DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
BRIEFING PACKAGE REVIEW

Date:	August 11, 2005
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From:	Sally Seymour, M.D., Medical Officer, DPADP, HFD-570
Through:	Eugene Sullivan, M.D., Deputy Director, DPADP
Through:	Badrul Chowdhury, M.D., Division Director, DPADP
Subject:	Pulmonary safety evaluation of Exubera (inhaled human insulin)

General Information

NDA/IND#:	NDA# 21-868, N000
Sponsor:	Pfizer
Drug Product:	Inhaled human insulin (Exubera)
Materials Reviewed:	NDA# 21-868, N000: December 27, 2004; January 12, 2005; April 26, 2005; May 6, 2005; June 10, 2005; June 22, 2005; July 5, 2005

This is an interim review from the Division of Pulmonary and Allergy Drug Products regarding the pulmonary safety of inhaled insulin (Exubera). This review addresses the pulmonary safety of inhaled insulin (Exubera), specifically the respiratory related adverse events, pulmonary function tests, chest x-ray, and high resolution computed tomography (HRCT) findings in subjects with type 1 and type 2 diabetes. In addition, this review addresses the pulmonary safety of inhaled insulin in subjects with underlying lung disease (asthma and COPD). It should be noted that this review is not final.

In NDA# 21-868, the Applicant has developed an inhaled insulin drug product (Exubera) for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. This is the first NDA for an inhaled insulin drug product. The clinical efficacy and overall safety of inhaled insulin (Exubera) was reviewed by Dr. Karen Mahoney of the Division of Metabolic and Endocrine Drug Products. Because of the novel method of delivery of insulin in this application, the Division of Pulmonary and Allergy Drug Products has provided input regarding assessment of the pulmonary safety of inhaled insulin during clinical development. The focus of this review is the pulmonary safety of inhaled insulin (Exubera), which supplements Dr. Mahoney's clinical review of the efficacy and overall safety of inhaled insulin.

The Executive Summary contains an overview of the pulmonary safety of inhaled insulin, while the body of the review contains a detailed review of the integrated pulmonary safety of inhaled insulin.

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1 Executive Summary

1.1 Summary of Clinical Findings

1.1.1 Brief Overview of Clinical Program for Pulmonary Safety

The Applicant's clinical program to evaluate the safety and efficacy of inhaled insulin includes 20 phase 2 and phase 3 clinical studies as well as 31 clinical pharmacology studies. The Applicant has completed 14 clinical studies evaluating the efficacy and safety of inhaled insulin in subjects with type 1 and type 2 diabetes. In addition, the Applicant has 6 ongoing clinical studies at the time of this review (1022, 1028, 1029, 1030, 1036, and 1017). The majority of the studies are controlled studies; however, two of the studies are extension studies (1036 and 111) and not controlled.

Most of the studies were limited to adult subjects (≥ 18 years) with diabetes; however, one study (1009) was conducted in subjects <18 years of age and two other studies (106, 107) included some subjects <18 years of age. The Applicant is not seeking an indication in subjects <18 years of age; therefore, the focus of this review was the pulmonary safety data in adult subjects.

The primary sources for the pulmonary safety database were the pooled controlled phase 2/3 studies in adult subjects with type 1 and type 2 diabetes. Pulmonary safety data from the ongoing studies was included in the pooled dataset primarily because the ongoing studies provide data for subjects exposed to inhaled insulin for 1 to 2 years.

To assess the pulmonary safety of inhaled insulin, the Applicant performed pulmonary function tests (PFTs) at baseline and at different time points during each clinical study. PFTs included spirometry, lung volumes, and DLCO. The focus of this review is on FEV_1 and DLCO; however, other key PFTs were reviewed. In addition, the Applicant performed a baseline chest x-ray (CXR) and end of study CXR in most of the clinical studies. High resolution computed tomography (HRCT) of the thorax was performed in a subset of subjects. In some of the later studies, the Applicant utilized a cough questionnaire and the Mahler Dyspnea Indices to further assess cough and dyspnea adverse events. This review addresses the PFTs, CXR, and HRCT findings in addition to the respiratory related adverse events.

The number of subjects exposed to inhaled insulin in the controlled clinical studies, greater than 600 subjects with type 1 diabetes and greater than 1200 subjects with type 2 diabetes is reasonable to assess the pulmonary safety of inhaled insulin in subjects without underlying lung disease. In addition, the duration of inhaled insulin exposure, up to 2 years in >200 subjects with type 1 diabetes and up to 2 years in approximately 150 subjects with type 2 diabetes, is reasonable to assess the pulmonary safety of inhaled insulin in subjects without underlying lung disease.

The Applicant's clinical program also includes two ongoing studies specifically designed to assess pulmonary safety in subjects with asthma (1028) and COPD (1030). The

limited pulmonary safety data in subjects with underlying lung disease is not adequate to assess the pulmonary safety of inhaled insulin in subjects with underlying lung disease.

1.1.2 Respiratory Related Adverse Events

In the controlled phase 2/3 studies, there were more respiratory related serious adverse events (SAEs) in the inhaled insulin group than in the comparator groups. All of the respiratory related SAEs were in subjects with type 2 diabetes. There were no respiratory related SAEs in the completed studies in subjects with type 1 diabetes. Of the respiratory-related SAEs, asthma and bronchitis SAEs were reported in more than one subject in the inhaled insulin group and were more common in the inhaled insulin group than the comparator group. It should be noted in the controlled phase 2/3 studies, there were no respiratory related deaths.

More subjects discontinued due to respiratory related AEs in the inhaled insulin group than in the comparator groups. Cough was the most common AE leading to discontinuation in subjects with either type 1 and type 2 diabetes. Twenty subjects discontinued due to cough AEs in the inhaled insulin group compared to none in the comparator groups. Asthma and dyspnea were the next most common AEs leading to discontinuation. In addition to permanent discontinuations due to respiratory AEs, there were more respiratory AEs leading to temporary discontinuation of therapy in the inhaled insulin group, than in the comparator groups.

Respiratory related adverse events were more common in the inhaled insulin group than in the comparator groups. Respiratory tract infection, increased cough, pharyngitis, and sinusitis were the most common respiratory related AEs reported in both treatment groups. Cough was the respiratory related adverse event reported at much greater incidence in the inhaled insulin group than in the comparator group. There were many other common respiratory related adverse events that were reported at a greater incidence in the inhaled insulin group than in the comparator group.

Cough adverse events were further assessed through the administration of a cough questionnaire in three individual studies. It should be noted that the cough questionnaire was not administered to every subject with a cough adverse event, but only to those subjects with cough AEs not attributed by the investigator to another condition. The cough questionnaire data suggested that for most subjects cough was rare or occasional during the day and rare or absent at night. For most subjects the severity of cough events was primarily mild. In general, the cough was not productive. Finally, a majority of subjects reported the timing of the cough event within seconds to minutes after inhaled insulin dosing; however, some subjects did report no relationship between cough and inhaled insulin dosing.

