials, TI + metformin was not superior (the sponsor's primary objective), but was non-inferior (this reviewer's analysis using the 0.4% NI margin), to metformin + secretagogue in lowering HbA1c in Study 103. The upper bound of the 95% CI of the treatment difference was 0.33% in this study (Table 25). TI + Lantus was non-inferior to Premixed 70/30 analog in reducing HbA1c in Study 102, but was **not** non-inferior to insulin aspart + Lantus in Study 014. The upper bounds of the 95% CI of the treatment differences were 0.29% and 0.58%, respectively, in these studies (Table 25). For all the active-controlled trials, the mean reductions in HbA1c from baseline to endpoint were numerically less in the TI arm than in the comparator arm. The treatment difference in Study 014 (+0.36%) showed statistical significance (p = 0.002), favoring the insulin aspart + Lantus treatment. Note that the sponsor's primary objective for Study 014 was an equivalence test defining as lower and upper bounds of the 95% CI of the treatment difference within $\pm 0.4\%$. It is apparent that the study did not have sufficient evidence to support the primary claim of equivalence.

Studies 102 and 103 had high dropout rates in the TI arms (32% and 31%, respectively). Therefore, statistical analyses were also performed for the completer cohort. Results were similar to the ones based on the ITT/LOCF population, indicating that the dropouts in each study did not have any major impact on the reduction of HbA1c.

Discussions of Type 1 Diabetic Trials

Technically speaking, there was only 1 confirmatory study submitted for the type 1 diabetes indication (Study 009). In this active-controlled trial, the mean reduction in HbA1c from baseline to endpoint in the TI + Lantus group was relatively small (-0.14%), which was statistically significantly less than that in the insulin aspart + Lantus group (treatment difference = +0.24%, $p = 0.003$, Table 25). The non-inferiority of TI + Lantus to insulin aspart + Lantus could **not** be established because the upper bound of the 95% CI of the treatment difference was 0.404%, greater than the pre-specified NI margin (0.4%) for this study. Since the dropout rate was high in the TI arm (32%), the completer cohort was analyzed as well. The results also showed that TI + Lantus was not non-inferior to insulin aspart + Lantus in lowering HbA1c because the upper bound of the 95% CI of the treatment difference was 0.45% (see Table 19 above). In addition, similar results were observed when a mixed model repeated measures (MMRM) analysis with contrast at Week 52 was performed to take missing data into consideration; the upper bound of the 95% CI of the treatment difference at endpoint in this case was 0.44% (see Table 19 above).

In Study 101, the mean reduction in HbA1c from baseline to endpoint was numerically less in the TI + Lantus group than in the insulin aspart + Lantus group. Although the treatment difference was not statistically significant, the upper bound of the 95% CI of the treatment difference was 0.58%, greater than the 0.4% non-inferiority margin (no pre-defined NI margin given by the sponsor). Note that HbA1c was not the primary efficacy variable in this study and the sample size was small.

Table 24 – Summary Statistics for HbA1c across Trials

Study (Duration)	Treatment Group (ITT with LOCF)	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change From Baseline	
					Raw Mean (SD)	LS Mean (SE)
Type 2 Diabetes Mellitus						
005 (11-week)	T (placebo)	41	8.70 (1.30)	8.94 (1.30)	0.24 (0.91)	0.23 (0.15)
	TI 14 U	43	8.91 (1.38)	8.55 (1.30)	-0.35 (1.15)	-0.29 (0.14)
	TI 28 U	43	8.59 (1.36)	8.05 (1.16)	-0.54 (1.15)	-0.59 (0.14)
	TI 42 U	41	8.68 (1.16)	8.21 (1.20)	-0.47 (0.91)	-0.49 (0.15)
	TI 56 U	42	8.82 (1.16)	8.20 (1.25)	-0.62 (1.11)	-0.59 (0.15)
Type 2 Diabetes Mellitus						
0008 (12-week)	TI	58	7.87 (1.15)	7.16 (1.09)	-0.71 (0.77)	-0.70 (0.09)
	T (placebo)	61	7.78 (1.11)	7.48 (1.12)	-0.30 (0.72)	-0.31 (0.09)
Type 2 Diabetes Mellitus						
026 (12-week)	TI	75	9.58 (1.39)	8.18 (1.12)	-1.40 (1.15)	-1.38 (0.10)
	No Treatment Control	15	9.33 (1.50)	8.09 (1.06)	-1.24 (0.93)	-1.35 (0.23)
Type 2 Diabetes Mellitus						
014 (24-week)	TI + Lantus	150	8.85 (1.10)	7.96 (1.34)	-0.89 (1.14)	-0.92 (0.08)
	Insulin aspart + Lantus	155	9.00 (1.31)	7.69 (1.09)	-1.31 (1.08)	-1.28 (0.08)
Type 2 Diabetes Mellitus						
102 (52-week)	TI + Lantus	302	8.69 (1.12)	8.11 (1.26)	-0.58 (1.22)	-0.59 (0.06)
	Premixed 70/30 analog	316	8.68 (1.08)	7.98 (1.16)	-0.70 (1.16)	-0.71 (0.06)
Type 2 Diabetes Mellitus						
103 (12-week)	TI alone	176	8.92 (0.95)	9.15 (1.27)	0.23 (1.19)	0.21 (0.07)
	Metformin + Secretagogue	162	8.90 (0.94)	8.15 (1.04)	-0.75 (0.90)	-0.78 (0.08)
	TI + Metformin	169	8.95 (0.97)	8.25 (1.09)	-0.70 (1.01)	-0.67 (0.07)
Type 1 Diabetes Mellitus						
009 (52-week)	TI + Lantus	277	8.41 (0.92)	8.28 (1.19)	-0.14 (1.03)	-0.13 (0.06)
	Insulin aspart + Lantus	262	8.48 (0.97)	8.09 (1.13)	-0.39 (0.93)	-0.37 (0.06)
Type 1 Diabetes Mellitus						
101 (12-week)	TI + Lantus	51	9.01 (1.22)	8.19 (1.10)	-0.81 (1.10)	-0.78 (0.12)
	Insulin aspart + Lantus	56	8.88 (1.18)	7.89 (0.95)	-0.99 (1.07)	-1.02 (0.12)

Table 25 – Efficacy Results for HbA1c across Trials Using the ITT/LOCF population

Study (Phase)	Duration	Treatment Group (ITT no.)	Primary Hypothesis Test	Treatment Difference (TI – control)			Reviewer’s Conclusion
				LS Mean (SE)	95% CI	p-value	
Type 2 Diabetes Mellitus							
005 (2)	11-week	<ul style="list-style-type: none"> TI 14, 28, 42, 56 U + Lantus (43, 43, 41, and 42, respectively) T (placebo) + Lantus (41) 	Superiority	14: -0.52 (0.21)	(-1.03, -0.01)	0.0439	➤ All doses (especially 28, 42, and 56 U) significantly better than placebo
				28: -0.82 (0.21)	(-1.33, -0.31)	0.0004	
				42: -0.72 (0.21)	(-1.24, -0.21)	0.0026	
				56: -0.82 (0.21)	(-1.33, -0.31)	0.0004	
0008 (2b)	12-week	<ul style="list-style-type: none"> TI (58) T (placebo) (61) 	Superiority	-0.39 (0.13)	(-0.64, -0.13)	0.003	➤ Significantly better than placebo
026 (2b)	12-week	<ul style="list-style-type: none"> TI (75) No Treatment (control) (15) 	Not specified	-0.03 (0.25)	(-0.52, 0.46)	0.90	<ul style="list-style-type: none"> ➤ Significant change from baseline ➤ No difference from no-treatment group
014 (3)	24-week	<ul style="list-style-type: none"> TI + Lantus (150) Insulin aspart + Lantus (155) 	Equivalence	+0.36 (0.11)	(0.14, 0.58)	0.002 a	<ul style="list-style-type: none"> ➤ Not NI (NI margin not pre-defined) ➤ Statistically worse
102 (3)	52-week	<ul style="list-style-type: none"> TI + Lantus (302) Premixed 70/30 analog (316) 	NI	+0.12 (0.09)	(-0.05, 0.29)	0.16 a	➤ NI
103 (3)	12-week	<ul style="list-style-type: none"> TI alone (176) Met. + Secretagogue (162) TI + Metformin (169) 	Superiority	TI+M vs. M+S (primary test): +0.10 (0.10)	(-0.13, 0.33)	0.51 a	<ul style="list-style-type: none"> ➤ Not Superior (TI + M vs. M + S) ➤ NI (NI margin not pre-defined)
Type 1 Diabetes Mellitus							
009 (3a)	52-week	<ul style="list-style-type: none"> TI + Lantus (277) Insulin aspart + Lantus (262) 	NI	+0.24 (0.08)	(0.08, 0.404)	0.003 a	<ul style="list-style-type: none"> ➤ Not NI ➤ Statistically worse
101 (2)	12-week	<ul style="list-style-type: none"> TI + Lantus (51) Insulin aspart + Lantus (56) 	Not specified	+0.25 (0.17)	(-0.09, 0.58)	0.15 a	➤ Not NI (NI margin not pre-defined)
a Regardless of statistical significance, the TI group showed a numerically less reduction in HbA1c when compared with the comparator.							

The proportions of subjects achieving HbA1c level $\leq 7.0\%$ at endpoint for Studies 014, 102, 103, 009, and 101 are presented in Table 26. It is shown that across the 5 comparative trials, regardless of type of diabetes mellitus, no more than 25% of the ITT subjects in the TI arm had reached 7% or less of HbA1c at endpoint. This phenomenon may be attributed to the high mean HbA1c at baseline ($\geq 8.5\%$ in general, see Table 8 above) with less than 1% of mean change at endpoint (Table 24) across the trials.

Table 26 – Summary of Responder Rate for HbA1c $\leq 7.0\%$ (ITT Population with LOCF)

Study	End of Treatment	TI	Comparator	Difference in Proportion	Asymptotic 95% CI
014 (T2DM)	Week 24	36/150 (24.0%)	51/155 (32.9%)	-8.9%	(-19.0%, 1.2%)
102 (T2DM)	Week 52	59/302 (19.5%)	71/316 (22.5%)	-2.9%	(-9.4%, 3.5%)
103 (T2DM)	Week 12	24/169 (14.2%)	20/162 (12.3%)	+1.9%	(-5.5%, 9.2%)
009 (T1DM)	Week 52	37/277 (13.4%)	37/262 (14.1%)	-0.8%	(-6.6%, 5.1%)
101 (T1DM)	Week 12	5/51 (9.8%)	10/56 (17.9%)	-8.1%	(-21.0%, 4.9%)

The 2-hour postprandial glucose after a standardized meal challenge (one of the secondary efficacy endpoints) was analyzed by the sponsor for Studies 102 and 009. Their statistical results are presented in Appendix II of this report.

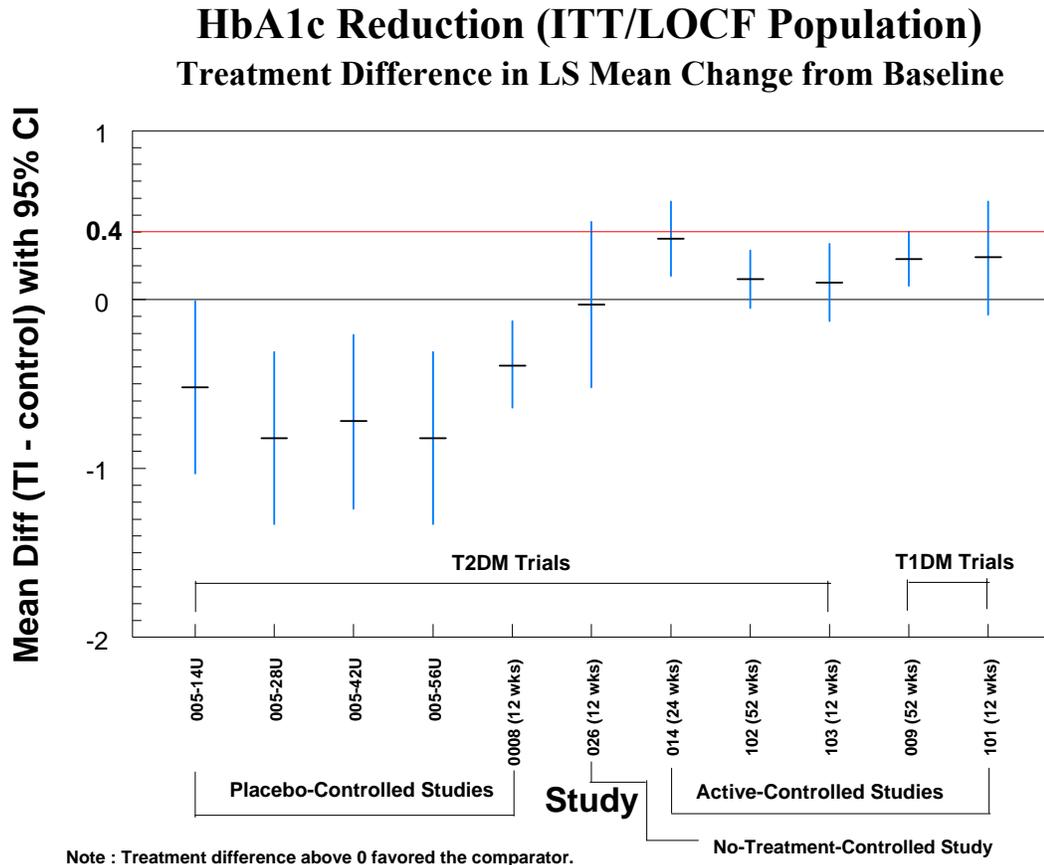
5.2 Conclusions and Recommendations

In this Technosphere[®] Insulin (TI) Inhalation Powder development program, data have demonstrated that TI, when combined with either insulin glargine (Lantus[®]) or OAD(s), was effective in lowering HbA1c when compared with placebo for type 2 diabetic patients.

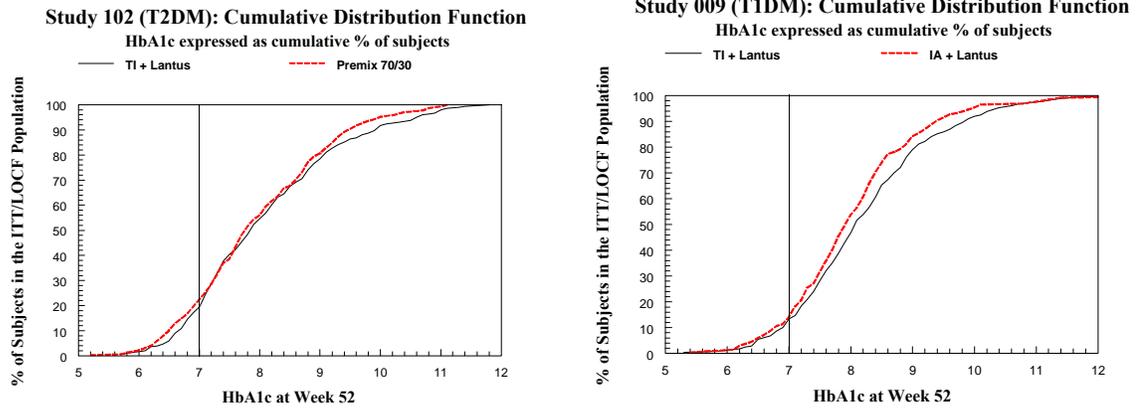
In the type 2 and type 1 diabetes mellitus (T2DM and T1DM) active-controlled trials, the mean reductions in HbA1c from baseline to endpoint were all numerically less in the TI arm than in the comparator arm. Assessment of non-inferiority with respect to active controls produced varying results. Specifically, in Study 103, treatment with TI + metformin was found to be non-inferior to metformin + secretagogue in lowering HbA1c for type 2 diabetic patients, since the upper bound of the 95% confidence interval (CI) of the treatment difference was 0.33%, smaller than the 0.4% non-inferiority margin. Treatment with TI + Lantus was also found to be non-inferior to Premixed 70/30 insulin analog in reducing HbA1c in Study 102 for type 2 diabetic patients, but was **not** non-inferior to treatment with insulin aspart + Lantus in Study 014 for type 2 diabetic patients and in Study 009 for type 1 diabetic patients. The upper bounds of the 95% CI of the treatment differences were 0.58% and 0.404% (0.45% for completers), respectively, and the mean HbA1c reductions were statistically significantly different between the 2 study groups, favoring the insulin aspart + Lantus treatment in both studies. Treatment with TI + Lantus was also shown to be not non-

inferior to insulin aspart + Lantus in Study 101 for type 1 diabetic patients. However, this was not a confirmatory study and HbA1c was not the primary efficacy variable. In other words, the study may not have enough power to make a sound conclusion for HbA1c.

The figure below clearly depicts the statistical results across all trials.



The 2 figures below compare responder rates in the long-term trial (52-week) of each type of diabetes mellitus. The TI + Lantus group consistently showed a similar % of subjects reaching any level of HbA1c at endpoint when compared with the Premixed 70/30 analog group (Study 102), but a smaller % of subjects reaching any level of HbA1c at endpoint was observed when compared with the insulin aspart + Lantus group (Study 009).



In summary, treatment with TI was effective in lowering HbA1c when compared with placebo. Based on the statistical criteria, non-inferiority of TI + metformin or TI + insulin glargine (Lantus[®]) to OAD(s) or Premixed 70/30 insulin analog, respectively, in the reduction of HbA1c was established in adult patients with type 2 diabetes mellitus. However, when TI + Lantus was compared with insulin aspart + Lantus, data were not sufficient to support the non-inferiority claim in adult patients with either type 2 or type 1 diabetes mellitus. Since there was only 1 confirmatory study submitted for the indication of type 1 diabetes mellitus, making a solid conclusion regarding efficacy for this type of diabetes mellitus is problematic.

Nevertheless, the final conclusions for approval of the drug/device should also take the comparability of insulin and non-insulin doses as well as safety factors such as hypoglycemia and lung function into consideration.

5.3 Labeling Comments

The following bullets summarize this reviewer’s comments for the sponsor’s proposed labeling.

- [Redacted]
- [Redacted]

(b) (4)



Primary Statistical Reviewer: Cynthia Liu, MA

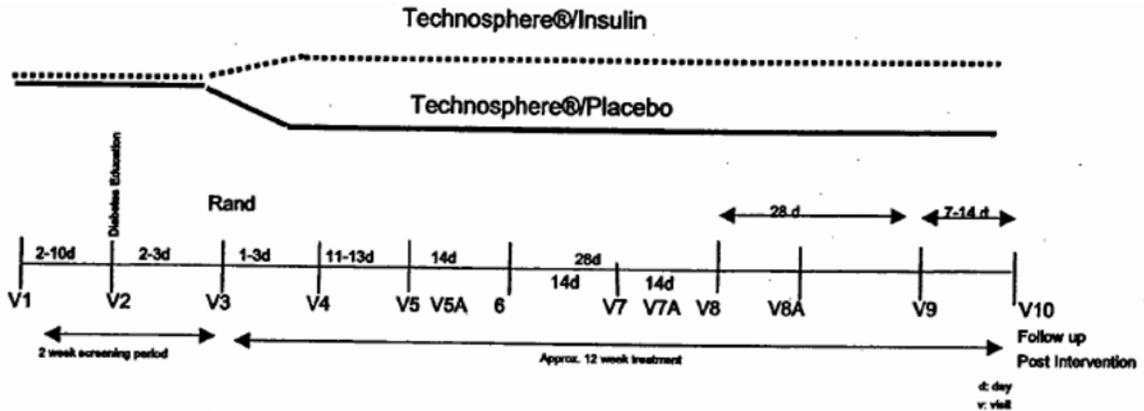
Concurring Reviewer: Todd Sahlroot, Ph.D.
Statistical Team Leader and Deputy Director of Biometrics II

CC: HFD-510/RHartford, MParks, HJoffe, LYanoff
HFD-715/TPermutt, TSahlroot, CLiu, JMele
HFD-700/LPatrician

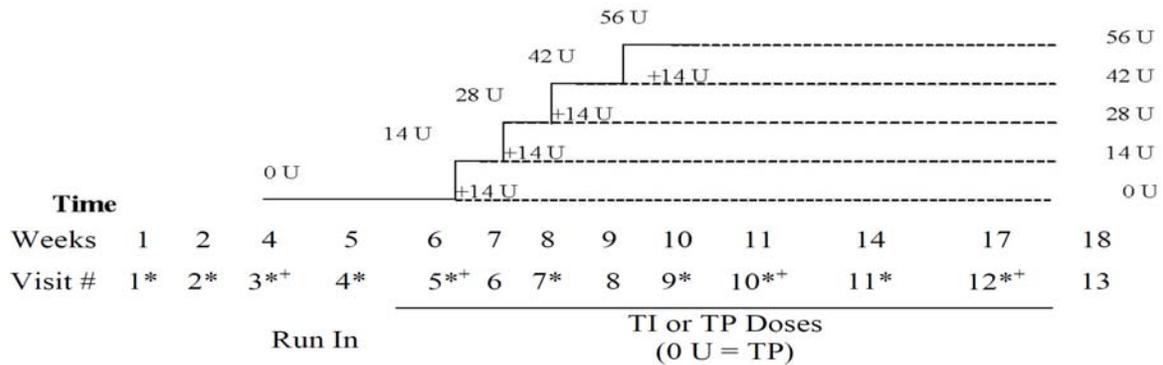
6. APPENDIX I

TYPE 2 DIABETES MELLITUS (T2DM)

Schematic Diagram for Study 0008 (a placebo-controlled trial)

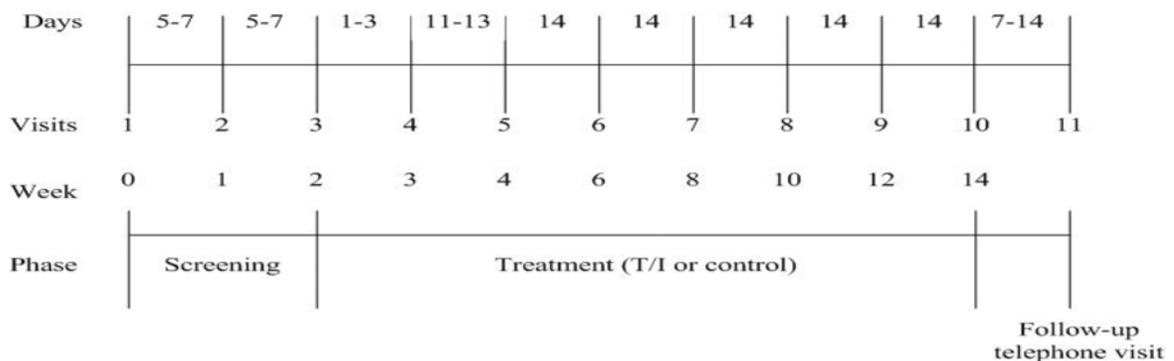


Schematic Diagram for Study 005 (a placebo-controlled trial)

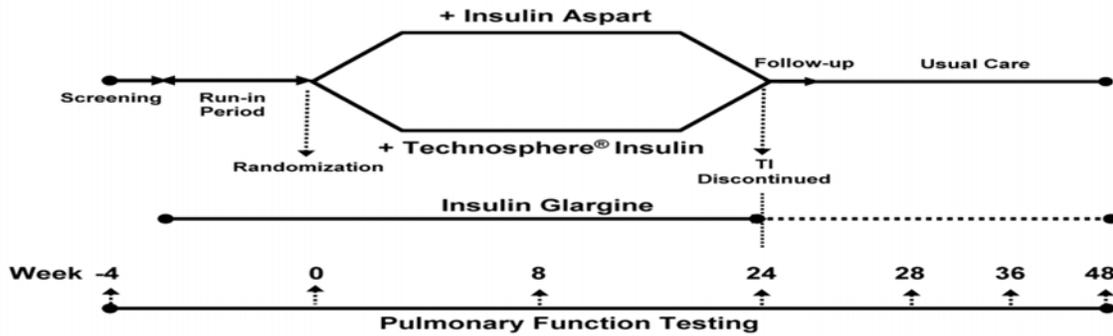


*Indicates in-clinic visit
 + Indicates a meal challenge

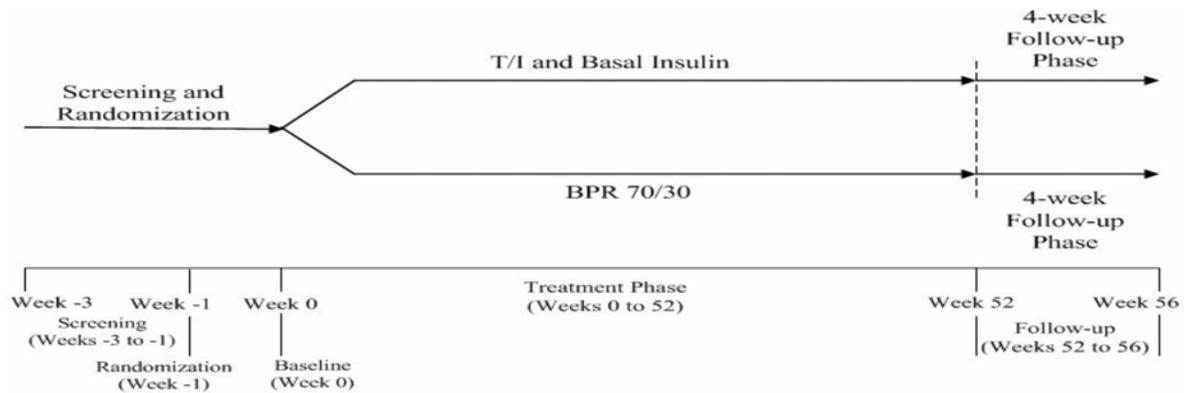
Schematic Diagram for Study 026 (a no-treatment control trial)



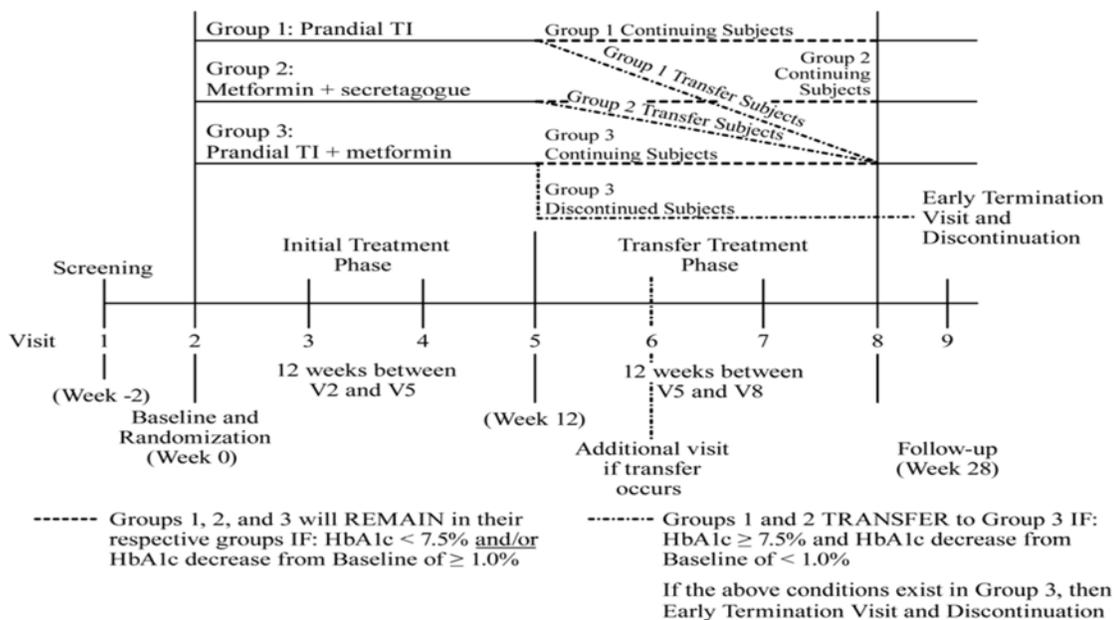
Schematic Diagram for Study 014 (an active-controlled trial)



