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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-868/N-000
Name of drug:	Exubera (Insulin [RDNA Origin] INH powder
Indication:	For use in controlling the hyperglycemia associated with type 1 and type 2 diabetes mellitus (DM) in adults
Applicant:	Pfizer Inc.
Dates:	Received 12/27/04
Review priority:	S
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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Twelve completed and 2 ongoing Controlled Phase 2/3 studies were included in the submission. The main focus of this review was to assess the quality of the data, to assess the computation techniques used by the applicant and to assist the medical officer Dr. Sally Seymour with her clinical review of the pulmonary safety of the inhaled insulin (Exubera) in adult (age 18 years and over) subjects with Type 1 or Type 2 diabetes mellitus (DM).

I conclude that the data quality and analytical techniques used by the applicant in analyzing the pulmonary safety data are acceptable.

In Pooled Type 1, I find that respiratory adverse events were higher in the inhaled insulin group compared to the comparator group, particularly on increased cough. Only 2% of the 698 subjects in the inhaled insulin group discontinued due to respiratory events. There is evidence that inhaled insulin consistently showed a greater decline in FEV_1 and DLco from baseline over time particularly at early timepoints compared to the comparator group. Treatment differences were of a magnitude of about 40 mL for FEV1 at the end of the study and about 0.5 mL/min/mmHg for DLco at the end of the study. Although there are declines in FRC, FVC, and TLC scores in each of the treatment groups (i.e. inhaled insulin and comparator), the treatments were comparable over time. There is no evidence of any consistent correlation between the change from baseline in pulmonary function tests and antibody titers. In terms of PFT measures and insulin dose, correlations were generally small, usually no greater in absolute value than 0.15.

In Pooled Type 2, I find that respiratory adverse events were higher in the inhaled insulin group compared to the comparator group, particularly on increased cough. Only 2% of the 1277 subjects in the inhaled insulin group and 0.1% of the 1132 subjects in the comparator discontinued due to respiratory events. There is evidence that inhaled insulin consistently showed a greater numerical decline in FEV_1 and DLco from baseline over time compared to the comparator group. However, the majority of these differences were not statistically significant as indicated by the confidence intervals for these changes. Treatment differences were of a magnitude of about 40 mL for FEV1 at the end of the study (same as Type 1 data) and about 0.4 mL/min/mmHg for DLco at week 84/91. A similar conclusion can be drawn for FRC, FVC, and TLC scores. Although treatment group differences slightly favored the comparator group, the differences were comparable in the sense that the confidence intervals include the zero difference. There is no evidence of consistent correlation between the change from baseline in pulmonary function tests and antibody titers. In terms of PFT measures and insulin dose, correlations were generally small, usually no greater in absolute value than 0.15.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

1.2.1 BACKGROUND

The primary objective of this statistical review is to assess the quality of the data, to assess the computation techniques used by the applicant and to assist the medical officer Dr. Sally Seymour with her clinical review of the pulmonary safety of the inhaled insulin (Exubera) in adult (age 18 years and over) subjects with Type 1 or Type 2 diabetes mellitus (DM). This includes detailed evaluations and treatment comparisons of the five pulmonary function tests (PFT), namely, the forced expiratory volume in 1 second (FEV1), carbon monoxide diffusion capacity (DLco), forced vital capacity (FVC), total lung capacity (TLC), and the functional residual capacity (FRC). In this review, I also evaluated the respiratory adverse events, the results from chest x-rays and thoracic high resolution computed tomography scan (HRCT). The relationships between PFT and antibody titers, as well as on dosing exposure were also assessed.

In my review, I focused mainly on the 12 completed and 2 ongoing Controlled Phase 2/3 studies included in the submission (Table 1). Most of the safety data and serious adverse event data presented in this review are based on cut-off dates of June 25, 2004 and September 1, 2004, respectively. I also included in my review the new safety update for the ongoing Study 1022 that was submitted on April 26, 2005 (actual data was submitted on July 5, 2005). Individual, pooled type 1, and pooled type 2 data from these Controlled Phase 2/3 studies with interim (Study 1029 and 1022) and final study reports have been re-analyzed and will be discussed in this review.

To simplify the discussion of pulmonary safety, subjects are grouped based on the treatment actually received. Subjects treated with INH with or without subcutaneous basal insulin, or oral antidiabetic agents (OAs) are considered to be INH- treated subjects. Subjects treated with subcutaneous short- acting (SC) insulin or with OAs alone are considered to be Comparator-treated subjects. No subjects were randomized to receive SC regular insulin with INH or OAs. All subjects with type 1 DM received basal insulin in addition to INH or SC insulin.

In the pooled studies, PFT measurements were summarized by treatment and analysis timepoints by descriptive statistics and graphical presentations. Treatment effects on the selected pulmonary function tests were analyzed and summarized with the unadjusted and adjusted models using all treated subjects. In this case, treated subjects are defined as subjects who received at least one dose of study treatment and have a baseline PFT measurement. An unadjusted model was fitted to the observed change from baseline PFT measurements by visits (time). Because of the longitudinal nature of the data, a repeated measure with treatment, time and, protocol as fixed effects, and a random effect associated with each subject was fitted to the observed change from baseline PFT measurements. Two additional repeated analyses conducted by the applicant were also included in the summary that includes covariates in the model. One of the adjusted models by the applicant was the repeated measures model with the categorical variables (treatment, month, center, gender) and the continuous variables (baseline, age, height) fitted to the change from baseline PFT measurements, and the other adjusted model was the repeated measures model with only treatment and time fitted to the change from baseline PFT measurements.

Missing PFT measurements were not imputed in the final model. However, to assess the robustness of the observed PFT measurements, imputation using last observation carried forward (LOCF) was also carried out.

Incidence of respiratory adverse events, and the results from chest x-rays and the thoracic high resolution computed tomography scan (HRCT) were summarized by treatment by descriptive statistics. The relationships between the change from baseline of PFT measurements and the antibody titer, as well as the dosing exposure were also summarized by treatment and analysis timepoints by graphical presentations.

1.2.2 SPONSOR'S RESULTS AND CONCLUSION

The following summarizes some of the applicant's results and conclusions:

> Pre- clinical studies of inhaled insulin (INH) pulmonary safety, with up to 6 months of INH exposure, were unremarkable. In clinical studies, involving controlled INH treatment for up to 24 months and uncontrolled INH treatment for up to approximately 84 months, cough, dyspnea, epistaxis, and increased sputum occurred in a greater proportion of INH- treated than comparator- treated subjects. Respiratory serious adverse events occurred at similar incidence among subjects receiving INH or comparator therapies. Discontinuations due to respiratory adverse events were more common among INH- than comparator- treated subjects.
>
> Pre- and post- exposure chest x- rays and high resolution computed tomography (HRCT) scans have not demonstrated lung pathology associated with INH treatment.
>
> Pulmonary function test result declines associated with INH treatment were small, nonprogressive beyond 2 weeks, and reversible following cessation of treatment. Small differences in change from baseline lung function (forced expiratory volume in 1 second [FEV1] and carbon monoxide diffusion capacity [DLco]) favoring comparator therapy have been observed in most of the 3- and 6-month controlled Phase 2/ 3 studies in the INH development program. Importantly, the treatment group differences were not driven by outlier values among INH- treated subjects. In long- term controlled studies these small treatment group differences did not progress beyond 3 months, with ongoing exposure up to 2 years. In Study 1027, in which FEV1 and DLco were measured frequently, the treatment group differences were fully manifest by 2 weeks of treatment and did not progress thereafter. Cessation of INH therapy following controlled exposure for as long as 2 years has shown rapid resolution of the treatment group differences in FEV1 and DLco. That these treatment group differences in lung function arise early and are small, non- progressive, and reversible supports the overall respiratory safety of INH therapy.
>
> Subjects with mild to moderate asthma or COPD did not experience any unexpected findings related to the safety and efficacy of INH in Phase 2/ 3 studies. Specifically, there was no evidence that these special populations experience altered INH absorption or clinical deteriorations in the status of their diabetes or underlying respiratory disease.
>
> Overall, the safety and efficacy of INH among subjects with and without notable pulmonary function test (PFT) declines were comparable. INH therapy was well tolerated by subjects in the clinical development program.

1.3 STATISTICAL ISSUES AND FINDINGS

Overall, the quality of the data provided by the applicant was good. There were some minor data problems encountered during the re-analyses process such as discrepancies between combined and individual data (e.g. Data for Studies 1001 and 1002, Updated data for Study 1002), as well detection of outliers (Study 1001). It is difficult to understand the origin of these outliers (i.e. whether it is typographical, measurement error, or true and actual measure) such that deletion of these outliers may not be an ideal approach. Post-hoc analyses showed the removing these outliers will change the outcome for DLco at Week 104. Meanwhile, post-hoc analyses comparing the combined and the manually-combined individual studies showed no considerable differences that would affect the overall findings.

Several statistical issues were identified after reviewing this NDA submission. These issues did not affect the overall conclusion of the pulmonary safety of the inhaled insulin, but I find that it is worth noting in this review. Post-hoc analyses had been conducted to address and clarify some of these issues.

The first issue is on the study population used to evaluate the PFT measurements. This is with regards to the concern I have for the inconsistency of baseline values and consequently the number of subjects with baseline values in the pooled Type 1 and Type 2 data with the individual studies. An inquiry was made on June 7, 2005. In the response letter dated July 5, 2005, the applicant wrote:

> In Table 15, only subjects with a nonmissing baseline measurement and a nonmissing postbaseline measurement captured in at least one of the tabulated nominal visit windows contribute to the count of subjects (n) at baseline. Based on this logic, Table 15's requirement for a baseline and a post- baseline tabulated measurement can alternatively be expressed as a requirement for a non- missing change from baseline (pft_ c) at one of the tabulated visits. In some of the individual CSR tables cited, the only requirement was the presence of a nonmissing baseline value. Implicit in the calculation of change from baseline is the requirement to have both a baseline and post- baseline measurement thus explaining the observation that the change from baseline values and the treatment differences from the pooled results agree with the results from the individual CSRs.

Although the overall findings were not affected by the exclusion of subjects with no post-baseline measures, I find that it is best to capture all subjects who had PFT measures (intent-to-treat approach), instead of restricting to only subjects who had post-baseline PFT measurements. The restriction should only be applied when imputation (such as last observation carried forward) is applied. Therefore, all subjects who received at least one dose of study treatment and have a baseline PFT measurement should be evaluable for the analyses of PFT decline. Furthermore, analyses should also not be restricted to completers (Combined Studies 1001 – 1002).

The second issue is on missing PFT measurements. In some of the individual studies, missing data were imputed using last observation carried forward (LOCF), while in some individual studies, specifically designed to study PFT measures, missing data were not imputed. The applicant also did not impute missing data in the pooled population. I find that this approach is more reasonable than to impute missing data using LOCF. Most of the concern about missing data comes from subject discontinuation. Discontinuation can be due to treatment-related adverse events, lack of efficacy, lost to follow-up, protocol violation, or subject's voluntary withdrawal. Typically, there is a natural decline of PFT measures in each individual over time. LOCF approach may not account for this decline. Instead, missing data will be imputed with a PFT that is potentially higher (better) than what the actual PFT should be. If the discontinuation is due to treatment-related adverse or treatment-related lack of efficacy, then the imputed value may actually be more favorable to the study drug. To account for the natural decline of PFT measures, imputation should take into account the slope of the observed values.

As stated, the applicant did not impute missing data, in studies specifically designed to study PFT measures (long-term studies) and the pooled data. The statistical model they chose to apply is the likelihood-based mixed model repeated measures analyses (MMRM) to account for intra-subject variation. In their primary model, they pre-specified covariates that they wanted to include in the model such as the categorical variable visits/time, protocols, sex, and in some instance centers, and continuous variables such as baseline PFT measures, baseline age, and height. I find that this is a reasonable approach considering that this model takes into account missing data. The only caveat in this type of modeling is that the missing data must be Missing at Random (MAR) which is a common assumption for this type of data. Post-hoc analyses have been conducted in Type 1 data to see the effects of imputed data versus using observed cases only. Comparison was also made between unadjusted (PROC GLM by visit/week) treatment difference and adjusted (using MMRM) treatment difference. All results from different PFT measures showed no differences using either one of the approaches. The question remains as to the usefulness of conducting a more complicated modeling technique (MMRM) versus using unadjusted analysis when the results are comparable. MMRM has the added advantage of accounting for within-subject variation (as well as known and clinically relevant covariates).

The third issue is related to the mixed model approach the applicant used in their analysis and the choice of variance-covariance structure. The variance-covariance structure chosen by the applicant is the Spatial Power,

which assumes higher correlation between neighboring time points than farther time points. This model appears to be reasonable particularly when there are a lot of time points. There was a concern that the results from the first-order autoregressive structure, AR(1) would be very similar with the result from the Spatial Power since the time variable in the pooled Type 1 (or Type 2) data only has a maximum of 8 timepoints. Post-hoc analyses have shown that the unstructured model generally yields a lower (more favorable) information criterion (AIC, AAIC, BIC) compared to the spatial power model. However, the difference is not large. The analyses also showed no difference between the AR(1) model and the Spatial Power model. Although the spatial power model is acceptable, I thought this concern is worth noting.

2 INTRODUCTION

2.1 OVERVIEW

This is a review of the pulmonary safety data of the inhaled human insulin therapeutic regimen (Exubera) in adult (age 18 years and over) subjects with Type 1 or Type 2 diabetes mellitus (DM). The study drug is indicated for use in controlling the hyperglycemia associated with Type 1 and Type 2 diabetes mellitus (DM) in adults. Exubera is proposed to be administered before each meal as part of an individualized DM control regimen that may include other insulin formulation or oral hypoglycemic agents.

Currently, the applicant, Pfizer Inc, is seeking FDA approval of EXUBERA (insulin [rDNA origin] powder for oral inhalation) 1 mg and 3 mg unit dose blisters in accordance with the proposed package insert. EXUBERA (also referred to as INH) is a novel treatment system for diabetes mellitus (DM) which combines a dry powder formulation of a recombinant human insulin with a customized inhaler and was designed to permit the easy and reproducible delivery of insulin for the control of hyperglycemia in patients with DM. It is delivered with a novel, reusable pulmonary inhaler that is purely mechanical, and requires no batteries, electronics or external power source

The primary objective of this statistical review is to assess the quality of the data, to assess the computation techniques used by the applicant and to assist the medical officer Dr. Sally Seymour with her clinical review of the pulmonary safety of the inhaled insulin (Exubera) in adult (age 18 years and over) subjects with Type 1 or Type 2 diabetes mellitus (DM).

In my review, I focused mainly on the 12 completed and 2 ongoing Controlled Phase 2/3 studies included in the submission (Table 1). Most of the safety data and serious adverse event data presented in this review are based on cut-off dates of June 25, 2004 and September 1, 2004, respectively. I also included in my review the new safety update for the ongoing Study 1022 that was submitted on April 26, 2005 (actual data was submitted on July 5, 2005). Individual, pooled type 1, and pooled type 2 data from these Controlled Phase 2/3 studies with interim (Study 1029 and 1022) and final study reports have been re-analyzed and will be discussed in this review.

Table 1: Controlled PFT Phase 2/3 Studies

Diabetes Type	Contributing Study	PFT	INH	Comparator	Total
Type 1 DM	Controlled Studies*	Total	698	705	1403
	102, 106, 107, 1022**, 1026, 1027	FEV1	686	692	1378
		FVC	686	692	1378
		DLco	684	691	1375
		FRC	686	689	1375
		TLC	686	690	1376
Type 2 DM	Controlled Studies*	Total	1277	1132	2409
	103, 104, 108, 109, 110, 1001**, 1002**, 1029***	FEV1	1267	1119	2386
		FVC	1266	1118	2384
		DLco	1234	1094	2328
		FRC	1247	1100	2347
		TLC	1264	1115	2379

*All Phase 2/3 Controlled Studies
**Studies 1022, 1001, and 1002 include 2 years of exposure data.
*** Study 1029 is truncated at 1 year of exposure, consistent with the 1-year interim analyses

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

A detailed clinical review of the efficacy of Exubera can be found in Dr. Karen M. Mahoney's review. Meanwhile, a detailed statistical review of the efficacy of Exubera can be found in Ms. Joy Mele's review.

3.2 EVALUATION OF SAFETY

The overall clinical review of the safety of Exubera can be found in Dr. Karen M. Mahoney's review. Meanwhile, a detailed review of the pulmonary safety of Exubera can be found in Dr. Sally Seymour's review.

The safety review in this section consists of two parts. The first part includes a brief description of the safety assessments such as the pulmonary function tests, adverse events reports, and some laboratory exams such as chest X-rays and thoracic high resolution computed tomography, as well as a brief summary of the statistical analysis plan of the applicant. The second part of this safety review section includes a collective summary of the pooled pulmonary safety data by type of diabetes.

3.2.1 SAFETY EVALUATIONS

1. Safety Assessments

According to the applicant, extensive safety analyses have been conducted to screen for safety signals in the INH clinical development program. The following are some of the safety monitoring programs the applicant has conducted:

a. Pulmonary Function Test

Comprehensive pulmonary function testing (spirometry, lung volumes, diffusion capacity and oxygen saturation) was performed (see Table 2 and Table 3 for individual studies). In early Controlled Phase 2/ 3 studies (Studies 102, 103, 104, 106, 107, 108, 109, 110, 1009, 1001 and 1002), PFT's were measured in local laboratories according to standards of the American Thoracic Society or local country standards. Subjects were to repeat the pulmonary function test 3- times at each evaluation, and the maximum test result from the 3 was to be recorded on the subject's CRF. However, no further attempt was made to standardize the equipment or methodologies. In Studies 1022, 1026, 1027, and 1029, standardized pulmonary function testing equipment and centralized data analysis were used.

b. Adverse Events

All observed or volunteered adverse events were recorded by the investigator on the CRF regardless of treatment group or suspected causal relationship to study drug. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre- existing illnesses were recorded. Objective test findings (e. g., ECG changes, abnormal laboratory test results) that resulted in a change in study drug dosage or resulted in discontinuation, and clinically significant changes in physical examination findings, as judged by the investigator, were also recorded as adverse events.

Exacerbation of pre- existing illness, including the disease under study, was defined as a manifestation (sign or symptom) of the illness that indicated a significant increase in the severity of the illness as compared to the severity noted at the start of the study. It may include worsening or increase in severity of signs or symptoms

of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/ complication. Exacerbation of a pre- existing illness was to be considered when a subject required new or additional concomitant drug or non- drug therapy for the treatment of that illness during the study. Lack of or insufficient clinical response, benefit, efficacy, or therapeutic effect was not to be recorded as an adverse event. The investigator was required to make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

For all adverse events, the investigator pursued and obtained information adequate to determine both the outcome of the adverse event and to assess whether it met the criteria for classification as a serious adverse event. The investigator was to obtain sufficient information to determine the causality of the adverse event and record the causality assessment on the CRF. If the adverse event or its sequelae persisted, follow- up was performed until resolution or stabilization at a level acceptable to the investigator and sponsor.

c. Other

Chest x-rays were performed at baseline and end of study for most Controlled Phase 2/ 3 studies (Studies 106, 107, 108, 109, 110, 1001, 1002, and 1027). Additional chest x-rays were performed at 1 year in controlled 2- year Studies 1022, and 1029. In extension studies, chest x-rays were performed at approximately yearly intervals. Baseline and end- of- study High Resolution Computed Tomography (HRCT) of the thorax were performed in subjects randomized to participate in the HRCT sub- study in Studies 106, 107, and 108. In Study 1029, thoracic HRCT is to be performed in a sub-set of subjects at baseline, 1 year, and 2 years.

2. Analysis Plan

To simplify the discussion of pulmonary safety, subjects are grouped based on the treatment actually received. Subjects treated with INH with or without subcutaneous basal insulin, or oral antidiabetic agents (OAs) are considered to be INH- treated subjects. Subjects treated with subcutaneous short- acting (SC) insulin or with OAs alone are considered to be Comparator-treated subjects. No subjects were randomized to receive SC regular insulin with INH or OAs. All subjects with type 1 DM received basal insulin in addition to INH or SC insulin.

For the Controlled PFT Phase 2/ 3 Studies, the objective was to estimate treatment group differences in change from baseline PFT parameters over time. Analyses were performed separately for the Type 1 and Type 2 pooled protocol sets. The pooled Type 1 data includes information and data from Studies 102, 106, 107, 1022 (two-year study report), 1026, and 1027, while the pooled Type 2 data includes information and data from Studies 103, 104, 108, 109, 110, 1001, 1002, and 1029. The accuracy of the data from individual studies was confirmed by re-analyzing each of the individual data sets. In this section, an overview of the pooled data will be described. Some analyses were added as per the request by Dr. Seymour, some data were re-analyzed because of the addition of new data, and some analyses were done to assist Dr. Seymour in understanding the pulmonary safety of the inhaled insulin.

The analysis population evaluable for adverse events includes all subjects who received study drug for at least one day. All studies in the INH clinical program were open- label, making assignment of causality to adverse events subject to bias. Therefore, all-causality adverse events were emphasized by the applicant, as well as in my review. Respiratory adverse event data are presented for adults (subjects >= 18 years old) only. In terms of the PFT measurements, all subjects who received at least one dose of study treatment and have a baseline PFT measurement were evaluable for the analyses of PFT decline. Additionally, according to the applicant, for a subject to be included in the analysis for DLco, the subject must have a baseline and a post-baseline DLco measurement. This approach by the applicant (i.e. restricting subjects who only have post-baseline for DLco score) may not be ideal unless imputation (such as last observation carried forward) is carried out.

Therefore, all subjects who received at least one dose of study treatment and have a baseline PFT measurement were included in the analyses of PFT decline. For insulin antibodies, population used includes all available data from all subjects regardless of whether they have baseline and/ or post- baseline data.

In the pooled data, the applicant specified in their study report (NOT protocol) that repeated measures analysis of variance was used to simultaneously estimate the mean change from baseline for each treatment group and its corresponding treatment difference at each assessment time point. Treatment comparison based on group means (inhaled insulin minus comparator insulin) was also done using the PROC MIXED procedure for mixed model repeated measure (MMRM) analysis in SAS. A random coefficients model was fitted to the observed PFT data where a random intercept and a random slope were associated with each subject. The variance-covariance structure chosen by the applicant was the Spatial Power form, which assumes higher correlation between neighboring time points than farther time points. From these estimates, treatment group differences (Inhaled Insulin – Comparator) and associated 95% confidence intervals in change from baseline PFTs were estimated at each assessment time point. Two statistical models were used for the MMRM analysis:

(1) Unadjusted Model • Treatment group, categorical variable • Visit, categorical variable • Subject, random effect
(2) Covariate Adjusted Model • Treatment group, categorical variable • Visit, categorical variable • Protocol, categorical variable • Baseline PFT, continuous variable • Age at baseline (years), continuous variable • Baseline height (meters), continuous variable • Gender (1= Male, 0= Female), categorical variable • Subject, random effect

According to the applicant, this analysis was to provide information on the profile of group mean change in FEV1 and DLco during early treatment of inhaled insulin. A detailed discussion of this MMRM model is described in the Statistical Issues and Findings Section

Although the variance-covariance structure (i.e. Spatial Power) chosen by the applicant appears to be reasonable, I also conducted additional analyses using unstructured correlation matrix and compound symmetry as the within-subject variance-covariance structure to determine whether the applicant had selected an appropriate covariance structure.

I also carried out additional analyses that looked into the effects of data imputation based on last observation carried forward in each of the individual studies, and using the imputed data in the pooled analysis. This approach was tricky since the treatment duration across studies was different thereby the imputed data were also at different time points. Furthermore, as noted previously, the analysis population in this type of approach should be restricted to subjects who had at least one post-baseline PFT measurements.
I compared the results from the imputed data with the results using the observed cases only, as well as with the mixed model.