Some uncommon respiratory related adverse events are worth noting. There were four cases of malignant lung neoplasms reported in the clinical studies. Three cases were in the inhaled insulin group and one in the comparator group. One case in the inhaled insulin group is likely not related to study medication since the subject had a lung nodule at screening. Three cases of "pulmonary fibrosis" were noted in the uncontrolled

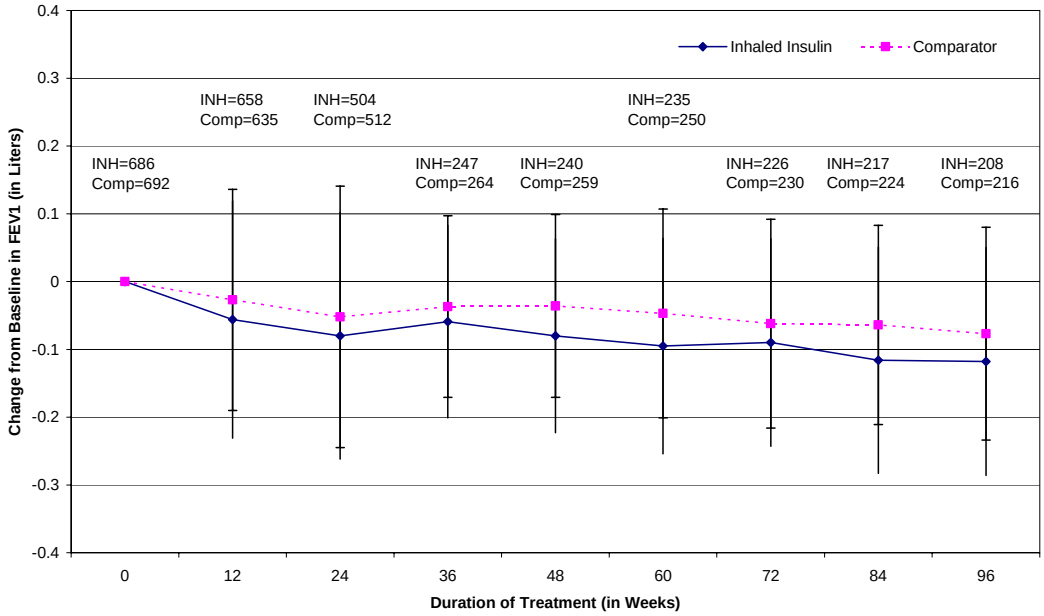
extension studies; however, in two of the cases an HRCT was not performed, which calls into question the diagnosis of pulmonary fibrosis.

1.1.3 Effect on Pulmonary Function in Type 1 Diabetes

1.1.3.1 FEV_1

Subjects with type 1 diabetes treated with inhaled insulin consistently showed a greater mean decline from baseline FEV_1 over time compared to the comparator group. One study suggested inhaled insulin has an effect on FEV_1 within the first few weeks of exposure. The effect of inhaled insulin on FEV_1 progressed during the first year of exposure then stabilized between the first and second year as shown below in Figure 1.

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



Source: Dr. Joan Buenconsejo's Biometrics Review

In the phase 2/3 controlled studies, after 2 years of treatment, subjects in the inhaled insulin group had a mean decline from baseline FEV_1 of 118mL while subjects in the comparator group had a mean decline from baseline FEV_1 of 77mL. Both treatment groups demonstrated a larger mean FEV_1 decline than what would be expected in non-smoking subjects without significant lung disease. The 2-year mean treatment group difference between inhaled insulin and the comparator group was approximately 40mL, favoring the comparator group.

Controlled data is not available to assess if the treatment group difference increases after 2 years. However, non-controlled extension studies have exposed subjects to inhaled insulin for up to 84 months. The non-controlled PFT data from two extension studies suggest that the mean decline from baseline FEV_1 continues with continued exposure to

inhaled insulin. However, without a comparator group, it is unknown if the treatment group difference changes with time.

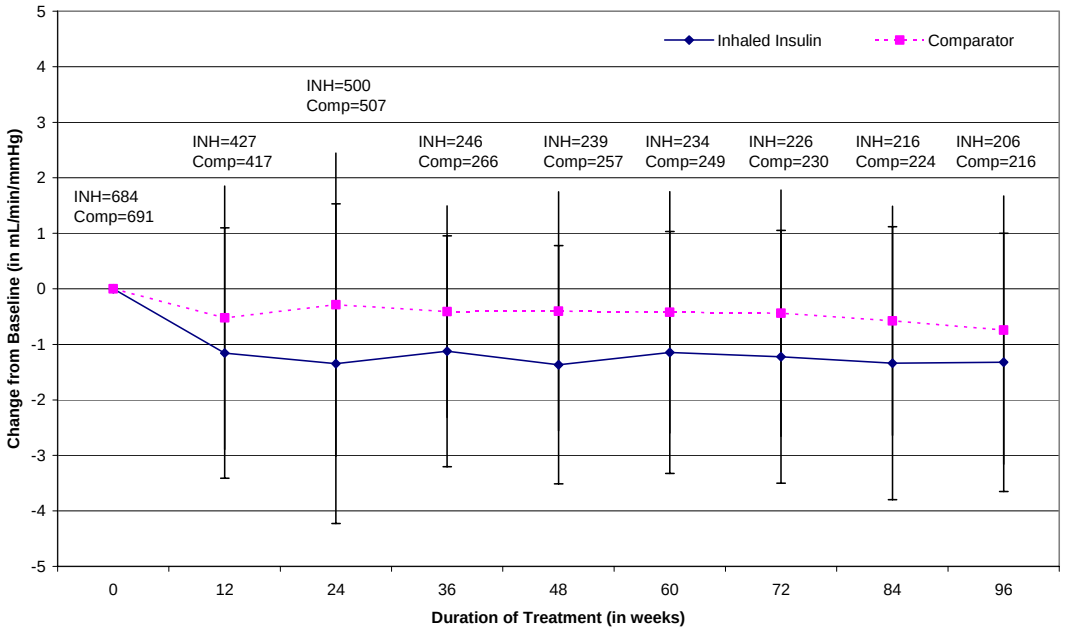
The reversibility of the effect of inhaled insulin on FEV_1 was evaluated in a controlled fashion in Study 1027. However, Study 1027 does not adequately address the reversibility of the effect of inhaled insulin on FEV_1 in type 1 diabetes primarily because there was essentially no difference in the mean change from baseline FEV_1 at Week 12 prior to discontinuation of inhaled insulin and the mean change from baseline FEV_1 after 12 weeks of discontinuation of inhaled insulin. Reversibility of the effect of long term inhaled insulin use was assessed in the non-controlled extension Study 111. However, the study design and results have issues which limit the interpretability of the reversibility data. Thus, the submitted data is not adequate to support that the change from baseline FEV_1 treatment group difference noted with inhaled insulin in type 1 diabetes is reversible.