Schematic Diagram for Study 102 (an active-controlled trial)

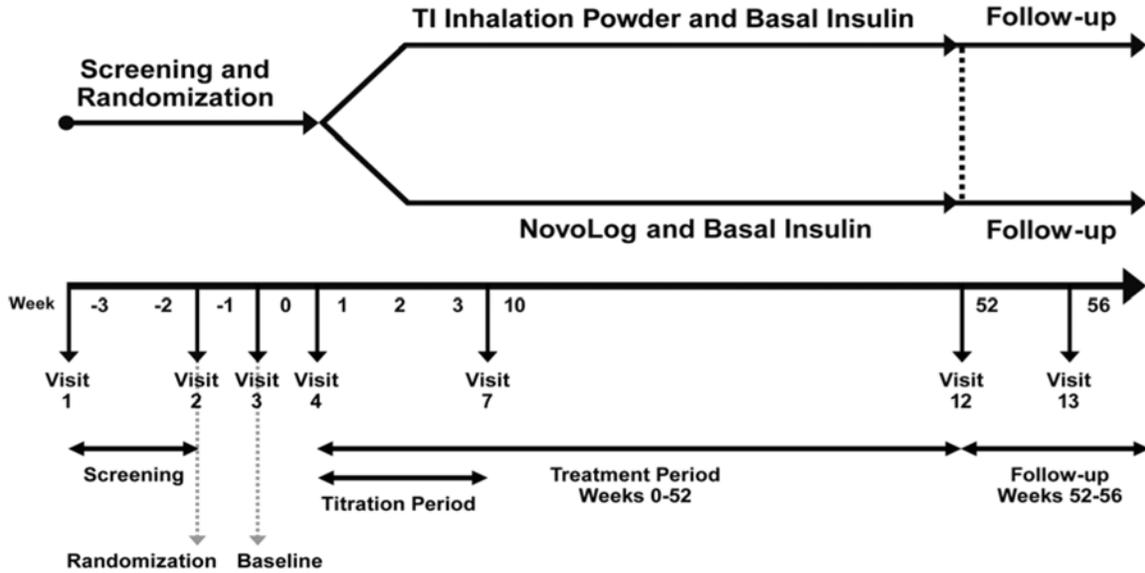


Schematic Diagram for Study 103 (an active-controlled trial)

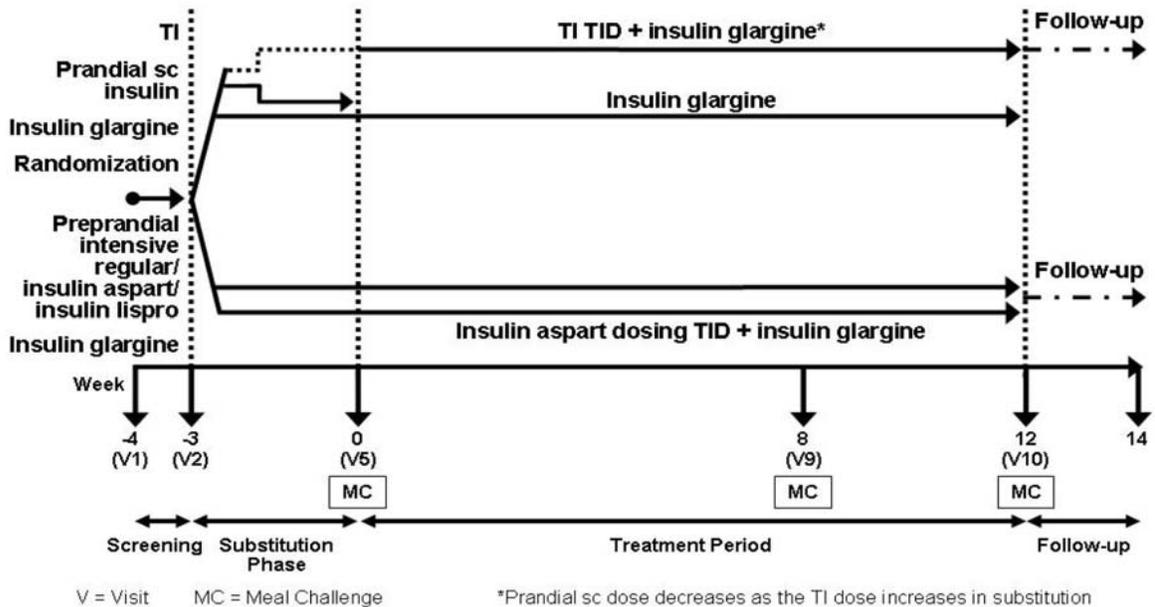


TYPE 1 DIABETES MELLITUS (T1DM)

Schematic Diagram for Study 009 (an active-controlled trial)



Schematic Diagram for Study 101 (an active-controlled trial)



7. APPENDIX II

The 2-hour postprandial glucose (PPG) after a standardized liquid meal (12 ounces Boost Plus[®], Novartis) was evaluated by the sponsor as one of the secondary efficacy endpoints. Change from Time 0 after the meal challenge in PPG at 2 hours was analyzed for Studies 102 (T2DM) and 009 (T1DM) using an ANCOVA model with treatment and pooled site as class variables and Time 0 plasma glucose as the covariate. The sponsor's results for Week 52 are summarized below.

Appendix II, Table 1 – 2-Hour PPG (mg/dL) after a Meal Challenge (ITT Population)

Study (Week)	Change from Time 0 in PPG at 2 hours LS Mean ± SE (N)		Treatment Difference		
	TI	Comparator	LS Mean (SE)	95% CI	p-value
102 (Week 52)	75.8 ± 4.4 (193)	56.4 ± 4.0 (213)	19.4 (5.7)	(8.2, 30.6)	0.0007
009 (Week 52)	74.6 ± 6.1 (170)	57.3 ± 5.8 (180)	17.3 (8.1)	(1.4, 33.2)	0.0332

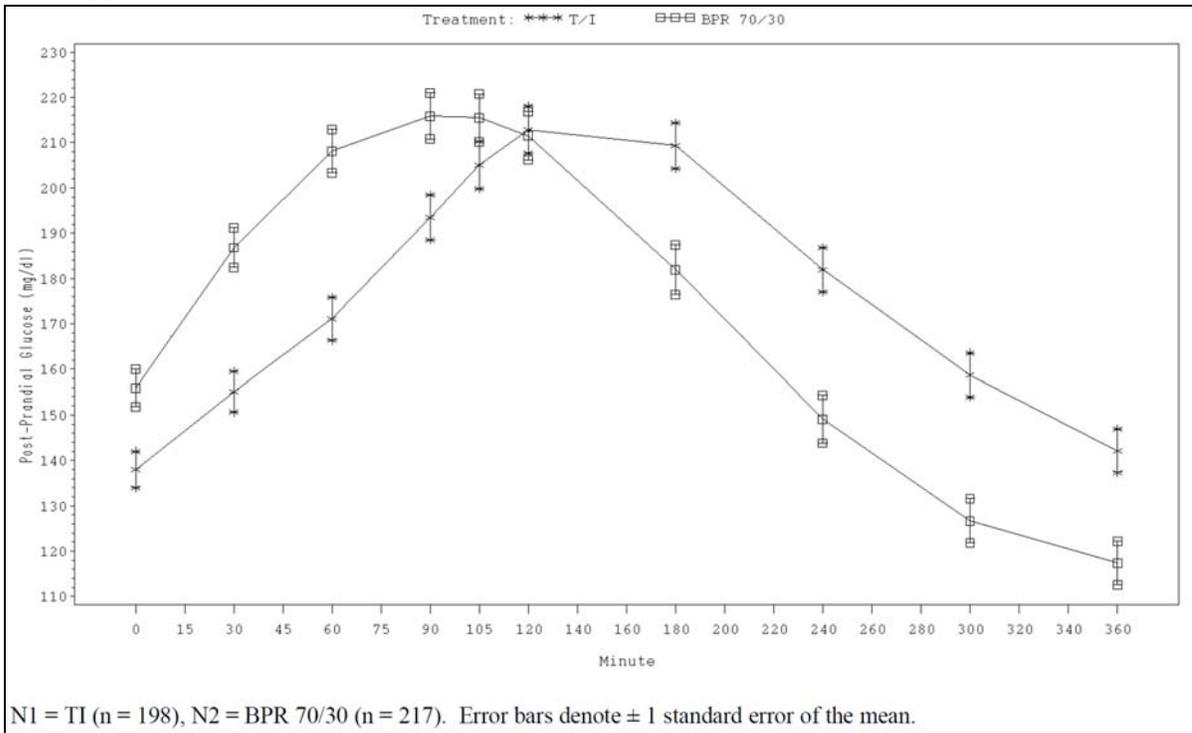
The ANCOVA model included treatment and pooled site as fixed factors and Time 0 glucose as the covariate.

For both studies, at Week 52, the Time 0-corrected 2-hour PPG was significantly better in the comparator arm than in the TI arm, which was probably due to the higher Time 0 glucose value in the comparator arm (thus yielding a smaller change), as there was no marked difference in the 2-hour PPG value between the 2 treatment arms (see Figures 1 and 2 below for Studies 102 and 009, respectively). The % of subjects reaching 140 mg/dL or less in the 2-hour PPG at Week 52 was 15.6% and 18.7% for the TI and Premixed 70/30 analog arms, respectively, for Study 102, and 16.8% and 19.1% for the TI and insulin aspart arms, respectively, for Study 009.

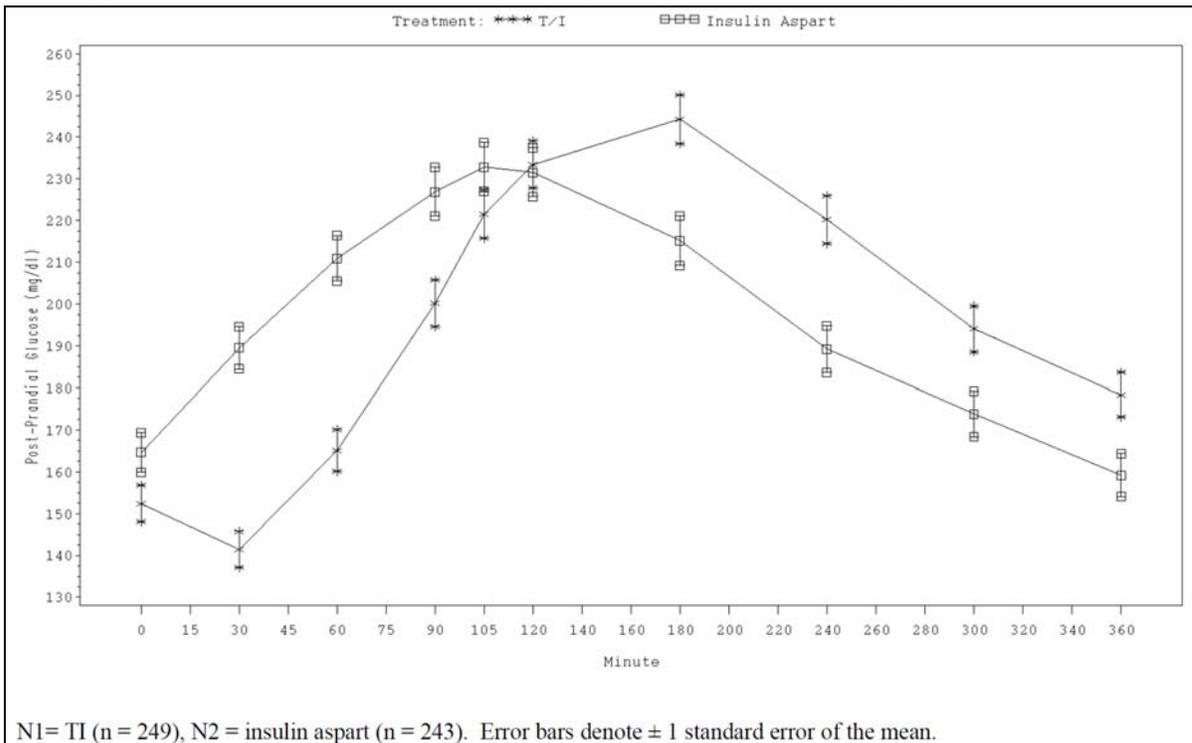
Figure 3 here shows that for Study 103, at Week 12, the Time 0-corrected 2-hour PPG was better in the TI + Metformin group (about 40 mg/dL) than in the Metformin + Secretagogue group (about 60 mg/dL).

Figure 4 shows that for Study 101, at Week 12, the Time 0-corrected 2-hour PPG was also better in the TI arm (about 20 mg/dL) than in the insulin aspart arm (about 36 mg/dL).

Appendix II, Figure 1 – Study 102: PPG (mg/dL) after a Meal Challenge at Week 52 (ITT)



Appendix II, Figure 2 – Study 009: PPG (mg/dL) after a Meal Challenge at Week 52 (ITT)

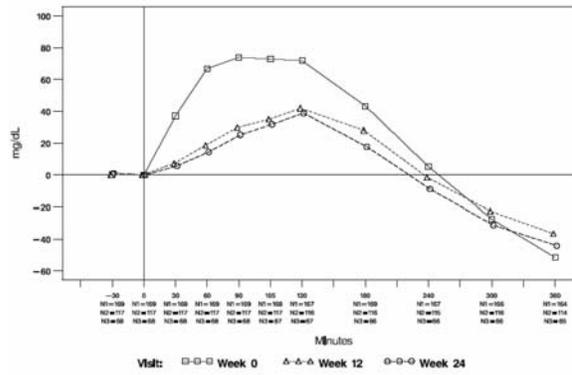


Appendix II, Figure 3 – Study 103

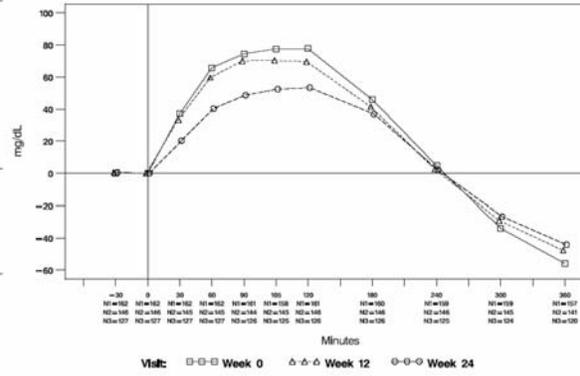
Time 0-Corrected PPG (mg/dL) after a Meal Challenge at Weeks 0, 12, and 24 (ITT)

TI + Metformin Randomization Group

Metformin + Secretagogue Randomization Group



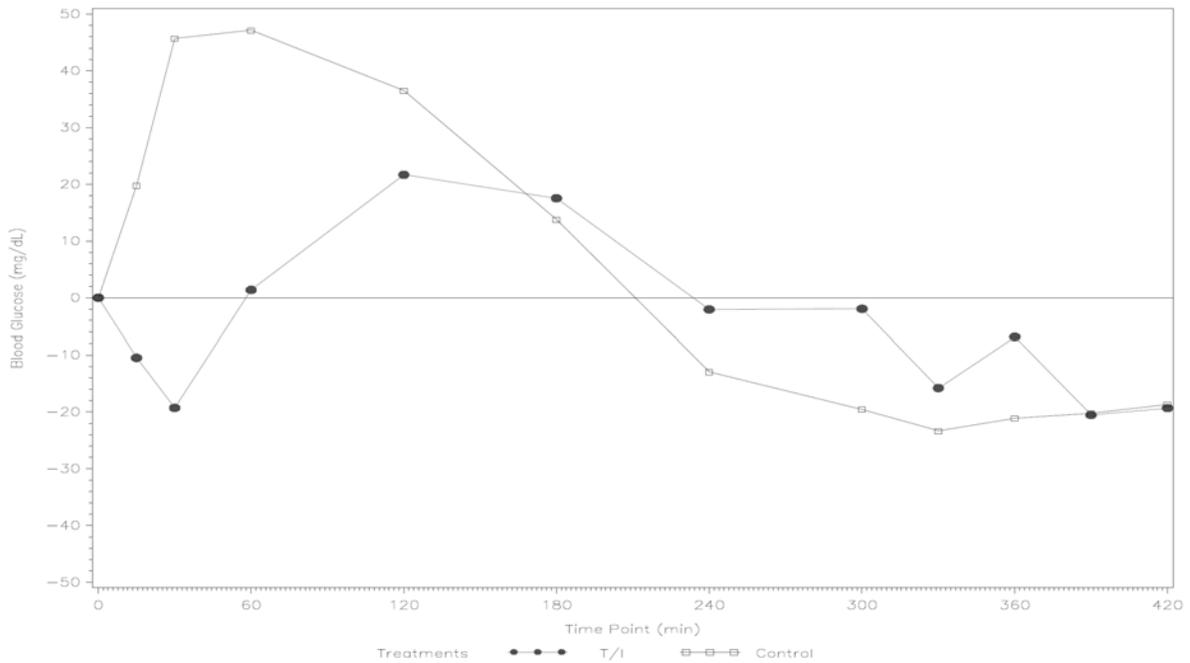
N1 = Week 0, N2 = Week 12, and N3 = Week 24. Data Source: Table 7.4.1.1.1; Figure 7.7.4.8



N1 = Week 0, N2 = Week 12, and N3 = Week 24. Data Source: Table 7.4.1.1.1; Figure 7.7.4.7

Appendix II, Figure 4 – Study 101

Time 0-Corrected PPG (mg/dL) after a Meal Challenge at Week 12 (ITT)



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

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/s/

CYNTHIA Y LIU
12/18/2009

JON T SAHLROOT
12/18/2009
Concur with reviewer's conclusions

THOMAS J PERMUTT
12/18/2009
concur



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22-472

Drug Name: AFREZZA inhalation powder (insulin monomer human [rDNA origin]
Inhalation Powder)

Indication(s): Diabetes mellitus in adults

Applicant: MannKind Corporation

Date(s): Submission: March 16, 2009
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1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The focus of this review is the safety of Technosphere Insulin Inhalation Powder (TI) as measured by two safety endpoints; forced expiratory volume (FEV₁) and hypoglycemia. The applicant presented the results of nine clinical trials (Table 1.2.1) to support the efficacy and safety of TI; this reviewer provides details on those studies that provided data on long-term safety (one year and greater).

Whereas the applicant primarily summarized safety by pooling studies in their integrated summaries, this reviewer shows the FEV₁ and hypoglycemia results by individual studies and bases conclusions on the evidence from these individual studies. This approach was taken for two reasons: 1) both of the safety endpoints under review here were measured and recorded over time for each trial so the data within trials is sufficient and pooling is not necessary nor desirable for assessing these endpoints 2) the trials differ in designs and populations so assessment of safety for each study provides valuable information.

FEV₁ results for individual trials generally showed greater decreases in FEV₁ during the first 3 months of therapy for TI compared to a variety of comparators. These treatment differences were small (on average about 50 ml) and not statistically significant particularly in trials of short duration (see Section 3.2.2.1). However the results from the long-term studies show that the early differences persist and that the endpoint results are statistically significantly different when TI is compared against a non-inhaled anti-diabetic product (Table 4.1.1). There was insufficient data to draw definitive conclusions regarding reversal of the FEV₁ effects with few patients (<25% of randomized patients) providing follow-up data after withdrawal of treatment.

Results for hypoglycemia suggest no important differences in rates of severe hypoglycemic events compared to both insulin and non-insulin comparators for both Type 1 and Type 2 diabetics. Generally higher rates of hypoglycemia are seen for TI versus non-insulin comparators and lower rates versus insulin comparators (see Section 3.2.2.2 and Appendix 5.1). The exception is Study 102 where TI was compared to a premixed (30/70) insulin analogue. For Study 102, statistically significantly lower hypoglycemic rates are seen for TI compared to the premixed insulin (Table 4.1.2); although, the fact that the majority of the severe events are defined by blood glucose alone may diminish the impact of these findings.

From a statistical perspective, the results for FEV₁ and for hypoglycemia both appear to support the safety of TI for the treatment of Type 1 and Type 2 diabetes because the treatment differences observed tend to be small and most likely clinically unimportant.

1.2 Brief Overview of Clinical Studies

The applicant has reported the results of 9 Phase 3 clinical studies (Table 1.2.1) to demonstrate the safety and efficacy of Technosphere Insulin Inhalation Powder (TI) for the treatment of Type 1 and Type 2 diabetes. Six of the studies were studies of 6 months duration or shorter; two studies (MKC-TI-009 and MKC-TI-102) were one-year studies and one was a two-year study (MKC-TI-030). Three studies enrolled patients with Type 1 (T1) diabetes and seven studies enrolled patients with Type 2 (T2) diabetes. For the remainder of this review, studies are generally referred to only by their numeric number, for example Study MKC-TI-030 is referred to as Study 030.

The control group varied across these studies with insulin as a comparator in about half the trials (Studies 009, 101, 014 and 102), placebo or no treatment in three trials (Studies 0008, 005 and 026) and usual care (UC) or oral anti-diabetics in two trial (Studies 103 and 030).

The primary objectives of this statistical review are the review of pulmonary safety and the review of hypoglycemia. Studies highlighted below were examined in detail to examine these two safety issues.

Table 1.2.1 Clinical Trials designed to assess efficacy and safety

Study	Patient Population	TI Group	Comparator Group	Duration of treatment
PDC-INS-0008	Type 2	Stable oral anti-diabetic Plus TI 3-4 times/day w/meals NR=61 NC=54 (93%)	Stable oral anti-diabetic Plus Inhalation powder without insulin NR=62 NC=53 (87%)	12 weeks
MKC-TI-005	Type 2	Lantus sc Plus TI w/meals Dose response TI doses of 14, 28, 42 and 56 U NR=181 NC=165 (91%)	Lantus sc Plus Inhalation powder without insulin NR=46 NC=40 (87%)	11 weeks
MKC-TI-014	Type 2	Insulin glargine Plus TI NR=151 NC=123 (82%)	Insulin glargine Plus Insulin aspart NR=158 NC=153 (97%)	24 weeks
MKC-TI-026	Type 2	Oral anti-diabetics taken at baseline Plus TI NR=75 NC=69 (92%)	Oral anti-diabetics taken at baseline NR=15 NC=14 (93%)	12 weeks
MKC-TI-102	Type 2	TI 2-4 times/day w/meals or snacks plus sc basal insulin 1 time/day at bedtime NR=334 NC=216 (65%)	sc biphasic rapid acting insulin (BPR 70/30) given at breakfast & evening meal NR=343 NC=246 (72%)	1 year
MKC-TI-103	Type 2	Metformin +TI NR=175 NC=119 (68%) TI alone NR=183 NC=133 (73%)	Metformin+secretagogue NR=170 NC=152 (89%)	12 weeks rand. trt.
MKC-TI-030	Type 1 & 2	TI T1 NR=267 NC=126 (47%) T2 NR=656 NC=349 (52%)	Usual care T1 NR=271 NC=199 (73%) T2 NR=678 NC=463 (68%)	2 years
MKC-TI-009	Type 1	basal insulin+TI NR=301 NC=198 (66%)	basal insulin+ sc aspart NR=288 NC=220 (76%)	1 year
MKC-TI-101	Type 1	basal insulin+TI NR=54 NC=49 (91%)	basal insulin+ sc NovoRapid NR=56 NC=56 (100%)	12 weeks

NR=number randomized NC=number of completers;

The applicant also conducted two extension studies (Table 1.2.2); MKC-TI-010 and MKC-TI-126. MKC-TI-010 was a long-term study where Type 2 patients completing studies Study 005 or Study 0008 could be followed for up to four years on TI treatment; there was no comparator group. Study 126 provided 2 months of follow-up where patients were withdrawn from TI treatment and followed on usual care (UC). This study provided data for assessing whether changes in FEV₁ seen on randomized treatment were reversed within two months. The extension data was not used by this reviewer to examine hypoglycemia.

Table 1.2.2 Extension Clinical Trials

Study	Patient Population	Duration
MKC-TI-010	Type 2 pts completing MKC-TI-005 and PDC-INS-0008	4 years all treated with TI
MKC-TI-126	Type 1 & 2 pts completing MKC-TI-009, 102, 103 and 030	8 weeks follow-up after withdrawal of randomized treatment

Pulmonary safety data was also analyzed by the applicant for the clinical pharmacology studies and summarized in Appendix 2 of the ISS; those data have not been reviewed here because those studies are of short duration and do not provide sufficient safety data supporting the use of the product long-term.

2. Introduction

2.1 Overview

The focus of this review is the safety of TI as measured by two safety endpoints; forced expiratory volume (FEV₁) and hypoglycemia. FEV₁ is considered by the FDA clinicians to be a good measure of the impact of TI, as an inhaled product, on pulmonary function. All studies collected FEV₁ data. Study 030 was specifically designed to assess pulmonary function and named FEV₁ as a primary endpoint.

Hypoglycemia is assessed by counting hypoglycemic episodes. The episodes considered severe are the primary focus of this review. All studies collected data on hypoglycemic events.

See Tables 1.2.1 and 1.2.2 for a listing of the studies reviewed for this application.

2.2 Data Sources

Datasets and study reports for the NDA reviewed here are available at the following link: [\\CDSESUB1\EVSPROD\NDA022472](https://cdsesub1.evsprod.nda022472).

3. Statistical Evaluation

3.1 Evaluation of Efficacy

For the statistical evaluation of efficacy, see FDA statistical reviewer Cynthia Liu's review.

3.2 Evaluation of Safety

This review of the safety of Technosphere inhaled insulin (TI) focuses on pulmonary safety measured by the pulmonary function test, FEV₁ and on events of hypoglycemia, emphasizing severe events. For the FDA clinical review of safety endpoints, see the reviews of Dr. Yanoff and Dr. Karimi-Shah.

To evaluate FEV₁ and hypoglycemia, this reviewer has taken the following approach:

- Describe the applicant's and the reviewer's statistical methods
- Summarize overall results for all studies
 - Three-month FEV₁ results
 - Total and severe hypoglycemic events
- Review long-term results
 - Long-term studies; 030, 009 and 102 plus extension data from Study 126
 - 4-year extension Study 010

This review includes detailed reviews of the safety populations for Studies 030, 009 and 102 and also includes summaries of the data from extension Studies 126 and 010. The safety population in these studies was defined as all patients taking at least one dose of treatment.

The applicant's summary of the results for FEV₁ reports that small changes are "fully manifested" at the first recorded post-baseline in the TI group and further decreases are not seen for up to 4 years. Also the summary states that the changes are reversed after stopping treatment. One of the objectives then of this review is to determine if the data supports the applicant's conclusions. To address whether further decreases are seen after the initial decreases, this reviewer looked at the 3 month results of all studies and then examined the long term effects in the studies of one year or longer. In addition, this reviewer summarizes the FEV₁ data collected in extension Study 010 which provided uncontrolled data out to nearly 4 years. To assess reversal of effect, the FEV₁ data collected after withdrawal of treatment was examined using data collected in Study 126.