As an added exploratory analysis, I also carried out responder analysis to assess the response (i.e. reduction of PFT scores) profile of the subjects in the Inhaled insulin group and the comparator group. The responder analysis in this scenario is based on percent reduction in mean PFT values from baseline. In other words, these are proportion of subjects who had a decline in PFT score from baseline. The percent decrease was classified in 1-percent increments (e.g. > 0% decrease, ≥1%, ≥2%, …. ≥10% reduction in PFT scores from Baseline), and in 5-percent increments (e.g. ≥15%, ≥20%,…, ≥60%) giving cumulative distribution functions of PFT reduction from Baseline by treatment groups. In this analysis, patients who withdrew from the study were not included in the analysis since it is difficult to predict what their PFT measures would be after discontinuation.

Incidence of respiratory adverse event, and the results from chest x-rays and the thoracic high resolution computed tomography scan (HRCT) were summarized by treatment by descriptive statistics. The relationships between the change from baseline of PFT measurements and the antibody titer, as well as the dosing exposure were also summarized by treatment and analysis timepoints.

Table 2: Analysis Population of Type 1 Data

PFT	Study	Treatment Duration (in weeks)	Number of Subjects INH	Number of Subjects Comparator	Overall Week	Overall Inhaled	Overall Comparator
DLco	102	12	35	37	12	447	452
	106	24	135	134	24	549	551
	107	24	102	105	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290
FEV1	102	12	35	37	12	686	692
	106	12 and 24	136	135	24	552	552
	107	12 and 24	103	105	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24,	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290
FRC	102	12	35	35	12	447	450
	106	24	136	135	24	552	551
	107	24	103	104	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290
FVC	102	12	35	37	12	686	692
	106	12 and 24	136	135	24	552	552
	107	12 and 24	103	105	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24,	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290
TLC	102	12	35	35	12	447	450
	106	24	136	135	24	552	552
	107	24	103	105	36	290	290
	1022	12, 24, 36, 48, 60, 72, 84, 96	290	290	48	290	290
	1026	12, 24	23	22	60	290	290
	1027	12	99	103	72	290	290
					84	290	290
					96	290	290

Table 3: Analysis Population for Type 2 Data

			Number of Subjects		Overall		
PFT	Study	Treatment Duration (in weeks)	INH	Comparator	Week	INH	Comparator
DLco	103	12	27	28	12	644	530
	104	12	33	36	24	896	866
	108	24	146	147	36	305	301
	109	12	205	98	48	750	719
	110	12	74	67	65	445	418
	1001	24, 48, 65, 78, 91, 104, 110, 116	221	202	78	445	418
	1002	24, 48, 65, 78, 91, 104, 110, 116	224	216	91	445	418
	1029	12, 24, 36, 48	305	301	104	445	418
					110	445	418
					116	445	418
FEV	103	12	28	28	12	798	682
	104	12	33	36	24	926	890
	108	12, 24	149	149	36	777	741
	109	12	207	99	48	777	741
	110	12	75	68	65	471	439
	1001	24, 36, 48, 65, 78, 91, 104, 110, 116	232	209	78	471	439
	1002	24, 36, 48, 65, 78, 91, 104, 110, 116	239	230	91	471	439
	1029	12, 24, 36, 48	306	302	104	471	439
					110	471	439
					116	471	439
FRC	103	12	28	28	12	643	527
	104	12	30	33	24	911	877
	108	24	149	148	36	762	729
	109	12	206	99	48	762	729
	110	12	73	66	65	456	428
	1001	24, 36, 48, 65, 78, 91, 104, 110, 116	226	205	78	456	428
	1002	24, 36, 48, 65, 78, 91, 104, 110, 116	230	223	91	456	428
	1029	12, 24, 36, 48	306	301	104	456	428
					110	456	428
FVC	103	12	28	28	12	798	682
	104	12	33	36	24	925	889
	108	12, 24	149	149	36	776	740
	109	12	207	99	48	776	740
	110	12	75	68	65	470	438
	1001	24, 36, 48, 65, 78, 91, 104, 110, 116	231	208	78	470	438
	1002	24, 36, 48, 65, 78, 91, 104, 110, 116	239	230	91	470	438
	1029	12, 24, 36, 48	306	302	104	470	438
					110	470	438
					116	470	438
TLC	103	12	28	28	12	649	532
	104	12	33	36	24	922	885
	108	24	149	149	36	773	736
	109	12	207	99	48	773	736
	110	12	75	68	65	467	435
	1001	24, 36, 48, 65, 78, 91, 104, 110, 116	232	208	78	467	435
	1002	24, 36, 48, 65, 78, 91, 104, 110, 116	235	227	91	467	435
	1029	12, 24, 36, 48	306	301	104	467	435
					110	467	435
					116	467	435

3.2.2 DETAILED REVIEW OF POOLED TYPE 1 AND POOLED TYPE 2 STUDIES

For the purposes of evaluating the pulmonary safety of INH, protocols were grouped and their data pooled according to study completion status and the population under study. The first part of this section will focus mainly on the pooled Type 1 data, and the second part of this section will focus of Pooled Type 2 data. One of the goals of this section is to discuss and evaluate overall pulmonary safety of Exubera on adults with either Type 1 or Type 2 diabetes mellitus. This will include pooled analysis of the pulmonary function tests, pooled discussion of the respiratory adverse events, and lastly, the relations between the pulmonary function tests and antibody titers, as well as with the insulin dosing. Note that my interpretations of findings are based wholly on statistical interpretation of the results. **I defer all clinical interpretations to Dr. Seymour's review**. This section is divided into two parts based on the type of diabetes.

I. Type 1 Data

Demographic Characteristics:

Demographic characteristics of subjects in the pooled Type 1 data are comparable between the two treatment groups. Majority of the subjects was white. There appears to be more males in each of the treatment group across all studies. The male subjects were heavier and taller than females in each of the treatment group. Age appears to be comparable between males and females (Table 4).

Table 4: Mean Demographic Characteristics of Adults Type 1 Data (SD)

	Inhaled Insulin		Comparator	
Variables	Male	Female	Male	Female
No. of Subjects*	385	302	377	315
Age (years)	38 (10.4)	38 (10.9)	38 (10.5)	37 (11.4)
Race (White)	341 (89%)	265 (88%)	344 (91%)	287 (91%)
Weight (kg)	83 (12.4)	66 (9.3)	81 (11.9)	67 (9.9)
Height (cm?)	179 (7.5)	164 (6.5)	178 (7.7)	164 (6.5)
BMI	26 (2.9)	25 (3.1)	26 (2.9)	25 (3.4)

* No. of Subjects are slightly smaller than the total number who were randomized in the studies. Includes only subjects who were treated and have PFT measurements.

Respiratory Adverse Events:

Respiratory adverse events by individual studies are presented in Table 5. In the pooled analysis, the number of subjects with respiratory events was higher in the inhaled insulin group compared to the comparator group (Figure 1). Using preferred COSTART term and severity for all-causality adverse events, the proportion of subjects with respiratory system adverse events was generally slightly higher in the inhaled insulin group than the comparator groups, particularly increased cough (INH 28% vs. Comparator 8%). There were also more subjects in the inhaled insulin group with dyspnea, rhinitis, respiratory disorder, pharyngitis, and sinusitis than the comparator group (Figure 2). The most common respiratory system adverse event was respiratory tract infection and this was comparable between the two treatment groups.

Almost all respiratory system adverse events were either mild or moderate in severity. There are a total of 11 subjects out of 698 (2%) who **permanently discontinued** due to respiratory events (Table 6). These events include increased cough, respiratory disorder, sinusitis, sputum increased, dyspnea, rhinitis, pharyngitis, laryngitis, and asthma. Most of these events were considered mild to moderate except for one subject with severe asthma and one subject with severe cough increased. None permanently discontinued in the comparator group

Table 5: Number of subjects (%) with Respiratory adverse events for all Adults Type 1 DM Subjects: All Causality

	Study 102		Study 106		Study 107		Study 1022		Study 1026		Study 1027	
	INH	Comp	INH	Comp	INH	Comp	INH	Comp	INH	Comp	INH	Comp
No. of Subjects	35	37	137	136	103	105	290	290	23	22	110	116
Total Respiratory	19 (54)	18 (49)	95 (69)	84 (62)	77 (75)	61 (58)	242 (83)	202 (70)	11 (48)	12 (55)	71 (65)	51 (44)
Asthma	0	1(3)	1 (1)	2 (1)	2 (2)	0	3 (1)	4 (1)			1 (1)	1 (1)
Bronchiolitis							1 (0)	0				
Bronchitis	0	1 (3)	4 (3)	4 (3)	3 (3)	3 (3)	9 (3)	17 (6)	1 (4)	0	3 (3)	2 (2)
Cough Increased	5 (14)	3 (8)	33 (24)	7 (5)	21 (20)	4 (4)	99 (34)	36 (12)	4 (17)	0	34 (31)	9 (8)
Dyspnea			4 (3)	1 (1)	3 (3)	1 (1)	18 (6)	2 (1)			2 (2)	0
Edema Pharynx							0	2 (1)				
Epistaxis			4 (3)	1 (1)	1 (1)	0	4 (1)	0			0	1 (1)
Hyperventilation					0	1 (1)					1 (1)	0
Hypoventilation											1 (1)	0
Laryngitis	1 (3)	0	2 (1)	1 (1)			4 (1)	1 (0)			1 (1)	1 (1)
Lung Edema							0	1 (0)				
Nasal Polyp							1 (0)	1 (0)				
Pharyngitis	5 (14)	5 (14)	22 (16)	19 (14)	25 (24)	19 (18)	52 (18)	45 (16)	1 (4)	3 (14)	18 (16)	12 (10)
Pleural Disorder							1 (0)	0				
Pneumonia			0	3 (2)	2 (2)	0	3 (1)	4 (1)				
Respiratory Disorder	3 (9)	1 (3)	10 (7)	8 (6)	6 (6)	3 (3)	22 (8)	13 (5)			4 (4)	2 (2)
Respiratory Distress Syndrome							0	1 (0)				
Respiratory Tract Infection	8 (23)	12 (32)	54 (39)	50 (37)	46 (45)	36 (34)	146 (50)	142 (49)	7 (30)	11 (50)	29 (26)	28 (24)
Rhinitis	3 (9)	2 (5)	18 (13)	15 (11)	9 (9)	8 (8)	51 (18)	33 (11)			15 (14)	9 (8)
Sinusitis	3 (9)	1 (3)	11 (8)	7 (5)	7 (7)	10 (10)	37 (13)	27 (9)	2 (9)	0	4 (4)	3 (3)
Sputum Increased			5 (4)	4 (3)	4 (4)	0	14 (5)	1 (0)			4 (4)	3 (3)
Voice Alteration							1 (0)	1 (0)				
Yawn							1 (0)	1 (0)				

Source: Study Report 217-102, 106, 107, 1022, 1026, 1027

Figure 1: Total Percentage of Respiratory Events by Individual and Pooled Studies in Controlled Phase 2/3 Type 1 Adults

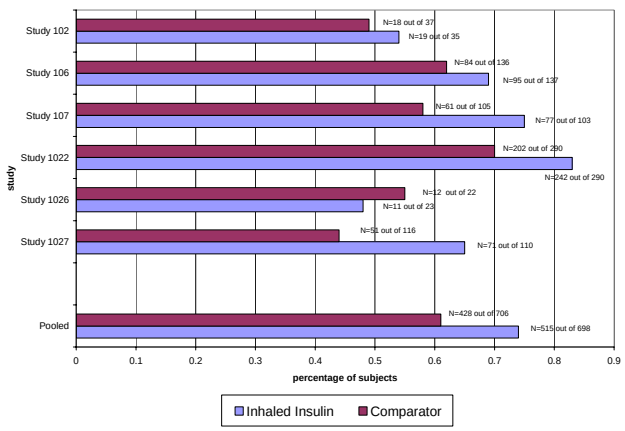


Figure 2: Respiratory Adverse Events by Treatment Group, Pooled Type 1 Controlled Phase 2/3 Studies

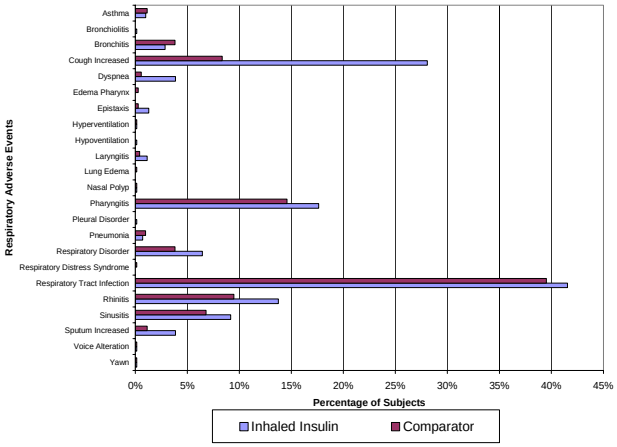


Table 6: Respiratory Adverse Events Resulting in Permanent Discontinuation from Individual Study

Study	Treatment Group	Subject	Severity	Adverse Event Preferred COSTART/Investigator Term
106	INH	5055 6135	Mild	Cough Increased
107	INH	5102 7141	Moderate	Respiratory Disorder including cough, wheezing and pulmonary obstruction
1022	INH	1005 241	Mild	Sinusitis
			Mild	Sputum Increased/Productive Cough
		1017 949	Mild	Cough Increased/Dry Cough
		1025 1425	Moderate	Dyspnea/Shortness of Breath
		1047 2728	Mild	Cough increased
			Mild	Dyspnea
			Mild	Respiratory Disorder/Decreased DLco
			Mild	Rhinitis/Nasal congestion
		5074 3085	Moderate	Cough increased/dry cough
			Moderate	Dyspnea/Shortness of breath
			Moderate	Asthenia/Weak Feeling
		5156 3797	Mild	Cough increased
			Moderate	Pharyngitis/sore throat
1027	INH	1004 154	Severe	Cough Increased/Cough
			Mild	Laryngitis
			Mild	Pharyngitis/Throat Irritation
		1006 249	Severe	Asthma/Reactive airways disease
		1006 251	Moderate	Cough increased/non-productive cough

Source: Study Report 217-102, 106, 107, 1022, 1026, 1027

Chest X-ray and Thoracic High Resolution Computed Tomography (HRCT)

In the four Type 1 DM clinical studies with chest X-ray (Studies 106, 107, 1022, 1027), only a very small proportion of subjects who had chest X-rays taken at final observation had abnormal findings compared to baseline. However, it appears that the incidences of change in chest x-ray results between baseline and last observation were numerically greater in the INH than the comparator treatment groups (INH 12, Comparator 9). Summary of the abnormal chest x-ray findings is available upon request.

In terms of HRCT, only selected sites, from the two Type 1 DM clinical studies (Study 106 and Study 107), had HRCT scan. It appears that there is only one subject in the inhaled insulin group with more abnormal HRCT, while there are four (three from Study 106 and one from Study 107) in the comparator group who had more abnormal HRCT scan. Summary of the abnormal HRCT scan is also available upon request.

Pulmonary Function Test:

One of the main objectives of the Phase 2/3 clinical studies was to determine the safety and potential (early) effects of INH insulin on lung function as measured by pulmonary function tests (PFT). This was achieved by comparing the treatment effect (change from baseline) of inhaled insulin to the comparator group over time, as well as the response rates over time. The applicant defined response as the decline in PFT results relative to a baseline intra-subject variation criterion; the response rate was the percentage of evaluable subjects who met the response criteria.

In Type 1 Adults studies, pulmonary function was monitored in Studies 102, 106, 107 using non-standardized methodologies available in local PFT laboratories. These studies were short-term studies, usually 3 or 6 months of exposure. Pulmonary function has also been monitored in studies (1026, 1027, and updated 2-year data of Study 1022), in which standardized pulmonary testing equipment, testing procedures, and centralized data analysis were used to measure PFTs.

As noted earlier, to simplify the discussion of pulmonary safety, subjects are grouped based on the treatment actually received. Subjects treated with INH with or without subcutaneous basal insulin, or oral anti-diabetic agents (OAs) are considered to be INH- treated subjects. Subjects treated with subcutaneous short-acting (SC) insulin or with OAs alone are considered to be Comparator-treated subjects. All subjects with Type 1 DM received basal insulin in addition to INH or SC insulin.

To begin, comparison of the mean baseline values between the two treatment groups and the percent predicted at baseline are presented in Table 7. It appears that mean baseline values and the % predicted mean values at baseline are comparable between the treatment groups across pulmonary function tests.

Table 7: Baseline PFT Measurements and Percent Predicted Mean Values at Baseline in Pooled Controlled Phase 2/3 Studies in Adults Type 1 Diabetes

	INH			Comparator		
Variables	N	Mean % Predicted (SD)	Mean (SD)	N	Mean % Predicted (SD)	Mean (SD)
FEV1	686	95.01 (11.8)	3.48 (0.8)	692	94.84 (12.5)	3.45 (0.8)
FVC	686	92.11 (21.0)	4.34 (1.0)	692	92.47 (21.1)	4.31 (1.0)
DLco	684	95.40 (14.4)	27.87 (6.6)	691	95.07 (15.0)	27.52 (6.6)
FRC	686	95.92 (11.7)	2.99 (0.9)	689	96.03 (12.4)	3.02 (0.9)
TLC	686	96.20 (11.7)	5.93 (1.3)	690	96.65 (12.2)	5.92 (1.3)

* N is based on the number of subjects who had a mean baseline score. N for the % Predicted Value may be smaller

As noted in the Analysis section, missing PFT measurements were not imputed in the pooled analysis by the applicant. Instead, the applicant conducted a mixed model repeated measures (MMRM) analysis to simultaneously estimate the mean change from baseline for each treatment group and its corresponding treatment differences at each assessment time point. The variance-covariance structure chosen by the applicant was the Spatial Power form, which assumes higher correlation between neighboring time points than more distant time points. From these estimates, treatment group differences (Inhaled Insulin – Comparator) and associated 95% confidence intervals in change from baseline PFTs were estimated at each assessment time point.

To explore whether using Observed Cases only (Pooled – Observed) will provide a sensible estimate of the treatment difference, I conducted two different types of sensitivity analysis. These two types of analysis were then compared to unadjusted (using the Generalized Linear Model method) treatment difference. One type of sensitivity analysis was simple LOCF imputation and analyzed using the GLM method, and the other was the mixed model repeated measures (MMRM) the applicant used. In the MMRM model, I used the model[1] the applicant proposed. Note that you will find in the discussion of individual PFT measurements that the Applicant's unadjusted MMRM model and the covariate-adjusted MMRM model yielded comparable results (Table 10, Table 12, Table 14, Table 16, and Table 18) , thus alleviating our concern that the results of these sensitivity analyses may not be applicable to the applicant's primary model (i.e. Covariate-adjusted MMRM). Furthermore, I used four different covariance structures[2] to determine how appropriate the selection of Spatial Power is. All these exploratory analyses were done before the new update for Study 1022 was submitted by the applicant, so the analyses were done with four timepoints only (weeks 12, 24, 36, and 48/52).

The following figures (Figure 3 to Figure 7) are the results of the individual and pooled studies for each PFT measurements. It includes pooled observed using GLM model, the imputed data (LOCF), and the analysis using Mixed Model Repeated Measures. From the figures, it appears that results from the observed cases are consistent with results from imputation and from using Mixed Model Repeated Measures. This is true regardless of the variance-covariance structure. From careful examination of the information criterion (AIC, BIC, AICC) and the -2xResidual (or REML) Log Likelihood, it appears that the unstructured covariance is the most appropriate choice for the data, since it minimized the information criterion value (AIC, BIC, AICC) in its -2 times the residual log-likelihood form. Therefore, unstructured covariance model is the preferred model (Table 8). Note that in theory, the greater the residual log likelihood, the better the fit of the model. Therefore, the smaller the -2 times the residual log-likelihood, the better the fit of the model. However, since the result from Spatial Power model is not extremely different compared to the unstructured covariance model, the applicant's choice is acceptable. Therefore, the result is not sensitive to the choice of covariance structures, as well as to the use of observed data only.

[1] Model • Treatment group, categorical variable • Visit, categorical variable
[2] Variance-Covariance Structures: Unstructured (UN), Spatial Power (SP), First-order Autoregressive (AR1), and Compound Symmetry (CS)

Figure 3: Treatment Difference in DLco (mL/min/mmHg) in Controlled Phase 2/3 Studies in Adults Type 1 Diabetes

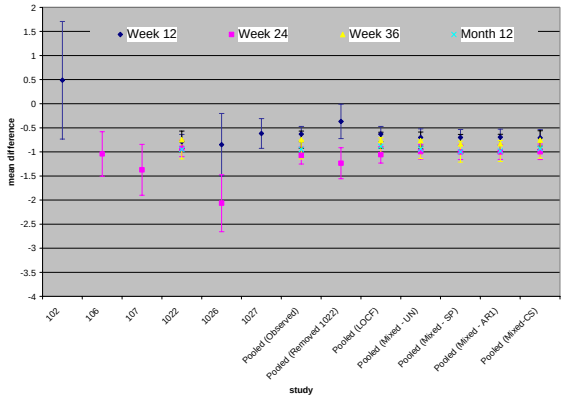


Figure 4: Treatment Difference in FEV1 (L) in Controlled Phase 2/3 Studies in Adults Type 1Diabetes

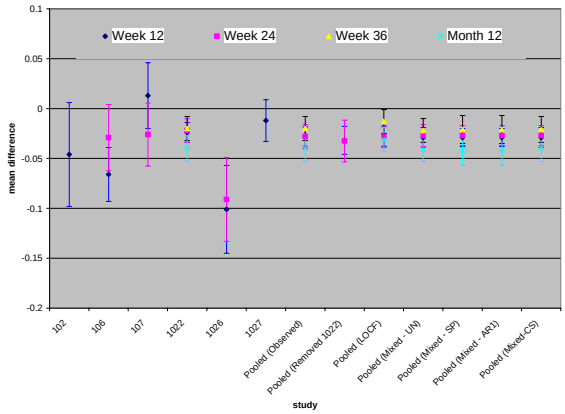


Figure 5: Treatment Difference in FVC (L) in Controlled Phase 2/3 Studies in Adults Type 1Diabetes

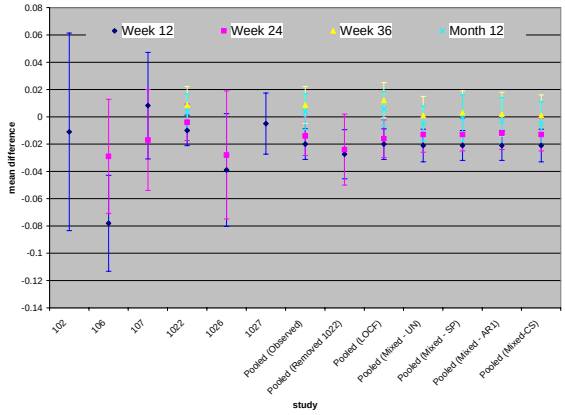


Figure 6: Treatment Difference in FRC (L) in Controlled Phase 2/3 Studies in Adults Type 1Diabetes

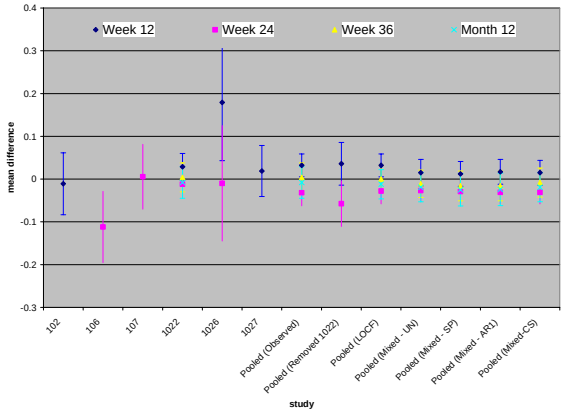


Figure 7: Treatment Difference in TLC (L) in Controlled Phase 2/3 Studies in Adults Type 1Diabetes

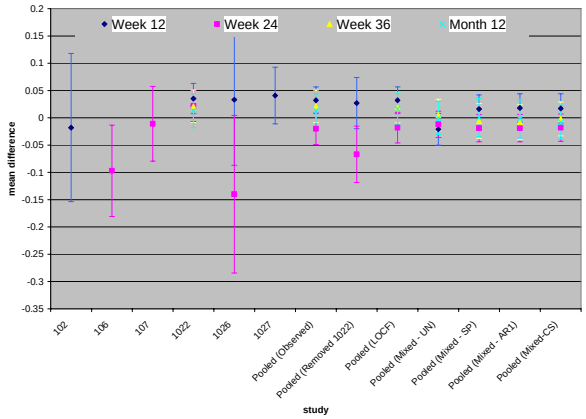


Table 8: Comparison of Covariance Models in Pooled Adult Type 1 Data

PFT	Variance-Covariance Structure	AIC	AICC	BIC	-2RLL
DLC	Spatial Power	12550.0	12550.0	12570.9	12542.0
	Unstructured	12419.7	12419.8	12497.9	12389.7
	AR(1) (no random)	12546.5	12546.5	12556.9	12542.5
	Compound	12428.5	12428.5	12438.9	12424.5
FEV	Spatial Power	-3135.1	-3135.1	-3114.2	-3143.1
	Unstructured*	-3235.8	-3235.8	-3235.8	-3235.8
	AR(1) no random	-3133.9	-3133.9	-3123.5	-3137.9
	Compound	-3232.3	-3232.3	-3221.9	-3236.3
FRC	Spatial Power	2691.8	2691.8	2712.7	2683.8
	Unstructured	2531.9	2532.1	2610.1	2501.9
	AR(1) no random	2697.0	2697.0	2707.4	2693.0
	Compound	2557.4	2557.4	2567.8	2553.4
FVC	Spatial Power	-2122.9	-2122.9	-2102	-2130.9
	Unstructured	-2330.4	-2330.2	-2252.1	-2360.4
	AR(1) no random	-2125.3	-2125.3	-2114.8	-2129.3
	Compound	-2226.8	-2226.8	-2216.4	-2230.8
TLC	Spatial Power	2274.7	2274.7	2295.6	2266.7
	Unstructured	2053.9	2054.0	2132.1	2023.9
	AR(1) no random	2272.3	2272.3	2282.7	2268.3
	Compound	2082.5	2082.6	2093.0	2078.5

* requests an unstructured R matrix be estimated from the sum-of-squares-and-crossproducts matrix of the residuals since it appears that the default REML estimate is too slow and not converging.