1.1.3.2 DLCO

Subjects with type 1 diabetes treated with inhaled insulin consistently showed a greater mean decline from baseline DLCO over time compared to the comparator group in most of the individual studies as well as in the pooled adult controlled phase 2/3 studies in type 1 diabetes. A single study (1027) suggested that inhaled insulin affects the DLCO within the first two weeks of exposure. In the pooled phase 2/3 controlled studies in type 1 diabetes, the inhaled insulin group had a greater decline in DLCO than the comparator group, thus, there is a treatment group difference favoring the comparator.

In the pooled phase 2/3 controlled studies, the mean treatment group difference in change from baseline DLCO fluctuated throughout the treatment period. At Week 96, the mean treatment group difference was approximately -0.5 to -0.6mL/min/mmHg, favoring the comparator. The maximum mean treatment group difference favoring the comparator was -1 mL/min/mmHg, which was noted at Week 24. It should be noted, though that the Week 96 data and Week 12 DLCO data showed a similar mean treatment group difference. Thus, the effect of inhaled insulin on DLCO did not appear to progress over 2 years of treatment as shown below in Figure 2.

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



Source: Dr. Joan Buenconsejo's Biometrics Review

Exposure to inhaled insulin longer than 24 months in type 1 diabetes has not been studied in controlled studies. One non-controlled extension study (Study 1036) has exposed subjects to inhaled insulin up to 84 months. The data suggest that after a decline from baseline DLCO in the first 12 months, the mean change from baseline DLCO does not continue to progress through 84 months of exposure.

The reversibility of the effect of inhaled insulin on DLCO was evaluated in a controlled fashion in Study 1027. The data from Study 1027 does suggest that after discontinuation of inhaled insulin following 12 weeks of inhaled insulin treatment, the mean treatment group difference decreases and favors the inhaled insulin group (after 12 weeks of discontinuation) However, Study 1027 does not adequately address the effect of the reversibility of the effect of inhaled insulin. Even if the discontinuation data suggests the effects of inhaled insulin on DLCO are reversible after 12 weeks of inhaled insulin exposure, the effects may not be reversible after longer inhaled insulin exposure.

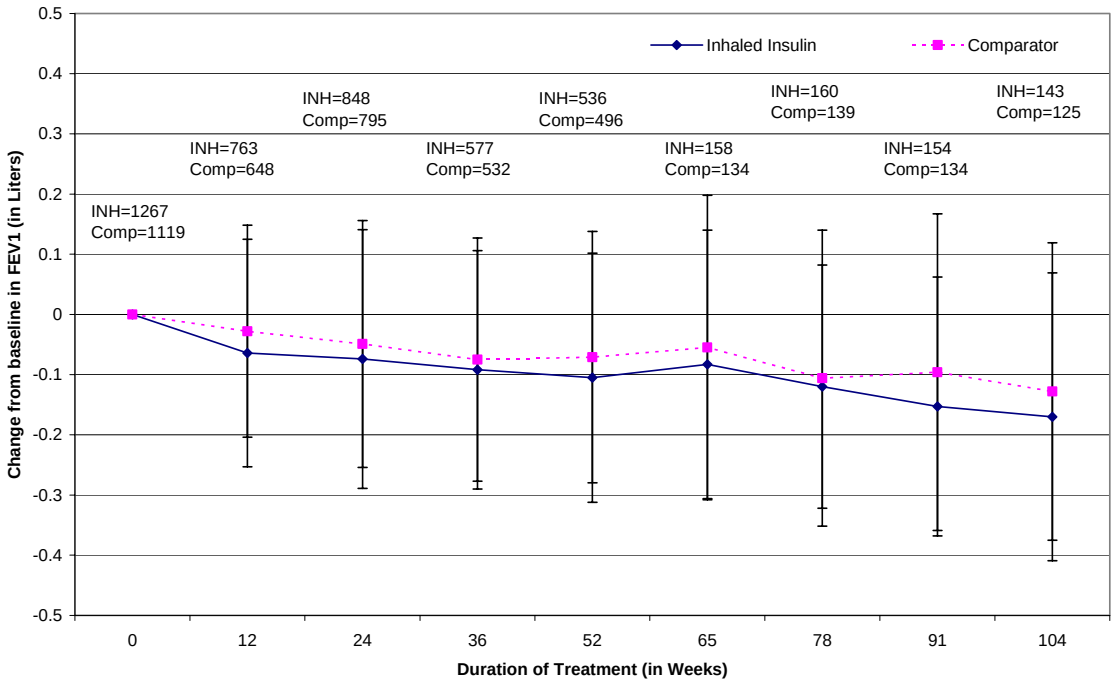
Reversibility of the effect of long term inhaled insulin use was also assessed in the extension Study 111. However, the study design and results have issues which limit the interpretability of the reversibility data. Thus, there is not adequate controlled data to determine if the long term effects on DLCO from exposure to inhaled insulin are reversible.

1.1.4 Effect on Pulmonary Function in Type 2 Diabetes

1.1.4.1 FEV_1

Subjects with type 2 diabetes treated with inhaled insulin showed a greater mean decline from baseline FEV_1 over time compared to the comparator group in most of the individual studies as well as in the pooled adult controlled phase 2/3 studies. The pooled controlled studies indicate that the mean treatment group difference favors the comparator within 3 months of exposure. The mean treatment group difference fluctuates during the 104 week treatment period; however, the mean treatment group difference at Week 12 and Week 104 are similar, which suggests that the effect of inhaled insulin on FEV_1 in type 2 diabetes is not progressive over 2 years.

Figure 3 Mean Change from Baseline FEV_1 over Time in the Phase 2/3 Controlled Studies in Type 2 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

In the phase 2/3 controlled studies, after two years of treatment, the inhaled insulin group demonstrated a mean decline from baseline FEV_1 of 170mL, while subjects in the comparator group demonstrated a mean decline from baseline FEV_1 of 128mL. Both treatment groups demonstrated a larger mean decline from baseline FEV_1 than would be expected in non-smoking subjects without significant lung disease. At Week 104, the mean treatment group difference is approximately 40mL, which is similar to the mean treatment group difference for change from baseline FEV_1 in subjects with type 1 diabetes.