The primary review issue addressed regarding hypoglycemia is whether there is sufficient evidence to support the applicant's assertion that fewer hypoglycemic events are seen with TI compared to insulin controls. The applicant has proposed labeling language (b) (4)

3.2.1 Statistical Methods

Whereas the applicant primarily summarized safety by pooling studies in their integrated summaries, this reviewer reviewed the FEV₁ and hypoglycemia results by individual studies. This approach was taken for two reasons: 1) both of the safety endpoints under review here were measured and recorded over time for each trial so the data within trials is sufficient and pooling is not necessary nor desirable for assessing these endpoints 2) the trials differ in designs and populations so assessment of safety for each study provides valuable information.

3.2.1.1 Methods for the Analysis of FEV₁

FEV₁ (forced expiratory volume in 1 second) was the focus of this review based on advice from the pulmonary medical reviewers.

The applicant presented results integrated for Studies 009 and 030 (Type 1 diabetics) and for Studies 102 and 030 (Type 2 diabetics). The applicant argued that the remaining studies were too dissimilar to allow for pooling and therefore the results of those studies were presented individually in the Integrated Summary of Safety. In addition, safety results were presented in the individual study reports although the presentation varied and therefore, the same results were not consistently shown for all studies. This reviewer focused on the individual study results because of the dissimilarities among the trials.

Pulmonary function tests were conducted in all studies according to the schedule in Table 3.2.1.1.1 below. Because all studies included a measure at about Month 3 (weeks 10-13), this reviewer summarized the FEV₁ results at this timepoint while focusing on the long-term studies (009, 030 and 102) of one to two years for more detailed regulatory review.

Table 3.2.1.1.1 Schedule of PFT tests by month in TI Studies

	0	3	6	9	12	18	24	FU
008	x	x						x
05	x	x						x
09	x	x	x	x	x			x
14	x	x	x					x
26	x	x						x
30	x	x	x	x	x	x	x	x
101	x	x	x					x
102	x	x	x	x	x			x

The applicant analyzed the FEV₁ change from baseline data using a mixed model with repeated measures and using analysis of covariance with baseline as a covariate. The mixed model with repeated measures (MMRM) contained terms for age, height, gender, baseline PFT, time(visit), treatment and region. For analyses of both Type 1 and Type 2 patients in the same model, a term for disease was included. The covariance structure was not pre-specified but was chosen based on the value of an information criterion (AIC, BIC or AICC). This model provided an overall estimate of the average treatment difference using all the data for each patient. To estimate an annual decline rate, the applicant used a random coefficients model. This model contained terms for age, height, gender and time (years). As for MMRM, a term for disease was included if both Type 1 and Type 2 patients were being analyzed.

Although the protocols defined an intent-to-treat population in each study, for some studies the applicant only analyzed observed cases or completers; this reviewer presents ITT results for long-term studies reviewed here in detail.

This reviewer also used the MMRM approach. In addition this reviewer performed last-observation-carried-forward, observed cases and completer analyses using an analysis covariance model with baseline FEV₁ as a covariate.

3.2.1.2 Methods for the Analysis of Hypoglycemia

Protocols for each of the studies defined hypoglycemia in different ways. Generally mild and moderate hypoglycemic events were identified by a blood glucose level less than 63 mg/dL or by the relief of symptoms by the addition of carbohydrates or glucagon injections. The definitions of severe hypoglycemia are shown in the table below (Table 3.2.1.2.1). Check marks indicate that all the symptoms needed to be seen to identify an event as severe; an X indicates that the symptom was sufficient alone to identify an event as severe.

The applicant performed analyses pooling across studies and for these analyses, the applicant defined a severe hypoglycemic event as one where the CRF indicated that the event was severe (this could only be done for Studies 009, 030, 102 and 103) or if the blood glucose was 36 mg/dL or less. This reviewer only used the definitions given in the study reports.

Table 3.2.1.2.1 Symptoms required for identifying an hypoglycemic event as severe for each study

	needed assistance	≥ 1 cognitive/neuro symptom	BG ≤ 49 mg/dL or symptoms reversed by carbo trt	BG ≤ 36 mg/dL w/ or wo symptoms	Required gluc inj or glucose infusion
030	✓	✓	✓	X	
102	✓	✓	✓	X	
009	✓	✓	✓	X	
101	✓	✓			X
005	✓	✓			X
014	✓	✓			X
026	✓	✓			X
0008	X				X
Exubera	✓	✓	✓		

✓ the checked symptoms needed to be seen together to constitute a severe hypoglycemic event while a symptom marked as X was sufficient to define an event BG=blood glucose

For the long-term studies (030, 009 and 102), a severe hypoglycemic event could be identified by a blood glucose level alone. In fact, the majority of the severe events were identified based on blood glucose level alone (for example, in Study 102, 85% of the severe events were identified on BG alone). Note that for the Exubera application (an inhaled insulin approved in 2005) the identification of a severe hypoglycemic event could not be made based on blood glucose levels alone. The significance of these details regarding the symptoms constituting a severe event to the interpretation of the results is clearly a clinical issue.

Hypoglycemia was analyzed using several methods by this reviewer and the applicant. The methods used to analyze first events seen for patients included both Cochran-Mantel-Haenzsel Test and logistic regression models (results from these tests were generally in agreement). To analyze the number of events observed for each patient, this reviewer used a Wilcoxon rank sum test. The applicant computed rates based on total number of events divided by total exposure time and analyzed rates using a Poisson regression model based on the generalized estimating equation. These methods together provide a full assessment of first events per patient, multiple events per patient and events adjusting for length of exposure.

3.2.2 Summary of Results for All Studies

3.2.2.1 FEV₁ Results

As shown previously in Table 3.2.1.1.1, all studies collected data at or close to Month 3. To assess the effect on FEV₁ for all studies, this reviewer summarized the results at the common timepoint of Month 3; some of the results were extracted from the applicant's reports and others were computed by the reviewer as noted. The results for Type 1 diabetics are summarized in Table 3.2.2.1.1 and for Type 2 diabetics in Table 3.2.2.1.2.

For most studies, the dropout rates at Month 3 were small (<15% except for Study 030 where higher dropout rates were seen) so the results using LOCF are consistent with results shown for observed cases. The choice of which results to present in the table was dependent on the availability of results in the study reports and the ease of computation for the reviewer (note that more details are available for the long-term studies in subsequent sections of this review).

The majority of trials showed more lowering of FEV₁ in the TI group than the comparator group (shaded values in the tables). The treatment differences were statistically significant for the 3 long-term studies (Studies 009, 102 and 030); these studies also showed statistically significant differences at endpoint (see Section 3.2.3 of this review for endpoint results).

Table 3.2.2.1.1 Type 1 FEV₁ Month 3 Change from Baseline Mean (SD)

Study	TI Group	Comparator Group	p-value
MKC-TI-009 OC	-0.06 (0.20)	-0.01 (0.16)	p<0.009**
MKC-TI-030 OC	-0.07 (0.21)	-0.05 (0.16)	p= 0.16**
MKC-TI-101 LOCF	-0.07 (0.18)	-0.07 (0.19)	p=0.84

**Computed by reviewer

Table 3.2.2.1.2 Type 2 FEV₁ Month 3 Change from Baseline Mean (SD)

Study	TI Group	Comparator Group	p-value
PDC-INS-0008 LOCF	-0.04 (0.20)	-0.01 (0.20)	p=0.42
MKC-TI-005 LOCF	-0.04 (0.26)	-0.09 (0.20)	p=0.34
MKC-TI-014 LOCF	-0.02 (0.22)	-0.01 (0.16)	p=0.19
MKC-TI-026 LOCF	-0.05 (0.34)	-0.05 (0.33)	p=0.98
MKC-TI-030 OC	-0.07 (0.20)	-0.05 (0.17)	p=0.02**
MKC-TI-102 OC	-0.09 (0.20)	-0.03 (0.17)	p<0.001**
MKC-TI-103 OC ¹	-0.04 (0.19)	-0.02 (0.14)	p=0.6

**Computed by reviewer 1 TI+met vs. Met+sec

Overall the Month 3 results support the applicant's statement that early drops in FEV₁ are seen. The treatment differences range from about 0.01L (10 ml) to 0.06L (60 ml) in those studies where a larger drop is seen for TI. Details regarding changes in FEV₁ with long-term treatment are provided in the review of Studies 030, 102 and 009 in Section 3.2.3.

3.2.2.2 Hypoglycemia Results

Hypoglycemia events are counted over the full duration of the treatment periods for all the trials. Incidences of first hypoglycemic event and first severe hypoglycemic event are shown for all trials in Tables 3.2.2.2.1 and 3.2.2.2.2 below. Plots of odds ratios for all studies are provided in Appendix 5.1. Studies with insulin as a comparator are highlighted in blue; Study 030 had usual care as a comparator so some Type 2 patients were taking insulin. Studies with lower hypoglycemic rates for TI than comparator are highlighted in grey; differences that were statistically significant either in favor or against TI are starred.

Generally lower rates of hypoglycemia are seen for TI against an insulin comparator; however, with the exception of Study 102, the differences are small and not statistically significant. For Study 102, both the total and severe rates are significantly lower for TI compared to PreMix 70/30; more details on these results are provided in Section 3.2.3 of this review.

Table 3.2.2.2.1 Type 1 Incidences of hypoglycemic events

Study	TI Group	Comparator Group
MKC-TI-009		
% pts w/at least 1 event	86% (252/293)*	93% (252/272)
% pts w/at least 1 severe event	33% (96/293)	38% (102/272)
MKC-TI-030		
% pts w/at least 1 event	62% (165/267)	66% (179/271)
% pts w/at least 1 severe event	16% (42/267)	17% (47/271)
MKC-TI-101		
% pts w/at least 1 event	89% (48/54)	93% (52/56)
% pts w/at least 1 severe event	0% (0/54)	0% (0/56)

Table 3.2.2.2.2 Type 2 Incidences of hypoglycemic events (trials in blue have insulin as head-to-head comparator)

Study	TI Group	Comparator Group
MKC-TI-0008		
% pts w/at least 1 event	43% (26/61)	36% (22/62)
% pts w/at least 1 severe event	0% (0/61)	0% (0/62)
MKC-TI-005		
% pts w/at least 1 event	28% (50/181)	15% (7/46)
% pts w/at least 1 severe event	0% (0/181)	0% (0/46)
MKC-TI-014		
% pts w/at least 1 event	37% (56/151)	53% (83/158)
% pts w/at least 1 severe event	7.3% (11/151)	8.9% (14/158)
MKC-TI-026		
% pts w/at least 1 event	40% (30/75)	33% (5/15)
% pts w/at least 1 severe event	0% (0/75)	0% (0/15)
MKC-TI-030		
% pts w/at least 1 event	30% (200/656)	28% (192/678)
% pts w/at least 1 severe event	3.2% (21/656)	4.6% (31/678)
MKC-TI-102		
% pts w/at least 1 event	48% (155/323)*	69% (228/331)
% pts w/at least 1 severe event	4.3% (14/323)*	10.0% (33/331)
MKC-TI-103 (TI vs. SEC)		
% pts w/at least 1 event	18% (31/177)*	9% (15/166)
% pts w/at least 1 severe event	0% (0/177)	0% (0/166)

*p ≤ 0.05, CMH Test

3.2.3 Review of Long-term Studies

This reviewer assessed FEV₁ and hypoglycemia using 4 databases with long term data as follows:

Studies	Duration	Patient Population
Study 030 plus extension data from Study 126	2 years Usual Care as comparator	Type 1 and 2 analyzed separately
Study 102 plus extension data from Study 126	1 year Insulin PreMix 70/30 as comparator	Type 2
Study 009 plus extension data from Study 126	1 year insulin aspart as comparator	Type 1
Studies 0008 and 005 plus extension data from Study 010	Maximum of 4 years uncontrolled	Type 2

3.2.3.1 Study MKC-TI-030

Study 030 was an open-label two-year pulmonary safety study with three arms; two arms were treatment arms (TI and usual anti-diabetic care) and one arm was an observational arm where non-diabetics (normal glucose tolerance test results) were followed untreated. Patients with diabetes for at least 2 years were randomized to TI or usual care stratifying on type of diabetes. After completion of two years, patients could be followed off treatment for an additional two months in Study MKC-TI-126. The primary objective of the trial was to assess pulmonary function as measured by change from baseline for FEV₁. The evaluation of severe hypoglycemia was named as a secondary objective.

Patient Disposition

A total of 1349 Type 2 diabetics and 540 Type 1 diabetics were randomized in Study 030 as shown in Table 3.2.3.1.1 below. The discontinuation rates were notably higher for the TI treated patients than the usual care (UC) treated patients with about 50% of the TI patients dropping by Month 24 compared to about 30% for the UC patients.

Table 3.2.3.1.1 Study 030 Patient disposition and reasons for discontinuing

	Type 1		Type 2		Non-diabetics Untreated
	TI	Usual Care	TI	Usual Care	
Randomized	269	271	669	680	<i>Enrolled</i> 164
Randomized and Treated	267 (99%)	271 (100%)	656 (98%)	678 (99+%)	163 (99%)
Month 3	191 (71%)	254 (94%)	520 (78%)	592 (87%)	159 (97%)
Month 24	126 (47%)	199 (73%)	349 (52%)	463 (68%)	127 (77%)
ITT	200 (74%)	246 (91%)	530 (79%)	578 (85%)	145 (88%)
Primary Reasons for withdrawal					
ADE	9%	0.4%	12%	1%	0%
Pt withdrew	29%	14%	21%	19%	11%
Lost to FU	4%	9%	7%	8%	3%

Percent was computed based on number randomized. The number of patients with at least 3 months of exposure was computed by the reviewer using the variable trtdurm; this number includes patients who do not have PFT data.

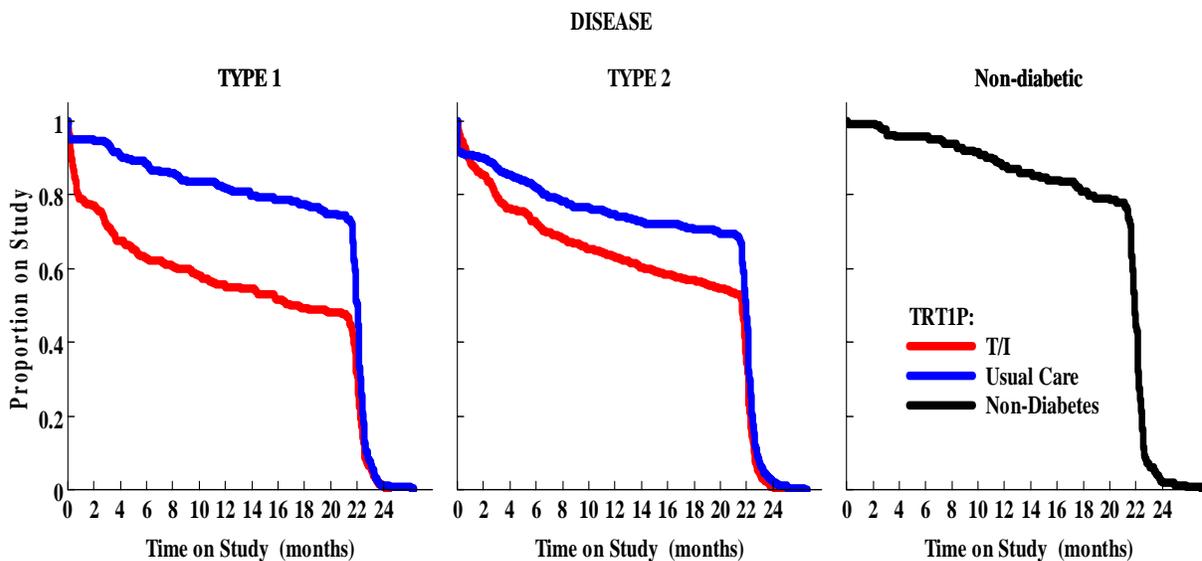
The most common reason for discontinuing from the study was patient withdrawing consent with about

half of those dropouts occurring during the first 3 months in the TI group regardless of type of diabetes (see Figure 3.2.3.1.1 below). In the usual care group, there were no Type 1 patients who dropped due to patient withdrawal in the first 3 months while about half of the Type 2 patients dropping due to patient withdrawal did so within the first 3 months.

The ITT population was defined as randomized patients who received at least one dose of treatment, had an FEV₁ baseline and at least one FEV₁ post-baseline value. The first FEV₁ post-baseline measurement was scheduled for Month 3. According to the protocol, patients who were discontinued early should have been brought into the clinic for a final visit which included pulmonary testing. The data suggests that the latter was not routinely done with about ¼ of the TI patients not included in the ITT population.

Figure 3.2.3.1.1 illustrates the patterns of discontinuation by treatment groups. Clearly significantly more patients on TI drop out earlier than UC patients or non-diabetics.

Figure 3.2.3.1.1 Proportion of patients on study by group and diabetes type



Baseline Demographics

There were no notable differences at baseline between treatment groups within each disease type (Table 3.2.3.1.2). The majority of patients were male and Caucasian. As would be expected, the age of Type 1 diabetics (mean 40 years) was less than the age of Type 2 patients (mean 55). Few patients were 65 or older. USA sites enrolled the most patients (~1/2).

Table 3.2.3.1.2 Study 030 Baseline demographics

	Type 1		Type 2		Non-diabetics Untreated n=164
	TI n=267	Usual Care n=271	TI n=669	Usual Care n=680	
Sex % male	58%	56%	61%	63%	44%
Race					
Caucasian	95%	94%	82%	84%	89%
Hispanic	3%	3%	8%	7%	7%
Age					
Mean (SD)	40 (12)	39 (12)	55 (8)	55 (8)	38 (12)
% ≥ 65	1.5%	1%	12%	11%	2%
Duration of diabetes (yrs)					
Mean (SD)	16 (11)	15 (10)	10 (7)	10 (7)	NA
Country					
USA	39%	39%	55%	55%	50%
Ukraine	14%	17%	11%	10%	15%
Russia	22%	22%	18%	18%	22%
Poland	8%	9%	4%	4%	4%
Great Brit	4%	4%	1%	2%	3%
Spain	<1%	1%	1%	1%	<1%
Czech	3%	2%	3%	3%	2%
Canada	9%	7%	8%	8%	4%

FEV₁ Results

Because there were a significant number of dropouts, this reviewer performed analyses on cohorts defined by the month completed (Months 3, 12 and 24) as well as an ITT population to assess the influence of dropouts on the results. An analysis of covariance model with baseline FEV₁ as a covariate was used for the analyses by month and for the last value analysis. In addition this reviewer ran the mixed model repeated measures model defined by the sponsor with a contrast at Month 24. The sponsor's computation of the average difference over the two years is also shown in the tables below.

What can be seen in the two tables on the following page (the first showing results for Type 1 diabetics and the second for Type 2 diabetics) is that the results consistently show a greater lowering of the FEV₁ in the TI group compared to the UC group. Statistically significant results are only observed in the Type 2 diabetic population although the magnitude of the effect is the same seen for Type 1 patients (treatment difference of about -0.04 L); the lack of significance for the Type 1 population is due to studying only half the number patients (i.e. there is not sufficient power to observe a statistically significant difference). Although, the largest drop in FEV₁ is seen during the first 3 month period, the data suggests that further decreases on average are seen. The latter is evident whether one considers only completers or the last value for the ITT population. Also the analysis of the last value for each patient produced results consistent with

the results produced using a repeated measures model; both of these analyses use data from all the ITT patients.

Table 3.2.3.1.3 FEV₁ change from baseline results (L) for Type 1 Diabetics

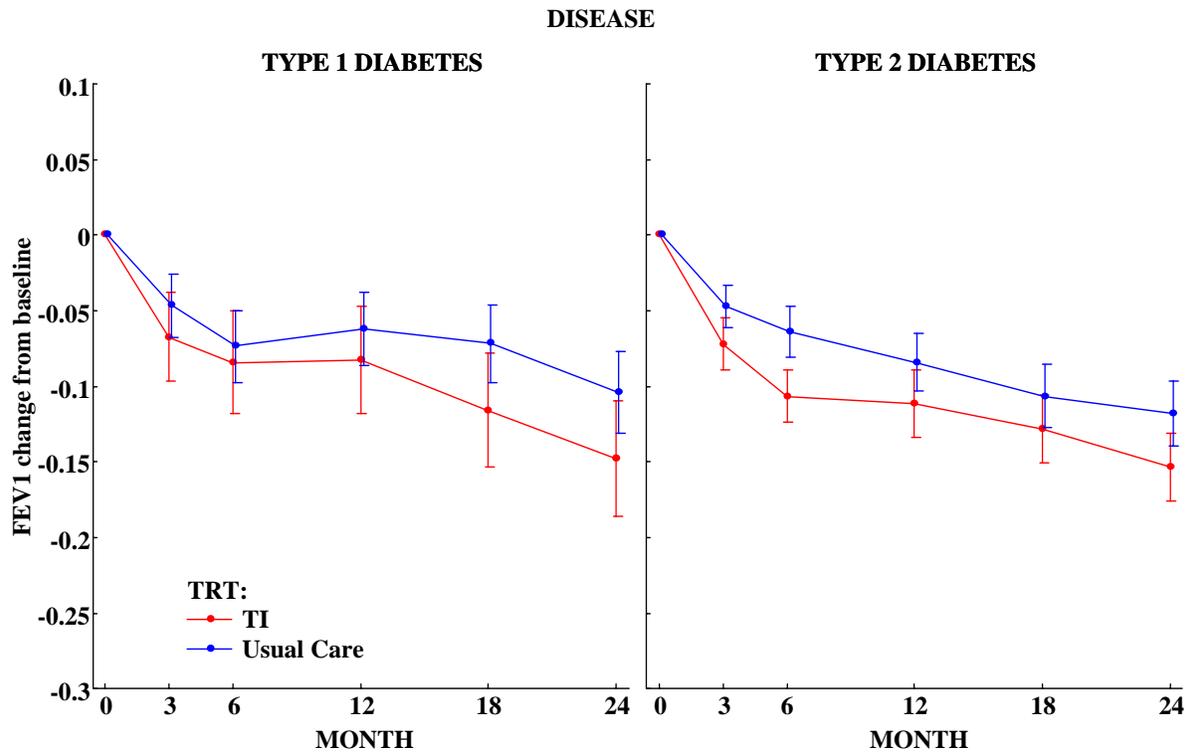
	TI Mean (SD) (n=200)	UC Mean (SD) (n=246)	p-value	Treatment Difference TI-UC (95% CI)
Baseline (ITT)	3.54 (0.72)	3.65 (0.84)	0.19	-0.10 (-0.25, 0.05)
Month 3 (Observed)	-0.07 (0.21) (n=197)	-0.05 (0.16) (n=236)	0.16	-0.02 (-0.06, 0.01)
Month 12 (Observed)	-0.07 (0.21) (n=148)	-0.06 (0.18) (n=217)	0.30	-0.02 (-0.06, 0.02)
Month 24 (Observed)	-0.15 (0.21) (n=115)	-0.10 (0.18) (n=182)	0.04	-0.05 (-0.09, -0.002)
Last Value (ITT)	-0.13 (0.22) (n=200)	-0.10 (0.19) (n=246)	0.04	-0.04 (-0.08, -0.001)
MMRM (ITT) Month 24 LSM (SE) Average difference over 24 mths	-0.15 (0.01)	-0.11 (0.01)	0.04	-0.04 (-0.08, -0.002) -0.03 (-0.05, -0.01)

Table 3.2.3.1.4 FEV₁ change from baseline (L) results for Type 2 Diabetics

	TI Mean (SD) (n=530)	UC Mean (SD) (n=578)	p-value	Treatment Difference 95% CI
Baseline (ITT)	3.09 (0.66)	3.15 (0.74)	0.13	-0.06 (-0.15, 0.02)
Month 3 (Observed)	-0.07 (0.20) n=521	-0.05 (0.17) n=559	0.02	-0.03 (-0.05, -0.005)
Month 12 (Observed)	-0.07 (0.20) n=414	-0.05 (0.17) n=504	0.04	-0.03 (-0.06, -0.002)
Month 24 (Observed)	-0.15 (0.20) n=319	-0.12 (0.22) n=436	<0.01	-0.04 (-0.07, -0.01)
Last Value (ITT)	-0.14 (0.21) n=530	-0.10 (0.22) n=578	<0.01	-0.04 (-0.06, -0.01)
MMRM (ITT) Month 24 LSM (SE) Average difference over 24 mths	-0.15 (0.01)	-0.12 (0.01)	<0.01	-0.04 (-0.06, -0.01) -0.03 (-0.04, -0.01)

Figure 3.2.3.1.2 illustrates the average FEV₁ change from baseline for patients with available data at any given timepoint (note that the table below the graph shows the number of patients at each timepoint). The FEV₁ continues to decrease overtime in both treatment groups with a greater decrease seen for the TI group. A graph of data for patients completing 24 months is shown in Appendix 5.2 and looks similar to the graph below indicating that the trajectory is similar when following the same cohort of patients overtime.

Figure 3.2.3.1.2 Mean change from baseline FEV₁ ± 2*standard error

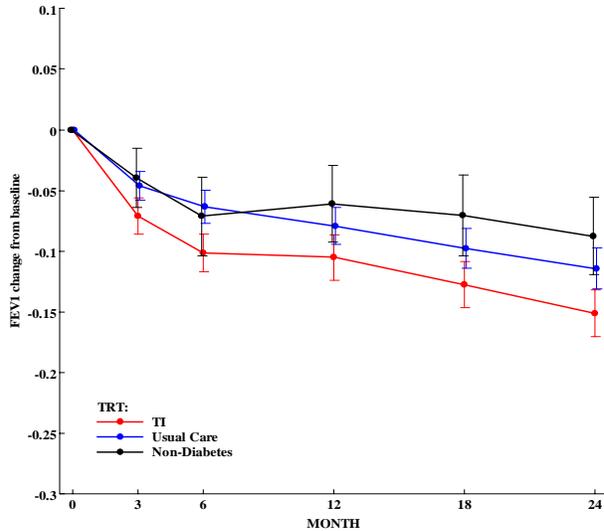


Sample Sizes for the above graphs

Type 1	0	3	6	12	18	24	Type 2	0	3	6	12	18	24
TI	266	197	167	149	134	115	TI	654	523	468	414	375	319
UC	268	236	230	217	207	182	UC	673	560	535	504	468	436

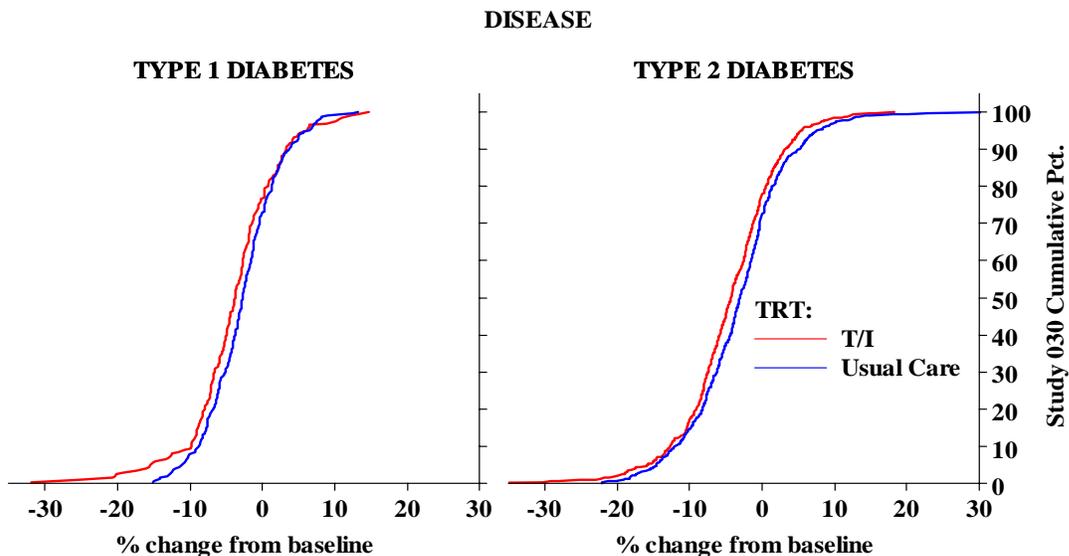
The drop in FEV₁ seen for the treatment groups during the first 3-6 months is also seen for the non-randomized non-diabetic group as illustrated below; however, this group shows essentially no further lowering after the 6 month timepoint.