In the following discussion, the results from the pooled analysis on each of the PFT measurements will be summarized.

Forced Expiratory Volume in 1 second (FEV_1)

From the individual studies, there appears to be small declines in mean FEV1 among INH- and comparator-treated subjects over 12, 24 weeks, up to 96 weeks (2 years) of exposure, with small but consistent treatment group differences favoring the comparator. This was supported for most part by the confidence interval for these changes. Note that the treatment group differences for FEV1 remained fairly constant and did not increase.

In the pooled data set, similar treatment group differences in mean change from baseline in FEV1 favoring comparator therapy are apparent among adult subjects with type 1 after 3 months of therapy. The treatment group differences remained fairly constant and only increased slightly after their first post-baseline measurement and these differences remained comparable at subsequent time points, which the applicant claims, supports the effect of INH on FEV1 is not progressive (Table 9, Table 10; Figure 8). The results were fairly robust when the adjusted model was used. Thus, the treatment differences were of a magnitude of about 40 mL for FEV1 at the end of the study.

Note that since most of the data in the pooled studies after week 24 are from Study 1022, the results from the Pooled analysis and from Study 1022 are fairly consistent.

Figure 8: Mean Change from Baseline in FEV_1 (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

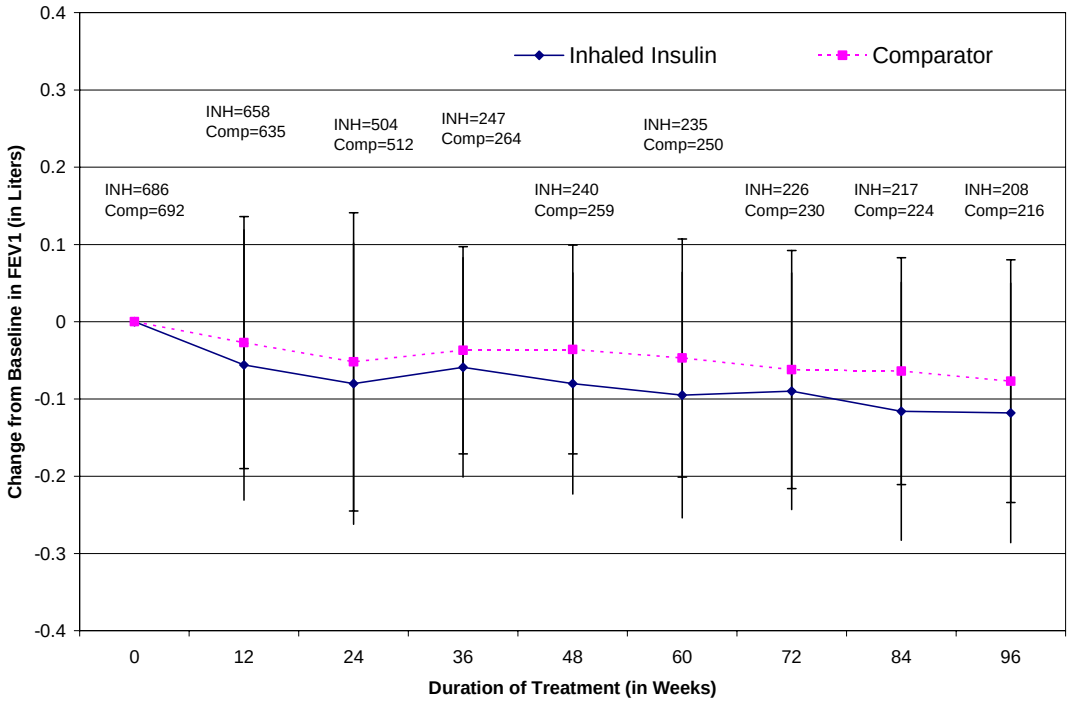


Table 9: Mean Change from Baseline in FEV1 Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	686	3.484	0.786				
	Week 12	658	3.434	0.782	-0.056	0.175	-0.029	-0.047, -0.011
	Week 24	504	3.442	0.772	-0.080	0.182	-0.029	-0.052, -0.006
	Week 36	247	3.473	0.740	-0.059	0.142	-0.022	-0.046, 0.002
	Week 48	240	3.465	0.733	-0.080	0.143	-0.044	-0.069, -0.020
	Week 60	235	3.450	0.760	-0.095	0.159	-0.047	-0.075, -0.019
	Week 72	226	3.457	0.742	-0.090	0.153	-0.029	-0.057, -0.0004
	Week 84	217	3.446	0.755	-0.116	0.167	-0.052	-0.082, -0.023
	Week 96	208	3.465	0.749	-0.118	0.168	-0.041	-0.072, -0.010
Comparator	Baseline	692	3.454	0.776				
	Week 12	635	3.436	0.783	-0.027	0.163		
	Week 24	512	3.442	0.789	-0.052	0.193		
	Week 36	264	3.432	0.789	-0.037	0.134		
	Week 48	259	3.432	0.770	-0.036	0.135		
	Week 60	250	3.424	0.767	-0.047	0.154		
	Week 72	230	3.426	0.800	-0.062	0.154		
	Week 84	224	3.423	0.777	-0.064	0.147		
	Week 96	216	3.400	0.788	-0.077	0.157		

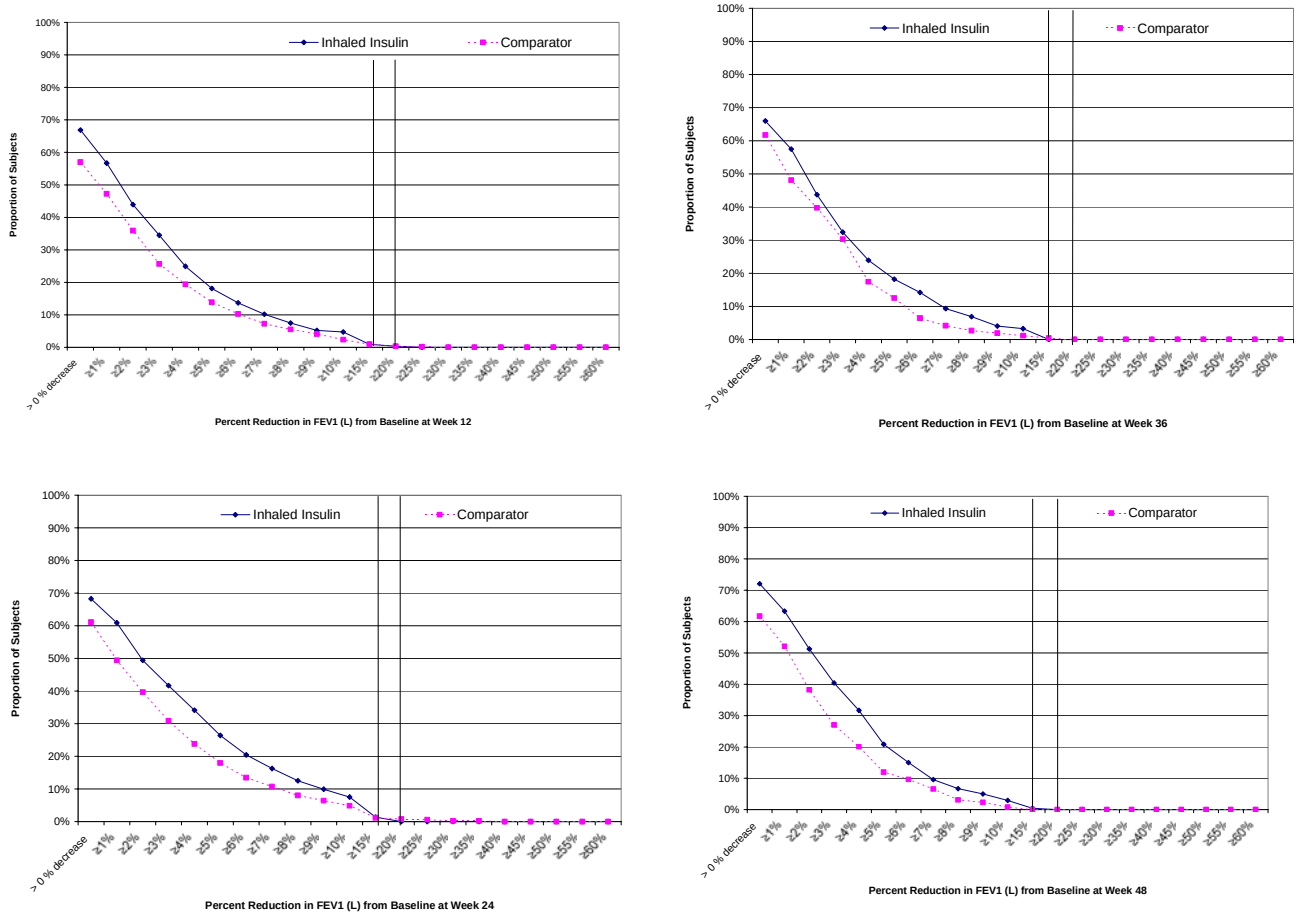
Table 10: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FEV1 Score in Controlled Phase 2/3 Studies in Type 1 Adults

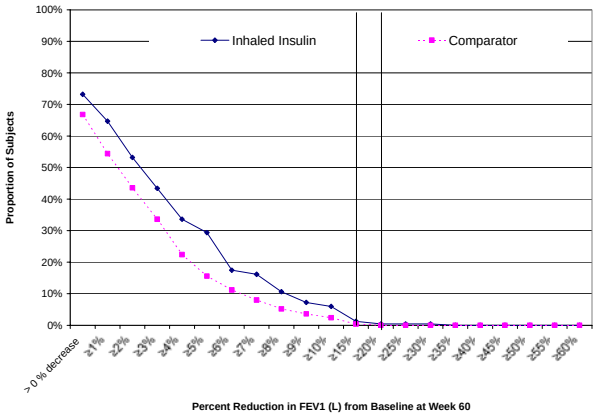
	Unadjusted		Adjusted*		Adjusted**	
Week	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	-0.029	-0.047, -0.011	-0.029	-0.047, -0.011	-0.028	-0.046, -0.011
24	-0.029	-0.052, -0.006	-0.027	-0.047, -0.008	-0.027	-0.046, -0.008
36	-0.022	-0.046, 0.002	-0.022	-0.048, 0.003	-0.021	-0.047, 0.004
48	-0.044	-0.069, -0.020	-0.045	-0.073, -0.017	-0.043	-0.071, -0.016
60	-0.047	-0.075, -0.019	-0.047	-0.076, -0.018	-0.046	-0.074, -0.017
72	-0.029	-0.057, -0.0004	-0.033	-0.063, -0.003	-0.032	-0.061, -0.002
84	-0.052	-0.082, -0.023	-0.051	-0.081, -0.020	-0.049	-0.079, -0.019
96	-0.041	-0.072, -0.010	-0.039	-0.071, -0.008	-0.038	-0.069, -0.007

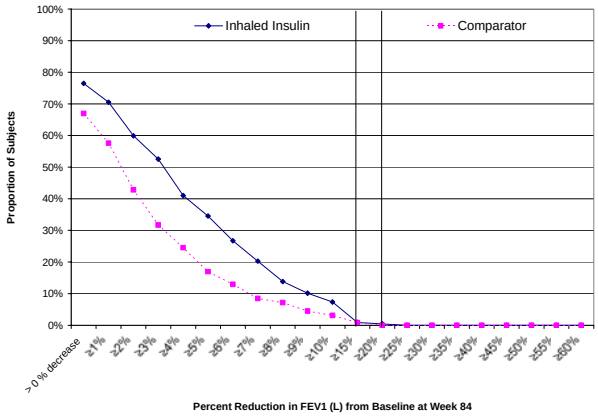
Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

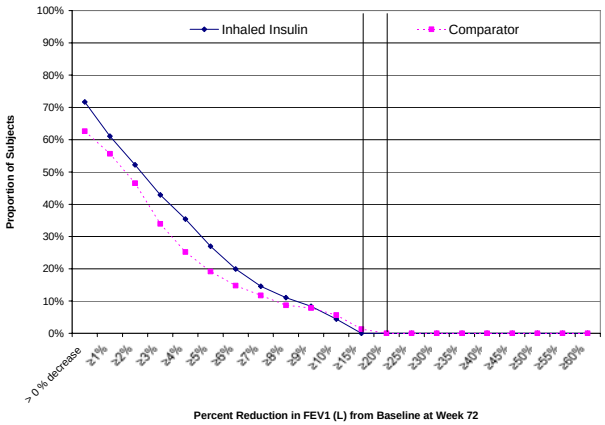
The proportions of subjects who had reduction in FEV1 from baseline at each timepoint (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions are presented in Figure 9. Inspection of these graphs suggests that there are apparent differences in the proportion of subjects who had reduction in FEV1 from baseline between the two treatment groups in favor of the comparator group. Note however, that these reductions are generally very small. In fact, only a small proportion of subjects (1% maximum) had reduction of more than 15%. Except for Week 36, there also appears to be an increasing proportion of subjects in the inhaled insulin group who had any reduction in FEV1 from baseline over time, while the comparator group remained fairly constant except at Week 96/104.

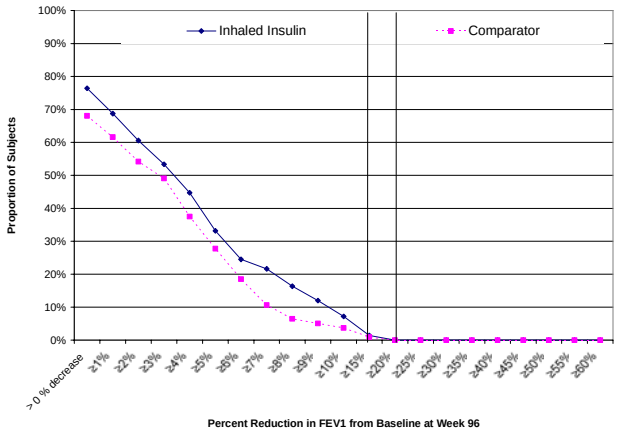
Figure 9: Proportion of Subjects by Percent Reduction from Baseline in FEV1 (L) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes




Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 (L) from Baseline at Week 60


Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 (L) from Baseline at Week 84


Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 (L) from Baseline at Week 72


Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 from Baseline at Week 96

Diffusion Lung Capacity (DLco)

From the individual studies, there appears to be decline during the first 12 weeks in mean change from baseline in DLco among INH- and comparator- treated subjects, but subsequent measurements remained steady up to 96 weeks (2 years) of exposure. In most of the individual studies, there was small but consistent treatment group differences favoring the comparator (Figure 3) and this was supported for most part by the confidence interval for these changes. Similar to the results from FEV1, the treatment group differences for Dlco remained fairly constant across time after week 12 (Week 96/104).

In the pooled data set, similar treatment group differences in mean change from baseline in DLco favoring comparator therapy are apparent among adult subjects with Type 1 diabetes after 3 months of therapy. The treatment group differences remained fairly close (ranged: -0.582 to -1.061) at subsequent time points, and had shown to be numerically smaller by the end of the study (Week 96/104), which the applicant claims, supports the effect of INH on DLco is also not progressive (Table 11, Table 12; Figure 10). The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 0.5 mL/min/mmHg for DLco at the end of the study.

Most of the data in the pooled studies after week 24 are from Study 1022, therefore the results from the Pooled analysis and from Study 1022 are fairly consistent

Figure 10: Mean Change from Baseline in DLco (mL/min/mmHg) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

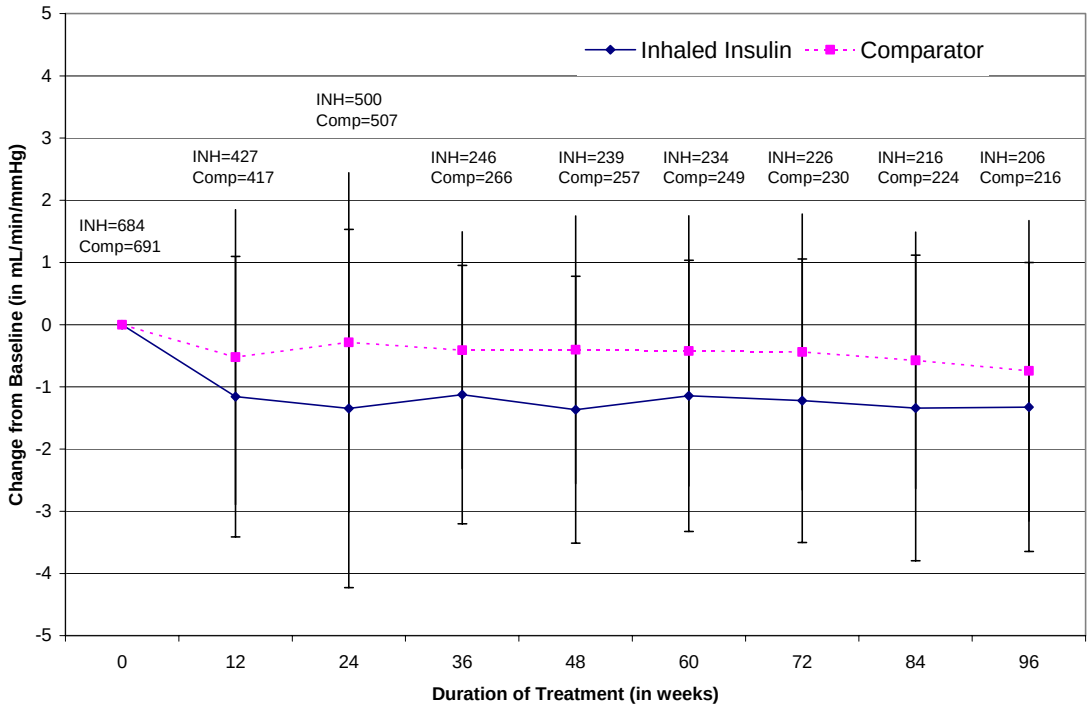


Table 11: Mean Change from Baseline in DLco Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	684	27.872	6.580				
	Week 12	427	26.733	6.284	-1.157	2.255	-0.634	-0.946, -0.321
	Week 24	500	26.898	6.257	-1.348	2.878	-1.061	-1.408, -0.715
	Week 36	246	26.998	6.064	-1.125	2.078	-0.714	-1.060, -0.368
	Week 48	239	26.931	6.004	-1.368	2.145	-0.964	-1.343, -0.584
	Week 60	234	27.170	6.178	-1.145	2.179	-0.723	-1.112, -0.334
	Week 72	226	27.070	6.029	-1.223	2.278	-0.783	-1.197, -0.370
	Week 84	216	27.083	6.053	-1.340	2.456	-0.765	-1.189, -0.341
	Week 96	206	27.089	5.974	-1.324	2.324	-0.582	-1.036, -0.128
Comparator	Baseline	691	27.521	6.552				
	Week 12	417	26.851	6.345	-0.523	2.371		
	Week 24	507	27.314	6.367	-0.286	2.730		
	Week 36	266	26.761	6.410	-0.411	1.904		
	Week 48	257	26.753	6.061	-0.404	2.152		
	Week 60	249	26.757	6.058	-0.422	2.173		
	Week 72	230	26.702	6.418	-0.439	2.218		
	Week 84	224	26.725	6.217	-0.575	2.062		
	Week 96	216	26.475	5.992	-0.742	2.415		

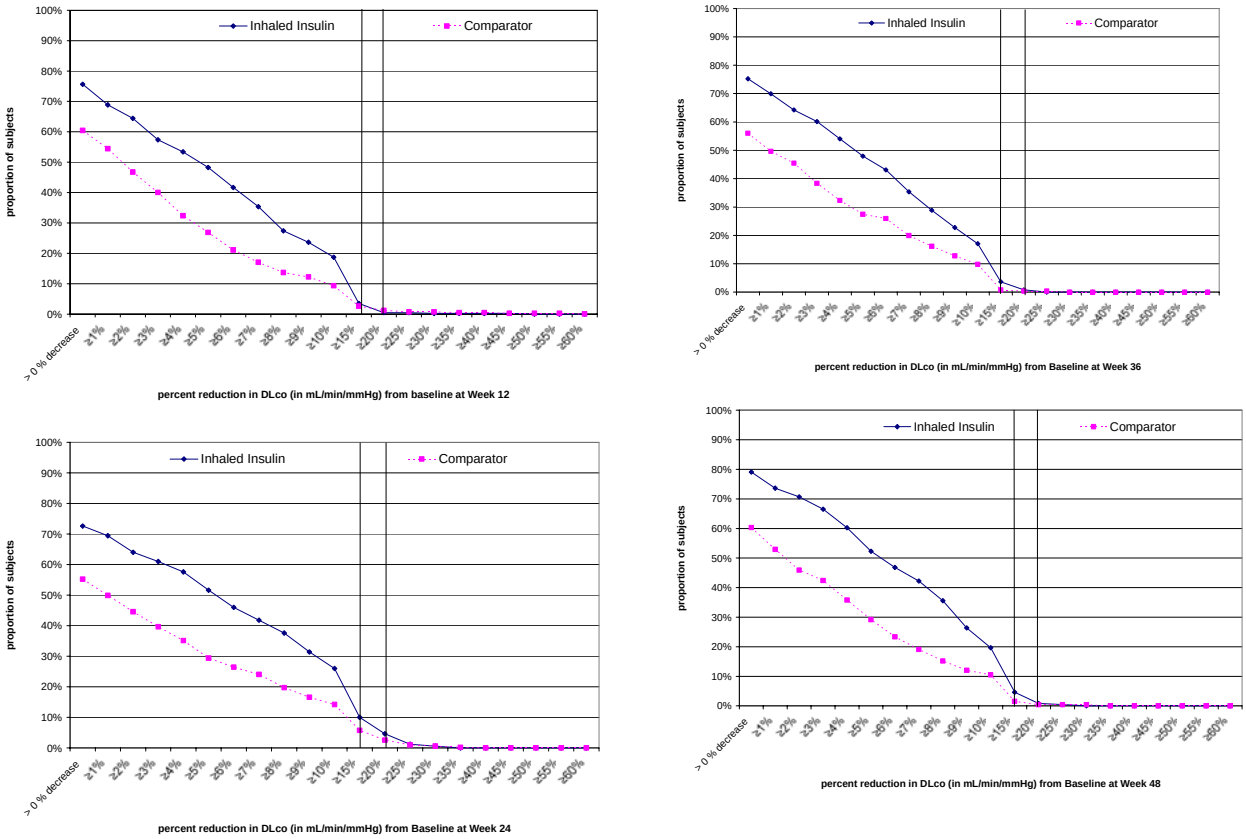
Table 12: Unadjusted and Sponsor-defined Adjusted Treatment Difference in DLco Score in Controlled Phase 2/3 Studies in Type 1 Adults