Exposure to inhaled insulin longer than 24 months in type 2 diabetes has not been studied in controlled studies. However, non-controlled extension studies have exposed subjects

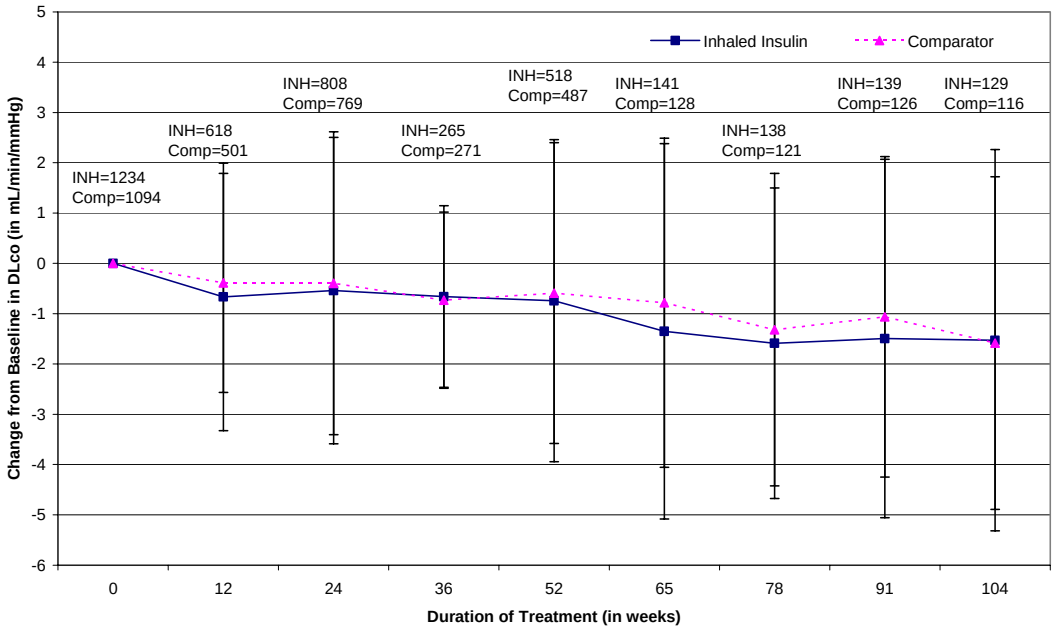
to inhaled insulin up to 84 months. The non-controlled PFT data from Study 1036 suggests that the mean decline from baseline FEV_1 continues with continued exposure. However, without a comparator group, it is unclear if the mean treatment group difference changes further with time.

The reversibility of the effect of inhaled insulin on FEV_1 was evaluated in combined Study 1001-1002. The results of combined Study 1001-1002 suggest that the mean treatment group difference after inhaled insulin treatment for 104 weeks was -40mL, favoring the comparator. However, after discontinuation of inhaled insulin for 6-12 weeks, there was minimal mean treatment group difference, which suggests the effects of inhaled insulin treatment (up to 104 weeks) on FEV_1 may be reversible.

1.1.4.2 DLCO

Subjects with type 2 diabetes treated with inhaled insulin in general showed a greater mean decline from baseline DLCO at most time points compared to the comparator group in most of the individual studies as well as in the pooled adult controlled phase 2/3 studies in type 2 diabetes. In the pooled phase 2/3 controlled studies in type 2 diabetes, the mean treatment group difference at most time points favored the comparator; however the mean treatment group difference fluctuated throughout the 104 week treatment period. The maximum mean unadjusted treatment group difference was approximately -0.6mL/min/mmHg at Week 65, favoring the comparator. This mean treatment group difference is similar to the mean treatment group difference noted in subjects with type 1 diabetes. However, at Week 104, the mean treatment group difference favored the inhaled insulin group. Thus, the effect of inhaled insulin on DLCO did not appear to progress over 2 years of treatment as shown below in Figure 4.

Figure 4 Mean Change from Baseline DLCO vs. Time in Adult Phase 2/3 Controlled Studies in Type 2 Diabetes



Source: Dr. Joan Buenconsejo's Biometrics Review

Exposure to inhaled insulin longer than 24 months in type 2 diabetes has not been studied in controlled studies. One non-controlled extension study (Study 1036) has exposed subjects to inhaled insulin up to 84 months and suggests that after a decline from baseline DLCO in the first 12 months, the mean change from baseline DLCO does not continue to progress.

The reversibility of the effect of inhaled insulin on DLCO was evaluated in a controlled fashion in combined Study 1001-1002. The results of combined Study 1001-1002 suggest that at Week 104 there is essentially no mean treatment group difference. Following discontinuation of study medication, both treatment groups showed an improvement in DLCO. After 12 weeks of discontinuation, there was a slight treatment group difference favoring the comparator.

1.1.5 Chest X-ray and High Resolution Computed Tomography

Baseline and end of study chest x-rays (CXRs) were performed in almost all of the clinical studies. The CXR data in the phase 2/3 adult controlled clinical studies demonstrates that there were more significant changes from baseline CXR in the inhaled insulin treatment group than in the comparator group. This was true in both type 1 and type 2 diabetes. The most common new significant findings on CXR were nodular density, opacity, nodule, atelectasis, cardiomegaly, and enhanced vasculature or pulmonary edema. Although the new finding of a nodule, opacity, or density was more common in the inhaled insulin group than in the comparator group, follow up imaging (CT scan, additional CXR) indicated resolution in most cases.

Baseline and two year high resolution computed tomography (HRCT) scans of the thorax in 50 subjects treated with inhaled insulin and 50 subjects treated with comparator were requested by the Agency to assess for parenchymal lung changes associated with inhaled insulin use. The Applicant submitted controlled HRCT data at baseline and 24 weeks in 116 subjects, controlled HRCT data at baseline and 24 months in 104 subjects, and "for cause" HRCT data in 48 subjects. The controlled HRCT data does not suggest an increase in abnormal findings associated with inhaled insulin use compared to SC insulin at 24 weeks or 24 months. Because the majority of the "for cause" HRCTs were performed in the extension studies in which all subjects received inhaled insulin, it is difficult to draw any conclusions from the "for cause" HRCT data.

1.1.6 Exploratory Analyses

Insulin is a polypeptide that may be associated with the formation of anti-insulin antibodies. The Biometrics reviewer performed exploratory analyses to assess for a correlation between change in pulmonary function and insulin antibody titer. The analyses in subjects with type 1 diabetes and type 2 diabetes do not suggest a correlation between mean change from baseline FEV_1, DLCO, FVC, TLC, FRC and insulin antibody titer.

The association between insulin exposure and change in pulmonary function was explored in several individual studies. The Biometrics reviewer analyzed the association between the average total daily insulin dose and change from baseline FEV_1, DLCO, FVC, TLC, and FRC as well as the association between the cumulative insulin dose and the change from baseline FEV_1, DLCO, FVC, TLC, and FRC at different time points in the individual studies. The analyses do not suggest a correlation between change from baseline FEV_1, DLCO, FVC, TLC, and FRC and the average total daily inhaled insulin dose or the cumulative inhaled insulin dose.

1.1.7 Underlying Lung Disease

The Agency requested the Applicant prospectively assess the effects of inhaled insulin in subjects with underlying lung disease, such as asthma and COPD. The Applicant's clinical program includes two ongoing studies: one in subjects with asthma and one in subjects with COPD. These studies were specifically designed to assess the efficacy and safety of inhaled insulin in these populations. The focus of this section is on the pulmonary safety in subjects with asthma and COPD.