Figure 3.2.3.1.3 Mean change from baseline FEV₁ ± 2*standard error



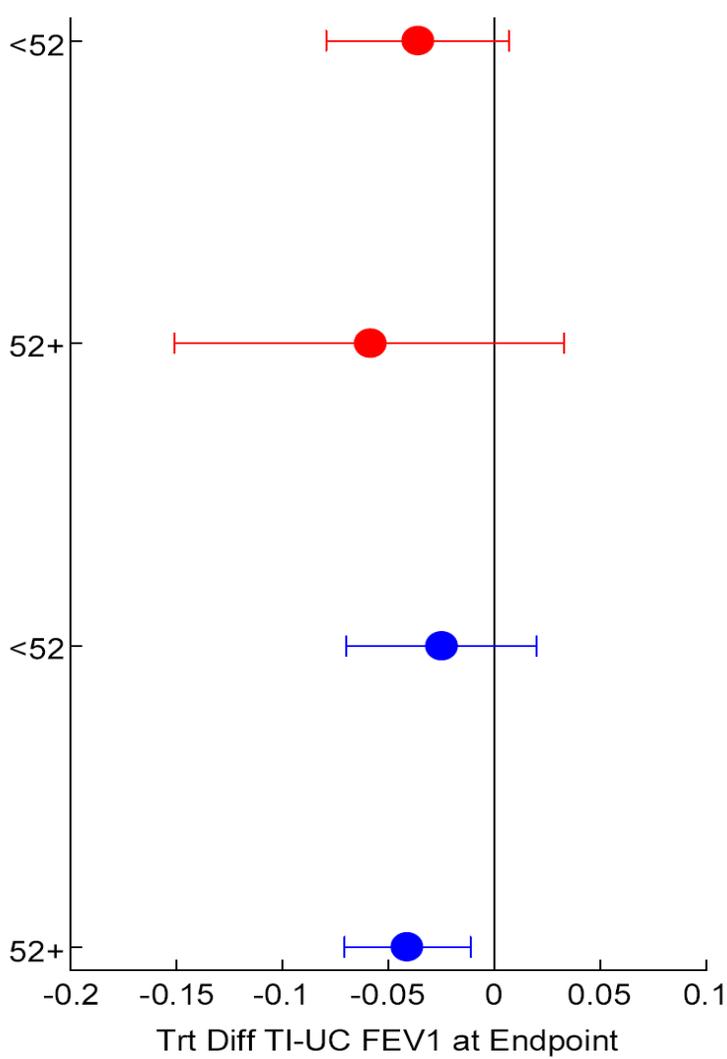
According to FDA medical reviewers, a change from baseline percent decrease in FEV₁ of 20% or more may be clinically important. For both Type 1 and Type 2 diabetics, there were statistically significantly more patients with a 20% or more drop (Type 1 diabetics: TI:2.5% UC:0% ; Type 2 diabetics: TI:1.9% UC:0.7%) using the last visit for the ITT population. A comparison of cumulative distribution plots (Figure 3.2.3.1.4) of percent change from baseline also yielded significant differences (p<0.03, Wilcoxon rank sum tests).

Figure 3.2.3.1.4 Cumulative distribution plot of percent change from baseline FEV₁ at the last visit for the ITT population.



This reviewer conducted subgroup analyses of FEV₁ change from baseline (ITT, last visit) defining subgroups based on age (by cutpoint of median of 52), sex, baseline FEV₁ and country (USA vs. other). Least square means treatment differences are shown on each graph by subgroup (labeled on y-axis) and by disease type; estimates to the left of zero favor usual care. Only country showed a differential treatment effect across subgroups with USA showing a larger decrease for TI over UC than other countries combined.

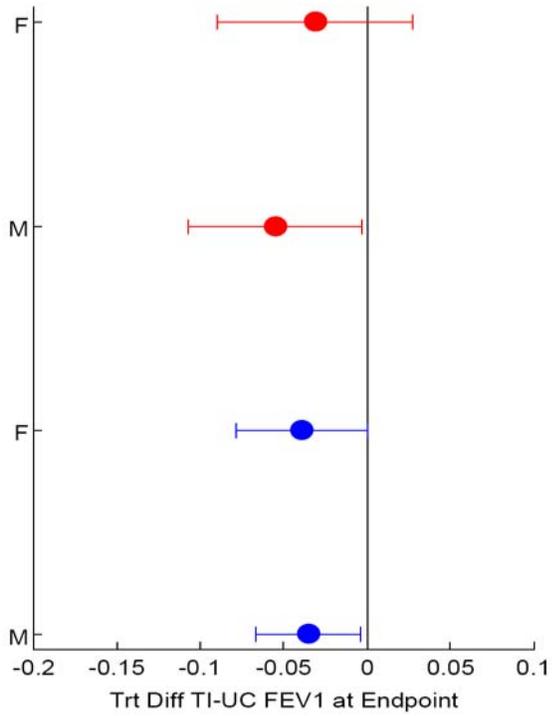
AGE



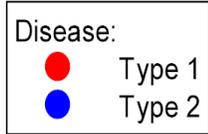
Disease:
 ● Type 1
 ● Type 2

The treatment effects by median age were consistent for both Type 1 and Type 2 diabetics (interaction $p > 0.9$). No differential treatment effects based on age were seen for FEV₁ in Study 030.

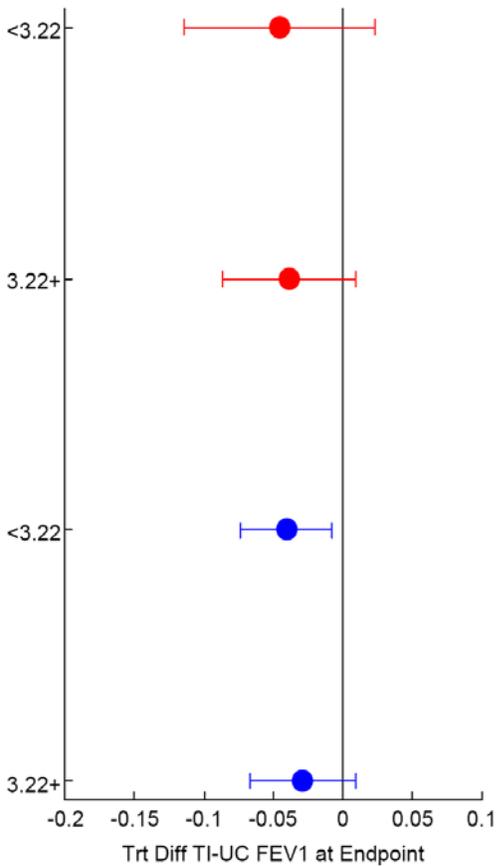
SEX



The treatment effects for females and males were consistent for both Type 1 and Type 2 diabetics (interaction $p > 0.9$). No differential treatment effects based on sex were seen for FEV₁ in Study 030.

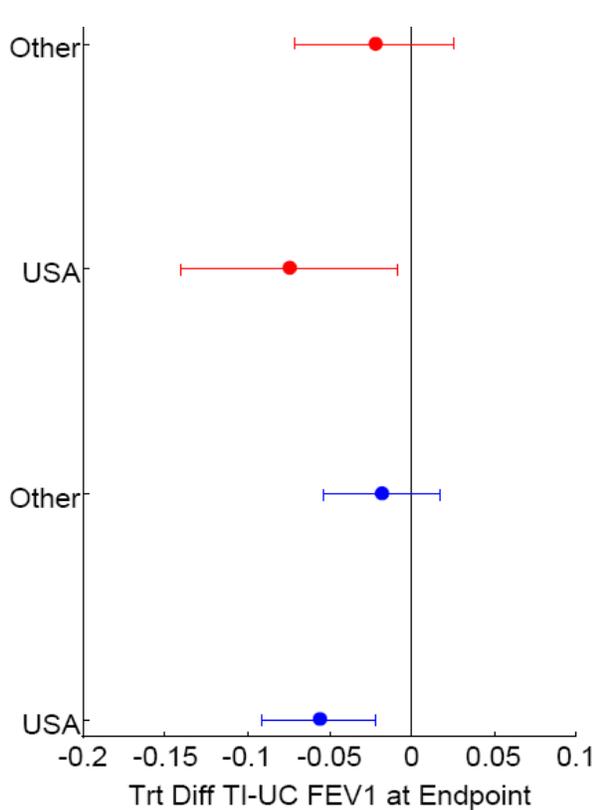


Baseline FEV₁



The treatment effects by baseline FEV₁ were consistent for both Type 1 and Type 2 diabetics (interaction $p > 0.6$). No differential treatment effects based on FEV₁ at baseline were seen for FEV₁ in Study 030.

COUNTRY



Disease:
 ● Type 1
 ● Type 2

The interaction for treatment by country (USA vs. Others) was statistically significant ($p < 0.06$). Statistically significant lowering of FEV₁ for TI compared to UC is seen for the USA sites but not for the sites pooled from other countries.

Each country had multiple sites with small numbers of subjects in each site (generally less than 20) so looking at results by site is not feasible.

This reviewer looked at other factors that may be related to country and only found that the BMI for the USA patients was on average higher than the BMI seen in other countries; however, no differential effect on FEV₁ was seen when considering BMI level.

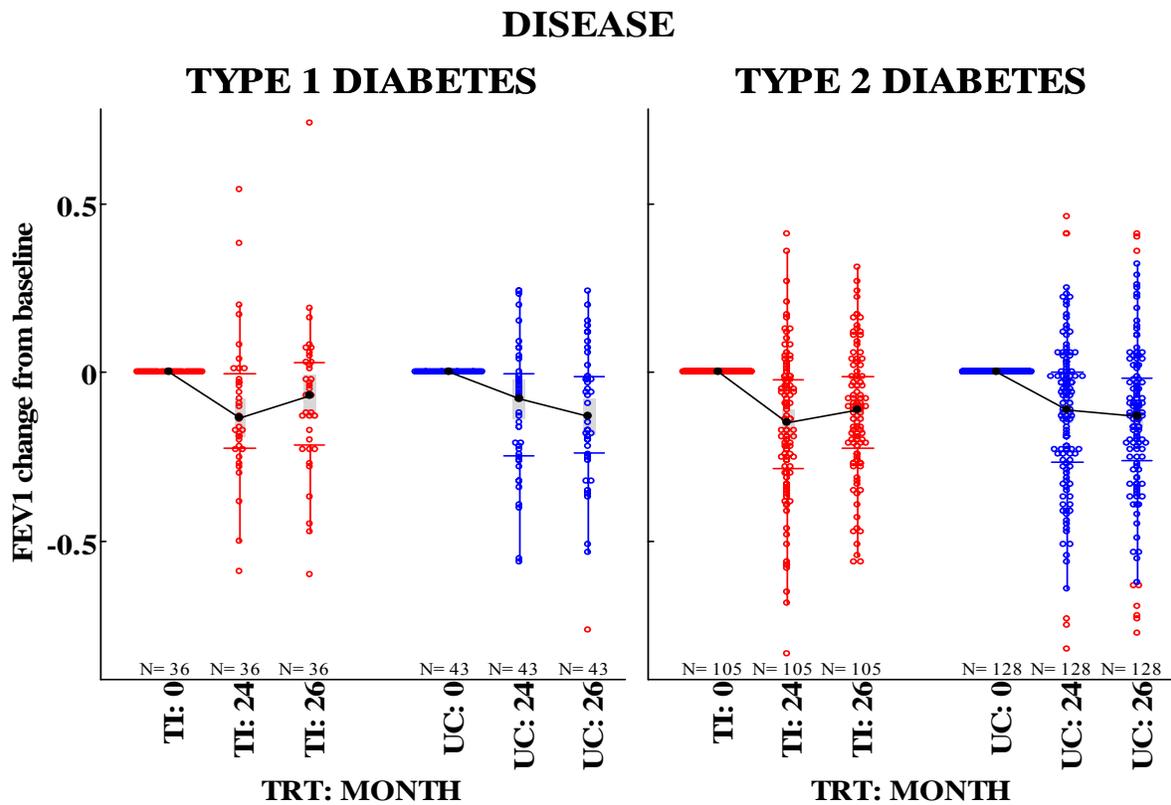
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FEV₁ Results After Removing TI Treatment

Patients enrolled in Canadian, Russian and US sites who completed Study 030 were eligible to enroll in Study 126. Upon entering Study 126, TI treatment was withdrawn and all patients were followed on usual care for about 2 months.

The boxplots below illustrate the distribution of FEV₁ change from baseline at Month 24 at the end of treatment and at Month 26 after 2 months without treatment.

Figure 3.2.3.1.5 Boxplots of FEV₁ change from baseline at Month 24 and at Month 26 (2 months off treatment) for all patients who entered Study 126 after completing Study 030



Although the graph indicates that most patients did not return to baseline FEV₁ after 2 months off therapy, the majority of the patients (60%) in the TI group did show an increase in FEV₁ levels during the follow-up period. About 44% of the comparator patients had an increase.

Among Type 1 diabetics, 23% (10/43) of usual care patients and 33% (12/36) of TI-treated patients returned to their baseline FEV₁ value or greater after two weeks off treatment. Among Type 2 diabetics, 24% (31/128) of usual care patients and 24% (25/105) of TI-treated patients returned to their baseline FEV₁ value or greater after two weeks off treatment.

With data only available on a small fraction of the originally randomized patients (~15%) and for a relatively short period of time, there is not definitive evidence for or against demonstration of reversal of the effect on FEV₁ based on this data from Study 030 and extension Study 126.

Hypoglycemia Results

The applicant performed analyses of hypoglycemia in Type 2 diabetics by comparing the total TI group to the UC group who took insulin while on study and separately to the UC group not taking insulin on study. This is not an appropriate comparison because dividing the control group based on administration of insulin results in non-randomized groups. In addition, the use of insulin was permitted in both treatment groups and the use was shown by the applicant to be comparable between the groups (63% in TI group and 67% in UC group, applicant’s table 12 in Study 030 report). The groups for comparison than within each disease type should be TI versus UC for the safety population.

The distribution of severe hypoglycemic events is shown in Table 3.2.3.1.5 for Type 1 diabetics and in Table 3.2.3.1.6 for Type 2 diabetics. A comparison of the distribution of all severe events (including multiple events per day) for the two treatment groups showed no significant difference between the groups for Type 1 diabetics (p=0.51, Wilcoxon rank sum test) and Type 2 diabetics (p=0.20, Wilcoxon rank sum test).

Table 3.2.3.1.5 Study 030 Type 1 diabetics tabulation of severe hypoglycemic events

	% (n/N) of pts. with at least 1 event	Number of patients with “n” events							
		0	1	2	3-5	6-10	11-15	16-20	>20
TI	16% (42/267)	225	24	8	8	2	0	0	0
UC	17% (47/271)	224	21	8	10	3	2	0	3

Variable HYDY7FL in dataset ADHY was used to identify cases of severe hypoglycemia. The applicant’s table 8.3.1.6.2.1.1 reports 3 UC pts for 11-20 and 2 for 21-30 while this reviewer computed 2 and 3 for those categories

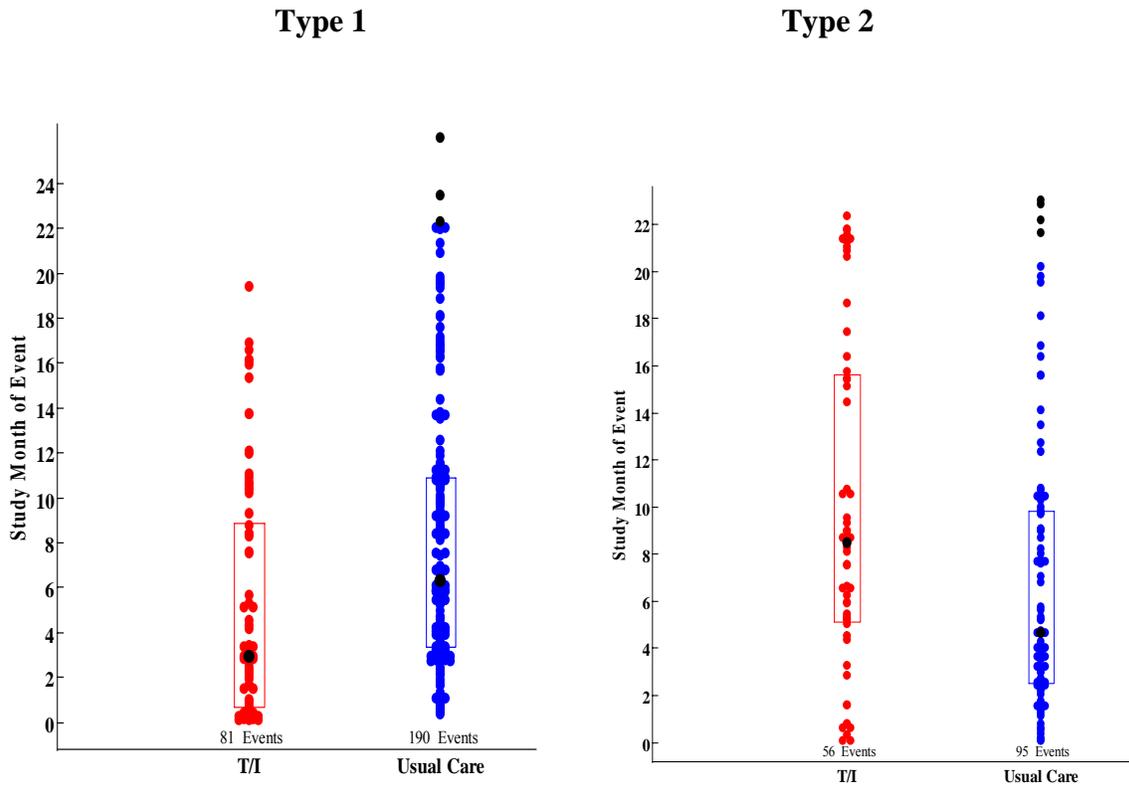
Table 3.2.3.1.6 Study 030 Type 2 diabetics tabulation of severe hypoglycemic events

	% (n/N) of pts. with at least 1 event	Number of patients with “n” events							
		0	1	2	3-5	6-10	11-15	16-20	>20
TI	3.2% (21/656)	635	8	8	4	0	1	0	0
UC	4.6% (31/678)	647	18	5	3	2	2	1	0

In addition, comparing the number of patients having at least one severe hypoglycemic event yielded a non-significant result based on an overall CMH test controlling for disease (p=0.23). Also a test of homogeneity showed consistent results for Type 1 and Type 2 diabetics. An odds ratio stratifying on diabetic disease of 0.80 (95% CI 0.6, 1.1) was statistically non-significant.

This reviewer looked at the timing of the severe events by plotting the times of the occurrences of the all the events by disease type and by treatment group. Figure 3.2.3.1.6 below suggests that fewer events occur with more time on study however, the interpretation of these results is confounded with the decrease in patient numbers with time.

Figure 3.2.3.1.6 Boxplots of time of occurrence of severe hypoglycemic events



Overall this reviewer concludes that the hypoglycemia data from Study 030 shows no statistically important difference between TI and usual care for either Type 1 or Type 2 diabetics.

Results for Change in Weight

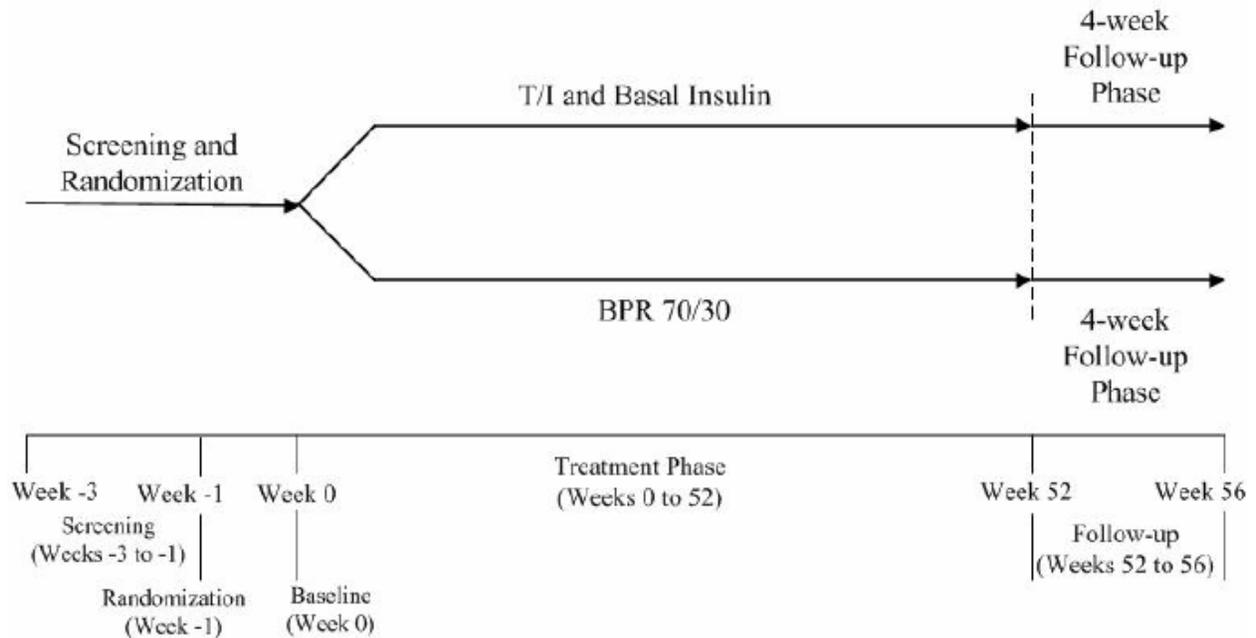
^{(b) (4)} For Study 030, more weight gain was seen at endpoint for usual care controls than TI-treated patients for both Type 1 and Type 2 diabetics (Type 1: UC +1.3 kg TI -0.06 kg, $p < 0.002$; Type 2: UC +1.5 kg TI +0.08 kg, $p < 0.02$). It is worth noting that non-diabetics showed an average increase of 1.1 kg similar to the UC controls.

3.2.3.2 Study MKC-TI-102

Study 102 was a one year trial in Type 2 diabetic patients suboptimally controlled with sc insulin with or without oral anti-diabetic drugs. Patients were randomized either to TI (given with meals) plus basal insulin or to BPR 70/30 (sc biphasic rapid acting insulin given twice daily) and followed as shown in the schematic below.

Figure 3.2.3.2.1 Applicant's schematic of Study 102 trial design

Figure 2. MKC-TI-102 Trial Design and Plan



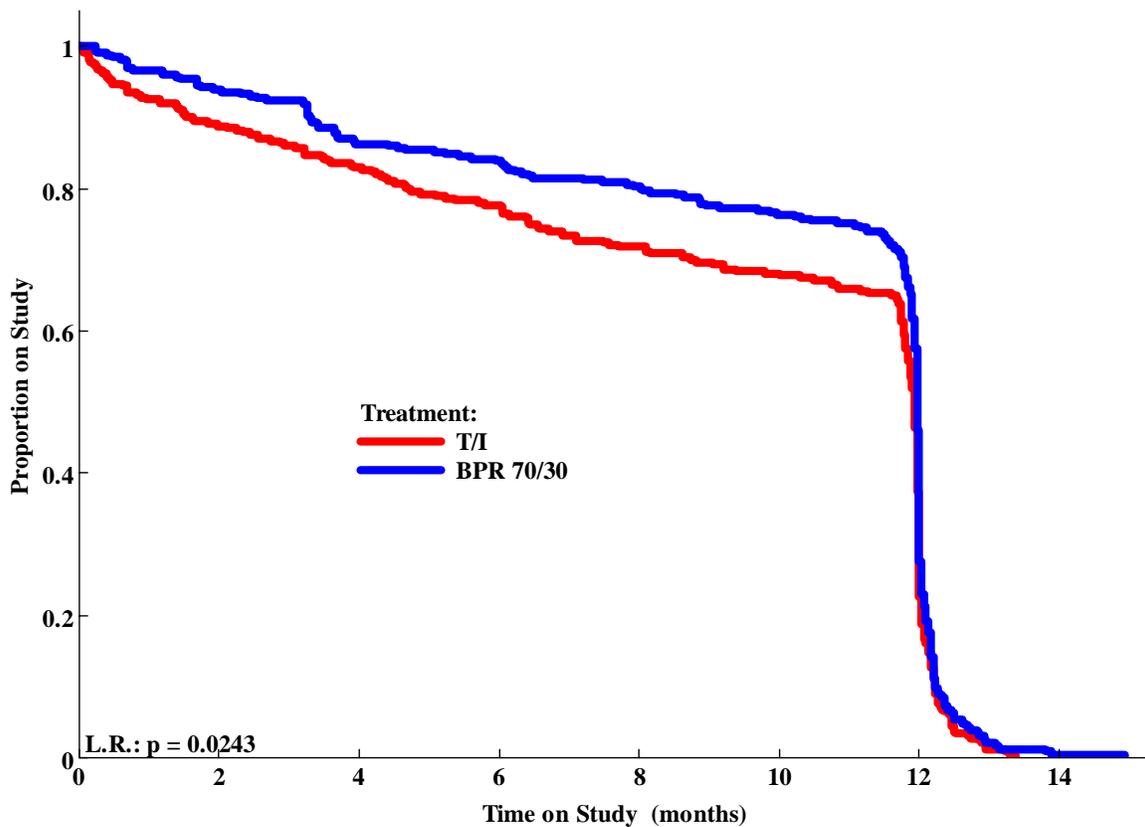
Over 600 patients were enrolled in Study 102 (Table 3.2.3.2.1 on the following page) at sites in Canada, Russia, US (44%), South America and Europe. About 70% of patients completed Study 102 although FEV₁ data was available on only about half the randomized patients at Month 12. Following completion of Study 102, patients could be followed for one month off drug and then enter Study MKC-TI-126 where patients were followed for an additional two months off randomized treatment. South American and European sites (about 1/3 of randomized patients) did not participate in Study 126. About 1/5 of the total randomized patients entered Study MKC-TI-126. The primary endpoint for follow-up period was change from baseline in FEV₁ where baseline was defined as the baseline from the parent study (i.e. Study 102). This follow-up data is only useful for illustrating the trajectory of FEV₁ after withdrawal of TI; it is not useful for comparisons to control since so few randomized patients continued into Study 126.