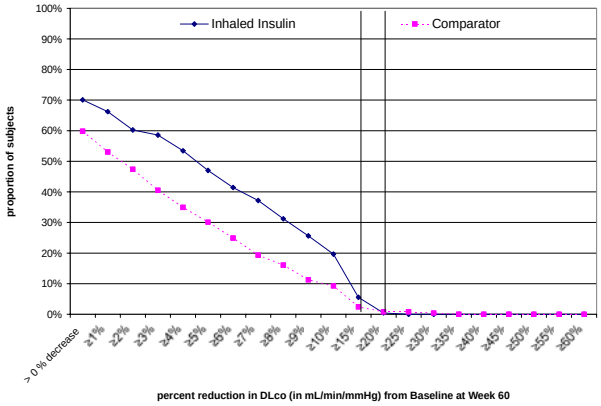
	Unadjusted		Adjusted*		Adjusted**	
Week	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	-0.634	-0.946, -0.321	-0.707	-1.023, -0.391	-0.680	-0.976, -0.384
24	-1.061	-1.408, -0.715	-0.995	-1.294, -0.696	-0.955	-1.233, -0.677
36	-0.714	-1.060, -0.368	-0.801	-1.178, -0.424	-0.716	-1.074, -0.359
48	-0.964	-1.343, -0.584	-1.008	-1.421, -0.594	-0.893	-1.283, -0.502
60	-0.723	-1.112, -0.334	-0.786	-1.220, -0.352	-0.653	-1.060, -0.246
72	-0.783	-1.197, -0.370	-0.718	-1.168, -0.268	-0.585	-1.005, -0.165
84	-0.765	-1.189, -0.341	-0.780	-1.241, -0.319	-0.646	-1.075, -0.216
96	-0.582	-1.036, -0.128	-0.645	-1.118, -0.171	-0.513	-0.953, -0.072

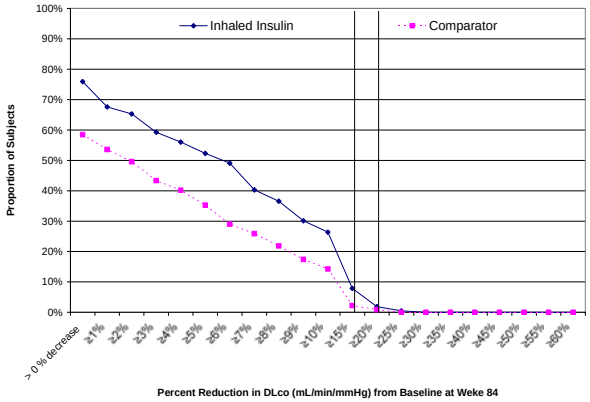
Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

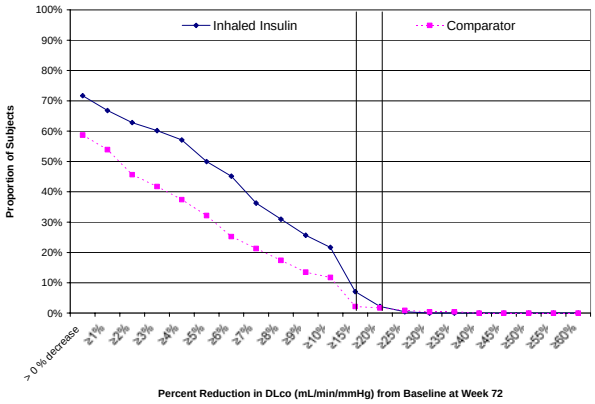
The proportions of subjects who had reduction in DLco at baseline at each timepoints (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions are presented in Figure 11. Inspection of these graphs suggests that there are apparent differences in the proportion of subjects who had reduction in DLco from baseline between the two treatment groups in favor of the comparator group. Although these reductions are generally very small (most subjects had at most 10% reduction), there are more subjects in the inhaled insulin group that had at least 15% reduction compared to the comparator group. The difference appears to be constant across different time intervals except for Week 96/104 in which there appears to be an upward shift (increase) in the proportion of subjects with any reduction in the comparator group. The reason for such increase is unknown.

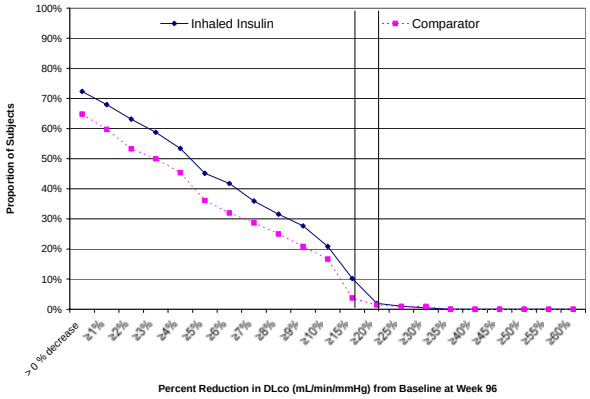
Figure 11: Proportion of Subjects by Percent Reduction from Baseline in DLco (mL/min/mmHg) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes




Inhaled Insulin
Comparator
proportion of subjects
percent reduction in DLco (in mL/min/mmHg) from Baseline at Week 60


Inhaled Insulin
Comparator
Proportion of Subjects
Percent Reduction in DLco (mL/min/mmHg) from Baseline at Weke 84


Inhaled Insulin
Comparator
Proportion of Subjects
Percent Reduction in DLco (mL/min/mmHg) from Baseline at Week 72


Inhaled Insulin
Comparator
Proportion of Subjects
Percent Reduction in DLco (mL/min/mmHg) from Baseline at Week 96

Forced Vital Capacity (FVC)

As seen from the individual studies, there appears to be a very small decline during the first 12 weeks in mean change from baseline in FVC among INH- and comparator- treated subjects, but measurements remained steady up to 96 weeks (2 years) of exposure. Treatment group differences were comparable between inhaled insulin group and the comparator group in the sense that all 95% confidence intervals included the zero difference, but numerically favored the comparator (Figure 5).

Similar conclusions can be drawn from the pooled data set. Treatment group differences were small and fairly consistent between the two treatment groups (Figure 12; Table 13, Table 14). The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 1 mL for FVC at the end of the study. Most of the data in the pooled studies after week 24 are from Study 1022, therefore the results from the Pooled analysis and from Study 1022 are fairly consistent.

The proportions of subjects who had reduction in FVC at baseline at each time points (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. In general, there are no differences in the proportion of subjects who had reduction in FVC from baseline between the two treatment groups. Furthermore, almost none had reduction of more than 15%.

Figure 12: Mean Change from Baseline in FVC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

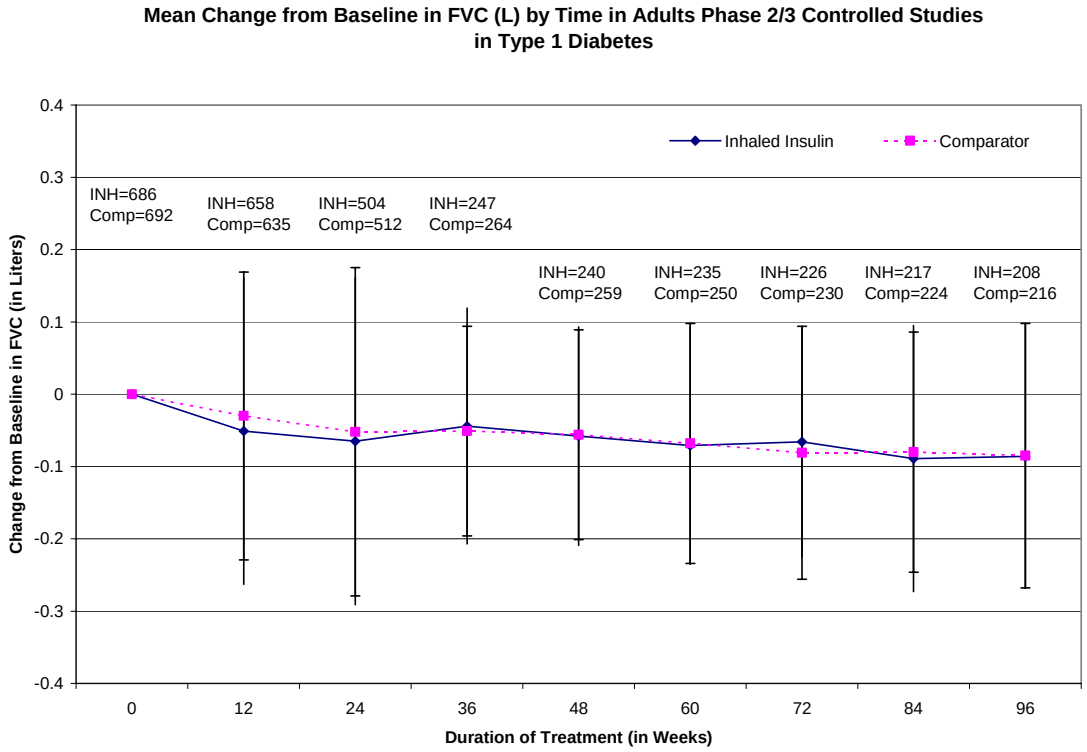


Table 13: Mean Change from Baseline in FVC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

			Observed		Change from Baseline		Inhaled - Comparator	
Treatment		N	Mean	SD	Mean	SD	Difference	95% CI
Inhaled	Baseline	686	4.338	1.006				
	Week 12	658	4.296	0.996	-0.051	0.212	-0.020	-0.043, 0.002
	Week 24	504	4.308	0.980	-0.065	0.226	-0.013	-0.041, 0.014
	Week 36	247	4.333	0.917	-0.044	0.163	0.007	-0.019, 0.034
	Week 48	240	4.336	0.919	-0.058	0.151	-0.002	-0.028, 0.024
	Week 60	235	4.326	0.936	-0.071	0.164	-0.003	-0.032, 0.027
	Week 72	226	4.335	0.923	-0.066	0.159	0.014	-0.016, 0.045
	Week 84	217	4.328	0.936	-0.089	0.184	-0.008	-0.041, 0.025
	Week 96	208	4.355	0.926	-0.086	0.182	-0.001	-0.036, 0.034
Comparator	Baseline	692	4.307	1.004				
	Week 12	635	4.293	1.003	-0.030	0.199		
	Week 24	512	4.291	1.027	-0.052	0.227		
	Week 36	264	4.256	0.983	-0.051	0.145		
	Week 48	259	4.254	0.968	-0.056	0.145		
	Week 60	250	4.244	0.961	-0.068	0.166		
	Week 72	230	4.240	0.992	-0.081	0.175		
	Week 84	224	4.251	0.980	-0.080	0.166		
	Week 96	216	4.239	0.986	-0.085	0.183		

Table 14: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FVC Score in Controlled Phase 2/3 Studies in Type 1 Adults

	Unadjusted		Adjusted*		Adjusted**	
Week	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	-0.020	-0.043, 0.002	-0.021	-0.043, 0.001	-0.021	-0.042, 0.000
24	-0.013	-0.041, 0.014	-0.012	-0.035, 0.011	-0.012	-0.035, 0.010
36	0.007	-0.019, 0.034	0.003	-0.027, 0.033	0.004	-0.026, 0.033
48	-0.002	-0.028, 0.024	-0.004	-0.037, 0.029	-0.003	-0.035, 0.029
60	-0.003	-0.032, 0.027	-0.004	-0.038, 0.030	-0.003	-0.036, 0.030
72	0.014	-0.016, 0.045	0.014	-0.021, 0.049	0.015	-0.019, 0.050
84	-0.008	-0.041, 0.025	-0.005	-0.042, 0.031	-0.004	-0.040, 0.031
96	-0.001	-0.036, 0.034	-0.002	-0.039, 0.035	-0.001	-0.037, 0.035

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

Forced Residual Capacity (FRC)

As seen from the individual studies, there appears to be a slow but steady decline over time in mean change from baseline in FRC among INH- and comparator- treated subjects. Treatment group differences were comparable between inhaled insulin group and the comparator group in the sense that all 95% confidence intervals included the zero difference, but numerically favored the comparator (Figure 6).

Similar conclusions can be drawn from the pooled data set. Treatment group differences were comparable between the two treatment groups. There appears to be a small separation between the two groups after Week 48 (Table 15, Table 16; Figure 13). The treatment differences were slightly bigger in the adjusted model, but they are still in the same direction as the unadjusted (i.e. favoring the comparator group). Thus, the treatment differences were of a magnitude of about 40 – 60 mL for FRC at the end of the study(taking into account the adjusted model).

Most of the data in the pooled studies after week 24 are from Study 1022 therefore the results from the Pooled analysis and from Study 1022 are fairly consistent.

Meanwhile, the proportions of subjects who had reduction in FRC at baseline at each time points (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. Inspection of each individual graph (by time points) suggests that at Week 12, there was no difference in the reduction profile of subjects in the inhaled insulin group and the comparator group. However, at Week 48 and onwards, the curves began to separate, and shows that there was some evidence of greater proportion of subjects in the inhaled insulin group who had a greater reduction in FRC compared to the comparator. Although reductions in FRC score were generally small, there were quite a few in both treatment groups (almost 20% in each group) that had reduction of more than 15%.

Figure 13: Mean Change from Baseline in FRC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

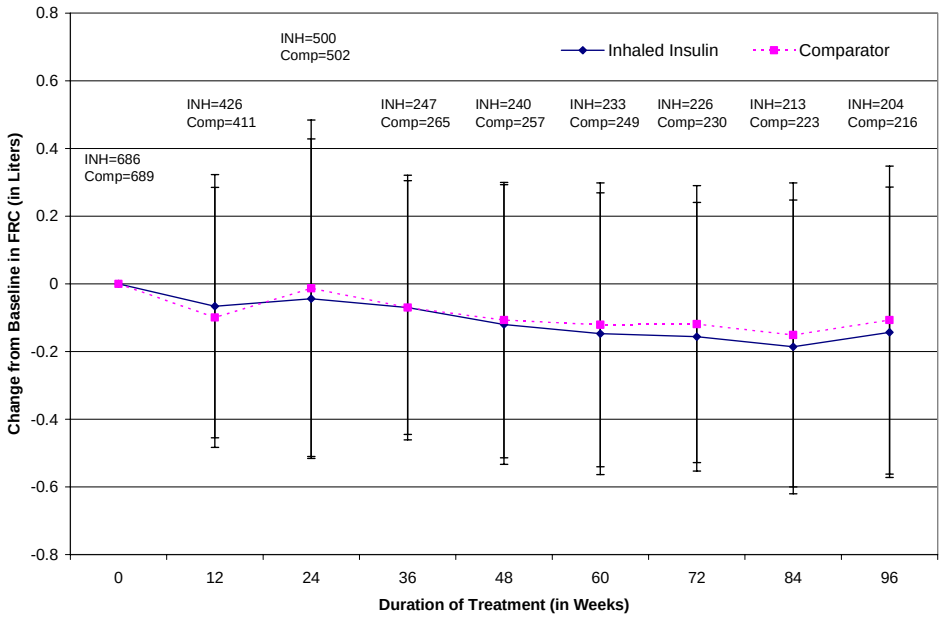


Table 15: Mean Change from Baseline in FRC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

			Observed		Change from Baseline		Inhaled - Comparator	
Treatment		N	Mean	SD	Mean	SD	Difference	95% CI
Inhaled	Baseline	686	2.991	0.861				
	Week 12	426	2.935	0.860	-0.066	0.389	0.033	-0.019, 0.086
	Week 24	500	2.976	0.818	-0.044	0.472	-0.031	-0.091, 0.029
	Week 36	247	2.929	0.831	-0.070	0.375	0.00003	-0.067, 0.067
	Week 48	240	2.900	0.833	-0.120	0.413	-0.012	-0.085, 0.060
	Week 60	233	2.881	0.801	-0.147	0.416	-0.026	-0.101, 0.049
	Week 72	226	2.880	0.816	-0.156	0.397	-0.037	-0.111, 0.037
	Week 84	213	2.833	0.823	-0.186	0.434	-0.035	-0.118, 0.048
	Week 96	204	2.902	0.818	-0.143	0.429	-0.037	-0.122, 0.048
Comparator	Baseline	689	3.020	0.857				
	Week 12	411	2.926	0.845	-0.099	0.384		
	Week 24	502	3.036	0.900	-0.013	0.497		
	Week 36	265	2.982	0.857	-0.070	0.391		
	Week 48	257	2.935	0.762	-0.107	0.407		
	Week 60	249	2.930	0.810	-0.121	0.419		
	Week 72	230	2.933	0.820	-0.119	0.409		
	Week 84	223	2.916	0.817	-0.151	0.449		
	Week 96	216	2.974	0.822	-0.107	0.455		

Table 16: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FRC Score in Controlled Phase 2/3 Studies in Type 1 Adults

	Unadjusted		Adjusted*		Adjusted**	
Week	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	0.033	-0.019, 0.086	0.014	-0.042, 0.070	0.002	-0.051, 0.055
24	-0.031	-0.091, 0.029	-0.030	-0.082, 0.023	-0.046	-0.095, 0.004
36	0.00003	-0.067, 0.067	-0.016	-0.083, 0.051	-0.032	-0.096, 0.032
48	-0.012	-0.085, 0.060	-0.029	-0.103, 0.044	-0.045	-0.115, 0.025
60	-0.026	-0.101, 0.049	-0.033	-0.110, 0.043	-0.048	-0.121, 0.024
72	-0.037	-0.111, 0.037	-0.040	-0.119, 0.039	-0.055	-0.129, 0.019
84	-0.035	-0.118, 0.048	-0.044	-0.125, 0.037	-0.061	-0.137, 0.015
96	-0.037	-0.122, 0.048	-0.041	-0.124, 0.041	-0.058	-0.136, 0.020

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

Total Lung Capacity (TLC)

As seen from the individual studies, there appears to be minimal to no decline in mean change from baseline in TLC among INH-treated group, while there appears to be very small decline in the comparator-treated subjects. These observations were consistent over time up to 96 weeks (2 years) of exposure. In the individual studies, treatment group differences were comparable between the inhaled insulin group and the comparator group, but it slightly favored the inhaled insulin group particularly in Studies 1022, 1026 and 1027 (Figure 7).

Similar conclusions can be drawn from the pooled data set. Treatment group differences were comparable between the two treatment groups (Figure 14), but from Table 17 and Table 18, there is a small numerical difference between the two groups favoring the inhaled insulin group except at Week 24. This appears to be not statistically meaningful and the differences could be due to random variation. The treatment differences shifted slightly in the adjusted model favoring the comparator group at Weeks 36, 48, 72, and 84. Since the actual differences are very small, this shift is not surprising at all. Thus, the treatment differences were of a magnitude of about 6 - 18 mL for TLC by the end of the study favoring the inhaled insulin group (taking into account the adjusted model).

Most of the data in the pooled studies after week 24 are from Study 1022, therefore the results from the Pooled analysis and from Study 1022 are fairly consistent except at Week 24. The small difference at Week 24 could be due to Studies 106 and 107 that have Week 24 data and showed a more favorable comparator group. Nonetheless, it appears that treatment difference in TLC slightly favored the inhaled insulin group.

Figure 14: Mean Change from Baseline in TLC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

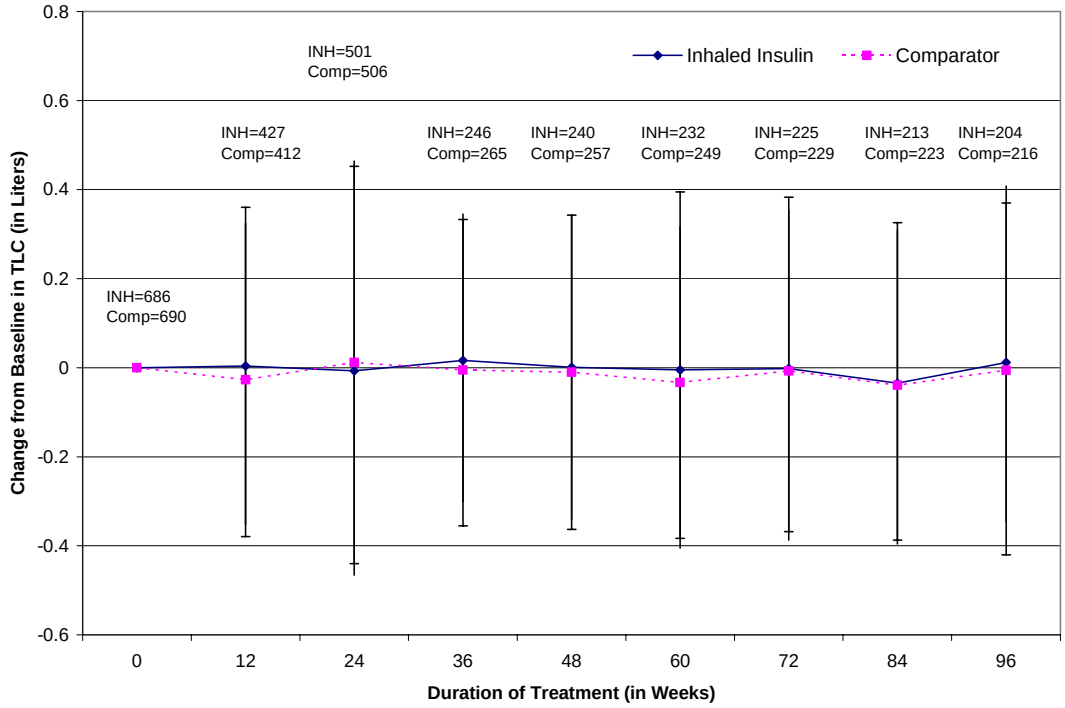


Table 17: Mean Change from Baseline in TLC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

			Observed		Change from Baseline		Inhaled - Comparator	
Treatment		N	Mean	SD	Mean	SD	Difference	95% CI
Inhaled	Baseline	686	5.927	1.316				
	Week 12	427	5.901	1.322	0.004	0.356	0.031	-0.017, 0.079
	Week 24	501	5.963	1.283	-0.007	0.459	-0.019	-0.076, 0.037
	Week 36	246	5.870	1.248	0.016	0.317	0.021	-0.038, 0.079
	Week 48	240	5.888	1.253	0.0006	0.342	0.011	-0.050, 0.072
	Week 60	232	5.897	1.261	-0.005	0.400	0.028	-0.039, 0.095
	Week 72	225	5.901	1.238	-0.002	0.385	0.006	-0.063, 0.075
	Week 84	213	5.853	1.240	-0.035	0.361	0.004	-0.063, 0.070
	Week 96	204	5.953	1.239	0.012	0.358	0.018	-0.057, 0.092
Comparator	Baseline	690	5.916	1.334				
	Week 12	412	5.822	1.282	-0.027	0.352		
	Week 24	506	5.971	1.383	0.012	0.452		
	Week 36	265	5.816	1.302	-0.005	0.350		
	Week 48	257	5.810	1.260	-0.010	0.353		
	Week 60	249	5.799	1.279	-0.033	0.350		
	Week 72	229	5.824	1.300	-0.007	0.361		
	Week 84	223	5.822	1.295	-0.039	0.348		
	Week 96	216	5.878	1.292	-0.006	0.414		

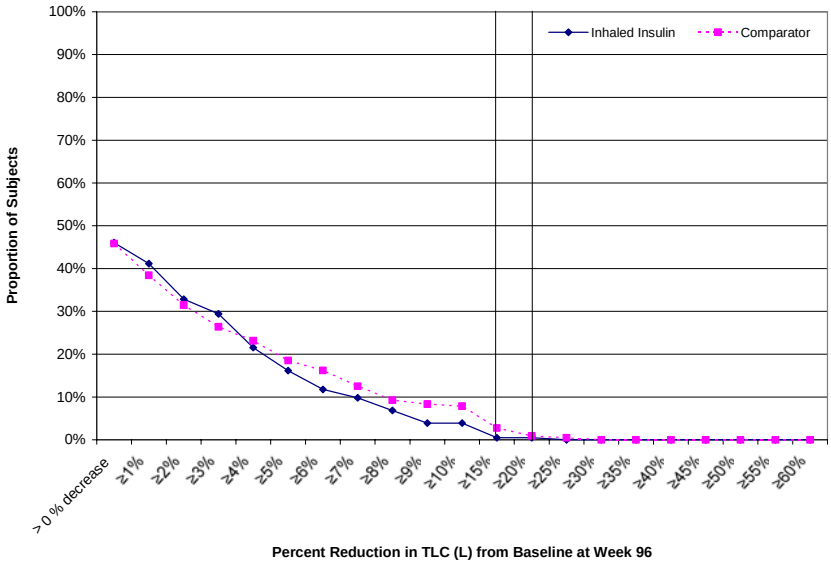
Table 18: Unadjusted and Sponsor-defined Adjusted Treatment Difference in TLC Score in Controlled Phase 2/3 Studies in Type 1 Adults

	Unadjusted		Adjusted*		Adjusted**	
Week	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	0.031	-0.017, 0.079	0.014	-0.037, 0.065	0.008	-0.042, 0.057
24	-0.019	-0.076, 0.037	-0.019	-0.066, 0.029	-0.029	-0.074, 0.018
36	0.021	-0.038, 0.079	-0.007	-0.069, 0.055	-0.016	-0.077, 0.044
48	0.011	-0.050, 0.072	-0.004	-0.071, 0.063	-0.013	-0.078, 0.053
60	0.028	-0.039, 0.095	0.024	-0.046, 0.094	0.016	-0.052, 0.083
72	0.006	-0.063, 0.075	0.005	-0.068, 0.077	-0.004	-0.073, 0.066
84	0.004	-0.063, 0.070	-0.002	-0.076, 0.072	-0.011	-0.083, 0.060
96	0.018	-0.057, 0.092	0.017	-0.059, 0.092	0.006	-0.067, 0.079

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

The proportions of subjects who had reduction in TLC at baseline at each time points (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. Inspection of each individual graphs (by time points) suggests that the reduction profile of subjects is more in favor of the inhaled insulin group than the comparator group, particularly at the end of the study (Figure 15). Note however that these differences in proportions of subjects with some reductions in TLC score were generally small. There were only a few subjects in both treatment groups that had reduction of more than 15%.