1.1.7.1 Asthma

Data regarding the pulmonary safety of inhaled insulin in subjects with asthma comes from two sources: the ongoing Study 1028 and a cohort of retrospectively identified subjects with asthma in the controlled phase 2/3 studies. Of these two sources, Study 1028 provides the best source of data because Study 1028 was specifically designed to prospectively assess the effects of inhaled insulin in subjects with asthma. The Applicant also retrospectively identified 54 subjects with asthma who participated in the controlled phase 2/3 studies. Although subjects with asthma could have enrolled in the phase 3 studies, the data from the retrospectively identified cohort is less robust because the

diagnosis of asthma is based upon a subject reported history of asthma and the diagnosis was not confirmed.

Study 1028

Study 217-1028 is an ongoing 15 month controlled study which provides interim data on 139 subjects with asthma; however, 12 month PFT data is only available for 27 subjects. The results from Study 1028 indicate that there were a similar number of subjects in each treatment group (inhaled insulin or SC insulin) with respiratory AEs. In general, the types of respiratory AEs noted in subjects with asthma were similar to AEs noted in subjects without asthma. Of the respiratory AEs reported in Study 1028, increased cough and respiratory tract infection were the AEs with the greatest difference between treatment groups favoring the comparator. In addition, dyspnea, pharyngitis, respiratory disorder, respiratory tract infection, and voice alteration were more common in the inhaled insulin group than in the SC insulin group.

Overall, asthma AEs were more common in the comparator group. The protocol specifically defined a non-severe asthma exacerbation (home-monitored FEV_1<80% baseline for two or more consecutive days or <60% of baseline at any time) and severe asthma exacerbation (oral corticosteroids or physician/ER visit/hospitalization). The event rates of both non-severe and severe asthma exacerbations were higher in the inhaled insulin group than in the SC insulin group. However, the number of subjects requiring systemic corticosteroid treatment was similar between treatment groups.

The interim PFT data from Study 1028 suggest that subjects treated with inhaled insulin demonstrated a greater mean decline from baseline FEV_1 (pre-BD) than the comparator group. In general, from Week 1 through Week 18 there was a treatment group difference usually favoring the comparator. However, by Week 52, the treatment group difference for change from baseline FEV_1 (pre-BD) had increased, further favoring the comparator. At Week 52, the inhaled insulin group had a mean decline from baseline FEV_1 of 296mL, while the comparator group had a mean decline from baseline FEV_1 of 113mL. The decline in FEV_1 in both groups at Week 52 is greater than the expected annual rate of decline in FEV_1 for non-smoking subjects with asthma – a decline of FEV_1 of approximately 30-33mL/year.[3] The mean treatment group difference at Week 52 (-183mL) is much greater than what was noted at one year in the pooled controlled phase 2/3 studies (without underlying lung disease), which was approximately -30 to -40mL. It should be noted that the 52 week data in Study 1028 is based upon only 27 subjects. The post-bronchodilator FEV_1 showed a similar pattern as the pre-BD FEV_1.

The interim PFT data from Study 1028 suggest that subjects treated with inhaled insulin demonstrated a greater mean decline from baseline DLCO (pre-BD) than the comparator group. The mean unadjusted treatment group difference for change from baseline DLCO (pre-BD) fluctuated between -0.1 to -0.8mL/min/mmHg until Week 39. At Week 52, the mean treatment group difference for change from baseline DLCO had increased further favoring the comparator (-1.75mL/min/mmHg). At Week 52, the inhaled insulin group had a mean change from baseline (pre-BD) DLCO of -2.394mL/min/mmHg, while the comparator group had a mean change from baseline (pre-BD) DLCO of

-0.646mL/min/mmHg. The treatment group difference is greater than the treatment group difference noted at one year in the pooled controlled phase 2/3/ studies (without underlying lung disease), which was approximately -0.1 and -0.9mL/min/mmHg in type 2 and type 1 diabetes, respectively. It should be noted that the 52 week data in Study 1028 is based upon only 27 subjects. The post-bronchodilator DLCO showed a similar pattern as the pre-BD DLCO.

Asthma control was assessed by the Asthma Control Questionnaire, which is a validated patient reported outcomes instrument measuring asthma control. The instrument includes 6 questions and FEV_1. The questions are on a scale of 0 to 6, with higher scores reflecting poor control. At Week 52, the inhaled insulin group showed a small increase in both the subject and clinical evaluation score suggesting a decline in asthma control, while the SC insulin group showed a small decrease in both the subject and clinical evaluation score, suggesting an improvement in asthma control. Again, it should be noted that the 52 week data in Study 1028 is based upon only 27 subjects.

Retrospectively Identified Subjects with Asthma
In the 54 subjects retrospectively identified with asthma (24 inhaled insulin, 30 comparator), the number of subjects with respiratory AEs was similar between treatment groups. Of the respiratory AEs reported asthma, bronchitis, increased cough, dyspnea, pharyngitis, respiratory tract infection, and sputum increased were reported in more than one subject and in a higher percentage of subjects in the inhaled insulin group than subjects in the comparator group,

The PFT data from the 54 subjects retrospectively identified with asthma indicate that subjects in the inhaled insulin group had a greater mean decline from baseline FEV_1 and DLCO than subjects in the comparator group. The mean treatment group difference for change from baseline FEV_1 is fairly consistent throughout the treatment period. After 12 months, the inhaled insulin group demonstrated a decline from baseline FEV_1 of 61mL while the comparator group demonstrated a decline from baseline FEV_1 of 18mL. It should be noted that the 12 month PFT data is based upon 12 subjects.

The treatment group difference for change from baseline DLCO is not as consistent because in the first 3 months of exposure, the treatment group difference favors the inhaled insulin group; however, after 3 months, the treatment group difference favors the comparator. After 12 months, the inhaled insulin group demonstrated a decline from baseline DLCO of 1.802 mL/min/mmHg while the comparator group demonstrated a decline from baseline DLCO of 0.145mL/min/mmHg. However, it should be noted that the 12 month PFT data is based upon 12 subjects.

1.1.7.2 COPD

Data regarding the pulmonary safety of inhaled insulin in subjects with COPD comes from two sources: the ongoing Study 1030 and a cohort of retrospectively identified subjects with COPD in the controlled phase 2/3 studies. Of these two sources, Study 1030 provides the best source of data because Study 1030 was specifically designed to prospectively assess the effects of inhaled insulin in subjects with COPD. The Applicant

also retrospectively identified 101 subjects with COPD who participated in the controlled phase 2/3 studies. Although subjects with COPD could have enrolled in the phase 3 studies, the data from the retrospectively identified cohort is likely not as robust because the diagnosis of COPD is based upon a retrospective diagnosis of COPD (history of smoking and FEV_1/FVC <70% at baseline).

Study 1030

Study 217-1030 is an ongoing 15 month controlled study which provides interim data on 72 subjects with COPD; however, 12 month PFT data is only available for 30 subjects. The interim results from Study 1030 indicate that the inhaled insulin group had more respiratory related SAEs (4 – pneumonia, COPD exacerbation (2), and URI) than the SC insulin group (0). There were a similar number of subjects in each treatment group with respiratory AEs. In general, the types of respiratory AEs noted in subjects with COPD were similar to AEs noted in subjects without COPD. Of the respiratory AEs reported in Study 1030, bronchitis, increased cough, dyspnea, and voice alteration were reported more frequently in more subjects treated with inhaled insulin than subjects treated with the comparator.