Table 3.2.3.2.1 Sample sizes at Randomization, Month 12 and Entrance into Study 126

	TI	BPR
Randomized	334	343
Safety population	323 (97%)	331 (97%)
Completed 102	216 (65%)	246 (72%)
Primary reasons for discontinuation from 102		
ADE	9%	4%
Patient withdrew consent	15%	9%
Lost to follow up	2%	6%
Entered 126	69 (21%)	69 (20%)

The treatment exposure was statistically significantly less in the TI group compared to the BPR group as illustrated below.

Figure 3.2.3.2.2 Proportion of patients on study by group



FEV₁ Results

Table 3.2.3.2.2 on the following page summarizes the FEV₁ results for Study 102. At Month 3 and also at endpoint, a statistically significant drop of 0.06 L (60mL) in FEV₁ for TI compared to BPR was seen. The applicant reported no significant difference between the groups based on the Month 12 observed cases

results (note that the applicant reported data nearly identical to the data below but for 175 TI and 199 BPR patients at Month 12). Data for observed cases at Month 12 does not adequately describe the results for randomized patients. Conclusions should be based on the last value for the ITT population which shows a statistically significant treatment effect.

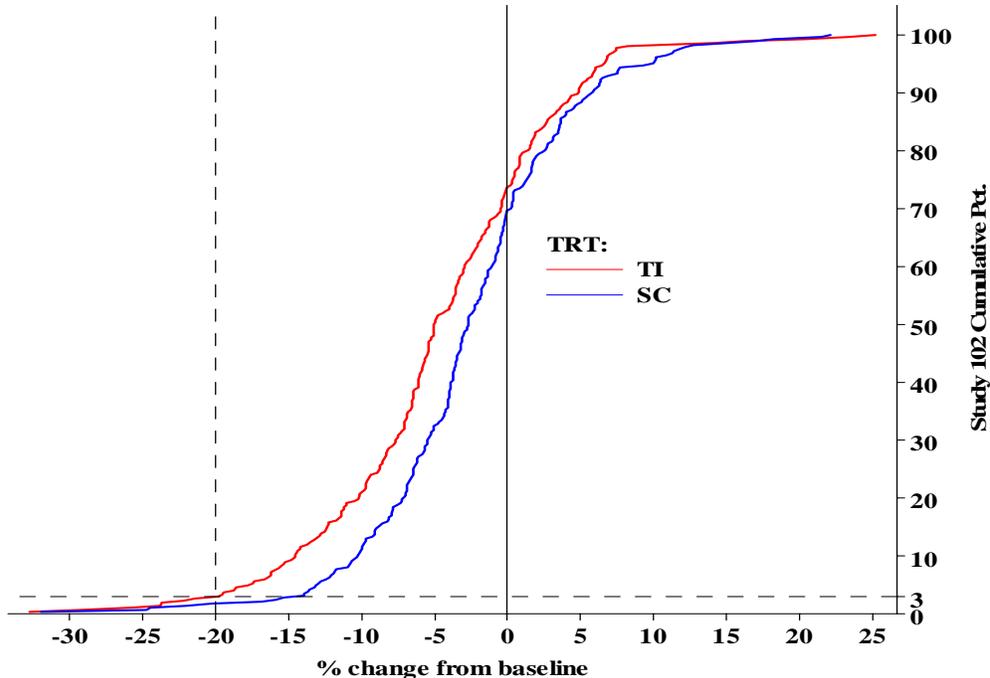
Table 3.2.3.2.2 Study 102 FEV₁ baseline and change from baseline mean (SD)

	TI (n=266)	BPR (n=283)	p-value	Treatment Difference 95% CI ^a
Baseline	2.86 (0.69)	2.77 (0.69)	0.14	
Month 3 OC	-0.09 (0.20) (n=264)	-0.03 (0.17) (n=259)	<0.001	-0.06 (-0.09, -0.03)
Month 12 OC	-0.13 (0.22) (n=141)	-0.09 (0.20) (n=139)	0.22	-0.03 (-0.08, +0.02)
Applicant's Month 12	-0.13 (0.22) (n=175)	-0.09 (0.20) (n=199)	0.22	NR
Last Value (ITT)	-0.13 (0.23) (n=266)	-0.07 (0.19) (n=283)	<0.001	-0.06 (-0.10, -0.03)

a – Results are based on ANCOVA model with baseline as a covariate.

A cumulative distribution plot of percent change from baseline in FEV₁ at endpoint also illustrates the significant difference between the groups (p<0.001, Wilcoxon rank sum test). About 2.6% of TI patients and 1.8% of BPR patients had a 20% or more drop in FEV₁.

Figure 3.2.3.2.3 Cumulative distribution plot of percent change from baseline FEV₁ at the last visit for the ITT population comparing TI versus BPR (SC)



Clearly TI statistically significantly lowers FEV₁ compared to BPR. (b) (4)

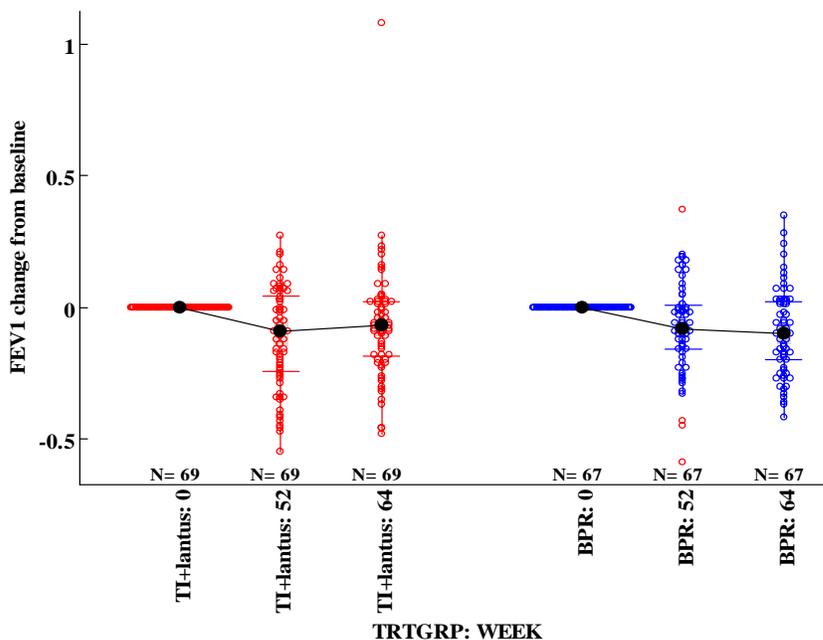
As shown earlier, a small number of patients from Study 102 were followed into Study 126 so their results cannot be considered representative of the results of randomized groups. This reviewer is therefore only presenting some descriptive statistics of the FEV₁ results for Study 126. The patients exposed to TI show an average decrease in FEV₁ of 0.11 L (110 mL) at the end of Study 102 and then a small mean increase of about 0.04 after 3 months without TI treatment. About 65% of the TI-treated patients had an increase in FEV₁ at the end of Study 126 with about 1/3 of the patients returning to the Study 102 baseline or higher. The latter observation is reassuring but not definitive given the paucity of data in Study 126.

Table 3.2.3.2.3 FEV₁ results for patients completing Study 102 and continuing into Study 126

	TI (n=69) Mean (SD)	BPR (n=67) Mean (SD)
Last FEV ₁ on 102		
Observed	2.89 (0.7)	2.80 (0.7)
Change from baseline	-0.11 (0.19)	-0.08 (0.17)
Last FEV ₁ on 126		
Observed	2.93 (0.7)	2.78 (0.7)
Change from 102	+0.04 (0.18)	-0.02 (0.15)
% patients with increase in FEV ₁ during 126	45/69 65%	29/67 43%
% patients returning to 102 baseline FEV ₁ or higher	22/69 32%	21/67 31%

The distribution of FEV₁ change from Study 102 baseline values illustrate that there were no notable outliers and the distributions for the two treatment groups are similar.

Figure 3.2.3.2.4 Boxplots of FEV₁ change from baseline for patients with data at the end of Study 102 and during Study 126.



Hypoglycemia Results

Analyses of severe hypoglycemic events showed significantly fewer first events for TI (4.3%) versus BPR (10%) with p=0.005 (CMH test) and statistically significant odds ratio of 0.41 (95% CI 0.21, 0.79).

Also a comparison of the number of events experienced by each patient (Table 3.2.3.2.4) showed results favorable to TI (p=0.005, Wilcoxon rank sum test).

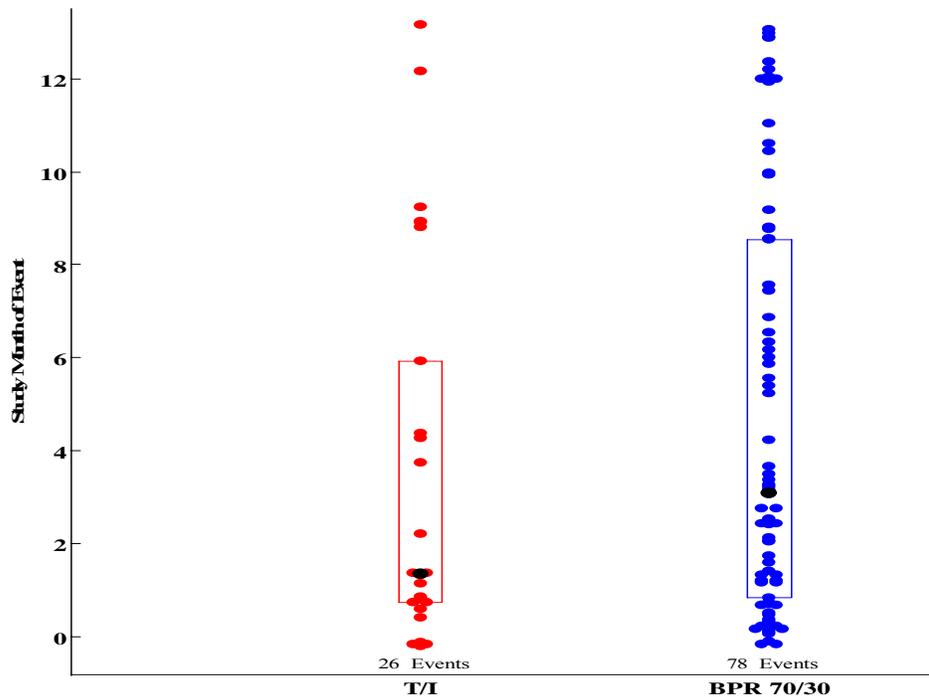
Table 3.2.3.2.4 Study 102 Tabulation of severe hypoglycemic events

	% (n/N) of pts. with at least 1 event	Number of patients with “n” events							
		0	1	2	3-5	6-10	11-15	16-20	>20
TI	4.3% (14/323)	309	9	3	1	1	0	0	0
BPR	10.0% (33/331)	298	17	8	6	1	0	1	0

In addition, the applicant reports rates of 0.72/100 subject months for TI versus 2.19 /100 subject months for BPR; clearly favoring TI although borderline significant (p=0.06).

A plot of the timing of the events shows events tending to occur during the first half of the study although interpretation is confounded by the large number of dropouts.

Figure 3.2.3.2.5 Boxplots of time of occurrence of severe hypoglycemic events

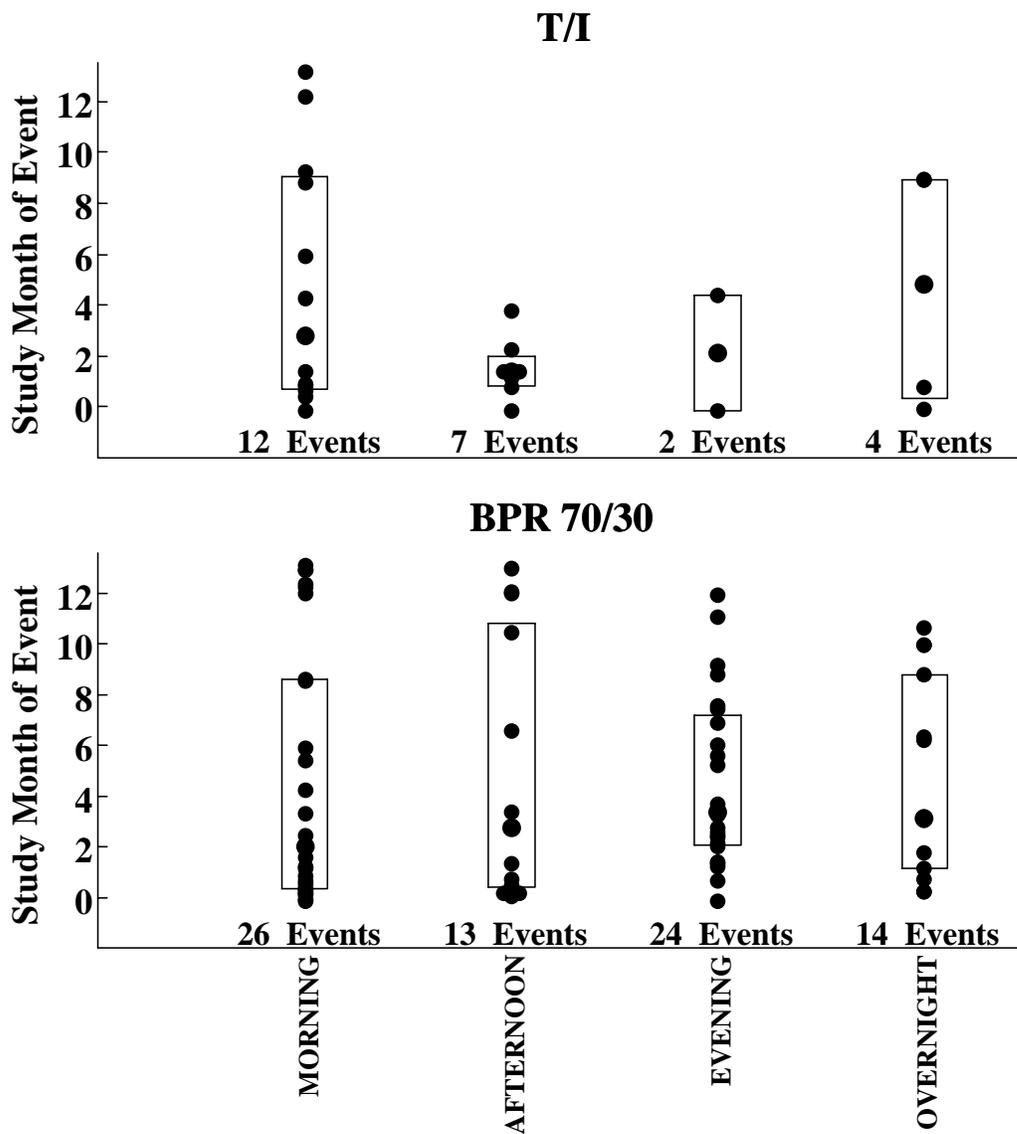


Similar results are seen when looking at all hypoglycemic events where also an odds ratio of 0.41 was seen

with 48% of TI patients and 69% of BPR patients experiencing a hypoglycemic event. As for severe events, most events were identified based on a glucose level (mild and moderate events are defined by a glucose of 49 or less).

Because of the differences in timing of the administration of drug in the TI group compared to the comparator BPR, this reviewer looked at the timing of all severe hypoglycemic events based on time of day of occurrence. For the TI group, about half the events occurred in the morning while for the BPR group the events appear somewhat evenly distributed over the day.

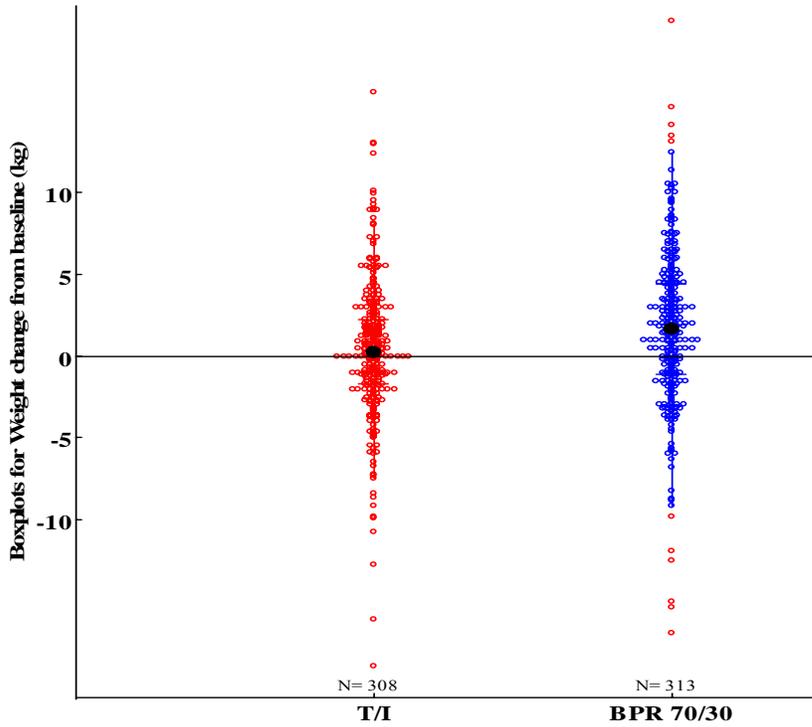
Figure 3.2.3.2.6 Boxplots of time of occurrence of severe hypoglycemic events by time of day and group



Results for Change in Weight

(b) (4) For Study 102, more weight gain was seen at endpoint for BPR controls (+1.6 kg) than TI-treated patients (+0.4 kg, $p < 0.0001$). This reviewer also did subgroup analyses to determine if there were any interactions and found none so these effects on weight were consistent for a number of subgroups.

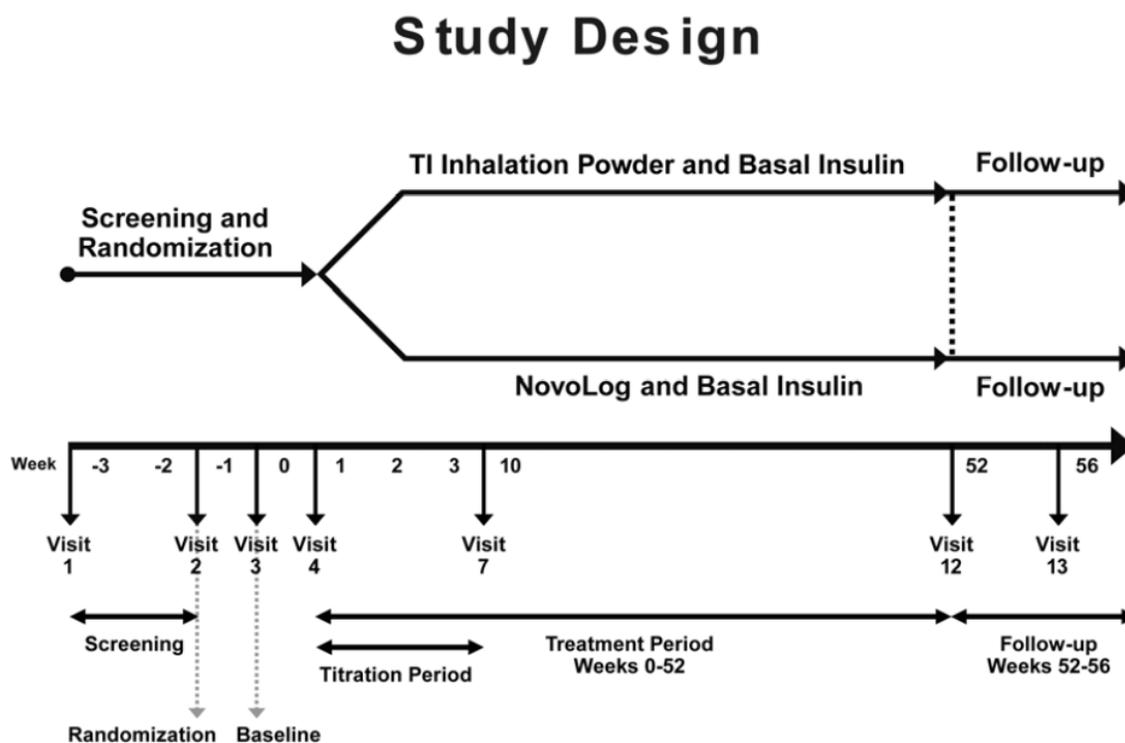
Figure 3.2.3.2.7 Change in weight (kg) at endpoint (ITT)



3.2.3.3 Study MKC-TI-009

Study MKC-TI-009 was an open label, randomized study comparing TI plus sc basal insulin to prandial insulin (insulin aspart) plus sc basal insulin in patients with Type 1 diabetes. This was a one-year study with a 4-week follow-up phase with some patients continuing to be followed in Study 126.

Figure 3.2.3.3.1 Applicant's schematic of the design for Study 009



Type 1 diabetics were enrolled in 10 countries with about half in the USA. As for the other long-term studies in this application, the dropout rate in the TI group was significantly greater than the rate in the insulin aspart group (see Table 3.2.3.3.1 and Figure 3.2.3.3.1). The primary reason for dropout in both groups was withdrawal of consent by the patient (TI 16% and Aspart 7%).

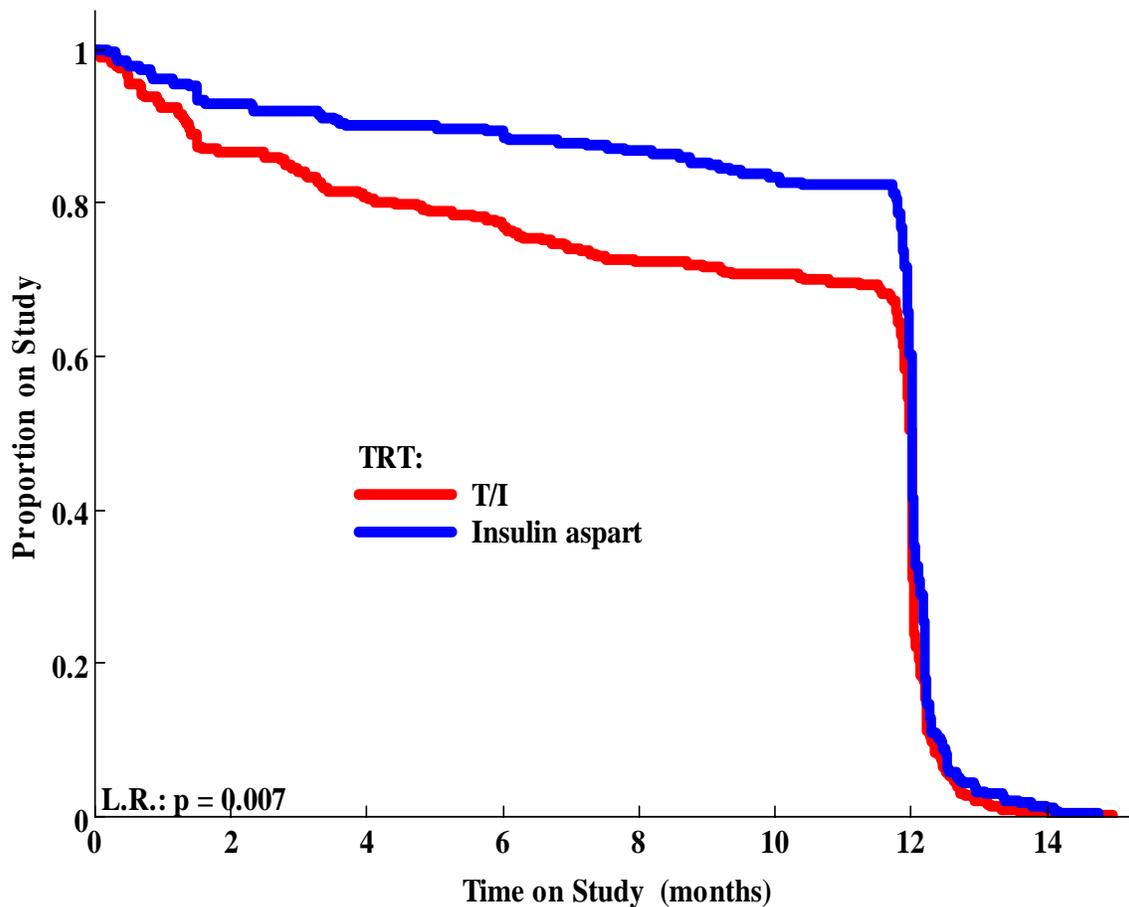
Table 3.2.3.3.1 Patient disposition for Study 009

	TI	Insulin Aspart
Randomized	301	288
Safety population	293 (97%)	272 (94%)
Completed 009	198 (66%)	220 (76%)
Primary reasons for discontinuation from 009		
ADE	6%	1%
Patient withdrew consent	16%	7%
Investigator decision	5%	2%
Entered 126 ¹	81	83

1-Patients with Study 009 baseline and endpoint FEV₁ and Study 126 FEV₁

As seen in Studies 102 and 030, dropouts occur early in the TI group with nearly half discontinuing by Month 2 (Figure 3.2.3.3.1). The dropout rates were significantly different with $p=0.007$.

Figure 3.2.3.3.1 Proportion of patients on study by treatment group



After a 4 week follow-up in Study 009, patients could be enrolled in Study 126 and followed for an additional 2 months open label off treatment with 2 visits, one on the last day of 009 (i.e. end of 1 month follow-up for patients who completed the trial) and the second two months later. Only about 28% of the randomized patients entered Study 126.

The table on the following page summarizes the FEV₁ results for Study 009. At Month 3 and also at endpoint, a statistically significant drop (40-50 mL) in FEV₁ for TI compared to insulin aspart was seen. The applicant reported no significant difference between the groups based on the Month 12 observed cases results and this reviewer confirmed no statistically significant difference although this reviewer calculated different results (this reviewer's results are based on the data provided in the Pulmonary ISS with subsetting on the visit variable AVISITN). However Month 12 OC results are based on a subset of the randomized

patients (<70%) and therefore the analysis should only be characterized as a sensitivity analysis designed to assess the impact of dropouts. The endpoint results computed using the last value for the ITT population should be considered as the primary results of importance and these results show a statistically significant difference between the groups.