Figure 15: Proportion of Subjects by Percent Reduction from Baseline in TLC (L) at Week 96 in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes



Pulmonary Function Test and Antibody Titer

One of the requests from Dr. Seymour is to assess at the relationship between the change in pulmonary function tests and the antibody titer. To explore this relation, I evaluated the change from baseline of PFT measurements with the antibody titer at that specific week using both the Pooled Data and Study 1022 (one-year interim) for this exercise. A regression line, to assess the relationship between the change from baseline of PFT measurements and the antibody titer, was plotted for the inhaled insulin-treated group. Note that since there is no increase in the antibody titer in the comparator group, no regression line was drawn. Correlation coefficients were calculated to indicate how the antibody titers are related to the change in PFT measurements. A negative correlation (or slope) implies decreased lung function with increased antibody titers, while a positive correlation (slope) implies increased (better) lung function with decreased antibody titers.

There is no evidence of any strong correlation between the change from baseline in pulmonary function tests and antibody titers. There might be some small negative correlation in terms of DLco, FRC, and TLC, but the correlations were not large enough to warrant a concern. Alternatively, there appears to be some small positive correlation in terms of FEV1 and FVC, but again these are small. It does not appear that the correlation increases or decreases over time, however there were numerically larger correlation at Week 36. As expected, the figures and the correlation coefficients are the same in the Pooled Study and Study 1022 after Week 24. There were slight differences in the direction and the magnitude at Week 24, but this could be due to more samples/studies in the population that have Week 24 data.

Pulmonary Function Test and Insulin Dose

Another request from Dr. Seymour is to look at the relationship between the change in pulmonary function tests and the dosing. The focus of interest is on short-acting drug. To explore this relationship, I looked at the change from baseline of PFT measurements with subject-reported average daily insulin doses by week. Average daily dose, according to the applicant, is calculated based on the average dose between the day of the previous visit and the day before the present visit. I also looked at the relationship between the change from baseline of PFT measurements and the subject's cumulative daily insulin doses by visit window. The cumulative dose was calculated based on the cumulative average daily insulin doses accounting for the number of days in the study. I looked at both Study 106 and Study 1022 (one-year interim) for this exercise. Because of the different study drugs (particularly on the comparator group) that the subjects were treated to, it is hard to look at the pooled data. Scatterplots and regression lines were drawn, and correlation coefficients were calculated.

Overall, it appears that there is no strong correlation between the change from baseline in any of the pulmonary function test and the average total or cumulative total daily dose in both inhaled insulin and comparator insulin. However, it is important to note that in DLco after Week 24, change from baseline in any of the pulmonary function test and the average total or cumulative total daily dose in the inhaled insulin group appears to be negatively correlated, but the correlation is not strong enough to warrant any claim. Meanwhile, the comparator-treated group appears to show a negative correlation between the change from baseline in FRC and the average total or cumulative total daily dose. It does not appear that the correlation increases or decreases over time.

II. Type 2 Data

Demographic Characteristics:

Demographic characteristics of subjects in the pooled Type 2 data are comparable between the two treatment groups. Majority of the subjects was white. There appears to be more males in each of the treatment group across all studies. The male subjects were heavier and were taller than females in each of the treatment group. Age appears to be comparable between males and females *(*Table 19*)*.

Table 19: Demographic Characteristics of Adults Type 2 Data

	Inhaled Insulin		Comparator	
Variables	Male	Female	Male	Female
No. of Subjects*	791	478	660	461
Age (years)	57 (9.3)	57 (9.6)	56 (9.9)	56 (10.4)
Race (White)	647 (82%)	391 (82%)	552 (84%)	359 (78%)
Weight (kg)	92 (15.5)	81 (13.9)	91 (15.0)	82 (15.5)
Height (cm?)	176 (7.4)	161 (6.6)	175 (7.3)	162 (7.2)
BMI	30 (4.2)	31 (4.7)	30 (4.2)	31 (5.1)

* No. of Subjects are slightly smaller than the total number who were randomized in the studies. Includes only subjects who were treated and have PFT measurements.

Respiratory Adverse Events:

Respiratory adverse events by individual studies are presented in Table 20. In the pooled study, the number of subjects with respiratory events, as expected, was higher in the inhaled insulin group compared to the comparator group (Figure 16). Using preferred COSTART term and severity for all-causality adverse events, the proportion of subjects with respiratory system adverse events was generally slightly higher in the inhaled insulin group than the comparator groups, particularly on increased cough (INH 21% vs. Comparator 5%). There were also more subjects with dyspnea, rhinitis, pharyngitis, and sputum increased (Figure 17). The most common respiratory system adverse event was respiratory tract infection and this was comparable between the two treatment groups.

Almost all respiratory system adverse events were either mild or moderate in severity. There are a total of 28 subjects out of 1277 (2%) who **permanently discontinued** due to respiratory events in the inhaled insulin group, while 2 out of 1132 (0.1%) in the comparator group (Table 21). These events include asthma, bronchitis, carcinoma of the lung, increased cough, dyspnea, respiratory disorder, sputum increased, pharyngitis, and respiratory tract infection. Most of these events were considered mild to moderate except two subjects with severe asthma, one with severe cough, one with severe bronchitis, one with severe carcinoma of the lung, and one with severe shortness of breath in the inhaled insulin group, and finally, in the comparator group, one subject had severe carcinoma of the lung and one had severe respiratory tract infection.

Table 20: Number of subjects (%) with Respiratory adverse events for all Adults Type 2 DM Subjects: All Causality

	Study 103		Study 104		Study 108		Study 109		Study 110		Study 1029		Study 1001 – 1002	
	INH	Comp	INH	Comp	INH	Comp	INH	Comp	INH	Comp	INH	Comp	INH	Comp
No. of Subjects	28	28	33	36	149	149	207	99	75	68	314	311	471	441
Total Respiratory	20 (71)	15 (54)	17 (52)	14 (39)	94 (63)	68 (46)	107 (52)	30 (30)	35 (47)	26 (38)	247 (79)	196 (63)	219 (46)	149 (34)
Apnea													1 (0)	0
Asthma	1 (4)	0			5 (3)	1 (1)	1 (0)	0			12 (4)	7 (2)	6 (1)	3 (1)
Atelectasis					0	1 (1)								
Bronchiectasis					0	1 (1)								
Bronchiolitis														
Bronchitis	0	2 (7)			4 (3)	4 (3)	4 (2)	2 (2)	2 (3)	1 (2)	26 (8)	11 (4)	25 (5)	23 (5)
Cough Increased	12 (43)	1 (4)	5 (15)	3 (8)	32 (22)	4 (3)	27 (13)	2 (2)	6 (8)	1 (2)	115 (37)	31 (10)	1 (0)	1 (0)
Dyspnea	1 (4)	0			9 (6)	1 (1)	2 (1)	0	3 (4)	1 (2)	13 (4)	8 (3)	71 (15)	18 (4)
Edema Pharynx											1 (0)	0	14 (3)	8 (2)
Emphysema					0	1 (1)								
Epistaxis					2 (1)	0	2 (1)	1 (1)	2 (3)	0	6 (2)	2 (1)	1 (0)	0
Hemoptysis					1 (1)	0							3 (1)	4 (1)
Hyperventilation														
Hypoventilation														
Laryngitis			0	1 (3)	0	1 (1)	1 (0)	0			4 (1)	1 (0)		
Lung Disorder							1 (0)	0			2 (1)	1 (0)	2 (0)	1 (0)
Lung Edema					1 (1)	0								
Nasal Polyp													0	1 (0)
Pharyngitis	7 (25)	2 (7)	3 (9)	3 (8)	14 (9)	11 (7)	18 (9)	7 (7)	4 (5)	2 (3)	37 (12)	30 (10)		
Pleural Disorder											0	1 (0)	36 (8)	26 (6)
Pneumonia					1 (1)	4 (3)					2 (1)	2 (1)		
Respiratory Disorder	4 (14)	4 (14)	2 (6)	1 (3)	8 (5)	8 (5)	11 (5)	3 (3)	5 (7)	1 (2)	25 (8)	29 (9)	8 (2)	4 (1)
Respiratory Distress Syndrome					0	1 (1)							10 (2)	6 (1)
Respiratory Tract Infection	4 (14)	7 (25)	5 (15)	8 (22)	48 (32)	40 (27)	49 (24)	19 (19)	19 (25)	19 (28)	130 (41)	119 (38)		
Rhinitis	4 (14)	5 (18)	4 (12)	1 (3)	13 (9)	13 (9)	17 (8)	2 (2)	5 (7)	3 (4)	40 (13)	28 (9)	102 (22)	81 (18)
Sinusitis	2 (7)	0	3 (9)	2 (6)	6 (4)	7 (5)	9 (4)	2 (2)	5 (7)	2 (3)	31 (10)	34 (11)	20 (4)	13 (3)
Sputum Increased	0	1 (4)			6 (4)	0	5 (2)	0	1 (1)	0	9 (3)	3 (1)	9 (2)	9 (2)
Voice Alteration					3 (2)	0	3 (1)	0	1 (1)	0	3 (1)	0	13 (3)	3 (1)
Yawn														

Source: Study Report 217-103, 104, 108, 109, 110, combined 1001 and 1002, and 1029

Figure 16: Total Percentage Respiratory Adverse Events by Individual and Pooled Controlled Phase 2/3 Studies in Type 2 Adults

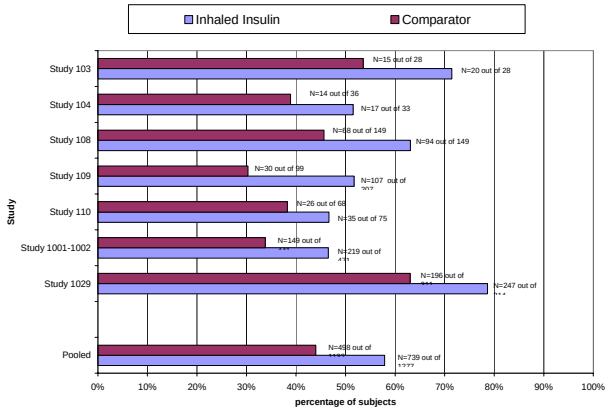


Figure 17: Respiratory Events by Treatment Group, Pooled Type 2 Controlled Phase 2/3 *Studies*

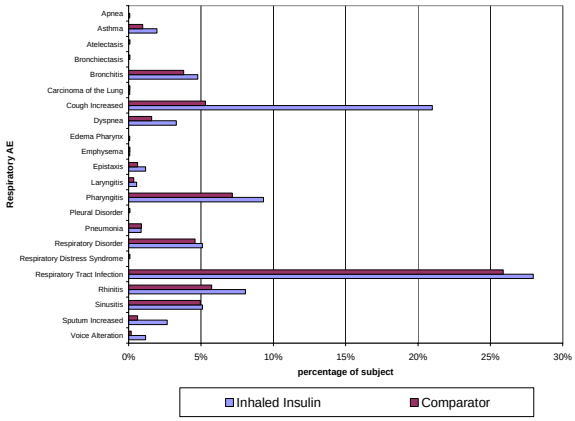


Table 21: Respiratory Adverse Events Resulting in Discontinuation from Individual Study

Study	Treatment Group	Subject	Severity	Adverse Event Preferred COSTART/Investigator Term
103	INH	5002 0002	Moderate	Increased Cough
109	INH	5026 0133	Mild	Respiratory Tract Infection
109	INH + 0A	5043 0031	Severe	Dyspnea/Shortness of Breath
110	INH	5103 1426	Moderate	Bronchitis
1001	INH	0018 0060	Mild	Cough increased
1001	INH	0049 0107		Bronchitis
1001	INH	0141 2043	Mild	Asthma
1002	INH	0037 5063		Asthma
1002	INH	0047 7049		Cough Increased
1002	INH	0048 5005		Cough Increased
1002	INH	0074 5150		Cough Increased
1002	INH	0108 6285		Dyspnea
1002	INH	0110 6223		Respiratory Tract Infection, Sputum Increased
1002	INH	0119 5236	severe	Carcinoma of the lung
1002	INH	0134 5269		Cough Increased
1002	INH	0141 8036		Cough Increased
1002	INH	0142 7408		Cough increased, dyspnea
1002	OA	0083 5165	severe	Carcinoma of the lung
1029	INH	1025 1913	Severe	Asthma
1029	INH	1029 788	Mild	Cough Increased
1029	INH	1045 2319	Severe	Asthma, possible bronchospasm, (reaction to INH)
				Cough Increased
			Moderate	Respiratory Tract Infection
			Moderate	
1029	INH	1065 2783	Mild	Cough Increased
			Mild	Respiratory disorder
1029	INH	1068 1197	Moderate	Asthma
1029	INH	1083 3445	Moderate	Asthma/Bronchospasm
			Moderate	Cough Increased
			Moderate	Dyspnea
1029	INH	1085 3552	Moderate	Dyspnea
1029	INH	1105 4681	Mild	Pharyngitis
1029	INH	1113 5158	Mild	Asthma

Chest X-ray

In the six Type 2 DM clinical studies with chest X-ray (Studies 108, 109, 110, 1001, 1002 and 1029), only a very small proportion of subjects who had chest X-rays taken at final observation had abnormal findings compared to baseline. However, it appears that the incidences of change in chest x-ray results between baseline and last observation were greater numerically in the INH than the comparator treatment groups (INH 46, Comparator 25).

In terms of HRCT, only selected sites, from the two Type 2 DM clinical studies (Study 108 and Study 1029), had HRCT scan. It appears that there is only six subjects in the inhaled insulin group with more abnormal HRCT, while there are 11 (2 from Study 108 and 9 from Study 1029) in the comparator group who had more abnormal HRCT scan.

Pulmonary Function Test:

In Type 2 Adults studies, pulmonary function was monitored in Studies 103, 104, 108, 109, 110, 1001, and 1002 using non- standardized methodologies available in local PFT laboratories. These studies were short-term studies, usually 3 or 6 months of exposure, except for 1001 and 1002 which are two-year studies. Pulmonary function has also been monitored in Study 1029 in which standardized pulmonary testing equipment, testing procedures, and centralized data analysis were used to measure PFTs.

As noted earlier, to simplify the discussion of pulmonary safety, subjects are grouped based on the treatment actually received. Subjects treated with INH with or without subcutaneous basal insulin, or oral antidiabetic agents (OAs) are considered to be INH- treated subjects. Subjects treated with subcutaneous short-acting (SC) insulin or with OAs alone are considered to be Comparator-treated subjects.

To begin, comparison of the mean baseline values between the two treatment groups and the percent predicted at baseline are presented in Table 22. It appears that mean baseline values and the % predicted mean values at baseline are comparable between the treatment groups across all pulmonary function tests. As noted previously in the individual studies Section, there is one questionable % predicted value in Study 109 on DLco (Subject 109 50600668). That subject's % predicted value is 1302.9 at baseline and 1346.1 at week 12. This is the reason why the mean % predicted value and its standard deviation in the INH group is slightly higher than the comparator group.

Table 22: Baseline PFT Measurements and Percent Predicted Mean Values at Baseline in Pooled Controlled Phase 2/3 Studies in Adults Type 2 Diabetes

	INH			Comparator		
Variables	N	Mean % Predicted (SD)	Mean (SD)	N	Mean % Predicted (SD)	Mean (SD)
FEV1	1267	96.05 (14.4)	2.92 (0.7)	1119	96.21 (15.0)	2.93 (0.7)
FVC	1266	94.88 (13.5)	3.66 (0.9)	1118	95.34 (14.1)	3.67 (0.9)
DLco	1234	97.41 (38.3)	25.09 (6.1)	1094	96.22 (16.5)	24.89 (6.2)
FRC	1247	89.96 (22.5)	2.82 (0.8)	1100	91.10 (21.5)	2.80 (0.8)
TLC	1264	95.87 (12.7)	5.74 (1.2)	1115	95.79 (12.5)	5.69 (1.3)

* N is based on the number of subjects who had a mean baseline score. N for the % Predicted Value may be smaller

Note that twenty four weeks data for Studies 1001 and 1002 were submitted separately by the applicant. In addition, the applicant also submitted the two-year combined safety report for Studies

1001 and 1002. Comparison of these two datasets yield inconsistent number of subjects and slight inconsistent in the baseline and week 24 data. However, the inconsistencies in the baseline and % predicted value were not substantial enough to warrant further exploration beyond asking the applicant's reasoning for such discrepancies. The applicant responded to an information request regarding this discrepancy. One reason they provided was that one site (site 0133) was removed from Study 1001 and no further explanation was provided as to the reason. After discussing with Dr. Sally Seymour and Dr. Jon T. Sahlroot, we decided to go ahead and analyze the Combined 1001-1002 data since that data is more complete.

Similar to Type 1 data, I explored whether using Observed Cases only (Pooled – Observed) will provide a sensible estimate of the treatment difference, I conducted different types of mixed model repeated measures (MMRM) analysis. Similar to pooled Type 1 data, I used the unadjusted model[3] the applicant proposed. Note that you will find in the discussion of individual PFT measurements that the Applicant's unadjusted MMRM model and the covariate-adjusted MMRM model yielded comparable results (Table 25, Table 28, Table 30, Table 32 and Table 34) , thus alleviating our concern that the results of these sensitivity analyses may not be applicable to the applicant's primary model (i.e. Covariate-adjusted MMRM). Furthermore, I used four different covariance structures[4] model to determine how appropriate the selection of Spatial Power is. All these exploratory analyses were done on the pooled Type 2 data. Note that LOCF was not conducted because of the difference in duration and designs of the individual studies. I find that it is not practical to impute the data with some studies having only two timepoints, while others have eight timepoints (e.g. in Study 1001: weeks 12, 24, 36, 48, 60, 72, 85, 96).

The following figures (Figure 18 to Figure 22) are the results of the individual and pooled studies for each PFT measurements. It includes pooled observed using GLM model and the analysis using Mixed Model Repeated Measures (MMRM). From the figures, it appears that results from the observed cases are consistent with results from imputation and from using Mixed Model Repeated Measures. This is true regardless of the variance-covariance structure. From careful examination of the information criterion (AIC, BIC, AICC) and the -2xResidual (or REML) Log Likelihood, it appears that unstructured covariance is the most appropriate choice for the data, since it minimized the information criterion value (AIC, BIC, AICC) in its -2 times the residual log-likelihood form. Therefore, unstructured covariance model is the preferred model (Table 23) Note that in theory, the greater the residual log likelihood, the better the fit of the model. Therefore, the smaller the -2 times the residual log-likelihood, the better the fit of the model. However, since the result from Spatial Power model is not extremely different compared to the unstructured covariance model, the applicant's choice is acceptable. Therefore, the result is not sensitive to the choice of covariance structures, as well as to the use of observed data only.