The total number of both non-severe (systemic corticosteroids, antibiotics, or oxygen) and severe (requiring hospitalization >24 hours) COPD exacerbations was higher in the inhaled insulin group than in the SC insulin group. The inhaled insulin group had 10 subjects who had 14 non-severe COPD exacerbations and the SC insulin group had 4 subjects who had 9 non-severe COPD exacerbations. For severe COPD exacerbations, the inhaled insulin group had 1 subject with 1 event, while the SC insulin group had none. The number of subjects requiring systemic corticosteroid treatment was slightly higher in the inhaled insulin group. The inhaled insulin group had 5 subjects requiring 6 systemic corticosteroid rescues, while the SC insulin group had 3 subjects requiring 5 systemic corticosteroid rescues.

The interim PFT data from Study 1030 indicate that subjects in both treatment groups demonstrate a mean decline from baseline FEV_1 (pre-BD) at Week 52. At Week 52, the inhaled insulin group had a mean decline from baseline FEV_1 of 127mL, while the comparator group had a mean decline from baseline FEV_1 of 145mL. At Week 52, the mean treatment group difference for change from baseline pre-BD FEV_1 favored the inhaled insulin group (17mL). For the post-BD FEV_1, the inhaled insulin group had a larger decline than the SC insulin group throughout the 52 week treatment period. The treatment group difference was -27 mL at Week 52 for the post-BD FEV_1, favoring the comparator. It should be noted that the Week 52 data is based upon 30 subjects.

Both treatment groups demonstrated a mean decline in pre-BD DLCO. Initially, the inhaled insulin group demonstrated a larger mean decline in pre-BD DLCO; however, by Week 12, the SC insulin group demonstrated a greater mean decline than the inhaled insulin group. At Week 52, the inhaled insulin group demonstrated a decline from baseline pre-bronchodilator DLCO of 0.338mL/min/mmHg while the SC insulin group demonstrated a decline from baseline pre-bronchodilator DLCO of 0.606mL/min/mmHg. Thus, at Week 52, the treatment group difference (0.268 mL/min/mmHg) favored the

inhaled insulin group. The post-BD DLCO also suggested that at Week 52 the SC insulin group had more of a decline than the inhaled insulin group. In fact, the inhaled insulin group actually demonstrated a slight increase from baseline post-bronchodilator DLCO at Week 52. It should be noted that the Week 52 data is based upon 30 subjects.

Retrospectively Identified Subjects with COPD

In the 101 subjects retrospectively identified with COPD in the controlled phase 2/3 studies (50 inhaled insulin, 51 comparator), the number of subjects with overall AEs, SAEs, and respiratory related AEs was similar between treatment groups. Two of the SAEs in the inhaled insulin group were respiratory related – epistaxis and vocal cord polyp. Bronchitis, increased cough, dyspnea, epistaxis, pharyngitis, respiratory disorder, sinusitis, and sputum increased were reported in more than one subject and in a higher percentage of subjects in the inhaled insulin group than subjects in the comparator group.

The PFT data from the 101 subjects retrospectively identified with COPD suggest that the mean treatment group difference in change from baseline FEV_1 is not consistent during the treatment period. Initially, the inhaled insulin group demonstrated a greater mean decline from baseline FEV_1 than subjects in the comparator group. However, after 6 months, the comparator group demonstrated a greater mean decline from baseline FEV_1 through 12 months. At 12 months, the inhaled insulin group demonstrated a mean decline from baseline FEV_1 of 13mL while the comparator group demonstrated a mean decline from baseline FEV_1 of 37mL, favoring the inhaled insulin group.

The inhaled insulin group demonstrated a greater mean decline from baseline DLCO than subjects in the comparator group throughout the treatment period. At 12 months, the inhaled insulin group demonstrated a mean decline from baseline DLCO of 1.407 mL/min/mmHg while the comparator group demonstrated a mean decline from baseline DLCO of 1.146mL/min/mmHg.

2 Introduction and Background

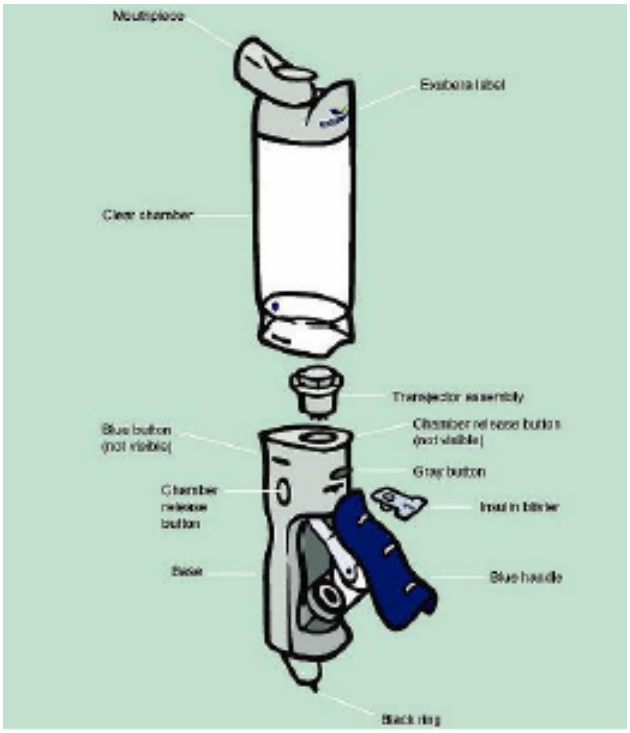
2.1 Product Information

The Applicant has developed a dry powder recombinant human insulin to be administered by oral inhalation via a specially designed pulmonary inhaler for the indication of the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. Inhaled insulin was developed as an alternative mode of delivery to injected insulin. The proposed trade name is Exubera. It is proposed to be administered immediately prior to meals.

The drug substance is , which is a recombinant human insulin produced by . The rDNA insulin is produced by *Escherichia coli*. The drug product is a white to off-white powder, which contains sodium citrate, mannitol, glycine, and sodium hydroxide.
Reviewer's Comment: The Agency's Inactive Ingredient Search for Approved Drug Products was accessed to assess if sodium citrate, mannitol, and glycine are common excipients in inhaled drug products. Mannitol and glycine were not listed as inactive ingredients in currently approved drug products. Sodium citrate is listed as an inactive ingredient at a maximum potency of 0.6% in an inhalation solution in the Agency's Inactive Ingredient Search for Approved Drug Products listing [www.accessdata.fda.gov/scripts/cder/iig/index.cfm].

The inhaled insulin comes as a unit dose in a foil blister. Inhaled insulin is supplied in a 1.0mg or 3.0mg nominal dose blister package. The inhaler is a reusable mechanical inhaler, which is illustrated in Figure 5, below.