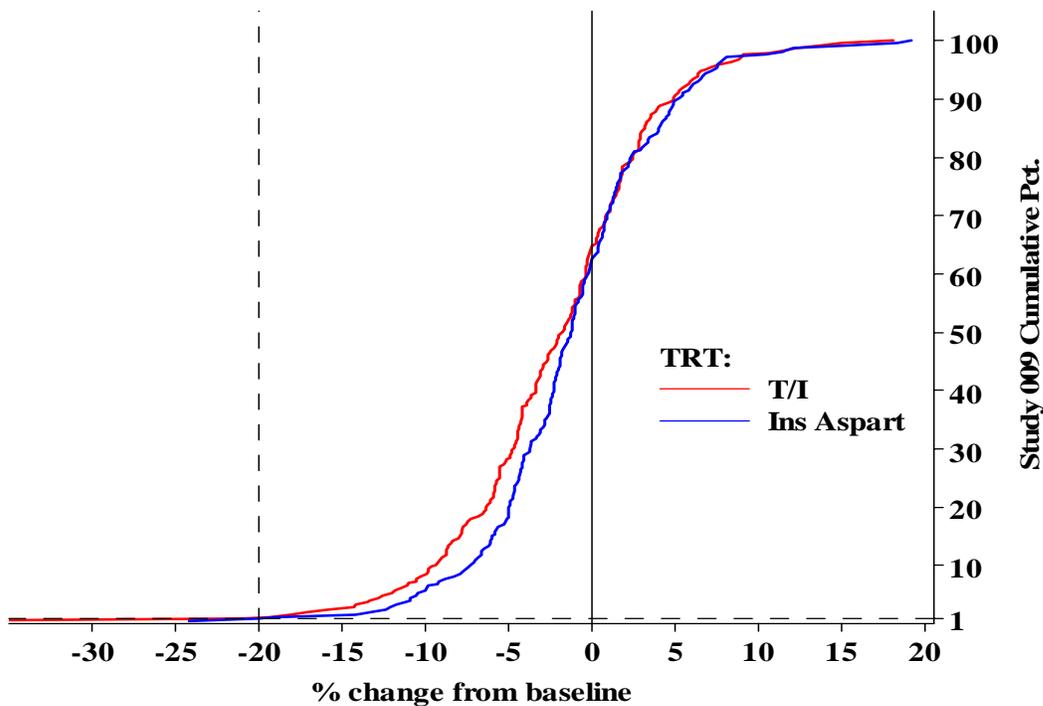
Table 3.2.3.3.2 Study 009 FEV₁ baseline and change from baseline mean (SD)

	TI (n=235)	Insulin Aspart (n=244)	p-value	Treatment Difference 95% CI ^a
Baseline	3.45 (0.77)	3.46 (0.79)	>0.5	
Month 3 OC	-0.05 (0.21) (n=229)	-0.01 (0.16) (n=226)	<0.009	-0.05 (-0.08, -0.01)
Month 12 OC	-0.07 (0.22) (n=134)	-0.04 (0.19) (n=138)	0.33	-0.02 (-0.07, +0.02)
Applicant's Month 12	-0.06 (0.21) (n=161)	-0.06 (0.20) (n=173)	0.72	NR
Last Value	-0.07 (0.22) (n=235)	-0.04 (0.17) (n=244)	0.03	-0.04 (-0.08, -0.005)

a – Results are based on ANCOVA model with baseline as a covariate.

When comparing, cumulative distribution curves of the percent change from baseline at endpoint, the results are borderline significant with p=0.06. Both treatment groups had 0.8% of patients with a 20% or greater decrease in FEV₁.

Figure 3.2.3.3.2 Cumulative distribution plot of percent change from baseline FEV₁ at the last visit for the ITT population comparing TI versus insulin aspart



As was seen with Study 102, a small number of patients (<1/3) from Study 009 were followed into Study 126 so their results cannot be considered representative of the results of randomized groups. This reviewer is therefore only presenting some descriptive statistics of the FEV₁ results for Study 126. The patients exposed to TI show an average decrease in FEV₁ of 0.07 L (70 mL) at the end of Study 009 and then a small mean increase of about 0.01 (10mL) after 3 months without TI treatment. About 51% of the TI had an increase in FEV₁ at the end of Study 126 with about 1/3 of the patients returning to the Study 009 baseline or higher. As for Study 102, the latter observation is reassuring but not definitive given the paucity of follow-up data from Study 126.

Table 3.2.3.3.3 FEV₁ results for patients completing Study 009 and continuing into Study 126

	TI (n=81) Mean (SD)	Ins Asp (n=83) Mean (SD)
Last FEV ₁ on 009		
Observed	3.54 (0.7)	3.53 (0.8)
Change from baseline	-0.07 (0.21)	-0.02 (0.19)
Last FEV ₁ on 126		
Observed	3.48 (0.7)	3.50 (0.8)
Change from last 009	+0.01 (0.14)	-0.02 (0.14)
% patients with increase in FEV ₁ during 126	42/82 51%	35/83 42%
% patients returning to 009 baseline FEV ₁ or higher	30/82 37%	43/83 52%

Results for Hypoglycemia

In this study of Type 1 diabetics, about 1/3 of the patients have at least one severe event; the difference in the incidence of severe events is not statistically significant with 33% of TI-treated patients and 38% of insulin aspart-treated patients having at least one severe event (p=0.24, CMH, OR 0.81 [95% CI 0.57, 1.15]). An analysis of the number of severe hypoglycemic events for each patient (Table 3.2.3.3.4) yielded a p-value of 0.12 (Wilcoxon rank sum test).

Table 3.2.3.3.4 Study 009 Tabulation of severe hypoglycemic events

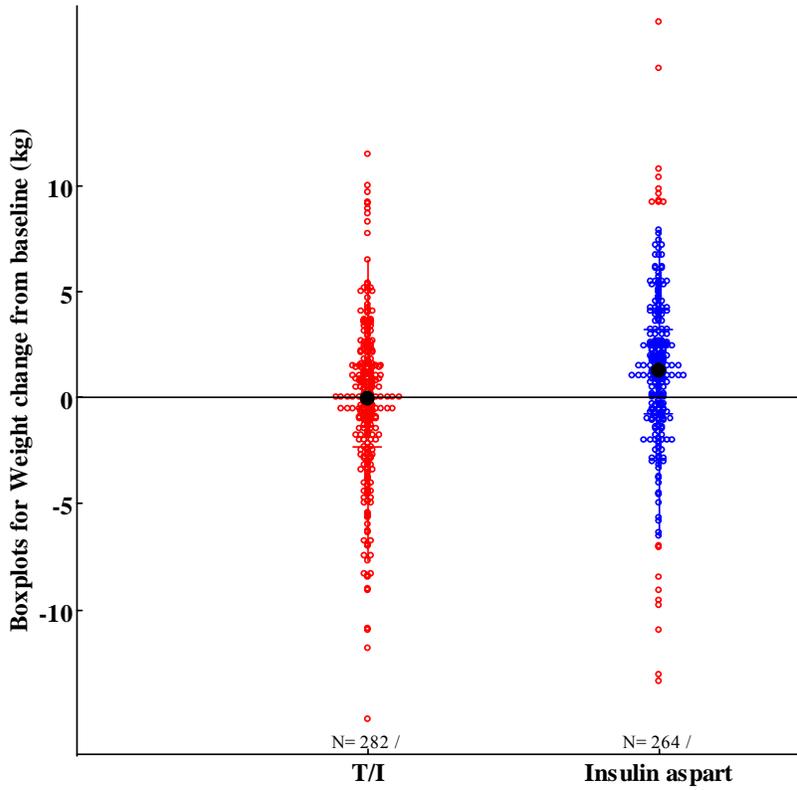
	% (n/N) of pts. with at least 1 event	Total # of severe events	Number of patients with “n” events							
			0	1	2	3-5	6-10	11-15	16-20	>20
TI	33% (96/293)	230	197	46	20	24	4	1	0	1
IA	38% (102/272)	292	170	39	22	28	10	1	2	0

In addition an analysis of event rates reported by the applicant showed no statistically significant difference between the groups with rates of 8.3/100 subject months for TI versus 9.9 /100 subject months for insulin aspart (p=0.18).

Results for Change in Weight

^{(b) (4)}. For Study 009, more weight gain was seen at endpoint for insulin aspart controls (+1.3 kg) than TI-treated patients (-0.3 kg, $p < 0.0001$). These results were also consistent across a number of subgroups.

Figure 3.2.3.3.3 Change in weight (kg) at endpoint (ITT)

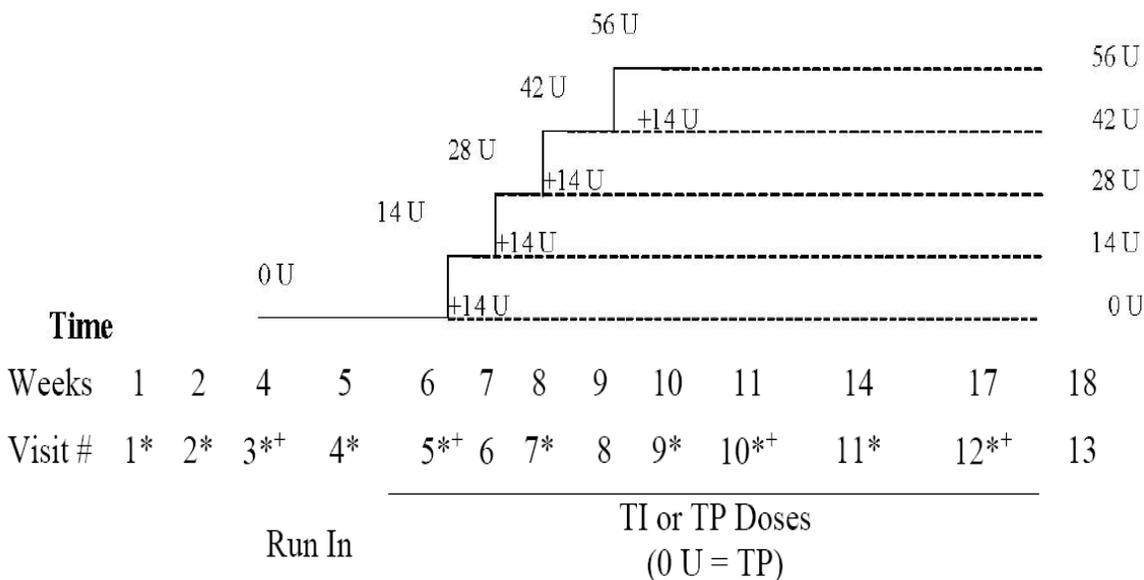


3.2.3.4 Studies PDC-INS-0008 and MKC-TI-005 plus Extension Study MKC-TI-010

Studies MKC-TI-005 and PDC-INS-0008 were Phase 2, placebo-controlled, double-blind studies conducted in Type 2 diabetics with about a 12-week treatment period. One of the objectives for each study was to evaluate the safety of the TI product (TP device plus insulin) compared to a placebo control of the TP device without insulin. Patients from both of these studies could enter into an extension study (Study 010) and be followed on TI for up to 4 years open label. Given the small number of patients evaluated in these studies and the short duration of the double-blind period, this reviewer thinks the extension data for FEV₁ is of most value. Therefore the results for these individual studies are briefly summarized and then followed by FEV₁ results from the extension study. The extension study with exposure out to nearly 4 years provides the longest follow-up data for FEV₁ provided in the application

The primary objective of Study 005 was to develop algorithms for dosing TI. A dose titration scheme as shown in Figure 3.2.3.4.1 was used. Patients were randomized to placebo, 14U, 28U, 42U or 56U. All patients received basal insulin (Lantus). All patients were treated with placebo (TP device without placebo) for 2 weeks; for patients randomized to TI, treatment with 14 U TI started at Week 6 as shown in Figure 3.2.3.4.1 and then the dose was titrated weekly until the randomized dose was reached. The total time on TI was 11 weeks; note that it takes 3 weeks to achieve the highest dose so the total time on the highest dose is only 8 weeks. Another goal of the study was to assess dose response; the statistical reviewer for efficacy shows in her review a difference between the low dose and the three higher doses but essentially no dose response for the 3 higher doses.

Figure 3.2.3.4.1 Study 005 schematic



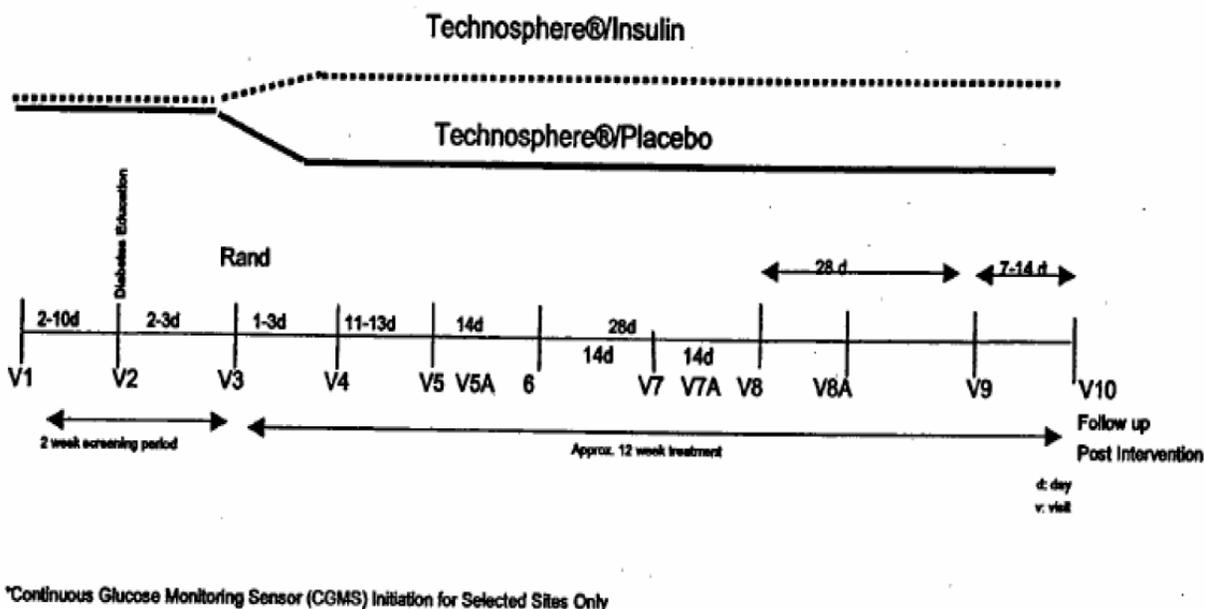
*Indicates in-clinic visit

⁺ Indicates a meal challenge

The patient population enrolled in this study was 99% Caucasian, 54% male and had an average age of 58 years (range 36 to 82). Baseline HbA1c was comparable across the groups with an overall mean of about 9%. The most commonly used oral anti-diabetic medication used at baseline was sulfonylureas (81%) and metformin (78%); about 18% of patients in each group used metformin while on study.

Study 0008 was a 12 week study with patients randomized to placebo or TI. The design is shown in the applicant's schematic below. Patients remained on their baseline oral anti-diabetic medications.

Figure 3.2.3.4.2 Study 0008 schematic



The patient population enrolled in this study was 69% Caucasian and 17% Hispanic. About 69% of patients were male and the average age was 56 years (range 34 to 72). [Note that this reviewer could not locate the baseline HbA1c values in the study report.]

In Study 005 approximately 45 patients were randomized to each treatment group while in Study 0008, 61 patients were randomized to TI and 62 to placebo. The completion rate was high in both studies with almost 90% of the patients completing about 12 weeks. About 60-70% of the randomized patients entered the uncontrolled extension study (Study 010) where all patients were treated with TI. The mean exposure in Study 010 was 2.5 years (minimum of 0.1 years and maximum of 3.9 years)

Table 3.2.3.4.1 Studies 0008 and 005 patient disposition

	Study 0008		Study 005				
	TP	TI Doses 6-48 U Mean 32 U	TP	TI 14 U	TI 28 U	TI 42 U	TI 56 U
Randomized	62	61	46	45	46	45	45
Completed ~12 weeks	53 (86%)	54 (89%)	40 (87%)	42 (93%)	41 (89%)	41 (91%)	41 (91%)
Entered Study 010	40 (65%)	45 (74%)	29 (63%)	30 (67%)	27 (59%)	32 (71%)	26 (58%)

The FEV₁ results and the hypoglycemia results for both studies are summarized in Section 3.2.2 of this review. Neither study showed a statistically significant drop in FEV₁ for TI compared to placebo after 12 weeks of therapy and the magnitude of the treatment effects were not consistent, with TI showing a larger

drop than TP in Study 0008 and smaller in Study 005. For hypoglycemia, there were no severe events in either trial; the incidences of all mild and moderate hypoglycemic events were higher in the placebo group but the difference was not statistically significant.

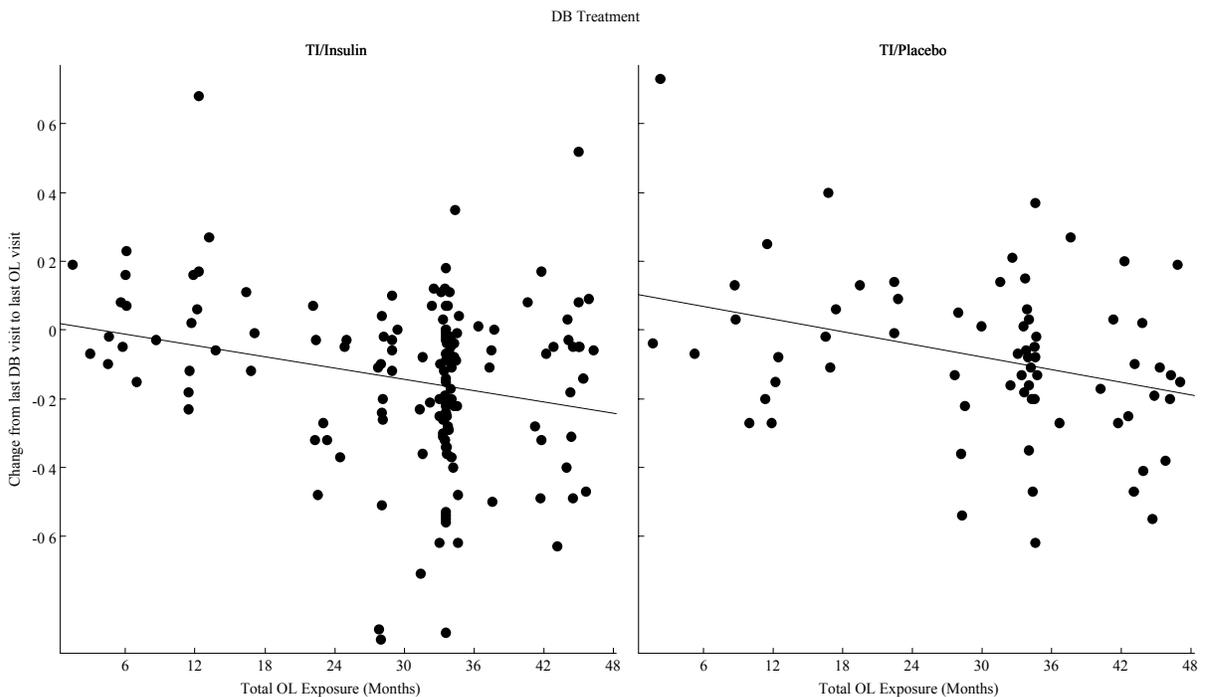
For Study 010, the applicant computed a mean annual rate of decline for FEV₁ of -0.048 L (95% CI of -0.06 to -0.04) using a random coefficients model. The mean change from baseline by time in the extension study is shown below. Baseline is the FEV₁ value at the end of Studies 005 and 0008. Higher mean decreases are seen after the first year suggesting that the FEV₁ continues to decline although the decline is small and not likely to be clinically important. Note also that the data is very limited after 2 years.

Table 3.2.3.4.2 FEV₁ mean change from baseline for Study 010

Month	N	Change from Baseline Mean (SD)
0 (end of DB)	229	Baseline 2.99 (0.7)
6	195	-0.03 (0.2)
12	205	-0.05 (0.2)
24	170	-0.15 (0.2)
36	56	-0.13 (0.2)
42	39	-0.15 (0.2)

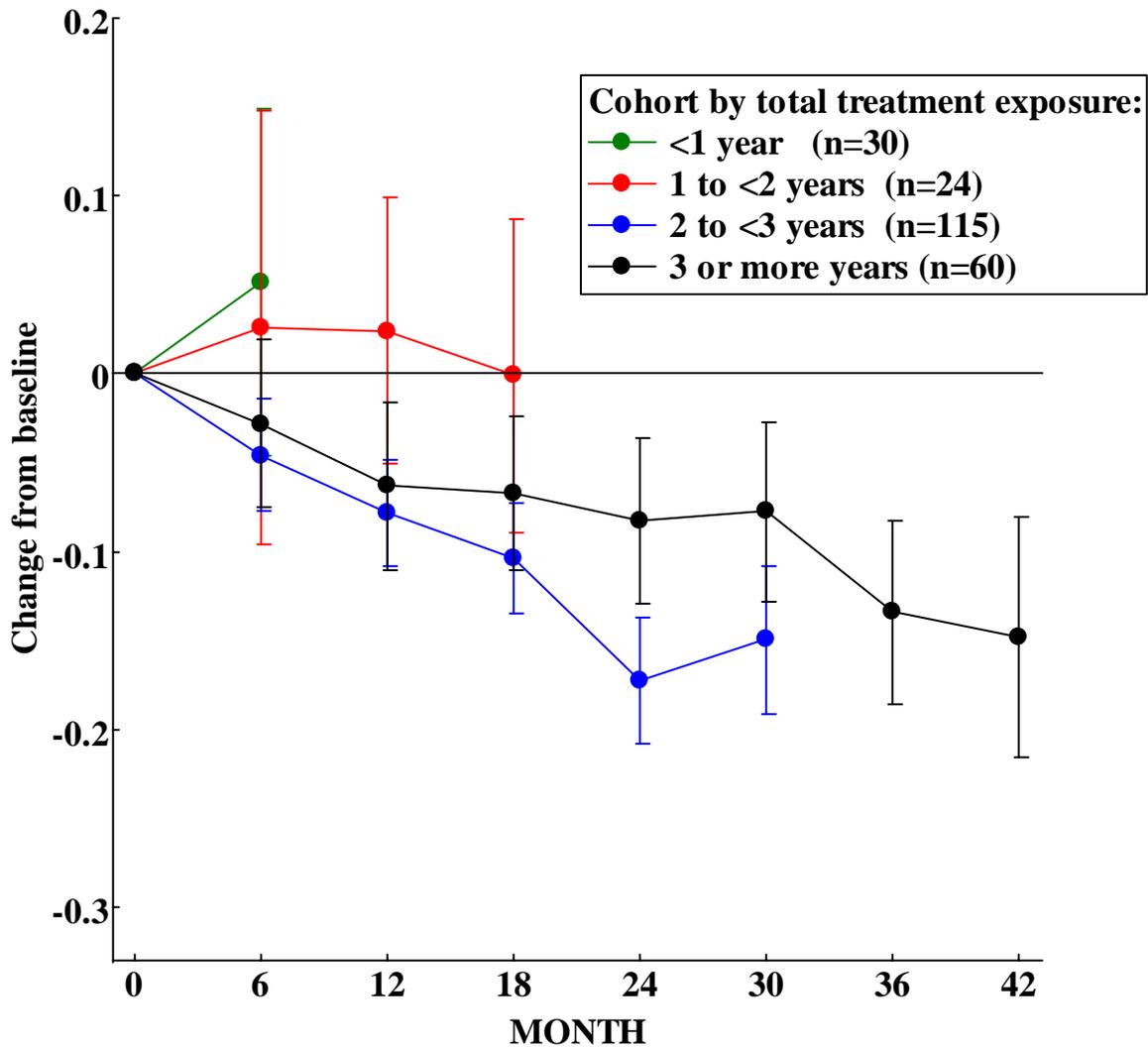
To illustrate the relationship between patient exposure to TI and the change in FEV₁, this reviewer provides the graphs below for patients exposed to TI in the parent study and for patients given placebo in the parent study. The fitted line suggests an average decline in FEV₁ with increased exposure.

Figure 3.2.3.4.3 Change from baseline (end of DB period) by time in extension study by originally randomized treatment



Similarly, plotting mean change from baseline in FEV₁ overtime by cohorts of patients defined by their time on Study 010 (Figure 3.2.3.4.4) also illustrates the decline in FEV₁ while remaining on TI treatment. Although these uncontrolled data in a relatively small sample do not provide definitive evidence of FEV₁ declining with long-term treatment, the data also does not provide evidence that FEV₁ stabilizes with time.

Figure 3.2.3.4.4 Change from baseline (end of DB period) during Study 010 for cohorts of patients defined by time in the extension study



4. Summary and Conclusions

4.1 Summary of Results

The focus of this review was the safety of TI for the treatment of Type 1 and Type diabetes measured by changes in FEV₁ and by events of hypoglycemia.

FEV₁ results for individual trials generally showed greater decreases in FEV₁ during the first 3 months of therapy for TI compared to a variety of comparators. These treatment differences were generally small and not statistically significant particularly in trials of short duration (see Section 3.2.2.1). However the results from the long-term studies show that the early differences persist and that the endpoint results are statistically significantly different when TI is compared against a non-inhaled anti-diabetic product (Table 4.1.1).

Table 4.1.1 FEV₁ (L) Endpoint Results for ITT Population for Long-term Studies

	TI	Comparator	Treatment Difference LS Mean (95% CI)	p-value
TYPE 1				
030				
N	200	246		
Baseline	3.54 (0.7)	3.65 (0.8)		
Change	-0.13 (0.2)	-0.10 (0.2)	-0.04 (-0.08, -0.001)	0.04
% pts with ≥ 20% drop	2.5%	0%		0.03
009				
N	235	244		
Baseline	3.45 (0.8)	3.46 (0.8)		
Change	-0.07 (0.2)	-0.04 (0.2)	-0.04 (-0.08, -0.005)	0.03
% pts with ≥ 20% drop	0.8%	0.8%		0.06
TYPE 2				
030				
N	530	578		
Baseline	3.09 (0.7)	3.15 (0.7)		
Change	-0.14 (0.2)	-0.10 (0.2)	-0.04 (-0.06, -0.01)	<0.01
% pts with ≥ 20% drop	1.9%	0.7%		0.003
102				
N	266	283		
Baseline	2.86 (0.7)	2.77 (0.7)		
Change	-0.13 (0.2)	-0.07 (0.2)	-0.06 (-0.10, -0.03)	<0.001
% pts with ≥ 20% drop	2.6%	1.8%		<0.001

P-value opposite % pts with ≥ 20% drop is for the comparison of cumulative distribution plots of % change from baseline at endpoint

There was insufficient data to draw definitive conclusions regarding reversal of the FEV₁ effects with few patients (<25% of randomized patients) providing follow-up data after withdrawal of treatment.

Generally higher rates of hypoglycemia are seen for TI versus non-insulin comparators and lower rates versus insulin comparators (see Section 3.2.2.2 and Appendix 5.1). However these differences are small and generally not statistically significant. The exception is Study 102 where TI was compared to a premixed (30/70) insulin analogue. For Study 102, significantly lower hypoglycemic rates are seen for TI compared to the premixed insulin (Table 4.1.2).

Table 4.1.2 Severe hypoglycemia (protocol defined severe hypoglycemia)

	TI	Comparator	p-values #events/pt; rates)	OR (95% CI) (1 st events)
TYPE 1				
030				
N	267	271		
# pts w/first event	42 (16%)	47 (17%)		0.89 (0.56, 1.40)
Total events	83	190	0.51;NR	
Rate	2.36	3.76		
009				
N	293	272		
# pts w/first event	96 (33%)	102 (38%)		0.81 (0.58, 1.15)
Total events	230	292	0.12; 0.18	
Rate	8.25	9.94		
TYPE 2				
030				
N	656	678		
# pts w/first event	21 (3.2%)	31 (4.6%)		0.69 (0.39, 1.21)
Total events	52	97	0.20;NR	
Rate	0.53	0.83		
102				
N	323	331		
# pts w/first event	14 (4.3%)	33 (10%)		0.41 (0.21, 0.79)
Total events	22	74	0.005 ; 0.06	
Rate	0.72	2.19		

Rate= # events /100 subject months; rates and p-values for comparison of rates were computed by applicant; NR=not reported

Bolded results are statistically significantly different comparing TI versus 30/70 premixed insulin analogue.

4.2 Conclusions

The results for FEV₁ and for hypoglycemia both support the safety of TI for the treatment of Type 1 and Type 2 diabetes. Although statistically significant decreases in FEV₁ are seen within 3 months of initiating therapy and there is no definitive evidence that these changes are reversed or do not increase, the changes are small (on average about 50 ml) and few patients (<3%) show decreases that are clinically relevant.