[3] Unadjusted Model • Treatment group, categorical variable • Visit, categorical variable

[4] Variance-Covariance Structures: Unstructured (UN), Spatial Power (SP), First-order Autoregressive (AR1), and Compound Symmetry (CS)

Figure 18: Treatment Difference in DLco (mL/min/mmHg) in Controlled Phase 2/3 Studies in Adults Type 2 Diabetes

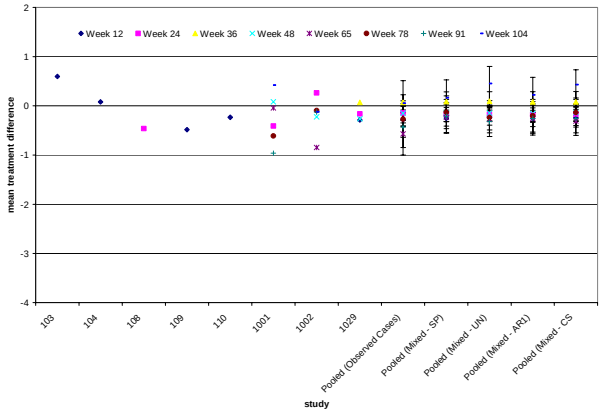


Figure 19: Treatment Difference in FEV1 (L) in Controlled Phase 2/3 Studies in Adults Type 2Diabetes

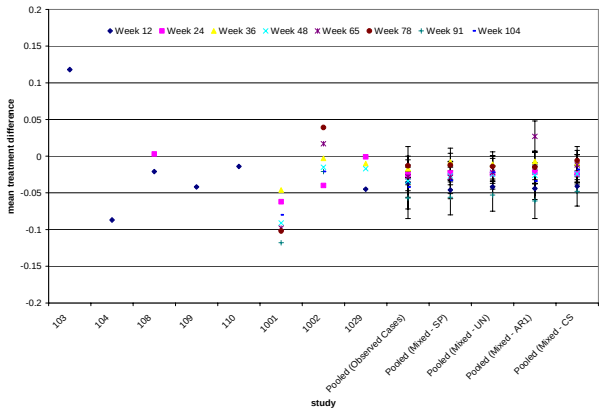


Figure 20: Treatment Difference in FVC (L) in Controlled Phase 2/3 Studies in Adults Type 2Diabetes

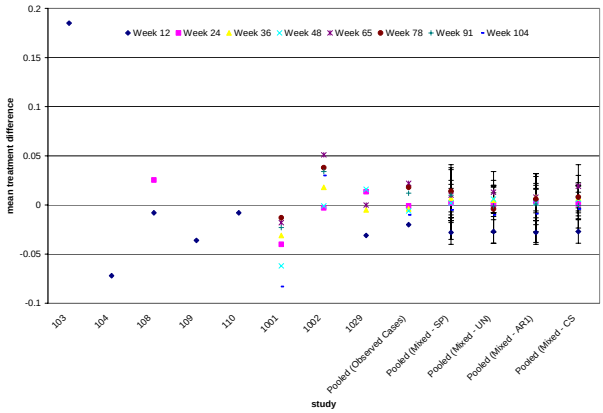


Figure 21: Treatment Difference in FRC (L) inControlled Phase 2/3 Studies in Adults Type 2Diabetes

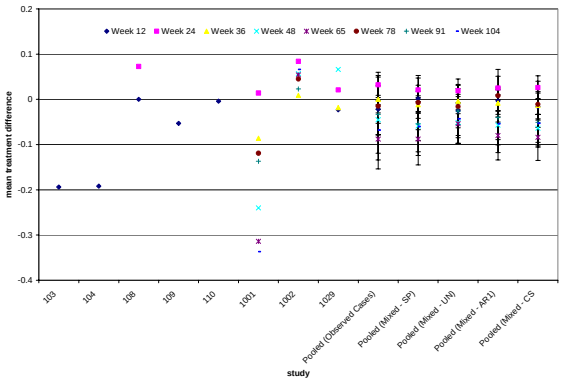


Figure 22: Treatment Difference in TLC (L) in Controlled Phase 2/3 Studies in Adults Type 2Diabetes

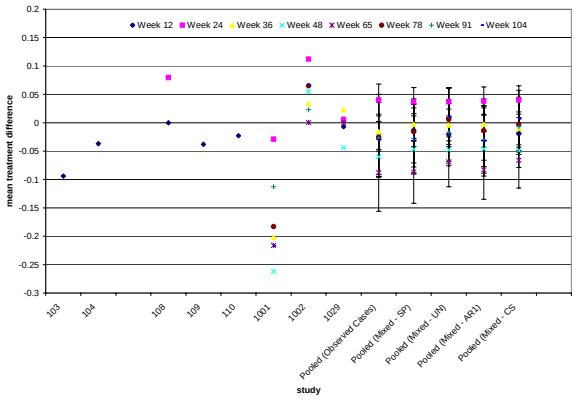


Table 23: Comparison of Covariance Models in Pooled Adult Type 2 Data

PFT	Variance-Covariance Structure	AIC	AICC	BIC	-2RLL
DLC	Spatial Power	24864.7	24864.8	24887.8	24856.7
	Unstructured	24670.8	24671.1	24831.9	24614.8
	AR(1) (no random)	25045.9	25045.9	25057.4	25041.9
	Compound	24819.8	24819.8	24831.3	24815.8
FEV	Spatial Power	-3589.6	-3589.6	-3566.5	-3597.6
	Unstructured*	-3751.8	-3751.8	-3751.8	-3751.8
	AR(1) no random	-3598.0	-3598.0	-3586.4	-3602
	Compound	-3774.5	-3774.5	-3762.9	-3778.5
FRC	Spatial Power	7890.9	7890.9	7913.9	7882.9
	Unstructured*	7825.4	7825.4	7825.4	7825.4
	AR(1) no random	7913.5	7913.5	7925.1	7909.5
	Compound	7708.8	7708.8	7720.4	7704.8
FVC	Spatial Power	-1607.8	-1607.8	-1584.7	-1615.8
	Unstructured	-2020.2	-2019.8	-1812.2	-2092.2
	AR(1) no random	-1616.0	-1616.0	-1604.4	-1620.0
	Compound	-1935.5	-1935.5	-1924.0	-1939.5
TLC	Spatial Power	7615.7	7615.7	7638.8	7607.7
	Unstructured	7196.7	7197.2	7404.6	7124.7
	AR(1) no random	7615.7	7615.7	7627.2	7611.7
	Compound	7292.6	7292.6	7304.2	7288.6

* requests an unstructured R matrix be estimated from the sum-of-squares-and-crossproducts matrix of the residuals since it appears that the default REML estimate is too slow and not converging.

In the following discussion, the results from the pooled analysis on each of the PFT measurements will be summarized.

Forced Expiratory Volume in 1 second (FEV_1)

As seen from the individual studies, there appears to be small declines in mean FEV1 among INH- and comparator- treated subjects over 12, 24 weeks, up to 96 weeks (2 years) of exposure, with small but consistent treatment group differences favoring the comparator (Figure 19). Some of these differences were supported by the confidence interval for these changes. Note that the treatment group differences for FEV1 remained fairly constant and did not increase. Meanwhile, although the mean change from baseline in FEV_1 score in the inhaled insulin group did not improve 6 weeks and 12 weeks after washout, the treatment different appears to be smaller and slightly in favor of inhaled insulin at 6 weeks after washout.

In the pooled data set, similar treatment group differences in mean change from baseline in FEV1 favoring comparator therapy are apparent among adult subjects with type 1 after 3 months of therapy. The treatment group differences remained fairly constant and only increased slightly after their first post-baseline measurement and these differences remained comparable at subsequent time points, which the applicant claims, supports the effect of INH on FEV1 is not progressive (Table 24, Table 25; Figure 23). The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 20 – 60 mL and around 30 – 40 mL at the end of study for FEV_1.

Most of the data in the pooled studies after week 48 are from Combined Studies 1001 and 1002 therefore the results from the Pooled analysis and from the combined studies 1001 and 1002 are fairly consistent.

Figure 23: Mean Change from Baseline in FEV_1 (L) by Time in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

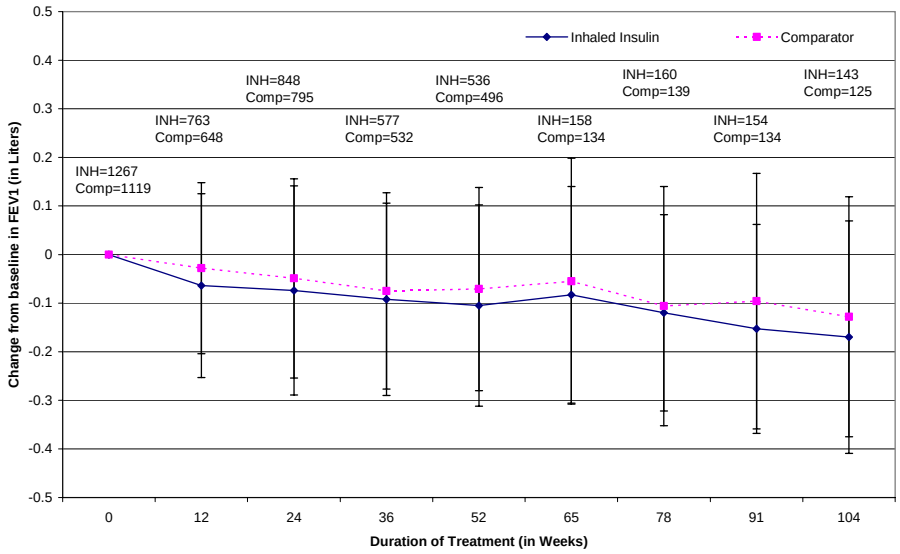


Table 24: Mean Change from Baseline in FEV1 Score and Unadjusted Treatment Group Difference in Controlled Type 2 Studies

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	1267	2.924	0.701				
	Week 12	763	2.866	0.681	-0.064	0.189	-0.036	-0.055, -0.017
	Week 24	848	2.831	0.702	-0.074	0.215	-0.025	-0.045, -0.005
	Week 36	577	2.839	0.694	-0.092	0.198	-0.017	-0.041, 0.006
	Week 48/52	536	2.819	0.691	-0.105	0.207	-0.034	-0.059, -0.009
	Week 65	158	2.784	0.687	-0.083	0.223	-0.028	-0.083, 0.027
	Week 78	160	2.736	0.691	-0.120	0.202	-0.013	-0.064, 0.038
	Week 91	154	2.706	0.668	-0.153	0.215	-0.057	-0.112, -0.001
	Week 104	143	2.663	0.676	-0.170	0.239	-0.042	-0.100, 0.017
	6 Week Washout	149	2.703	0.661	-0.139	0.214	0.008	-0.049, 0.065
	12 Week Washout	132	2.689	0.677	-0.164	0.237	-0.014	-0.073, 0.044
Comparator	Baseline	1119	2.928	0.728				
	Week 12	648	2.926	0.714	-0.028	0.176		
	Week 24	795	2.873	0.709	-0.049	0.205		
	Week 36	532	2.835	0.702	-0.075	0.202		
	Week 48/52	496	2.851	0.714	-0.071	0.209		
	Week 65	134	2.718	0.655	-0.055	0.253		
	Week 78	139	2.717	0.665	-0.106	0.246		
	Week 91	134	2.699	0.634	-0.096	0.263		
	Week 104	125	2.708	0.641	-0.128	0.247		
	6 Week Washout	138	2.707	0.670	-0.147	0.273		
	12 Week Washout	128	2.689	0.645	-0.150	0.243		

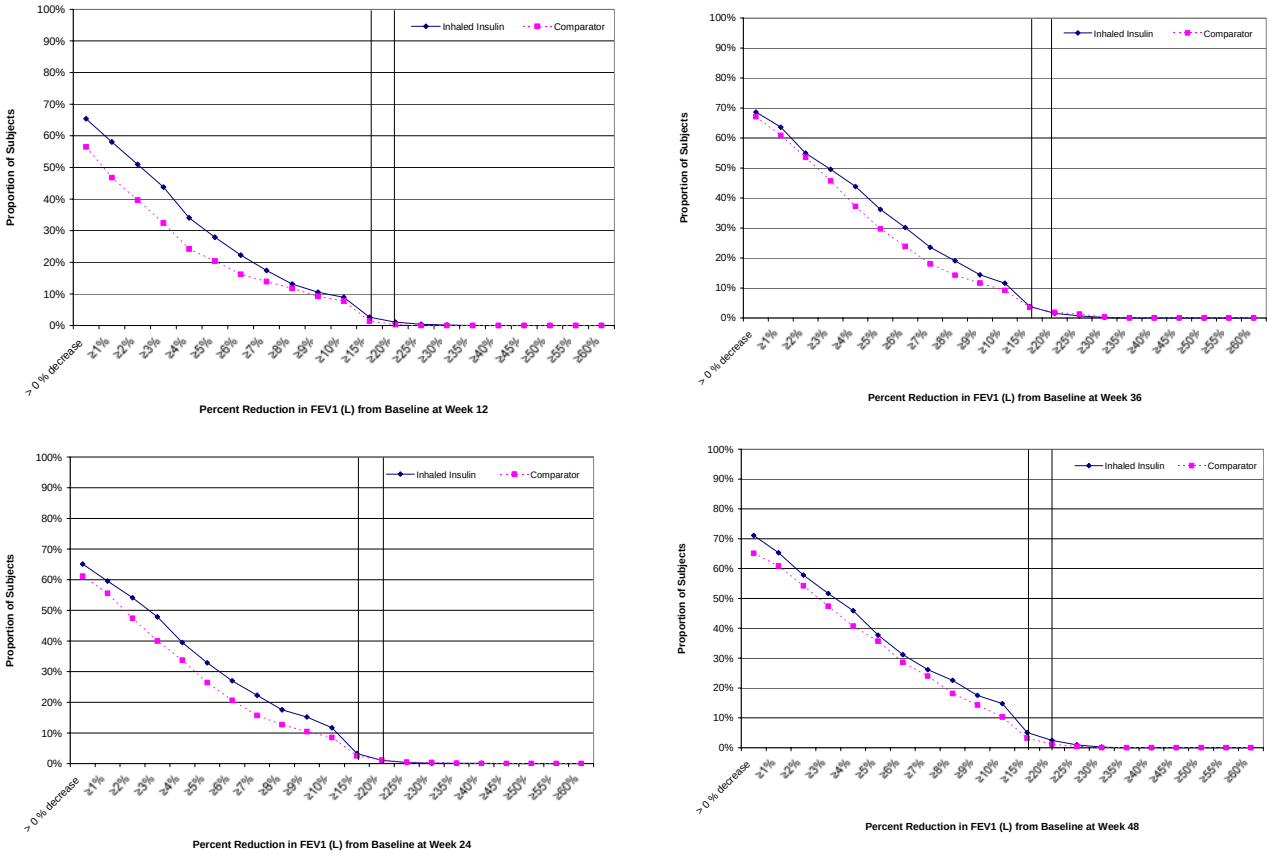
Table 25: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FEV1 Score in Controlled Phase 2/3 Studies in Type 2 Adults

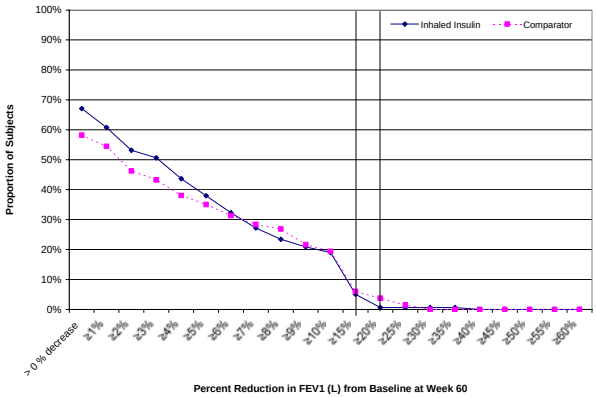
Week	Unadjusted Difference	95% CI	Adjusted* Difference	95% CI	Adjusted** Difference	95% CI
12	-0.036	-0.055, -0.017	-0.044	-0.065, 0.024	-0.043	-0.063, -0.022
24	-0.025	-0.045, -0.005	-0.023	-0.042, -0.004	-0.024	-0.043, -0.005
36	-0.017	-0.041, 0.006	-0.009	-0.031, 0.014	-0.009	-0.032, 0.013
52	-0.034	-0.059, -0.009	-0.027	-0.051, -0.002	-0.028	-0.052, -0.005
65	-0.028	-0.083, 0.027	-0.029	-0.072, 0.014	-0.027	-0.067, 0.013
78	-0.013	-0.064, 0.038	-0.012	-0.058, 0.033	-0.010	-0.054, 0.033
91	-0.057	-0.112, -0.001	-0.056	-0.103, -0.009	-0.053	-0.099, -0.008
104	-0.042	-0.100, 0.017	-0.033	-0.082, 0.016	-0.031	-0.078, 0.017

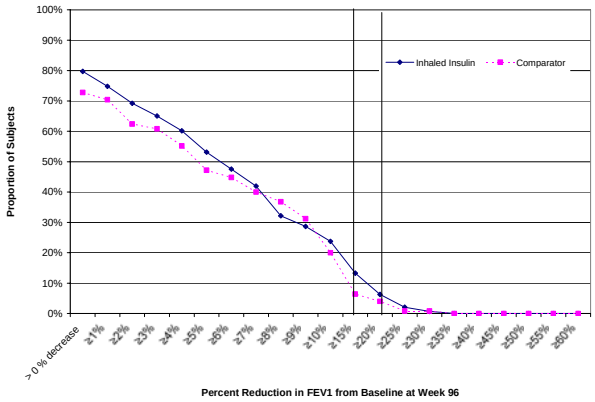
Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

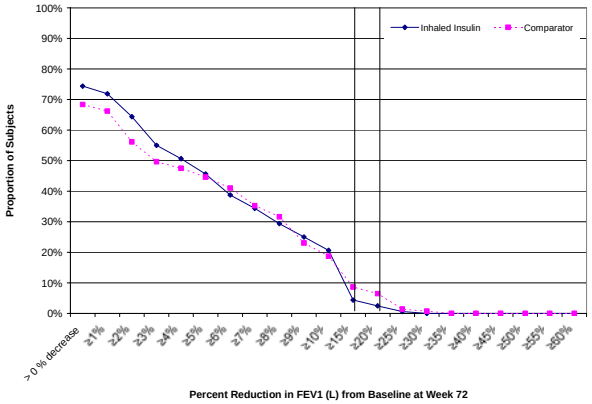
The proportions of subjects who had reduction in FEV1 from baseline at each timepoint (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions are presented in Figure 24. Inspection of these graphs suggests that there are apparent differences in the proportion of subjects who had reduction in FEV1 from baseline between the two treatment groups in favor of the comparator group before Week 48. The treatment difference appears to diminish slowly after Week 48 particularly those who had more than 6% reduction, except at Week 84. Note however, that these reductions are generally very small. In fact, only a small proportion of subjects (1% maximum) had reduction of more than 15%, although this appears to increase especially after Week 48 in the comparator group.

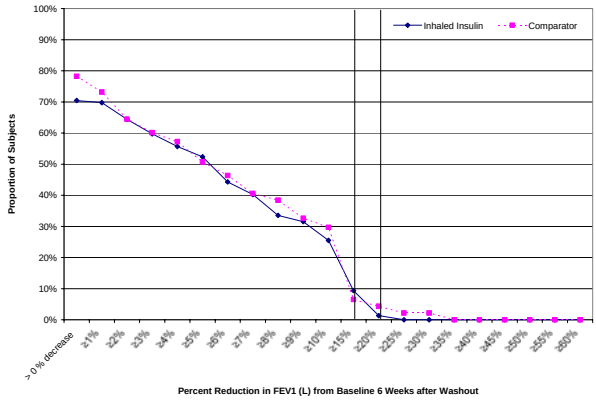
Figure 24: Proportion of Subjects by Percent Reduction from Baseline in FEV1 (L) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

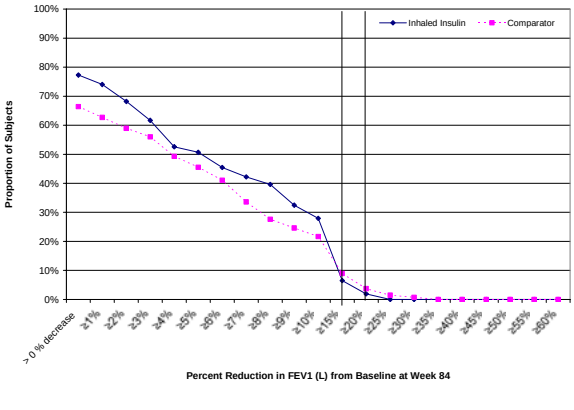


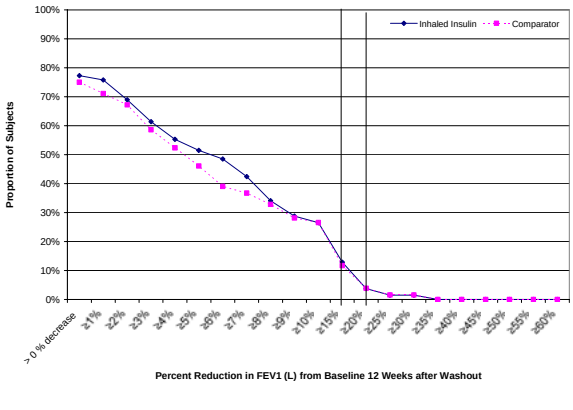

Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 (L) from Baseline at Week 60


Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 from Baseline at Week 96


Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 (L) from Baseline at Week 72


Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 (L) from Baseline 6 Weeks after Washout


Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 (L) from Baseline at Week 84


Inhaled Insulin
Comparator
Proportion of Subjects
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
> 0 % decrease
≥1%
≥2%
≥3%
≥4%
≥5%
≥6%
≥7%
≥8%
≥9%
≥10%
≥15%
≥20%
≥25%
≥30%
≥35%
≥40%
≥45%
≥50%
≥55%
≥60%
Percent Reduction in FEV1 (L) from Baseline 12 Weeks after Washout

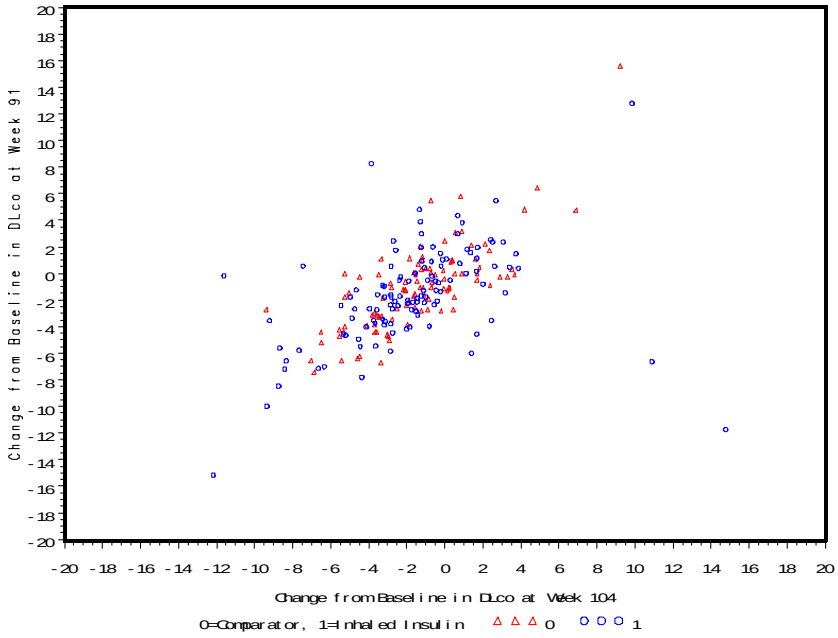
Diffusion Lung Capacity (DLco)

From the results of the individual studies, there appears to be a slow and steady decline in mean change from baseline in DLco among INH- and comparator- treated subjects up to 96 weeks (2 years) of exposure (Figure 18). In most of the individual studies, there was a consistent treatment group difference numerically favoring the comparator. However, these differences were not supported by the confidence interval. Note that one of the concerns Dr. Seymour had was in the change in direction on the treatment difference from Week 91 and Week 104 (i.e. -0.431 and 0.054, respectively) in combined studies 1001 and 1002. This phenomenon is seen also in the pooled analysis (Table 27 and Table 28). After careful exploration of the scatterplots in the between Weeks 91 and 104, I found that there were several outliers that could explain this shift in direction. Some of the extreme outliers are presented in Table 26. Removal of the two extremes (PID: 100101380278 and 100100590136) led to a negative treatment differences at Weeks 91 and 104, making them consistent. It is unknown what happened to these outliers, so removal of these subjects may not be the best way to handle this problem. Therefore, I would note of such problem, but will still include these subjects in the analysis.

Table 26: Change from Baseline in DLco at Weeks 91 and 104

PID	Treatment Group	Change from Baseline PFT at 91	Change from Baseline PFT at 104
100200477343	INH	0.5729	-7.4491
100100590133	Comparator	-0.0322	-5.2679
100201315262	INH	8.2805	-3.8506
100101380278	INH	-6.6139	10.9050
100100590136	INH	-11.7171	14.7865

Figure 25: Exploratory Analysis of the Change from Baseline in DLco at Week 91 by Change from Baseline in DLco at Week 104



In the pooled data set, there also appears to be a slow and steady decline in mean change from baseline in DLco among INH- and comparator- treated subjects up to 96 weeks (2 years) of exposure. Similar to the results from the individual studies, treatment group differences in mean change from baseline in DLco numerically favors the comparator therapy among adult subjects with Type 2 diabetes after 3 months of therapy, except at Weeks 36 and 96/104. Similar to the individual studies in 1001 and 1002, there is a change in direction from Weeks 91 and 104, which is the result of few outliers in the data. Meanwhile, data for Week 36 is only available in Study 1029, thus the samples are very small, and this shift in direction could again be due to some outliers. Note however, that in Study 1029, Week 24 is -0.163, Week 36 is 0.071, and Week 48 is -0.264, which in a sense are not that extreme, unlike the week 91 and 104 data. The applicant claims that the effect of INH on DLco did not appear to be progressive (Table 27, Table 28; Figure 26). Meanwhile, although the mean change from baseline in DLco score in both the inhaled insulin and the comparator groups did not improve 6 weeks and 12 weeks after washout, the treatment different appears to be smaller and slightly in favor of inhaled insulin at 6 weeks after washout. However, this observation appears to be false at 12 weeks after washout. The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 0.4 mL/min/mmHg for DLco at week 84/91.