Figure 5 Insulin Pulmonary Inhaler



Source: N21868/N_000/2004-12-27/summary/quality_summary.pdf, pg 120

The base contains the air pump system and valves that generate, store, and release compressed air. This compressed air is the source of energy to extract the powder and generate the aerosolized insulin cloud. No propellants are used. The patient manually pumps the base handle to store the compressed air and then compresses the trigger button, which raises the blister into the transjector for puncture. The valve releases the compressed air into the transjector, which leads to aerosolization of the powder from the blister pack [N21868/N_000/2004-12-27/summary/quality_summary.pdf, pg 119].

Reviewer's Comment: For more information regarding the drug substance and drug product as well as a detailed review of the CMC information, refer to the CMC review.

2.2 Pre-submission Regulatory Activity

The following is a list of key regulatory meetings between the Applicant and the Agency.

August 18, 2000, Industry Meeting

- The Agency recommended at least one year controlled data for the NDA submission to assess pulmonary safety.
- The Agency stated the development program should address the acute and chronic effects of inhaled insulin in subjects with underlying lung disease.
- The Agency stated that the NDA must include data on device performance for the entire life of the device.

April 16, 2001, Teleconference

- The Agency raised the following concerns:
  - Lack of adequate and long-term controlled pulmonary safety data
  - Relatively small number of subjects on Inhaled insulin
  - Relatively short duration of exposure data
  - Limited data in Type 1 diabetics
  - Potential bias introduced by non-random participation in the two proposed extension studies
  - Lack of adequate safety and efficacy data in subjects with concurrent lung disease.
- The Agency requested the long-term pulmonary safety database include safety and efficacy assessments on the following groups of subjects studied for ≥ 1 year in a controlled fashion:
  - Subjects with COPD (n≥100 subjects)
  - Subjects with asthma (n≥ 100 subjects)
  - Subjects with Type 1 diabetes and no underlying lung disease (n≥100)
- The Agency informed the Applicant that subjects enrolled in studies in which lung disease was an exclusion criterion, and classified post hoc as having asthma or COPD will not be sufficient.
- The Agency stated the presentation of the PFT should include shift tables
- The Agency reminded the Applicant that labeling precautions would not be accepted in lieu of further safety data

April 5, 2002, Teleconference

- The Agency reiterated the request for safety and efficacy assessment of the following additional groups of subjects, studied for ≥ 1 year in a controlled fashion:
  - Subjects with COPD (n≥100 subjects)
  - Subjects with asthma (n≥ 100 subjects)
  - Subjects with Type 1 diabetes and no underlying lung disease (n≥100)

November 15, 2002, Teleconference

- The Agency recommends approximately 50 subjects on drug and 50 subjects on standard therapy undergo HRCT at 0 and 24 months.
- The 2-year HRCT data may not be a filing issue, but the HRCT data requested will be necessary in order for the application to be complete.
- The Agency recommended the need for pulmonary consultation in subjects with the largest decline in FEV_1 and DLCO and highest titers of circulating anti-insulin IgG. In addition, a consideration of bronchoscopic lung biopsy with appropriate staining of the tissue (about 5-10) for subjects with high IgG titer.

June 9, 2004, Pre-NDA Meeting

- The Agency informed the Applicant that their proposal for the pulmonary safety database did not follow our recommendations and the adequacy of the safety database will be a review issue, not a filing issue.

- The Agency informed the Applicant that the NDA should include pulmonary safety data in subjects who developed antibodies.
- The Agency requested that the PFT data should include shift tables.
- The Agency reminded the Applicant that the NDA must include device performance data.

3 Significant Findings from Other Review Disciplines

3.1 Animal Pharmacology/Toxicology

The Applicant conducted inhalation toxicology studies in rats and monkeys of 6 months duration. The nonclinical studies were performed with an early formulation containing 20% insulin (Lilly). Later in the development, a 60% insulin (Aventis) formulation was developed. This 60% insulin formulation was used in the phase 3 clinical trials. A 1-month toxicology study in rats was performed to bridge the formulations. The following information is a synopsis of the pulmonary findings in the animal toxicology studies noted in pharmacology/toxicology review by Dr. Fred Alavi.

The 6-month rat studies demonstrated sporadic increases in lung weights, while the 6-month monkey study demonstrated a slight increase in lung weight in the low dose female group. Histologic examination of the lungs in the 6 month-monkey and rat study animals showed focal and multifocal inflammation and aggregation of alveolar histiocytes in all groups. There was no evidence of insulin related increase in lung cell proliferation in the in vitro studies in lung tissues from the 6 month rat and monkey studies. In terms of an effect of inhaled insulin on pulmonary function, the rat studies were unremarkable. In the 6-month monkey study, there was a decrease in lung compliance in the high dose males and an increase in minute volume in both sexes in the high dose groups. During the clinical observation, monkeys treated with excipient and insulin had frequent incidences of coughing and sneezing throughout the 6-month study.
Reviewer's Comment: For a detailed review of the pharmacology/toxicology studies, refer to Dr. Fred Alavi's review.

3.2 Clinical Pharmacology

The Applicant has conducted 32 clinical pharmacology studies. Several of the clinical pharmacology studies assess the effects of smoking, asthma, COPD, and rhinovirus infection on the bioavailability of inhaled insulin. These studies are of interest and are briefly discussed in this section.
Reviewer's comment: Although the results of these studies are briefly discussed in this section, it should be noted that this reviewer is not interpreting the significance of these findings because the clinical pharmacology studies are not meant to provide information regarding pulmonary safety but are meant to provide information regarding the effects of intrinsic (COPD and asthma) and extrinsic (smoking and rhinovirus infection) factors on the pharmacokinetics and pharmacodynamics of inhaled insulin. The pharmacokinetic and pharmacodynamic effects are most relevant to the overall efficacy/safety assessment of inhaled insulin.

Study 217-010 was a clinical pharmacology study to assess the effect of a rhinovirus challenge on the bioavailability and tolerability of inhaled insulin in 24 healthy subjects. Subjects were given a single dose of inhaled insulin followed by an intra-nasal dose of rhinovirus (20 subjects) or saline (4 subjects). Subjects then received two additional doses of inhaled insulin, 2 and 3 days later. There were no consistent differences in absorption of inhaled insulin between subjects who developed colds and controls. However, the number of subjects was small, especially in the control groups; thus, it is difficult to draw any definitive conclusions from this study [N21868/N_000/2004-12-27/hpbio/hupharm/010.pdf, pg. 6-10].