In general, results for hypoglycemia suggest no important differences in rates of severe hypoglycemic events compared to both insulin and non-insulin comparators for both Type 1 and Type 2 diabetics. Favorable findings showing significantly less hypoglycemia is seen in only study where TI is compared to a premixed insulin analogue; although the fact that the majority of severe events are defined by blood glucose alone may diminish the impact of these findings.

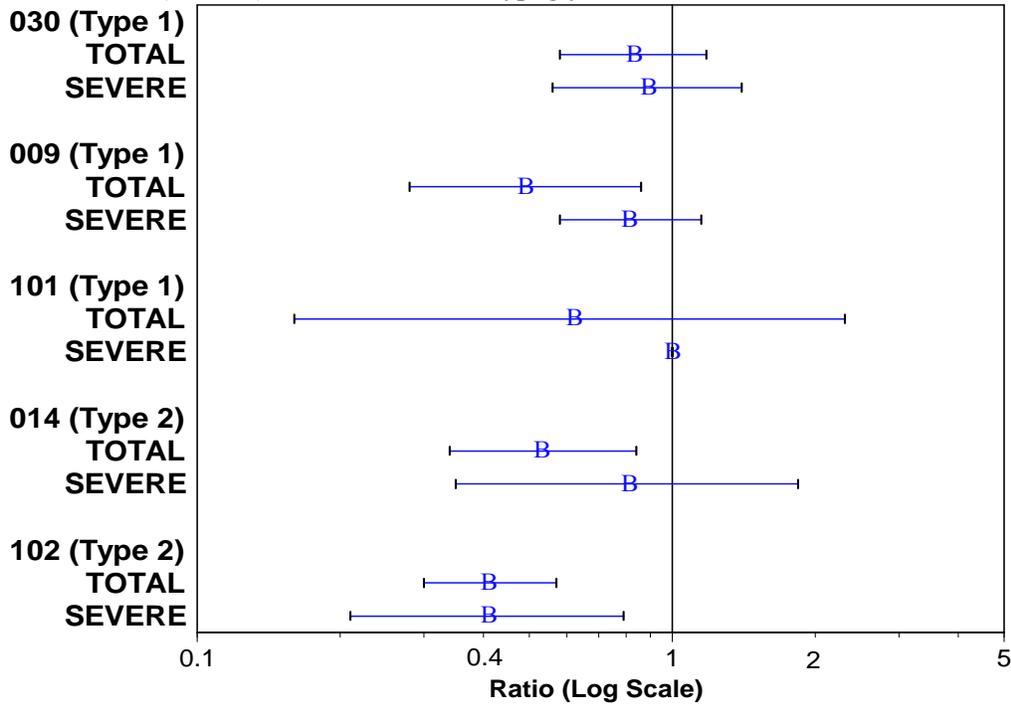
4.3 Labeling Recommendations

(b) (4)

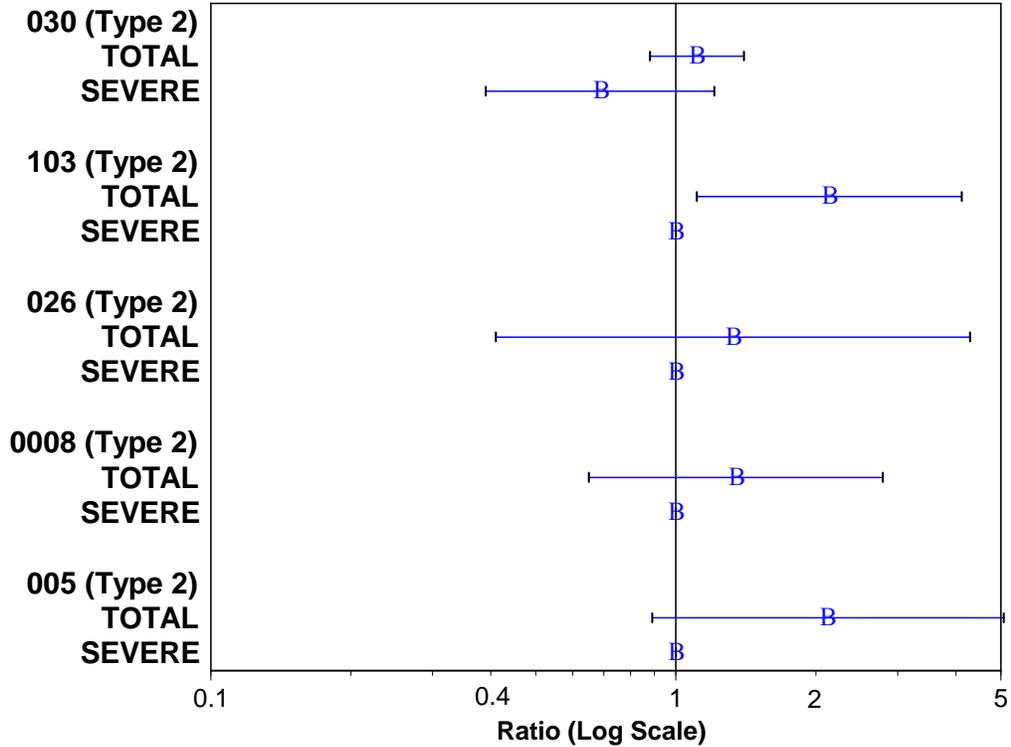
5. Appendices

5.1 Odds Ratios for Hypoglycemia by Type of Comparator and Study

Odds Ratios (95% CI) For At Least One Hypoglycemic Event: Studies With Insulin Comparator

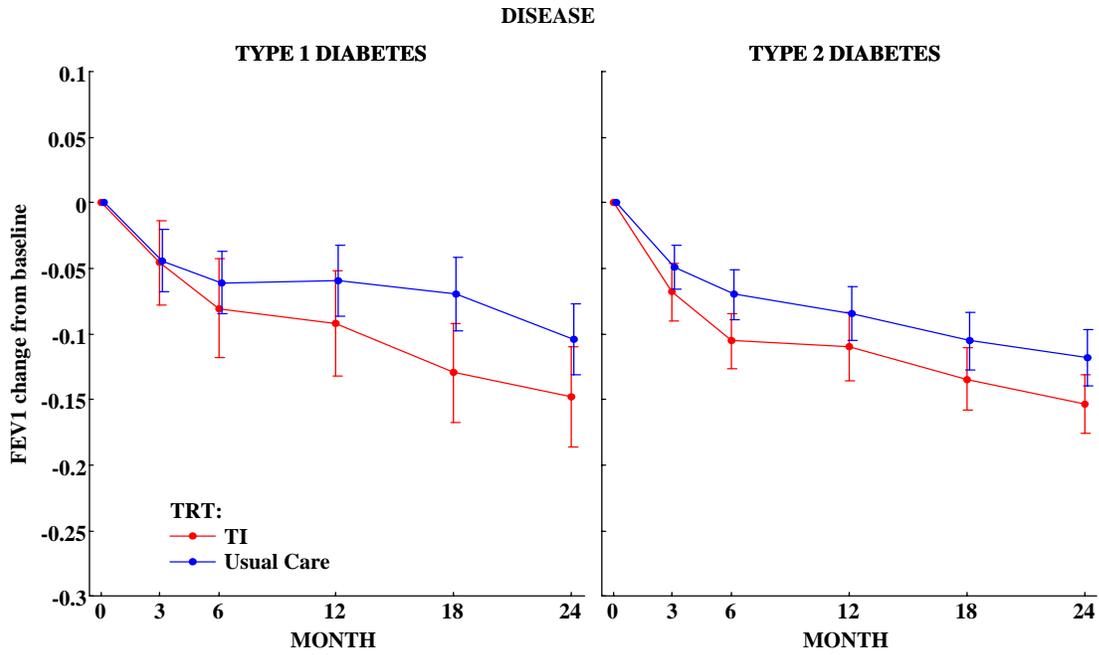


Odds Ratios (95% CI) For At Least One Hypoglycemic Event: Studies With Non-Insulin Comparator



Note that estimate of 1 with no CI indicates trial with no events in either arm.

5.2 Study 030 FEV₁ Change From Baseline For Completers



Sample sizes:

Type 1 TI n=115 Usual Care n=182

Type 2 TI n=319 Usual Care n=436

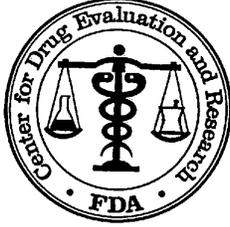
Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22472	ORIG-1	MANKIND CORP	INSULIN HUMAN (RDNA ORIG)INH POWDER

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JOY D MELE
12/08/2009

JON T SAHLROOT
12/09/2009



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Drug
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number: NDA 22-472

Drug Name: Technosphere Insulin

Indication(s): 104 weeks regular rat and 26 weeks transgenic mice carcinogenicity studies

Applicant: MannKind Corporation
28903 North Avenue Paine, Valencia, California 91355

Testing Facilities:

Rat: (b) (4)

Mouse: (b) (4)

Documents Reviewed: Submission: Submitted electronically on March 16, 2009
Data: Rat data submitted electronically on July 30, 2009 and
Mouse data submitted electronically on March 16, 2009

Review Priority: Standard

Biometrics Division: Division of Biometrics-6

Statistical Reviewer: Mohammad Atiar Rahman, Ph.D.

Concurring Reviewer: Karl Lin, Ph.D.

Medical Division: Division of Metabolism and Endocrine Products

Reviewing Pharmacologist: Miyun M. Tsai-Turton, Ph.D.

Project Manager: Haley Seymour

Keywords: Carcinogenicity, Dose-Response

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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of **technosphere insulin** when administered at appropriate drug levels via inhalation once daily for about 104 weeks in rats, and via subcutaneous injection for 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Tsai-Turton.

In this review, the phrase "dose-response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

104 Week regular rat study

1.1. Design

Two separate experiments, one in males and one in females were conducted. In each of these two experiments there were two treated groups (Group 4, and 5) and three control groups (Group 1, 2, and 3). Three hundred Sprague-Dawley [CrI:CD (SD) IGS BR] rats of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The Group 5 (High Dose) was selected by the Sponsor based on minimal toxicity observed during a 13-week inhalation toxicity study in rats. In that study the high dose of insulin administered as Technosphere® Insulin was 5 IU/kg/day for males and 3 IU/kg/day for females. The Group 4 (Low Dose) was selected based on a multiple of the anticipated human therapeutic dose. The Group 2 (Vehicle Control Low Dose) was exposed to aerosols of vehicle (Technosphere® particles) at a mass concentration equal to that of Group 5 (High Dose) and Group 3 (Vehicle Control High Dose) was exposed to aerosols of vehicle (Technosphere® particles) 25 times that of the anticipated human therapeutic dose. Group 1 was an air control group.

The targeted dose levels and durations of exposure were as follows:

Targeted Exposure Concentrations and Dose levels in Rat Study

Group	Group Designation	Targeted Dose Level ¹ (mg/kg/day)						Targeted Aerosol Concentration (mg/L)		
		Technosphere®		Insulin (IU)		Total		Technosphere®	Insulin	Total
		♂	♀	♂	♀	♂	♀			
1	Air Control	-	-	-	-	-	-	-	-	-
2	Technosphere® Control Low Dose	1.3259	0.7301	0	0	1.33	0.73	0.0419	0	0.0419
3	Technosphere® Control High Dose	50	50	0	0	50	50	1.58	0	1.58
4	Technosphere® Insulin Low Dose	0.7381	0.4429	0.0948 (2.5)	0.0569 (1.5)	0.83	0.50	0.0233	0.0030	0.0263
5	Technosphere® Insulin High Dose	1.3259	0.7301	0.1706 (4.5)	0.0948 (2.5)	1.50	0.82	0.0419	0.0054	0.0473

¹ Based on an estimated body weight of 0.250 kg using the formula presented below:

Mortality checks were performed twice a day (AM and PM) during all phases of the study. Moribund animals were euthanized for humane reasons at the discretion of the Study Director in consultation with the Clinical Veterinarian and, were subjected to detailed external and internal necropsy examination. Cage-side clinical

signs (signs of ill health, behavioral changes, etc.) were recorded once daily during the quarantine and pretreatment periods for all animals. During the treatment period the animals were evaluated once in the morning (pre-dose) and again before the end of the working day, following the end of dosing. In lieu of the morning cage-side examination on each relevant day, each animal was subjected to a detailed clinical examination (DCE) once during the pretreatment phase and on the first day of each week of the 104-week treatment period. As part of this procedure, from Week 13 onward, each animal was examined for the presence of palpable masses. In these examinations, particular attention was paid to the location, size, appearance and progression (time first seen and time of disappearance, when relevant) of each palpable mass potentially representing a benign or malignant tumor. Animals judged to be abnormal were examined by the Clinical Veterinarian or by a qualified technician working under the supervision of the veterinarian. Decisions to take additional action in the case of animals in deteriorating condition were made by the Study Director in consultation with the Clinical Veterinarian. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the experiment.

Body weights were recorded for all animals once prior to group assignment, and approximately one week prior to initiation of treatment. During the treatment period, body weights were recorded for all animals on Day 1 (before dosing), weekly until Week 26, and every 4 weeks thereafter. At the conclusion of the study (end of Weeks 104–107), during an overnight (12 to 16 hours) period of food (but not water) deprivation, each surviving animal was weighed again prior to blood sampling, euthanasia and necropsy.

1.2. Sponsor's analyses

1.2.1. Survival analysis

Survival function of each treatment group was estimated using the Kaplan-Meier product limit method. The number of animal died during the study, up to and including Week 104 (and beyond), was analyzed by the logrank tests. Males and females were analyzed separately. The following statistical tests were carried out:

- (1) a two-tailed test for a trend for Groups 1, 2, 4 and 5.
- (2) a two-tailed pairwise comparison test of Groups 2, 4 and 5 against Group 1.
- (3) a two-tailed test for a trend for Groups 2, 4 and 5.
- (4) a two-tailed pairwise comparison test of Groups 4 and 5 against Group 2.

1.2.1.1. Sponsor's findings

Sponsor's analysis showed the end of the study mortality rates of 32%, 37%, 28%, 32%, and 27% in male rats in Groups 1, 2, 3, 4 and 5, respectively, and 28%, 37%, 37%, 38% and 33% in female rats in Groups 1, 2, 3, 4 and 5, respectively.

The sponsor's analysis showed no statistically significant differences across the groups in the number of mortalities or final survival at the end of the study in either sex. The sponsor concluded that the end of the study survivals in all treatment groups were at acceptable levels of 65% – 73% for males and 62% – 72% for females. For survival analysis the dose response relationship tests were not significant, when Groups 1, 2, 4 and 5 or when Groups 2, 4 and 5 were included in the analysis ($p=0.531$ and $p=0.394$, respectively for males and $p=0.635$ and $p=0.745$, respectively for females). The pairwise comparisons of the control groups were not statistically significant.

1.2.2. Tumor data analysis

Each tumor was categorized as non-incident if the tumor was a factor contributing towards the death of the animal, incidental otherwise. For statistical purposes, all animals that died after terminal sacrifice commenced (Week 104) were considered terminal and the tumors observed in these animals were categorized as incidental.

Tumor types were selected for full statistical analysis where at least two tumors are observed over Groups 4 and 5. The analyses were carried out for benign, malignant and benign and malignant tumors combined. If an animal had a benign and a malignant tumor then only the malignant tumor was included in the analysis of both tumors together.

Statistical analysis was performed using the methodology suggested by Peto et al. (1980). For this analysis, for non-incident tumors, the strata were defined as those time points during which there were deaths and for incidental tumors, the time strata are defined using the CDER commonly used partitions (in weeks): 0 – 50, 51 – 80, 81 – 104, and terminal sacrifice. Log-rank methods were used to analyze the number of animals with tumors across treatment groups. The following statistical tests were carried out:

- (1) a one-tailed test for a trend for Groups 1, 2, 4 and 5.
- (2) a one-tailed test for a trend for Groups 2, 4 and 5.
- (3) a one-tailed pairwise comparison test of treatment Groups 2, 4 and 5 against treatment Group 1.
- (4) a one-tailed pairwise comparison test of treatment Groups 4 and 5 against treatment Group 2.

Significance levels were calculated using the χ^2 tests and adjusted with a continuity correction. If fewer than ten tumors were observed across all groups included in the test, exact p-values were calculated using permutation tests for stratified contingency tables.

Tumors with an historical frequency greater than 1% were designated as being "common" otherwise. For common tumor types, a significance level of 0.005 was used for the trend tests, and 0.01 for each pairwise test. Tumors with an historical frequency less than 1% were designated as being "rare". For rare tumors, a significance level of 0.025 was used for the trend tests, and 0.05 for each pairwise test. The classification of tumors was carried out based upon data from previous studies carried out in Sprague-Dawley rats and was retained with the raw data for the study.

1.2.2.1. Sponsor's findings

The sponsor's summary table showed that the adrenal cortical carcinoma occurred in three (5%) high-dose Technosphere® Insulin (Group 5) females. The sponsor's analysis showed this occurrence to have a statistically significant dose response relationship. None of the pairwise comparisons of high dose group with the controls was found to be statistically significant. The sponsor mentioned that this incidence rate was slightly higher than the historical control rate (1%).

1.3. Reviewer's analyses

To verify sponsor's results and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

In this review, the reviewer analyzed the survival and the tumor data. As mentioned before, in this study there were three control groups, namely the air control group, technosphere low dose control group, and technosphere high dose control group. The animals in air control group were left untreated, the animals in technosphere low dose control group were exposed to aerosols of vehicle (Technosphere® particles) at a mass concentration equal to that of the technosphere insulin high dose group (Group 5), and the animals in technosphere high dose control group were exposed to aerosols of vehicle (Technosphere® particles) 25 times that of the anticipated human therapeutic dose. Since the air control group remained unexposed to the insulin or technosphere particles, and technosphere level of technosphere low dose control group was the same as Group 5, in consultation with the reviewing pharmacologists, this reviewer determined that the three treatment groups namely Groups 1, 2, and 3 should be compared to determine the effect of technosphere particles, while the three groups namely Groups 2, 4, and 5 should be compared to determine the effect of insulin. Therefore, for both the survival and tumor data analyses this reviewer performed two sets of analysis once using groups 1, 2, and 3 (termed as particle groups) and once using groups 2, 4, and 5 (termed as insulin groups).

1.3.1. Survival analysis

The survival distributions of animals in all five treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the likelihood ratio test and log-rank test, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for males and females, respectively.

1.3.1.1. Reviewer's findings

Reviewer's analysis showed the end of the study mortality rates of 31.67%, 35.00%, 28.33%, 31.67%, and 26.67% in Groups 1, 2, 3, 4, and 5 respectively, for male rats and 28.33%, 36.67%, 36.67%, 38.33%, and 33.33% in Groups 1, 2, 3, 4, and 5 respectively, for female rats. Tests showed no statistically significant dose response relationship in survivals across treatment groups or pairwise differences between the control and any of the treated groups in either the particle or insulin groups in either sex of rat.

***Reviewer's comment:** This reviewer's analysis showed 35.00% (21/60) mortality of male rats in Group 2, while the sponsor's analysis showed 37.00% (22/60) mortality for this group. This difference is due to the fact that there was one animal (Animal number 2050B) in Group 2 males that died in Week 106 due to natural cause. Since this animal died during terminal sacrifice period (after Week 104), this reviewer counted it with the terminally sacrificed animals, while the sponsor counted it with the naturally dead animals.*

1.3.2. Tumor data analysis

The tumor data were analyzed for dose response relationship and pairwise comparisons of treated groups with control (separately for particle groups and insulin groups). The analysis of the tumor data were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for males and females, respectively.

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria recommended developed by Lin and Rahman (1998), which recommends the use a significance level $\alpha=0.025$ for rare tumors and $\alpha=0.005$ for common tumors for a submission with two in two species, and a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors for a submission with one specie study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. Adjustment for multiple pairwise comparisons was done using the criteria developed by Haseman (1983), which recommends to use a significance level $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the original recommendations of Lin and Rahman were for submissions with two long term studies (two year study). The recommendations were based on anticipated number of tumors per study. The present submission consists of one long term study in rats and one short term study in mouse. It is speculated that the short term two studies may produce fewer number of tumors compared to the long term studies. It is suspected that the recommend test levels of Lin and Rahman may not be suitable in this case. The most appropriate solution for this case is not known to this reviewer. To be conservative, this reviewer used the significance levels of $\alpha=0.05$ for rare tumors and $\alpha=0.01$ for common tumors for both dose response and pairwise comparisons in rat study. This issue for mouse study is discussed in mouse study review section (Section 1.6.2). Any positive finding was further assessed by histopathological consideration.

1.3.2.1.Reviewer’s findings

Following tumor type showed p-value less than or equal to 0.05 for dose response relationship.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons

Female Rats (Insulin Groups)						
Organ Name	Tumor Name	0 mg Cont N=60	0.44 mg Low N=60	0.73 mg High N=60	P_Value	
					Dose Resp	C vs. L C vs. H
ADRENAL	CARCINOMA, CORTICAL	0	0	3	0.0363*	0.1213

Based on the criteria of adjustment for multiple testing discussed above, the incidence of this adrenal cortical adenoma in the insulin group female rats was considered to have a statistically significant positive dose response relationship. None of the pairwise comparisons of treated groups with control were considered to be statistically significant.

26 Week Tg.rasH2 Transgenic Mouse study

1.4. Design

Two separate experiments, one in males and one in females were conducted. In total there were 12 treatment groups. Seven of these were for the carcinogenicity study in rasH2 mice (main study). The other five groups were for a toxicokinetic study. For carcinogenicity study 175 rasH2 mice (Model 001178-T (hemizygous),

CB6F1/Jic-TgrasH2@Tac) of each sex were randomized equally into the carcinogenicity study. The positive control group received N-methyl-N-nitrosurea (MNU). For toxicokinetic study 170 wild-type rasH2 (Model 001178-W (homozygous wild type), CB6F1/Jic-TgrasH2@Tac) mice were used. The treatment group size and dose levels were as follows:

Group Size and Dose Levels for Tg.rasH2 Mouse

Group ^{ab}	Group Designations and Dose Levels					
	No. of Animals		Dose Level (mg/kg/day)		Dose Concentration (mg/mL)	
	Male	Female	Male	Female	Male	Female
Toxicity Animals						
1 (Control - Sham)	25	25	0	0	0	0
2 (Vehicle Control - PBS)	25	25	0	0	0	0
3 (Technosphere® Particles - Low)	25	25	25	25	2.5	2.5
4 (Technosphere® Particles - High)	25	25	75	75	7.5	7.5
5 (Technosphere® Insulin - Low)	25	25	2.5	2.5/0.6*	0.25	0.25/0.06*
6 (Technosphere® Insulin - High)	25	25	5	5/1.25*	0.5	0.5/0.125*
7 (Positive Control - MNU)	25	25	75	75	7.5	7.5
Toxicokinetic Animals^{cd}						
8 (Vehicle Control - PBS)	18	18	0	0	0	0
9 (Technosphere® Particles - Low)	38	38	25	25	2.5	2.5
10 (Technosphere® Particles - High)	38	38	75	75	7.5	7.5
11 (Technosphere® Insulin - Low)	38	38	2.5	2.5/0.6*	0.25	0.25/0.06*
12 (Technosphere® Insulin - High)	38	38	5	5/1.25*	0.5	0.5/0.125*

a Group 1 received a sham dose only.
b Group 7 animals were dosed with one intraperitoneal dose of MNU on Day 1 of study at a dose volume of 10 mL/kg.
c Toxicokinetic animals were wild-type mice (Model 001178-W, CB6F1/Jic-TgrasH2@Tac) and were included solely for the purpose of blood sample collections; three/sex/group were bled for each collection time point, then discarded without necropsy.
d Two extra animals/test article groups were added as potential replacements.
e Beginning on Day 77 of the dosing phase, females in Groups 5 and 11 were dosed at 0.6 mg/kg/day and females in Groups 6 and 12 were dosed at 1.25 mg/kg/day.

Animals in Groups 1 through 6 and 8 through 12 received a subcutaneous injection once daily for at least 26 weeks (dosing phase). Group 1 received a sham injection using needles only; no test or control article was administered. Injections were rotated among four different injection sites each day. Doses were based on the most recently recorded body weight. Animals were dosed at the volume of 10 mL/kg. Treatment continued through the day prior to terminal sacrifice.

Group 7 animals were administered a dosing formulation of MNU via one intraperitoneal injection on Day 1. Doses were based on the most recently recorded body weight and animals were dosed at a volume of 10 mL/kg. Dosing of Group 7 was completed within 3 hours of MNU formulation.

Each animal was observed twice daily (AM and PM) for mortality, abnormalities, and signs of pain or distress. If the animal could not be visualized, the cage was opened. Findings were recorded as they were observed. Approximately 2 hours post dose during the dosing phase, cage side observations were made for each toxicity animal dosed; abnormal findings were recorded. Timing of the observations was based on the last time of each animal dosed per group. Once during the predose phase, before dosing on Day 1 and weekly thereafter, and on the day of scheduled sacrifice, detailed observations were made for each toxicity animal. Detailed observations were made for each toxicokinetic animal once during the predose phase. Abnormal findings or an indication of normal was recorded. Time of onset, location, size, appearance, and progression on each grossly visible or palpable mass were recorded weekly. Unscheduled observations were recorded.

Body weights were measured for all animals (toxicity and toxicokinetic) once during the predose phase, before dosing on Day 1 of the dosing phase, and weekly thereafter.

After at least 26 weeks of treatment, all surviving animals were anesthetized with carbon dioxide and oxygen inhalation, exsanguinated, and necropsied. Terminal body weights were recorded. All tissues from animals in the control and high-dose groups (Groups 1, 2, 4, 6 and 7) and from animals that died or were sacrificed at an unscheduled interval were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically. Macroscopic lesions were also examined microscopically for all animals.

Histopathology (lesions and target organs only) was peer reviewed by a second pathologist designated by (b) (4) prior to generation of the histopathology report.

1.5. Sponsor's analyses

The following statistical methods were used to analyze the continuous variables, such as body weight, body weight change, and food consumption data.

- Levene's test (Levene, 1960; Draper and Hunter, 1969) was done to test for variance homogeneity. In the case of heterogeneity of variance at $p \leq 0.05$, rank transformation was used to stabilize the variance. Comparison tests took variance heterogeneity into consideration.
- One-way analysis of variance [ANOVA (Winer, 1971)] was used to analyze data.
- If the ANOVA was significant ($p \leq 0.05$), Dunnett's t-test (Dunnett, 1955, 1964) was used for control versus treated group comparisons. For data that exhibited heterogeneous variances after the series of transformations, Dunnett's t-test for unequal variances with Welch's degrees of freedom (Welch, 1947) was employed.

For each sex, Groups 3 through 6 were compared with Group 2 (vehicle control) at the 5%, two-tailed probability level. Unless otherwise specified in the protocol, only data collected on or after the first day of treatment were analyzed statistically. None of the data collected from the toxicokinetic animals were statistically analyzed.

The sponsor did not mention of any statistical methodologies used for mortality and tumor data analyses.

1.5.1. Sponsor's Findings

1.5.1.1. Mortality

The sponsor's analysis showed 0, 1, 1, 0, 2, 1, and 22 deaths in male mice and 1, 0, 1, 1, 4, 6, and 17 deaths in female mice in Groups 1, 2, 3, 4, 5, 6, and 7 respectively. The sponsor considered these mortalities as low in the control and treated mice given Technosphere® Particles or Technosphere®/Insulin (compared to the positive control). The sponsor concluded that there was no evidence of compound-related histopathologic changes associated with mortality in the treatment groups. Many of the female mice (with an undetermined cause of death) were found dead early in the study and likely represent a pharmacologic effect (hypoglycemia), prompting a decrease in the dosing level for the Technosphere®/Insulin - low and Technosphere®/Insulin - high females.