Most of the data in the pooled studies after week 48 are from combined Studies 1001 and 1002, therefore the results from the Pooled analysis and from combined studies 1001 and 1002 are fairly consistent

Figure 26: Mean Change from Baseline in DLco (mL/min/mmHg) by Time in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

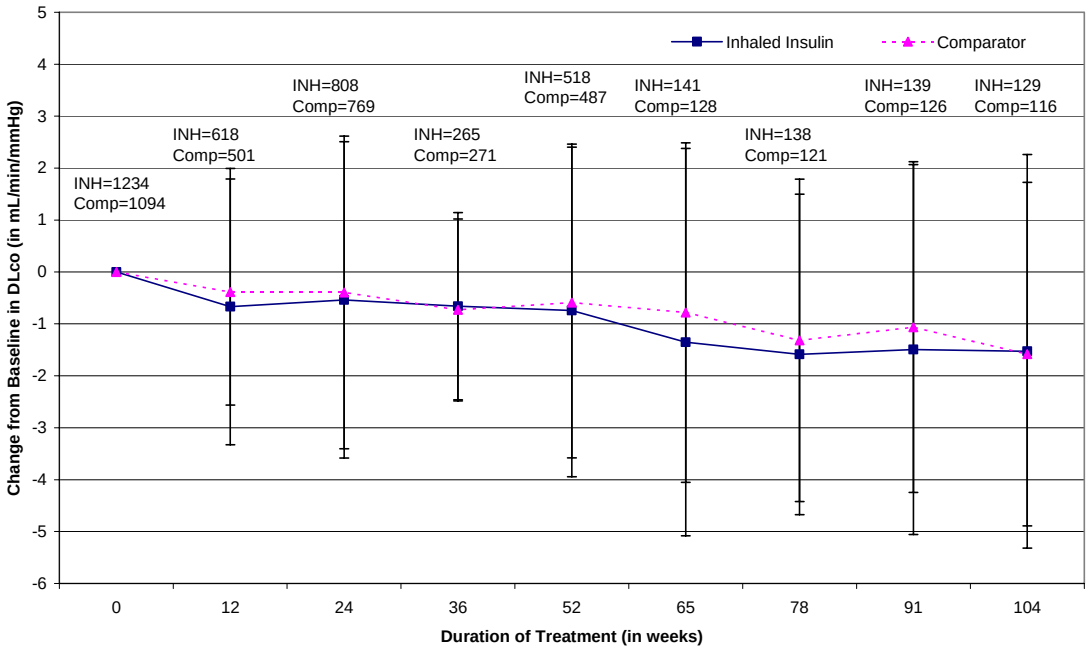


Table 27: Mean Change from Baseline in DLco Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 2 Adults

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	1234	25.091	6.152				
	Week 12	618	24.091	6.006	-0.666	2.660	-0.278	-0.568, 0.011
	Week 24	808	24.516	6.225	-0.540	3.046	-0.145	-0.445, 0.154
	Week 36	265	23.728	5.389	-0.660	1.804	0.071	-0.230, 0.373
	Week 48/52	518	24.559	6.297	-0.742	3.203	-0.151	-0.535, 0.233
	Week 65	141	24.550	5.748	-1.352	3.730	-0.570	-1.416, 0.276
	Week 78	138	24.200	5.922	-1.588	3.088	-0.270	-1.029, 0.489
	Week 91	139	24.251	5.830	-1.495	3.563	-0.431	-1.252, 0.390
	Week 104	129	24.017	5.743	-1.529	3.791	0.054	-0.846, 0.954
	6 Week Washout	132	24.114	5.998	-1.133	3.731	0.214	-0.628, 1.056
	12 Week Washout	112	24.218	5.735	-1.253	3.610	-0.103	-1.013, 0.806
Comparator	Baseline	1094	24.892	6.172				
	Week 12	501	24.135	5.934	-0.388	2.177		
	Week 24	769	24.411	6.057	-0.395	3.012		
	Week 36	271	23.239	5.562	-0.731	1.751		
	Week 48/52	487	24.195	6.033	-0.591	2.991		
	Week 65	128	24.288	5.810	-0.782	3.270		
	Week 78	121	24.243	5.686	-1.318	3.104		
	Week 91	126	24.135	5.582	-1.063	3.185		
	Week 104	116	24.056	5.664	-1.583	3.306		
	6 Week Washout	128	24.364	5.818	-1.347	3.127		
	12 Week Washout	119	24.569	5.765	-1.149	3.402		

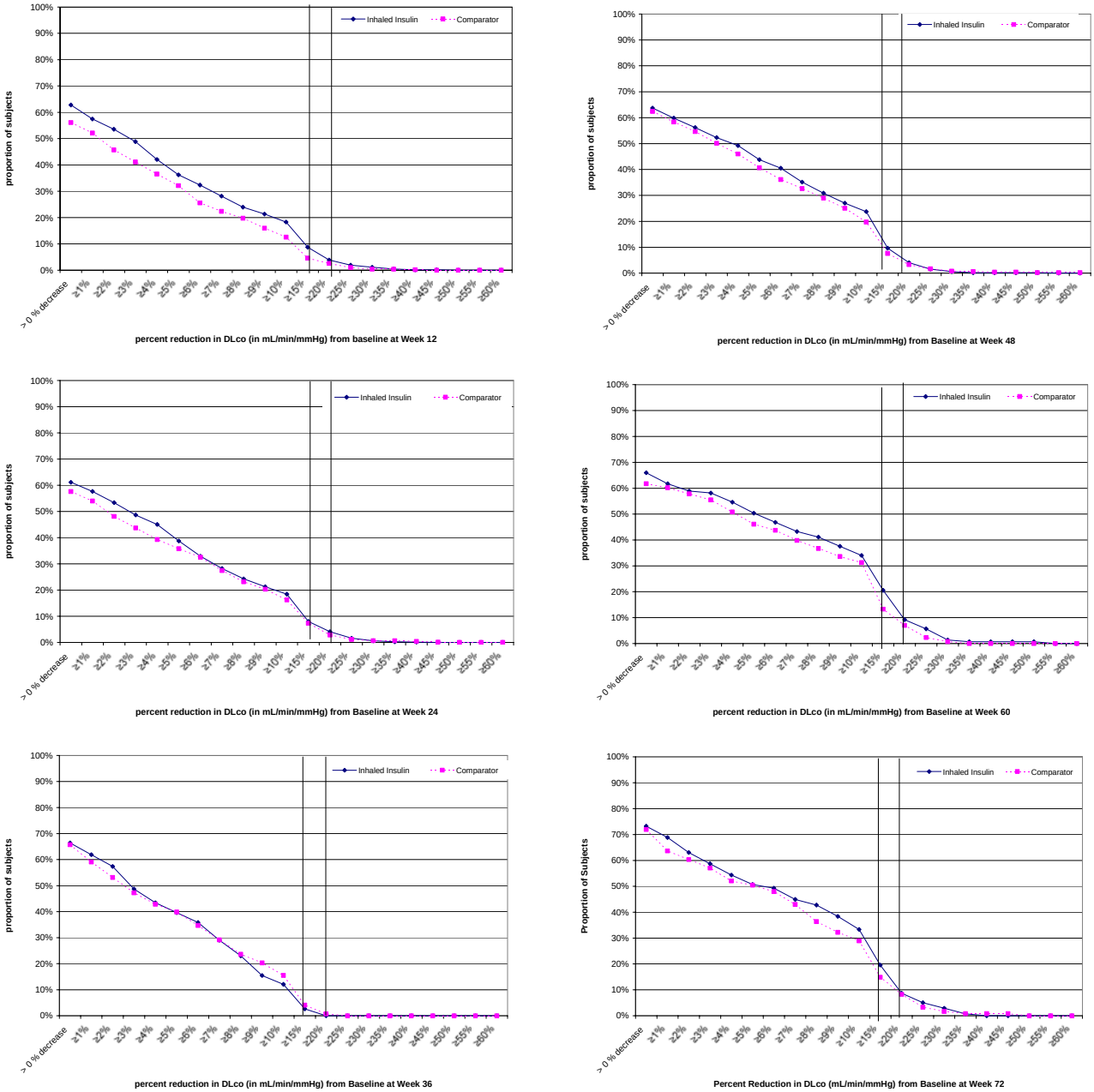
Table 28: Unadjusted and Sponsor-defined Adjusted Treatment Difference in DLco Score in Controlled Phase 2/3 Studies in Type 2 Adults

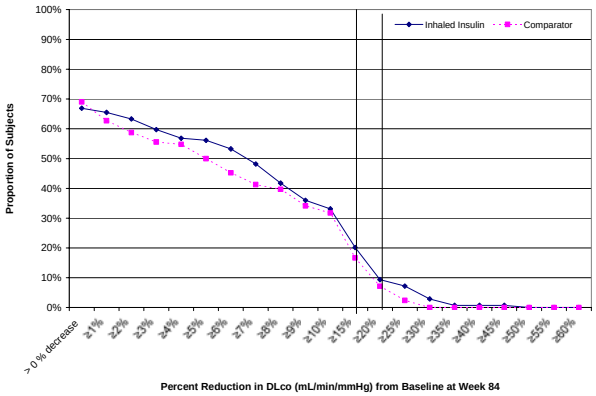
	Unadjusted		Adjusted*		Adjusted**	
Week	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	-0.278	-0.568, 0.011	-0.251	-0.572, 0.069	-0.230	-0.540, 0.079
24	-0.145	-0.445, 0.154	-0.175	-0.456, 0.107	-0.163	-0.429, 0.104
36	0.071	-0.230, 0.373	0.089	-0.305, 0.483	0.107	-0.277, 0.490
52	-0.151	-0.535, 0.233	-0.148	-0.497, 0.202	-0.122	-0.455, 0.210
65	-0.570	-1.416, 0.276	-0.213	-0.785, 0.358	-0.180	-0.737, 0.376
78	-0.270	-1.029, 0.489	-0.116	-0.761, 0.528	-0.075	-0.696, 0.546
91	-0.431	-1.252, 0.390	-0.204	-0.876, 0.469	-0.173	-0.814, 0.468
104	0.054	-0.846, 0.954	0.167	-0.543, 0.877	0.194	-0.481, 0.869

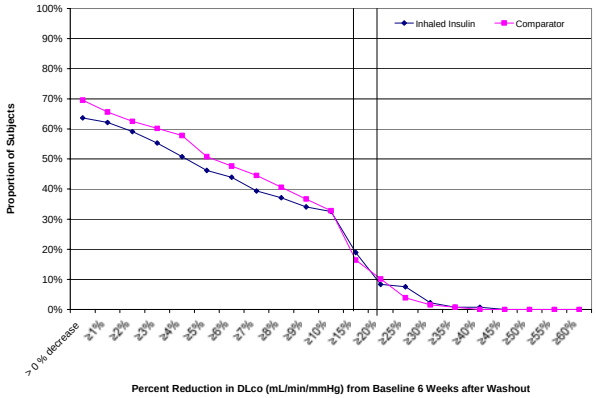
Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

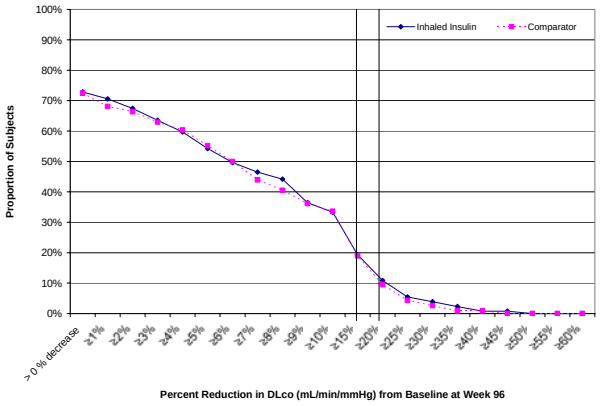
The proportions of subjects who had reduction in DLco at baseline at each timepoints (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions are presented in Figure 27. Inspection of these graphs suggests that there are some differences in the proportion of subjects who had reduction in DLco from baseline between the two treatment groups in favor of the comparator group at Weeks 12 and after Week 48. But these differences are small compared to the Type 1 data. Although these reductions are generally very small (most subjects had at most 10% reduction), same as the Type 1 data, there are quite a few in the inhaled insulin group that had at least 15% reduction compared to the comparator group.

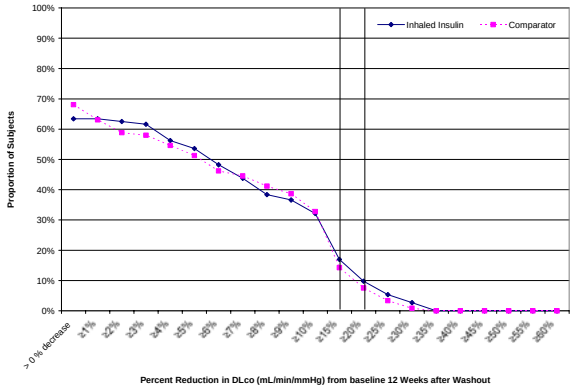
Figure 27: Proportion of Subjects by Percent Reduction from Baseline in DLco (mL/min/mmHg) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes











Forced Vital Capacity (FVC)

As seen from the individual studies, there appears to be a small decline that looks to be constant over time in mean change from baseline in FVC among INH- and comparator- treated subjects (Figure 20). Treatment group differences were comparable between inhaled insulin group and the comparator group in the sense that all 95% confidence intervals included the zero difference.

Similar conclusions can be drawn from the pooled data set. Treatment group differences were small and fairly consistent between the two treatment groups (Table 29, Table 30; Figure 28). The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 10 mL for FVC at the end of the study. In terms of the two washout data, the mean change from baseline in FVC score did not improve at 6 weeks or 12 weeks after washout in both treatment groups. However, the treatment different numerically appears to be in favor of inhaled insulin at 6 weeks and 12 weeks after washout.

Most of the data in the pooled studies after week 48 are from the combined studies 1001 and 1002, therefore the results from the Pooled analysis and from the combined studies 1001 and 1002 are fairly consistent.

The proportions of subjects who had reduction in FVC at baseline at each time points (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. In general, the graphs suggest that there are no differences in the proportion of subjects who had any reduction in FVC from baseline between the two treatment groups, except at week 12 (in favor of comparator) and during the

washout phase (slightly in favor of the inhaled insulin). Only few subjects (<1%) had reduction of more than 15% during the early phase of the treatment period, but this soon increased to 5% after week 48, particularly in the comparator insulin group.

Figure 28: Mean Change from Baseline in FVC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

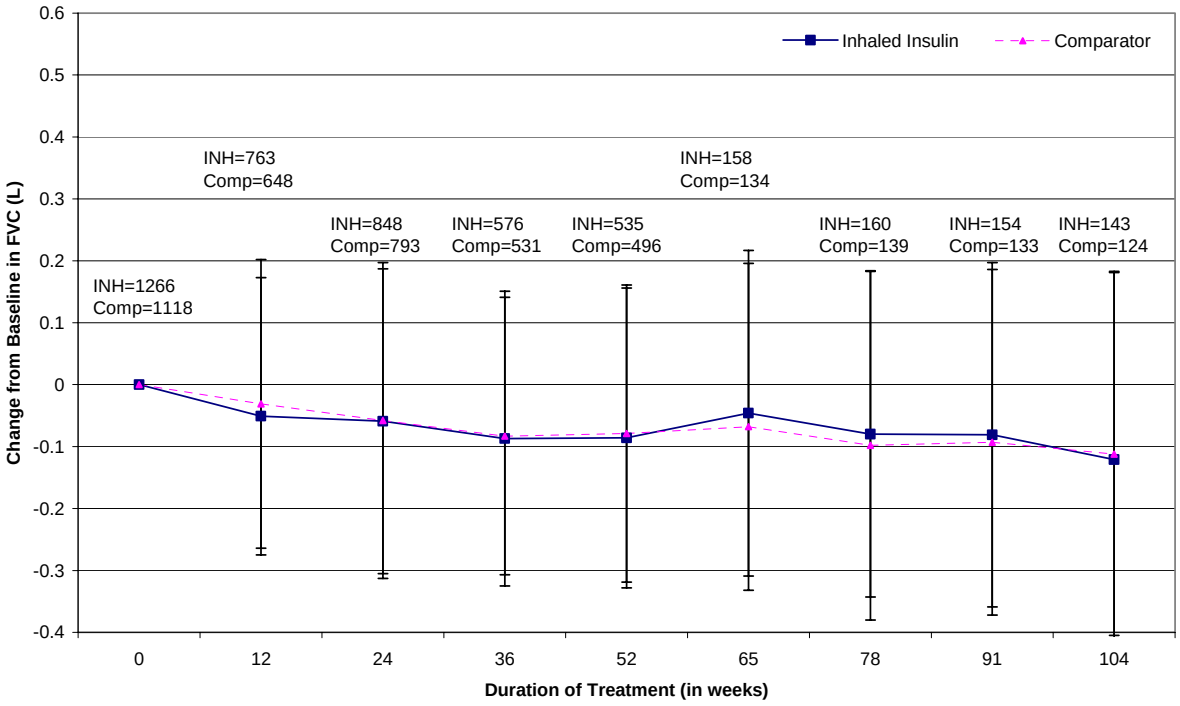


Table 29: Mean Change from Baseline in FVC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 2 Adults

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	1266	3.664	0.889				
	Week 12	763	3.665	0.877	-0.051	0.224	-0.020	-0.044, 0.004
	Week 24	848	3.576	0.883	-0.059	0.246	-0.001	-0.025, 0.023
	Week 36	576	3.578	0.870	-0.087	0.238	-0.004	-0.031, 0.023
	Week 48/52	535	3.575	0.871	-0.086	0.242	-0.006	-0.036, 0.023
	Week 65	158	3.458	0.830	-0.046	0.263	0.022	-0.039, 0.083
	Week 78	160	3.405	0.863	-0.080	0.263	0.018	-0.044, 0.080
	Week 91	154	3.388	0.843	-0.081	0.278	0.012	-0.053, 0.077
	Week 104	143	3.342	0.856	-0.121	0.304	-0.010	-0.082, 0.063
	6 Week Washout	149	3.358	0.846	-0.094	0.279	0.047	-0.020, 0.113
	12 Week Washout	132	3.345	0.864	-0.124	0.242	0.023	-0.045, 0.090
Comparator	Baseline	1118	3.666	0.926				
	Week 12	648	3.707	0.917	-0.031	0.233		
	Week 24	793	3.610	0.904	-0.058	0.255		
	Week 36	531	3.578	0.899	-0.083	0.224		
	Week 48/52	496	3.586	0.909	-0.079	0.240		
	Week 65	134	3.375	0.794	-0.068	0.264		
	Week 78	139	3.395	0.802	-0.098	0.282		
	Week 91	133	3.383	0.774	-0.093	0.279		
	Week 104	124	3.411	0.766	-0.112	0.293		
	6 Week Washout	137	3.402	0.804	-0.140	0.294		
	12 Week Washout	127	3.394	0.788	-0.147	0.308		

Table 30: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FVC Score in Controlled Phase 2/3 Studies in Type 2 Adults

	Unadjusted		Adjusted*		Adjusted**	
Week	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	-0.020	-0.044, 0.004	-0.028	-0.052, -0.004	-0.029	-0.054, -0.005
24	-0.001	-0.025, 0.023	0.002	-0.021, 0.025	-0.001	-0.024, 0.022
36	-0.004	-0.031, 0.023	0.007	-0.020, 0.034	0.003	-0.023, 0.030
52	-0.006	-0.036, 0.023	0.002	-0.027, 0.030	-0.002	-0.031, 0.026
65	0.022	-0.039, 0.083	0.009	-0.038, 0.057	-0.008	-0.039, 0.055
78	0.018	-0.044, 0.080	0.013	-0.039, 0.057	0.012	-0.040, 0.063
91	0.012	-0.053, 0.077	0.009	-0.046, 0.064	0.007	-0.047, 0.061
104	-0.010	-0.082, 0.063	-0.005	-0.063, 0.052	-0.008	-0.064, 0.049

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

Forced Residual Capacity (FRC)

As seen from the individual studies, there appears to be a very small decline that looks constant across time in mean change from baseline in FRC among INH- and comparator- treated subjects (Figure 21). Treatment group differences were comparable between inhaled insulin group and the comparator group, but numerically favored the comparator group after Week 12.

Similar conclusions can be drawn from the pooled data set. Treatment group differences were comparable between the two treatment groups in the sense that the confidence interval includes zero difference. There appears to be a small separation between the two groups after Week 36 (Table 31, Table 32; Figure 29). The treatment differences were slightly bigger in the adjusted model, but generally are in the same direction as the unadjusted (i.e. favoring the comparator group). Thus, the treatment differences were of a magnitude of about 0 – 90 mL for FRC (taking into account the adjusted model), and about 70 mL at the end of the study (week 96/104). In terms of the two washout data, the mean change from baseline in FRC score did not improve at 6 weeks or 12 weeks after washout in both treatment groups. The treatment difference improved a little at 12 weeks after washout, in favor of inhaled insulin.

Most of the data in the pooled studies after week 48 are from the combined studies 1001 and 1002, therefore the results from the Pooled analysis and from combined studies 1001 and 1002 are fairly consistent.

Figure 29: Mean Change from Baseline in FRC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

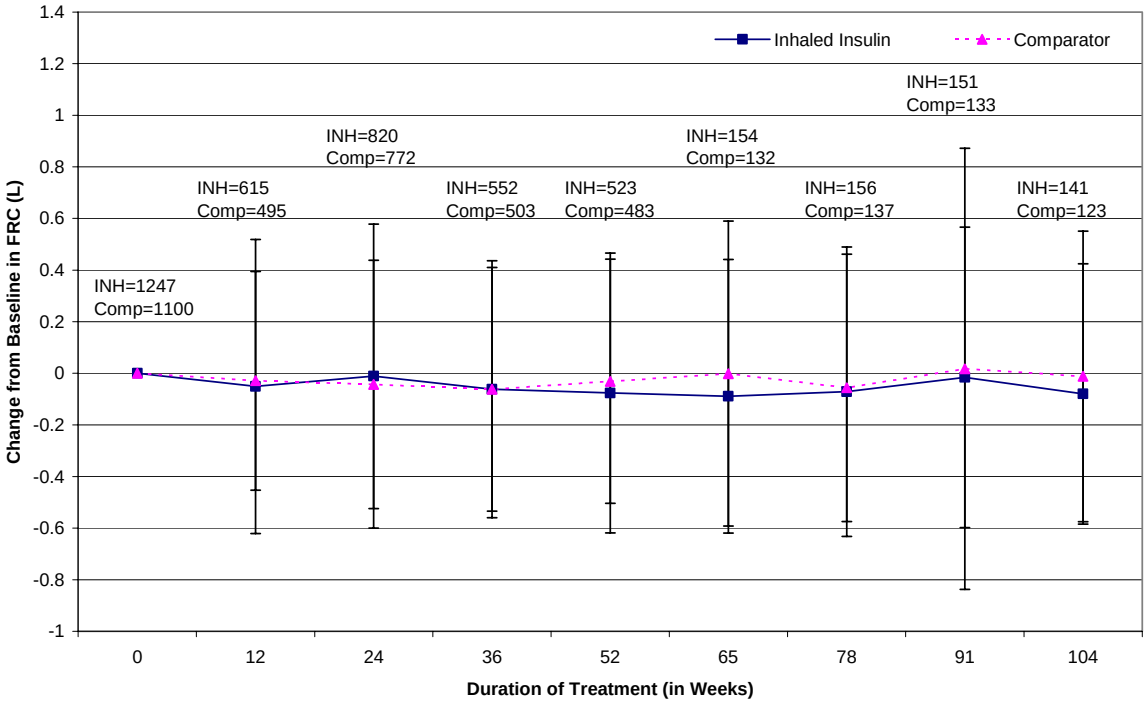


Table 31: Mean Change from Baseline in FRC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 2 Adults

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	1247	2.824	0.842				
	Week 12	615	2.728	0.816	-0.051	0.570	-0.022	-0.083, 0.038
	Week 24	820	2.828	0.876	-0.011	0.589	0.032	-0.022, 0.085
	Week 36	552	2.781	0.824	-0.062	0.498	0.00002	-0.059, 0.059
	Week 48/52	523	2.772	0.838	-0.076	0.542	-0.045	-0.109, 0.018
	Week 65	154	2.744	0.690	-0.089	0.530	-0.088	-0.218, 0.043
	Week 78	156	2.729	0.741	-0.071	0.561	-0.015	-0.140, 0.110
	Week 91	151	2.768	0.726	-0.016	0.582	-0.033	-0.202, 0.136
	Week 104	141	2.716	0.783	-0.080	0.504	-0.068	-0.197, 0.061
	6 Week Washout	147	2.653	0.763	-0.130	0.572	-0.081	-0.215, 0.053
	12 Week Washout	130	2.692	0.825	-0.067	0.620	-0.024	-0.176, 0.129
Comparator	Baseline	1100	2.798	0.824				
	Week 12	495	2.692	0.825	-0.029	0.424		
	Week 24	772	2.785	0.838	-0.043	0.481		
	Week 36	503	2.751	0.842	-0.062	0.472		
	Week 48/52	483	2.789	0.858	-0.031	0.473		
	Week 65	132	2.856	0.892	-0.001	0.591		
	Week 78	137	2.811	0.898	-0.056	0.518		
	Week 91	133	2.849	1.055	0.017	0.855		
	Week 104	123	2.835	0.856	-0.012	0.563		
	6 Week Washout	136	2.860	0.895	-0.048	0.575		
	12 Week Washout	126	2.858	0.866	-0.044	0.622		

Table 32: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FRC Score in Controlled Phase 2/3 Studies in Type 2 Adults

	Unadjusted		Adjusted*		Adjusted**	
Week	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	-0.022	-0.083, 0.038	0.000	-0.059, 0.059	-0.009	-0.066, 0.047
24	0.032	-0.022, 0.085	0.021	-0.030, 0.072	0.011	-0.036, 0.059
36	0.00002	-0.059, 0.059	-0.012	-0.071, 0.048	-0.021	-0.078, 0.035
52	-0.045	-0.109, 0.018	-0.059	-0.123, 0.005	-0.068	-0.128, -0.009
65	-0.088	-0.218, 0.043	-0.087	-0.193, 0.019	-0.096	-0.198, 0.006
78	-0.015	-0.140, 0.110	-0.006	-0.121, 0.109	-0.018	-0.127, 0.091
91	-0.033	-0.202, 0.136	-0.054	-0.174, 0.067	-0.064	-0.177, 0.049
104	-0.068	-0.197, 0.061	-0.060	-0.186, 0.065	-0.072	-0.190, 0.046

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

The proportions of subjects who had reduction in FRC at baseline at each timepoint (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. Inspection of each individual graphs (by timepoints) suggests no difference in the reduction profile of subjects in the inhaled insulin group and the comparator group except at Weeks 48 and 96. It appears that the differences are small that a slight separation of curves may be due to random variation. Although reductions in FRC score were generally small, there were quite a few in both treatment groups (almost 20% in each group) that had reduction of more than 15%.

Total Lung Capacity (TLC)

As seen from the individual studies, there appears to be minimal to no decline in mean change from baseline in TLC among INH-treated group, while there appears to be very small decline in the comparator-treated subjects. These observations were consistent over time up to 96 weeks (2 years) of exposure (Figure 22). Treatment group differences were comparable between the inhaled insulin group and the comparator group in the sense that the confidence intervals include zero difference, but numerically favored the comparator insulin group in most studies, which is the opposite of what is seen in the Type 1 data.

Similar conclusions can be drawn from the pooled data set. Treatment group differences were comparable between the two treatment groups (Figure 30), but from Table 33 and Table 34, it appears that numerically there is a small difference between the two groups favoring the comparator insulin group except at Week 24. The treatment differences were of a magnitude of about 10 – 90 mL for TLC (taking into account the adjusted model), and about 30 mL at the end of the study (week 96/104). In terms of the two washout data, the mean change from baseline in TLC score did not improve at 6 weeks or 12 weeks after washout in both treatment groups. The treatment difference improved a little at 12 weeks after washout, in favor of inhaled insulin.

Figure 30: Mean Change from Baseline in TLC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

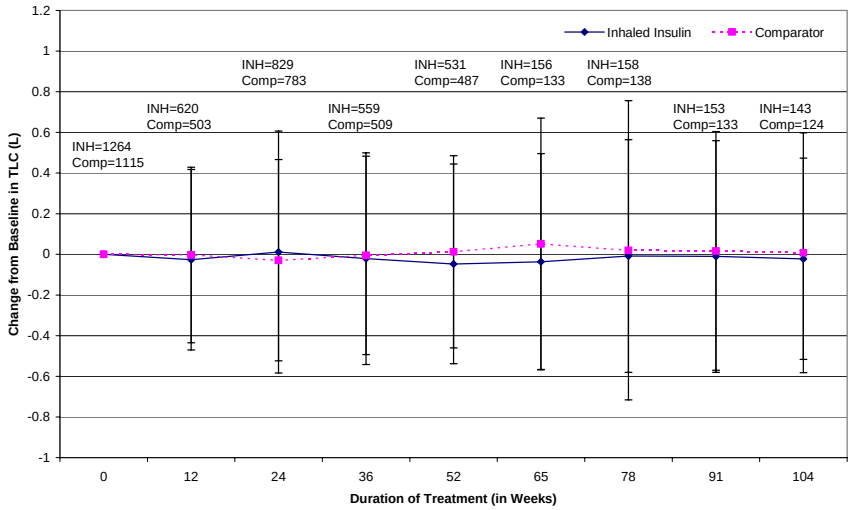


Table 33: Mean Change from Baseline in TLC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 2 Adults

Treatment Group		Observed			Change from Baseline		Inhaled - Comparator	
		N	Mean	SD	Mean	SD	Difference	95% CI
Inhaled	Baseline	1264	5.741	1.233				
	Week 12	620	5.720	1.279	-0.026	0.444	-0.024	-0.075, 0.028
	Week 24	829	5.707	1.281	0.011	0.595	0.040	-0.014, 0.094
	Week 36	559	5.692	1.274	-0.021	0.521	-0.016	-0.077, 0.045
	Week 48/52	531	5.662	1.226	-0.047	0.491	-0.060	-0.120, -0.001
	Week 65	156	5.570	1.254	-0.036	0.532	-0.088	-0.221, 0.046
	Week 78	158	5.566	1.285	-0.008	0.572	-0.027	-0.177, 0.122
	Week 91	153	5.556	1.233	-0.010	0.570	-0.027	-0.161, 0.108
	Week 104	143	5.559	1.264	-0.022	0.495	-0.030	-0.160, 0.101
	6 Week Washout	148	5.495	1.264	-0.058	0.552	-0.025	-0.161, 0.110
	12 Week Washout	132	5.515	1.374	-0.035	0.602	0.009	-0.137, 0.154
Comparator	Baseline	1115	5.686	1.251				
	Week 12	503	5.689	1.314	-0.003	0.432		
	Week 24	783	5.644	1.262	-0.029	0.495		
	Week 36	509	5.607	1.269	-0.005	0.488		
	Week 48/52	487	5.630	1.272	0.013	0.473		
	Week 65	133	5.605	1.284	0.052	0.618		
	Week 78	138	5.626	1.307	0.020	0.736		
	Week 91	133	5.555	1.245	0.017	0.587		
	Week 104	124	5.587	1.203	0.008	0.590		
	6 Week Washout	137	5.621	1.269	-0.032	0.610		
	12 Week Washout	127	5.582	1.262	-0.043	0.584		

Table 34: Unadjusted and Sponsor-defined Adjusted Treatment Difference in TLC Score in Controlled Phase 2/3 Studies in Type 2 Adults

	Unadjusted		Adjusted*		Adjusted**	
Week	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	-0.024	-0.075, 0.028	-0.013	-0.070, 0.044	-0.016	-0.072, 0.040
24	0.040	-0.014, 0.094	0.037	-0.012, 0.086	0.028	-0.019, 0.076
36	-0.016	-0.077, 0.045	-0.004	-0.061, 0.054	-0.011	-0.068, 0.045
52	-0.060	-0.120, -0.001	-0.047	-0.109, 0.014	-0.055	-0.116, 0.004
65	-0.088	-0.221, 0.046	-0.087	-0.189, 0.014	-0.094	-0.194, 0.007
78	-0.027	-0.177, 0.122	-0.016	-0.127, 0.095	-0.021	-0.131, 0.088
91	-0.027	-0.161, 0.108	-0.028	-0.144, 0.089	-0.032	-0.145, 0.082
104	-0.030	-0.160, 0.101	-0.028	-0.150, 0.094	-0.028	-0.146, 0.091

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

Most of the data in the pooled studies after week 48 are from the combined studies 1001 and 1002, therefore the results from the Pooled analysis and from combined studies 1001 and 1002 are fairly consistent.

The proportions of subjects who had reduction in TLC at baseline at each timepoint (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. Inspection of each of the individual graphs (by time points) suggests no difference in the reduction profile of subjects in the inhaled insulin group and the comparator group except at Weeks 60, 72 and 96. It appears that the differences are small that a slight separation of curves may be due to random variation. There were only a few in both treatment groups that had reduction of more than 15%.

Pulmonary Function Test and Antibody Titer

Similar to Type 1 data, I also explored the relationship between the change in pulmonary function tests and the antibody titer by week of treatment using pooled Type 2 data. A regression line, to assess the relationship between the change from baseline of PFT measurements and the antibody titer, was plotted for the inhaled insulin-treated group. Correlation coefficients were included in the graphs to indicate how the antibody titers are related to the change in PFT measurements.

In general, the graphs showed that most of the correlations are small and negative. These may even be significant in some cases since even small correlations can be significant if the dataset is large enough. However, statistical significance, in general and especially true for correlations, is not the same as clinical significance. Therefore I find that there is no strong evidence to suggest any correlation between the change from baseline in pulmonary function tests and antibody titers. There is also no evidence of a 'correlation' trend over time in each of the PFT measurements.

Pulmonary Function Test and Insulin Dosing

The relationship between pulmonary function tests and the dosing was also explored. I looked at the change from baseline of PFT measurements with subject-reported average daily inhaled insulin doses at that specific week, as well as subject's cumulative daily insulin doses at that specific visit window using the combined 1001 and 1002 studies. Because of the different study drugs (particularly on the comparator group) that the subjects were treated to, I did not explore this relationship in the comparator group, or the pooled data for that matter..

Numerically the correlation coefficients are very small between the change from baseline in any of the pulmonary function test and the average total or cumulative total daily dose in the inhaled insulin group. Although most of these coefficients (from DLco, FEV1, and FVC measures) are negative, indicating some decrease in lung function with increasing dose, but these correlations are not strong enough to warrant any concern. Similarly, in FRC and TLC, change from baseline appears to be negatively correlated with insulin dose at the beginning but became positive towards Week 36 and Week 64, respectively. Again, these correlations are small and may not be clinically significant.

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

Analyses to assess the pulmonary safety of INH in different subpopulations based on age, race, and gender were performed using pooled Type 1 and pooled Type 2 data from controlled Phase 2/3 studies. Data were summarized for subjects with Type 1 DM and Type 2 DM using inhaled insulin or comparative insulin (i.e. subcutaneous or oral agents). Results are shown for subjects ≥ 18 years of age. Treatment difference within each subgroups were analyzed using the unadjusted model (PROC GLM) and the mixed model repeated measures (PROC MIXED) with covariates (baseline PFT, height, visit/time, age, male, protocol/study) to be consistent with the analyses done in the pooled data. Adjusting for the categorical variable gender should not affect the results or lose degrees of freedom using MMRM when analyzing the gender subpopulations since it will just ignore the variable. Meanwhile, adjusting for the continuous variable age when analyzing the age subpopulation should make the confidence intervals tighter.

4.1 SEX, RACE AND AGE

In this review, I find that there appears to be a greater decline in pulmonary function among inhaled insulin treated group, specifically FEV1 and DLco, than the comparator groups in both Type 1 and Type 2 Diabetes. Age for Type 1 DM are categorized into two groups: 18 – 44 and ≥ 45. Because only a minority of subjects is > 64 years of age, Dr. Seymour and I decided it best to include these subjects in the ≥ 45 group. In Type 2 Diabetes, because subjects were a lot older than Type 1 (Table XX for Type 1 Demo; Table XX for Type 2), we decided to categorize age into three groups: 18 – 44, 45 – 64, and ≥ 65. Since majority of subjects were white, we collapsed Blacks, Hispanics, Asians and others into the non-white group.

4.1.1 TYPE 1 DATA

It appears that majority of the subjects were between ages 18 to 44 (72%) in both treatment groups. Male subjects accounted for close to 55% in the Type 1 population in both treatment groups, while around 90% of the Type 1 population was white.

FEV_1, DLco, FVC, FRC, and TLC data for subjects with Type 1 DM are presented by age groups, gender, and race groups in Figure 31 to Figure 35. Descriptive statistics for change from baseline in each treatment groups by strata are available upon request.

In general, there appears to be a small shift in the treatment difference in FEV1, FVC, FRC, and TLC among subjects who were older (>44 years of age) in favor of the comparator group. However, this increase in treatment difference does not appear to be a cause for alarm. One possible reason for this shift could be due the natural decline of most PFT scores as one gets older, or this could also be due to unbalance sample size between the subgroups (e.g. 27% age > 44 vs. 72% age 18 - 44). There is no difference between unadjusted and adjusted model accounting for age.

In terms of race, there is no apparent difference between male and female subgroups in both unadjusted and adjusted model except on FRC score. There appears to be a gender difference in terms of FRC score which is quite difficult to explain except that this may just be random occurrence.

There also appears to be disparity in treatment difference among white and non-white subjects. This could easily be due to the enormous discrepancy in the sample size between the subgroups (e.g. 10% non-whites vs. 90% whites).

Figure 31: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race using Unadjusted and Mixed Model (Spatial Power) in FEV_1 (L) Score

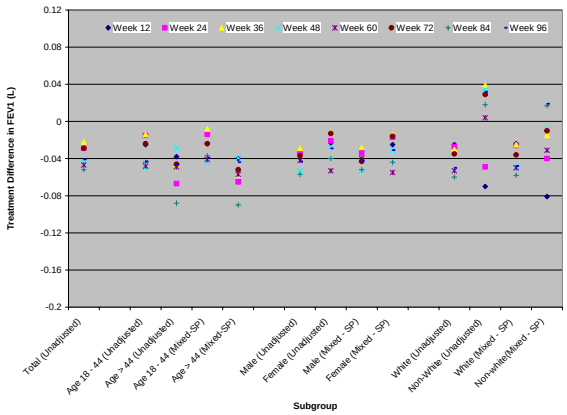


Figure 32: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race in DLco (mL/min/mmHg) Score

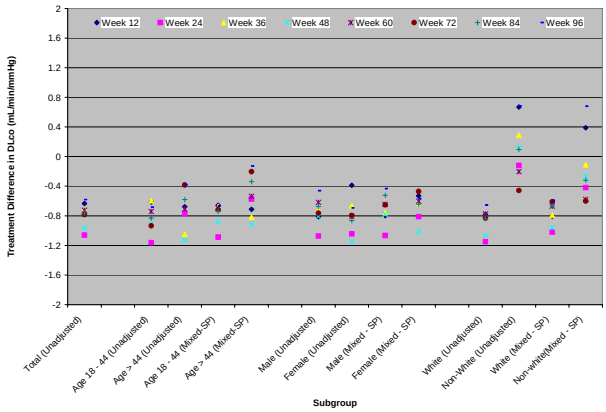


Figure 33: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race

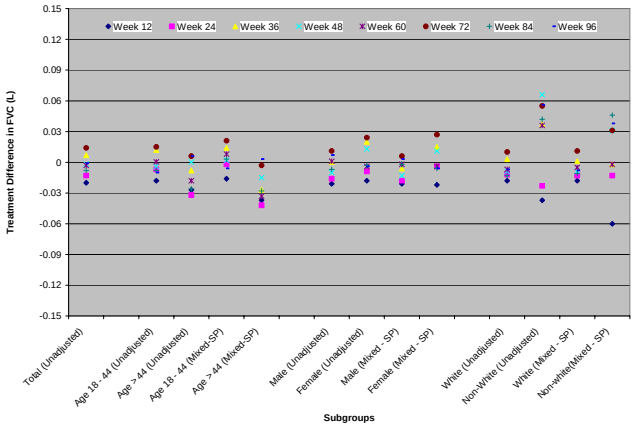


Figure 34: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race in FRC (L) Score

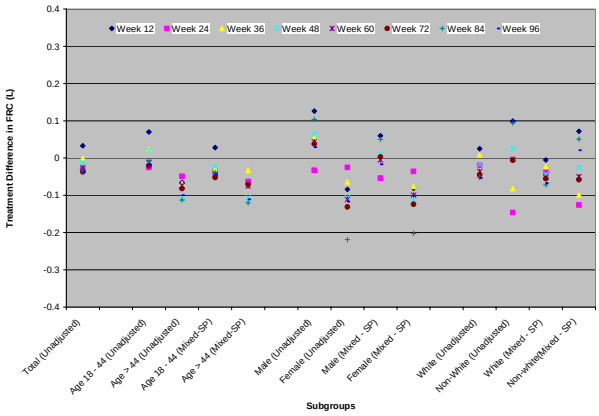
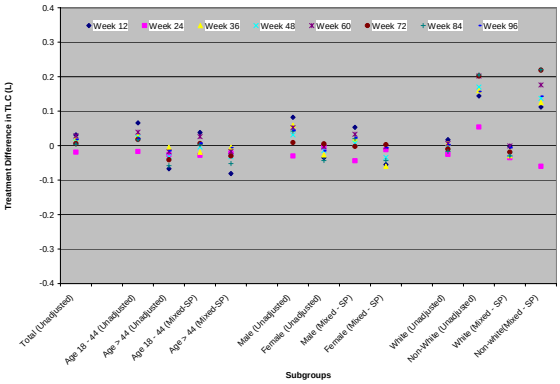


Figure 35: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race in TLC (L) Score



4.1.2 TYPE 2 DATA

It appears that majority of the subjects were between ages 45 to 64 (~65%) in both treatment groups. There are about 23% that were older than 64 and about 11% younger than 44. Male subjects accounted for close to 60% in the Type 2 population in both treatment groups. Almost 82% in the Type 2 population were white.

FEV_1, DLco, FVC, FRC, and TLC data for subjects with Type 2 DM are presented by age groups, gender, and race groups in Figure 36 to Figure 40.

In general, there appears to be a small shift in the treatment difference in FEV1, FVC, FRC, and TLC among subjects who were younger (<45 year of age) and older (>64 years of age) in favor of the comparator group. While subjects who are 45 to 64 years of age almost have identical treatment difference as the Type 2 pooled data. This increase in treatment difference does not appear to be a cause for alarm simply because subjects who are younger and subjects who are older accounts for only 11% and 23% respectively of the total population. Thus this shift should be cause for alarm. There is no difference between unadjusted and adjusted model accounting for age.

In terms of race, there appears to be a gender difference in terms of FEV1 and possibly TLC score, in which the average FEV1 score for the pooled Type 2 data seems to hover in the middle of the average FEV1 score of each of the gender. There is really no clear explanation as to why this occurs and this is not consistent with other PFT scores and with the Type 1 data.

There also appears to be disparity in treatment difference among white and non-white subjects. This could easily be due to the enormous discrepancy in the sample size between the subgroups (e.g. 18% non-whites vs. 82% whites).

Figure 36: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender, and Race using Unadjusted and Mixed Model (Spatial Power) in FEV_1 (L) Score

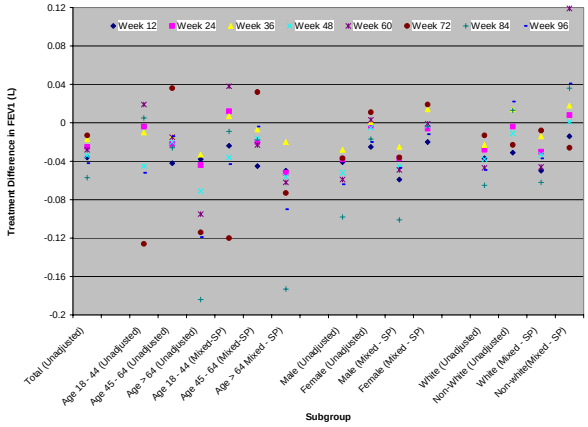


Figure 37: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender, and Race in DLco (mL/min/mmHg) Score

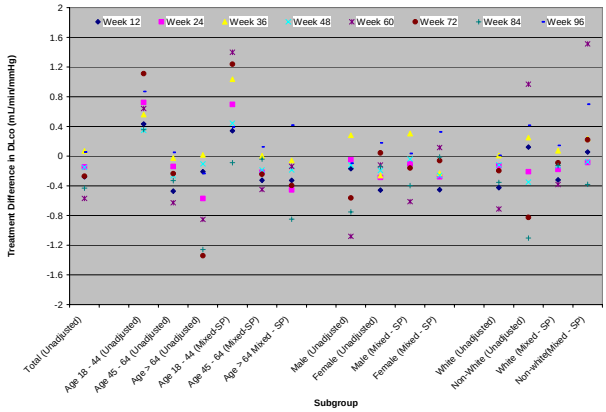


Figure 38: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender, and Race in FVC (L) Score

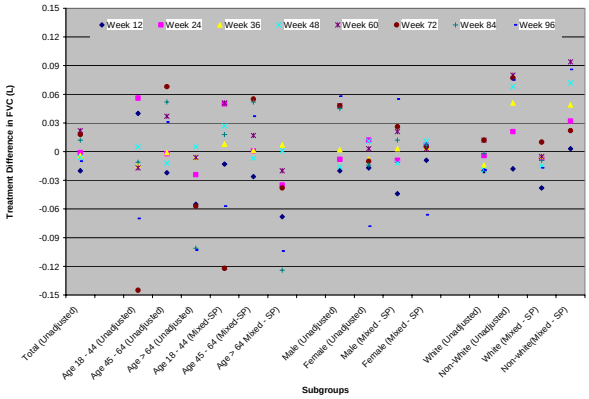


Figure 39: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender, and Race in FRC (L) Score

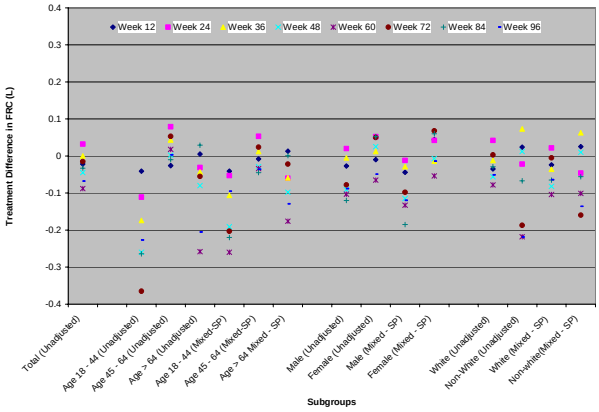
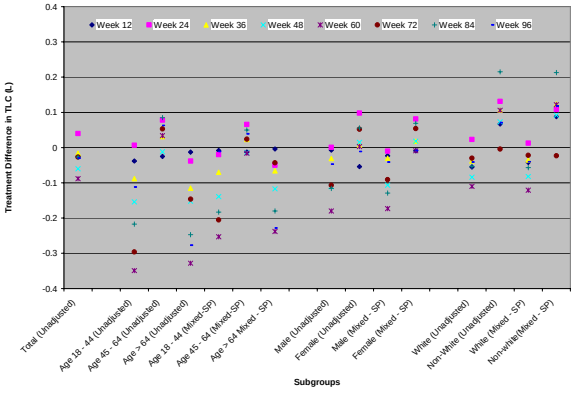



Figure 40: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender and Race in TLC (L) Score