1.5.1.2. Tumor occurrence

The sponsor concluded that compared to positive controls the overall incidence of neoplasia was low for all groups and there was no evidence of increased oncogenicity associated with the subcutaneous administration of the test articles Technosphere® Particles or Technosphere®/Insulin.

1.6. Reviewer's analysis

To verify sponsor's results and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

This reviewer analyzed only the data from carcinogenicity study groups (Groups 1, 2, 3, 4, 5, 6, and 7). As mentioned before, in this study there were three control groups and four treated groups. The three control groups were sham control, vehicle control and positive control, and the four treated groups were technosphere particle-low, technosphere particle-high, technosphere insulin-low, and technosphere insulin-high. Due to similar logical reasoning as explained in the rat review section, in mouse study for both the survival and tumor data analyses this reviewer performed two sets of analysis once using groups 2, 3, and 4 to compare the effect of technosphere particles, and once using groups 2, 5, and 6 to compare the effect of insulin.

1.6.1. Survival analysis

The survival distributions of animals in all seven treatment groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were separately tested for (1) all seven treatment groups, (2) control, technosphere particle-low, technosphere particle-high dose groups, and (3) vehicle control, technosphere insulin-low, and technosphere insulin-high dose groups. The tests were performed using the same statistical methods as this reviewer used to analyze the rat survival data. The intercurrent mortality data are given in Tables 4A and 4B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 2A and 2B in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

1.6.1.1. Reviewer's findings

Reviewer's analysis showed the end of the study mortality rates of 0 (0%), 1 (4%), 1 (4%), 0 (0%), 2 (8%), 1 (4%), and 22 (88%) in Groups 1, 2, 3, 4, 5, 6, and 7 respectively in male mice, and 1 (4%), 0 (0%), 1 (4%), 1 (4%), 4 (16%), 6 (24%), and 17 (68%) in Groups 1, 2, 3, 4, 5, 6, and 7 respectively in female mice. Tests showed statistically significant difference between vehicle control and low ($P=0.039$), vehicle control and high ($P=0.0097$) in female insulin.

1.6.2. Tumor data analysis

The tumor data were analyzed for dose response relationship and pairwise comparisons of control group with technosphere treated groups. Similar to survival data analysis, the tumor data were also separately analyzed for (1) control, technosphere particle-low, technosphere particle-high dose groups (particle groups), and (2) vehicle control, technosphere insulin-low, and technosphere insulin-high dose groups (insulin groups). The tests were performed using the same statistical methods as were used to analyze the rat tumor data.

Multiple testing adjustment: In this Tg.rasH2 mouse study, since the group sizes were small and the tested animals developed very small number of tumor types, this reviewer performed all tests (both dose response and pairwise comparisons) using significance level of $\alpha=0.05$.

1.6.2.1. Reviewer's findings

Based on the multiple testing adjustment criteria discussed above, the incidence of none of the tested tumor types was considered to have a statistically significant dose response relationship. Pairwise comparisons also did not show any statistically significant increased incidence of any tumor type in the treated groups compared to the control group.

2. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of **technosphere insulin** when administered at appropriate drug levels via inhalation once daily for about 104 weeks in rats, and via subcutaneous injection for 26 weeks in mice.

In this review, the phrase "dose-response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

2.1. Rat study

Two separate experiments, one in males and one in females were conducted. In each of these two experiments there were two treated groups (Group 4, and 5) and three control groups (Group 1, 2, and 3). Three hundred Sprague-Dawley [CrI:CD (SD) IGS BR] rats of each sex were randomly allocated to treated and control groups in equal size of 60 animals. The targeted dose levels and durations of exposure were as follows:

Group	Group Designation	Targeted Dose Level ¹ (mg/kg/day)						Targeted Aerosol Concentration (mg/L)		
		Technosphere®		Insulin (IU)		Total		Technosphere®	Insulin	Total
		♂	♀	♂	♀	♂	♀			
1	Air Control	-	-	-	-	-	-	-	-	-
2	Technosphere® Control Low Dose	1.3259	0.7301	0	0	1.33	0.73	0.0419	0	0.0419
3	Technosphere® Control High Dose	50	50	0	0	50	50	1.58	0	1.58
4	Technosphere® Insulin Low Dose	0.7381	0.4429	0.0948 (2.5)	0.0569 (1.5)	0.83	0.50	0.0233	0.0030	0.0263
5	Technosphere® Insulin High Dose	1.3259	0.7301	0.1706 (4.5)	0.0948 (2.5)	1.50	0.82	0.0419	0.0054	0.0473

¹ Based on an estimated body weight of 0.250 kg using the formula presented below:

The animals in Group 3 (Vehicle Control High Dose) were exposed to aerosols of vehicle (Technosphere® particles) 25 times that of the anticipated human therapeutic dose and the Group 2 (Vehicle Control Low Dose) was exposed to aerosols of vehicle (Technosphere® particles) at a mass concentration equal to that of Group 5 (High Dose) and Group 1 was an air control group. In this review, groups 1, 2, and 3 were termed as particle groups and groups 2, 4, and 5 were termed as insulin groups. This reviewer performed two separate analyses on these two sets of treatment groups.

Tests showed no statistically significant dose positive response relationship in survivals across treatment groups or pairwise differences between the control and any of the treated groups in either the particle or

insulin groups in either sex of rat. Tests showed statistically significant positive dose response in the incidence of adrenal cortical adenoma in the insulin groups of in female. None of the pairwise comparisons of treated groups with respective control were considered to be statistically significant.

2.2. Tg.rasH2 mouse study

Two separate experiments, one in males and one in females were conducted. In total there were seven treatment groups. One hundred and seventy five Tg.rasH2 mice (Model 001178-T (hemizygous), CB6F1/Jic-Tg.rasH2@Tac) of each sex were randomly allocated to treated and control groups in equal size of 25 animals. The treatment dose levels were as follows:

Group ^{ab}	No. of Animals		Dose Level (mg/kg/day)		Dose Concentration (mg/mL)	
	Male	Female	Male	Female	Male	Female
Toxicity Animals						
1 (Control - Sham)	25	25	0	0	0	0
2 (Vehicle Control - PBS)	25	25	0	0	0	0
3 (Technosphere® Particles - Low)	25	25	25	25	2.5	2.5
4 (Technosphere® Particles - High)	25	25	75	75	7.5	7.5
5 (Technosphere® Insulin - Low)	25	25	2.5	2.5/0.6*	0.25	0.25/0.06*
6 (Technosphere® Insulin - High)	25	25	5	5/1.25*	0.5	0.5/0.125*
7 (Positive Control - MNU)	25	25	75	75	7.5	7.5

b Group 7 animals were dosed with one intraperitoneal dose of MNU on Day 1 of study at a dose volume of 10 mL/kg
e Beginning on Day 77 of the dosing phase, females in Groups 5 and 11 were dosed at 0.6 mg/kg/day and females in Groups 6 and 12 were dosed at 1.25 mg/kg/day

Animals in Groups 1 through 6 received a subcutaneous injection once daily for at least 26 weeks. Group 1 received a sham injection using needles only with no test or control article. Group 7 was a positive control which received one intraperitoneal dose of MNU on Day 1 of study at a dose volume of 10 mL/kg.

In this review, groups 2, 3 and 4 were termed as particle groups and groups 2, 5 and 6 were termed as insulin groups. This reviewer performed two separate analyses on these two sets of treatment groups.

Tests showed statistically significant difference in survival between vehicle control and low dose group, and vehicle control and high dose group in female insulin. Tests showed no statistically significant positive dose responses relationship in any of the tested tumor types. Pairwise comparisons also did not show statistically significant increased incidence of any tumor type in the treated groups compared to the respective control group.

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3. Appendix

**Table 1A: Intercurrent Mortality Rate
Male Rats**

Week	Group 1		Group 2		Group 3		Group 4		Group 5	
	No. of Death	Cum. %								
0 - 52	2	3.33	.	.	2	3.33	.	.	1	1.67
53 - 78	6	13.33	4	6.67	3	8.33	6	10.00	4	8.33
79 - 91	7	25.00	5	15.00	5	16.67	6	20.00	4	15.00
92 - 104	4	31.67	12	35.00	7	28.33	7	31.67	7	26.67
Ter. Sac.	41	68.33	39	65.00	43	71.67	41	68.33	44	73.33
Total	60		60		60		60		60	

**Table 1B: Intercurrent Mortality Rate
Female Rats**

Death Cum. %	Group 1		Group 2		Group 3		Group 4		Group 5	
	No. of Death	Cum. %								
0 - 52	2	3.33	2	3.33	1	1.67	2	3.33	1	1.67
53 - 78	7	15.00	3	8.33	6	11.67	4	10.00	5	10.00
79 - 91	4	21.67	7	20.00	7	23.33	6	20.00	6	20.00
92 - 104	4	28.33	10	36.67	8	36.67	11	38.33	8	33.33
Ter. Sac.	43	71.67	38	63.33	38	63.33	37	61.67	40	66.67
Total	60		60		60		60		60	

**Table 2A: Intercurrent Mortality Comparison
Male Rats**

Particle			Insulin		
Test	Statistic	P_Value	Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.5441	Dose-Response	Likelihood Ratio	0.4836
Homogeneity	Log-Rank	0.7430	Homogeneity	Log-Rank	0.7831

**Table 2B: Intercurrent Mortality Comparison
Female Rats**

Particle			Insulin		
Test	Statistic	P_Value	Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.6892	Dose-Response	Likelihood Ratio	0.9820
Homogeneity	Log-Rank	0.2871	Homogeneity	Log-Rank	0.7551

**Table 3A: Dose Response Relationship Test and Pairwise Comparisons
Using Poly-3 test
Male Rats
(Particle Groups)**

Organ Name	Tumor Name	0 mg	1.33 mg	50 mg	P_Val ue	P_Val ue C vs. L	P_Val ue C vs. H
		Cont N=60	Low N=60	Hi gh N=60	Dos Resp		
////////////////////////////////////							
ADRENAL	ADENOMA, CORTI CAL	1	0	2	0.2722	0.5146	0.5291
	PHEOCHROMOCYTOMA, BENI GN	2	4	2	0.5821	0.3673	0.3312
	PHEOCHROMOCYTOMA, MALI GNANT	1	0	0	0.6795	0.5146	0.5146
BRAI N	ASTROCYTOMA, MALI GNANT	1	4	4	0.1911	0.2000	0.2000
	OLI GODENDROGLI OMA, MALI GNANT	1	1	0	0.6795	0.2623	0.5146
HEART	SCHWANNOMA, BENI GN	0	1	0	0.3397	0.5146	.
HEMOLYMPHORETI CULAR(LYMPHOMA, MALI GNANT	1	0	0	0.6795	0.5146	0.5146
	SARCOMA, HI STI OCYTI C	0	1	1	0.3463	0.5146	0.5146
LI VER	ADENOMA, HEPATOCELLULAR	2	0	0	0.8987	0.7668	0.7668
LUNG	ADENOMA, BRONCHI OLO-ALVEOLAR	1	0	0	0.6795	0.5146	0.5146
LYMPH NODE, MESENTER	HEMANGI OMA	0	0	1	0.3397	.	0.5146
MAMMARY GLAND	TUMOR, MI XED, MALI GNANT	1	0	0	0.6795	0.5146	0.5146
ORAL CAVI TY	CARCI NOMA, SQUAMOUS CELL	0	1	1	0.3463	0.5146	0.5146
PANCREAS	ADENOMA, ACI NAR-I SLET CELL	1	0	0	0.6795	0.5146	0.5146
	ADENOMA, I SLET CELL	5	6	1	0.9675	0.5546	0.9104
PI TUI TARY	ADENOMA, PARS DI STALI S	22	27	26	0.4038	0.3049	0.3731
	ADENOMA, PARS I NTERMEDI A	1	2	0	0.7528	0.5221	0.5146
	CARCI NOMA, PARS DI STALI S	0	0	1	0.3397	.	0.5146
PROSTATE	ADENOCARCI NOMA	2	0	0	0.8959	0.7619	0.7619
	ADENOMA	3	2	2	0.6080	0.5278	0.5278
SKI N & SUBCUTI S	FI BROMA	0	1	1	0.3463	0.5146	0.5146
	FI BROSARCOMA	0	0	2	0.1140	.	0.2623
	KERATOACANTHOMA, BENI GN	1	0	0	0.6795	0.5146	0.5146
	LI POMA	1	0	0	0.6795	0.5146	0.5146
	SCHWANNOMA, MALI GNANT	1	4	0	0.8827	0.2000	0.5146
TESTI S	ADENOMA, I NTERSTI TI AL(L EYDI G) C	2	3	0	0.9030	0.5278	0.7668
THORACI C CAVI TY	HI BERNOMA, MALI GNANT	3	3	2	0.6427	0.3574	0.5180
	LI POSARCOMA	0	1	0	0.3397	0.5146	.
THYROI D LOBE	ADENOMA, C-CELL	6	2	7	0.2051	0.8834	0.5454
	ADENOMA, FOLLI CULAR CELL	0	1	0	0.3397	0.5146	.
	CARCI NOMA, C-CELL	0	0	1	0.3397	.	0.5146

**Table 1A: Intercurrent Mortality Rate
Male Mice**

Week	0 mg kg day		1 mg kg day		2 mg kg day		3 mg kg day		4 mg kg day		5 mg kg day		6 mg kg day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
11 - 15	1	4.00	.	.	5	20.00
16 - 20	1	4.00	1	4.00	5	40.00
21 - 26	.	.	1	4.00	1	8.00	.	.	12	88.00
Ter. Sac.	25	100.00	24	96.00	24	96.00	25	100.00	23	92.00	24	96.00	3	12.00
Total	25		25		25		25		25		25		25	

**Table 1B: Intercurrent Mortality Rate
Female Mice**

Week	1 mg kg day		2 mg kg day		3 mg kg day		4 mg kg day		5 mg kg day		6 mg kg day		7 mg kg day	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 10	1	4.00	.	.	3	12.00	4	16.00	1	4.00
11 - 15	1	16.00	.	.	2	12.00
16 - 20	1	4.00	.	.	2	24.00	6	36.00
21 - 26	1	4.00	8	68.00
Ter. Sac.	24	96.00	25	100.00	24	96.00	24	96.00	21	84.00	19	76.00	8	32.00
Total	25		25		25		25		25		25		25	

**Table 2A: Intercurrent Mortality Comparison
Male Mice**

Particle			Insulin		
Test	Statistic	P_Value	Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.8775	Dose-Response	Likelihood Ratio	0.9969
Homogeneity	Log-Rank	0.6034	Homogeneity	Log-Rank	0.7652

**Table 2B: Intercurrent Mortality Comparison
Female Mice**

Particle			Insulin		
Test	Statistic	P_Value	Test	Statistic	P_Value
Dose-Response	Likelihood Ratio	0.9063	Dose-Response	Likelihood Ratio	0.3708
Homogeneity	Log-Rank	0.6034	Homogeneity	Log-Rank	0.0437

**Table 3A: Dose Response Relationship Test and Pairwise Comparisons
Using Poly-3 test
Male Mice
(Particle Groups)**

Organ Name	Tumor Name	0 mg	25 mg	75 mg	P_Val ue	P_Val ue C vs. L	P_Val ue C vs. H
		Cont N=25	Low N=25	Hi gh N=25	Dos Resp		
Body, Whol e/Cav	M-Hemangi osarcoma	1	1	1	0. 5987	0. 7551	0. 7551
Lung	B-Adenoma, Bronchi ol	2	0	2	0. 4595	0. 7449	0. 6954
Ski n/Subcuti s	B-Papi l l oma, Squamou	1	0	0	0. 6622	0. 4898	0. 5000

**Table 3A: Dose Response Relationship Test and Pairwise Comparisons
Using Poly-3 test
Female Mice
(Particle Groups)**

Organ Name	Tumor Name	0 mg Cont N=25	25 mg Low N=25	75 mg High N=25	P_Val ue Dos Resp	P_Val ue C vs. L	P_Val ue C vs. H
<i>ff</i>							
Body, Whole/Cav	B-Hemangi oma	1	0	0	0. 6575	0. 4898	0. 4898
	M-Hemangi osarcoma	1	0	1	0. 5525	0. 4898	0. 7449
	M-Myel oprol i ferati ve	1	0	0	0. 6575	0. 4898	0. 4898
GI, Harderian	B-Adenoma	1	0	0	0. 6575	0. 4898	0. 4898
	M-Carci noma	1	0	0	0. 6575	0. 4898	0. 4898
Lung	B-Adenoma, Bronchi ol	2	0	0	0. 8858	0. 7449	0. 7449
Stomach, Nongl	M-Carci noma, Squamou	0	0	1	0. 3378	.	0. 5000

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

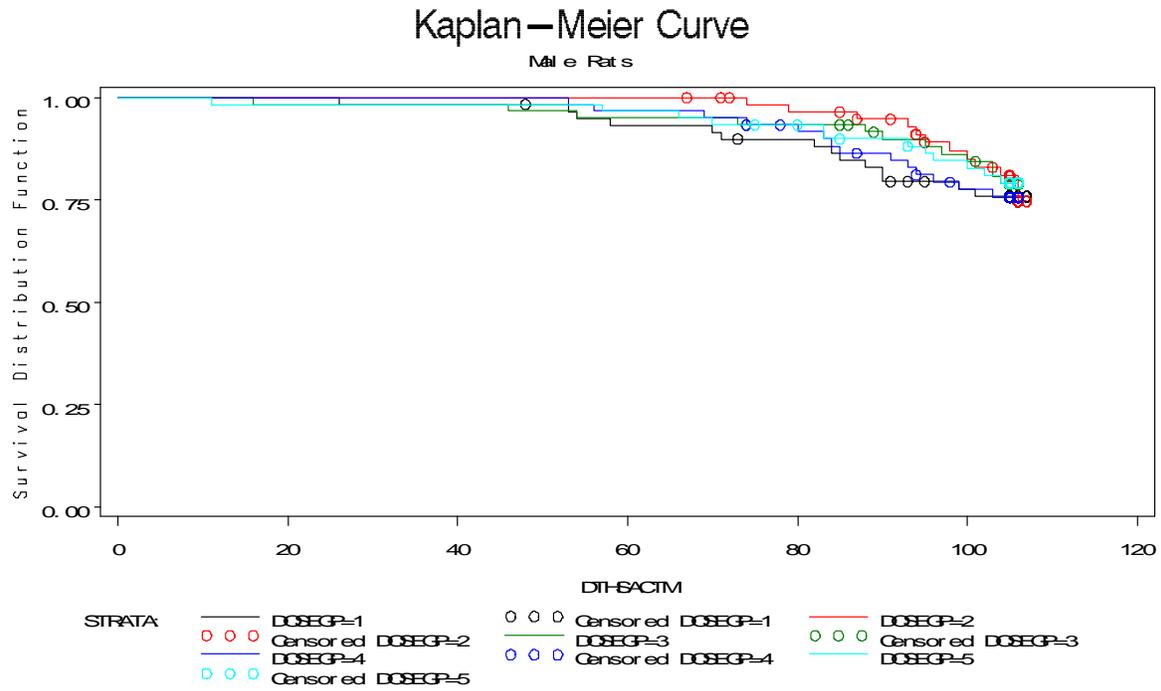


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

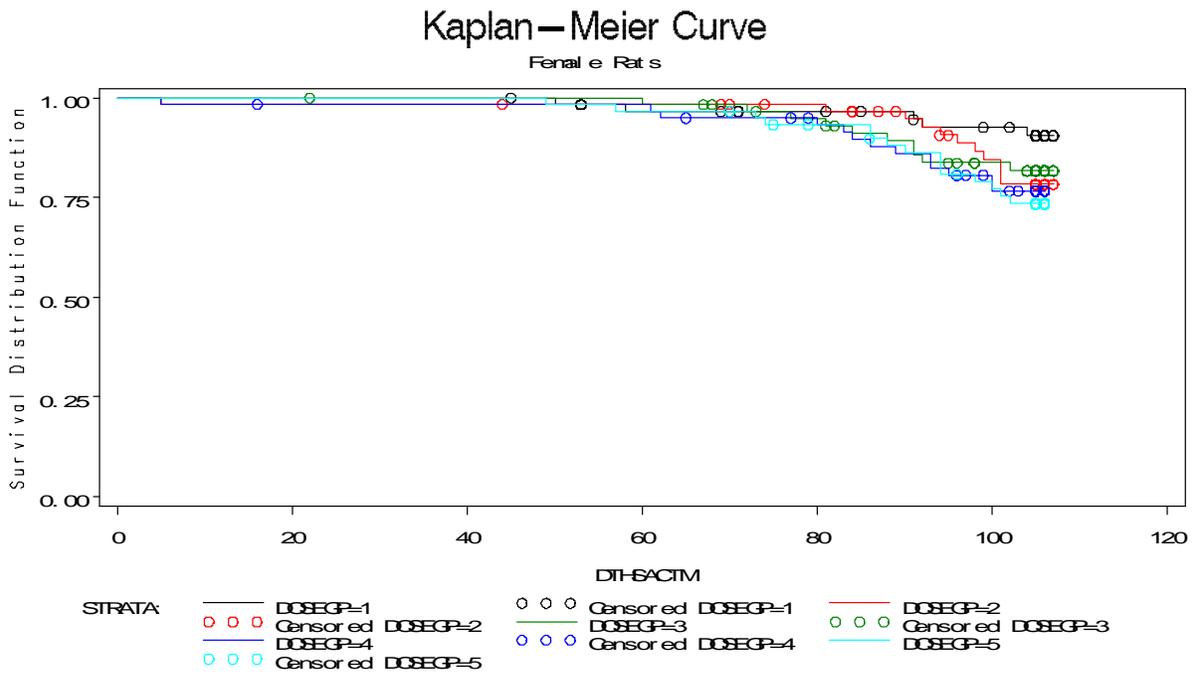


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

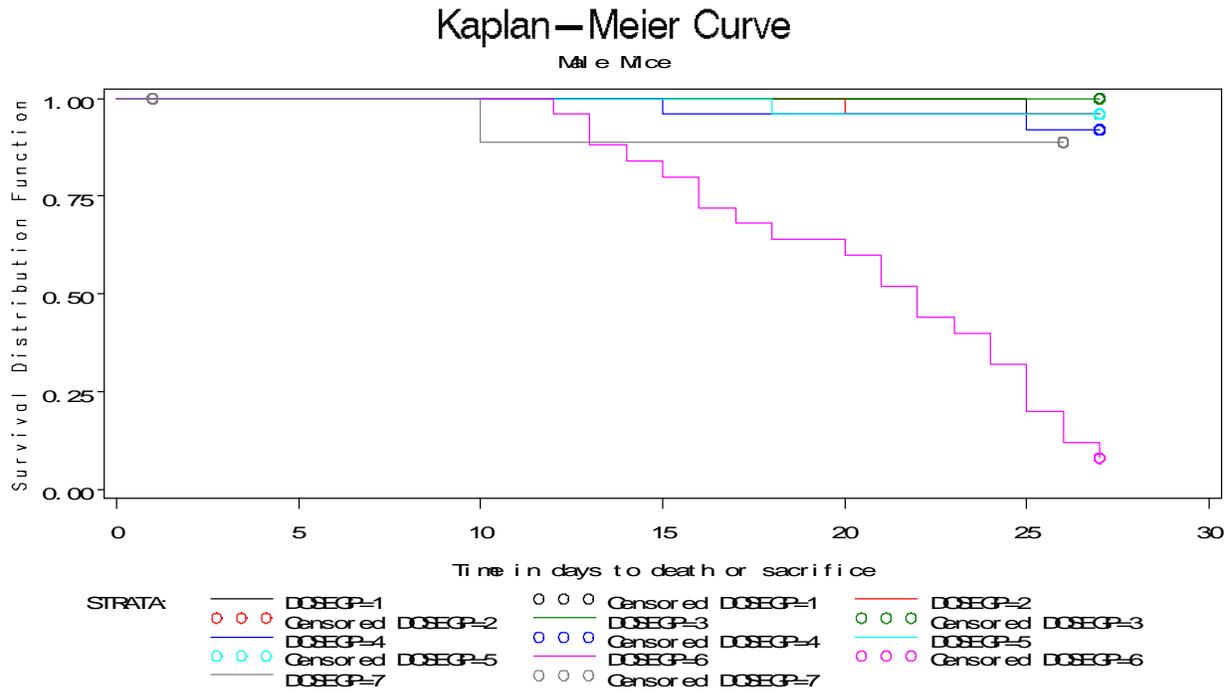
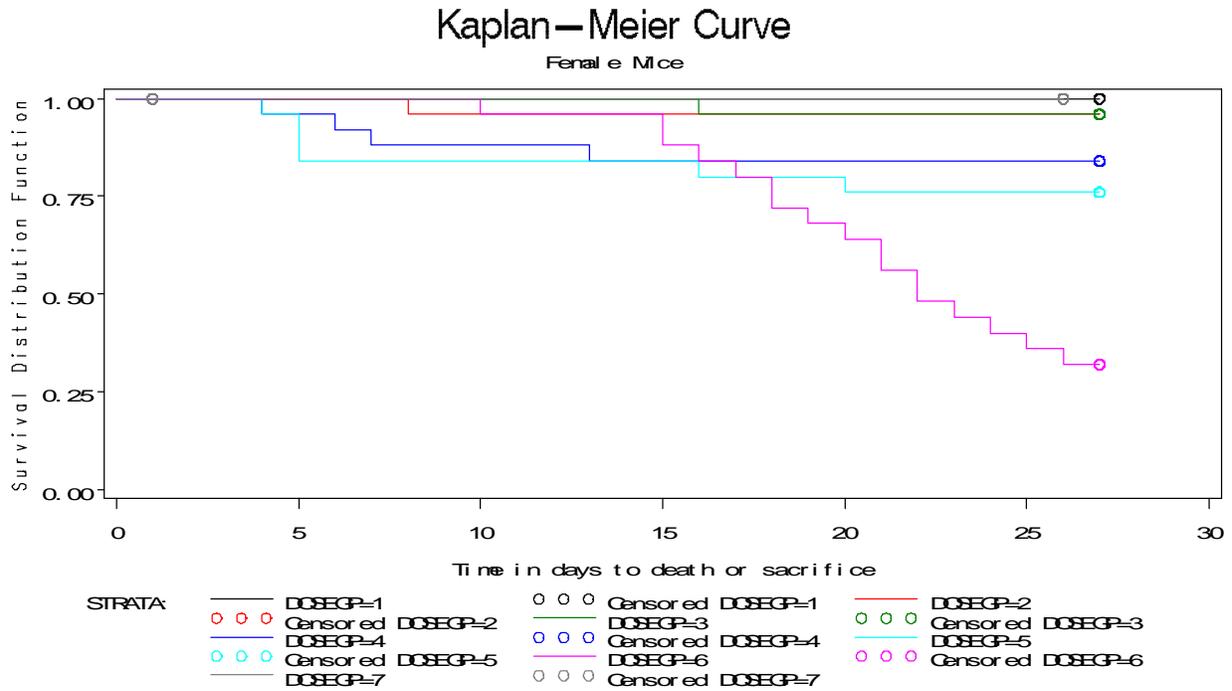


Figure 2.1B: Figure 2A: Kaplan-Meier Survival Functions for Female Mice



4. References

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

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/s/

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Concur with review