Study 217-009 was a clinical pharmacology study to assess the tolerability and bioavailability of inhaled insulin in 24 subjects with mild, controlled asthma compared with 12 healthy subjects. Study 217-009 was a crossover study in which subjects received two doses of inhaled insulin and one dose of SC insulin on 3 separate days with at least one week washout between doses. Inhaled insulin AUC_{0-360} and Cmax were consistently lower in subjects with asthma than in normal subjects; however, the differences in PK parameters were not statistically significant [N21868/N_000/2004-12-27/hpbio/hupharm/009.pdf, pg. 6-8].
Reviewer's Comment: In this study with inhaled insulin, the insulin exposure in subjects with mild, stable, controlled asthma was lower than the insulin exposure in healthy subjects. This study did not asses potential intra-subject PK variability related to variations in airflow resistance, which is a hallmark of asthma. Such a phenomenon would be potentially clinically significant.

Study 217-1005 was a clinical pharmacology study to assess the tolerability and bioavailability of inhaled insulin in 39 subjects with COPD (13 chronic bronchitis and 14 emphysema) compared with 12 healthy subjects. Subjects with COPD received one dose of inhaled insulin pre-albuterol, one dose of inhaled insulin post-albuterol, and one dose of SC insulin. Healthy subjects received one dose of inhaled insulin and one dose of SC insulin. The change from baseline insulin AUC and Cmax were greater in subjects with COPD compared to healthy subjects. Although the exposure was slightly higher in subjects with emphysema compared to subjects with chronic bronchitis, the difference was not statistically significant. The change from baseline AUC and Cmax were slightly higher when inhaled insulin was administered post- albuterol compared to pre-albuterol. Of note, two SAEs, myocardial infarctions, were reported in this study [N21868/N_000/2004-12-27/hpbio/hupharm/1005.pdf, pg. 8-13].
Reviewer's Comment: In this study with inhaled insulin, the exposure to inhaled insulin was higher in subjects with COPD compared to healthy subjects.

The Applicant conducted four clinical pharmacology studies to assess the effect of smoking (217-005), cessation of smoking (217-016), and cessation/resumption of smoking (217-1020) in non-diabetic subjects. In addition, the Applicant assessed the effect of smoking in subjects with Type 2 diabetes (217-1003).

In Study 217-005, inhaled insulin was compared to SC insulin in 24 chronic smokers (>15 cigarettes per day for at least 6 months). Inhaled insulin produced a more rapid rise

from baseline in insulin concentrations (25 minutes INH vs. 90 minutes SC) in smokers [N21868/N_000/2004-12-27/hpbio/hupharm/005.pdf, pg. 6-8].

In Study 217-016, the effect of cessation of smoking (for 3 and 13 weeks) was assessed in 38 chronic smokers and compared to non-smokers. Prior to cessation, smokers had significantly higher AUC and Cmax and a shorter Tmax than nonsmokers. After 3 weeks of smoking cessation, former smokers had a decrease in inhaled insulin absorption (~50%) and slightly longer Tmax; however, former smokers continued to have a higher bioavailability than nonsmokers. After 13 weeks of smoking cessation, no further significant decrease in AUC or Cmax was noted. Thus, after 13 weeks of smoking cessation, former smokers continued to have greater bioavailability than non-smokers. The results are shown below in Table 1 [N21868/N_000/2004-12-27/hpbio/hupharm/016.pdf, pg. 7-9].

Table 1 PK Parameters for Study 217-016 – Effect of Smoking Cessation on Bioavailability of Inhaled Insulin

Inhaled Insulin	Smokers N=38	Non-smokers N=30
AUC_{0-360} μU·min/ml – baseline	4850	1410
AUC_{0-360} μU·min/ml – Week 3 smoking cessation	2850	
AUC_{0-360} μU·min/ml – Week 13 smoking cessation	3260	
Cmax μUml – baseline	72.3	15.8
Cmax μUml – Week 3 smoking cessation	35.7	
Cmax μUml – Week 13 smoking cessation	43.1	
Tmax (min) – baseline	31	53
Tmax (min) – Week 3 smoking cessation	41	
Tmax (min) – Week 13 smoking cessation	40	

Source: N21868/N_000/2004-12-27/hpbio/hupharm/016.pdf, pg 8

In Study 217-1020, the Applicant assessed the effect of short term cessation and resumption of smoking on the bioavailability of inhaled insulin. In this study 20 smokers were compared to10 non-smokers. All subjects were administered inhaled insulin once at baseline. Smokers then stopped smoking for 7 days and had inhaled insulin administered on Day 1, 3, and 7 of the cessation period. Smoking was then resumed. Inhaled insulin was administered once after resumption of smoking. The PK results indicated than smokers had a greater exposure to inhaled insulin and shorter Tmax than non-smokers at baseline. Insulin exposure was slightly greater after cessation of smoking for 12 hours. However following cessation of smoking for 3 to 7 days, the insulin exposure decreased. However, the exposure increased after resumption of smoking for 2-3 days. The results of the PK parameters for inhaled insulin are shown below in Table 2 [N21868/N_000/2004-12-27/hpbio/hupharm/1020.pdf, pg. 11-20].

Table 2 PK Parameters for Study 217-1020 – Effect of Smoking Cessation and Resumption on Bioavailability of Inhaled Insulin

Inhaled Insulin	Smokers N=20	Non-smokers N=10
AUC_{0-6} µU·min/ml – baseline	2583	1645
AUC_{0-6} µU·min/ml – Day 1 smoking cessation	3165	
AUC_{0-6} µU·min/ml – Day 3 smoking cessation	2321	
AUC_{0-6} µU·min/ml – Day 7 smoking cessation	1887	
AUC_{0-6} µU·min/ml – After smoking resumption	3156	
Cmax µUml – baseline	26.8	9.7
Cmax µUml – Day 1 smoking cessation	33.3	
Cmax µUml – Day 3 smoking cessation	18.5	
Cmax µUml – Day 7 smoking cessation	15.9	
Cmax µUml – After smoking resumption	29.2	
Tmax (min) – baseline	20	53
Tmax (min) – Day 1 smoking cessation	20	
Tmax (min) – Day 3 smoking cessation	30	
Tmax (min) – Day 7 smoking cessation	38	
Tmax (min) – After smoking resumption	30	

Source: N21868/N_000/2004-12-27/hpbio/hupharm/1020.pdf, pg 17

Study 217-1003 was a clinical pharmacology study in type 2 diabetic smokers. As with the studies in non-diabetic smokers discussed above, the results indicated that the rate and extent of absorption of inhaled insulin was increased in type 2 diabetic smokers compared with type 2 diabetic non-smokers [N21868/N_000/2004-12-27/hpbio/hupharm/1003.pdf, pg. 7-12].

Reviewer's Comment: The clinical pharmacology studies to assess the effects of smoking on inhaled insulin exposure suggest the following:

- *Inhaled insulin exposure (Cmax and AUC) in smokers is increased compared to nonsmokers.*
- *The absorption of inhaled insulin is more rapid in smokers compared to non-smokers.*
- *Smoking cessation for 3 days results in a decrease in inhaled insulin exposure, but the exposure is still higher than non-smokers.*
- *The resumption of smoking returns the exposure to baseline.*

Reviewer's Comment: The changes in exposure with smoking appear to be clinically important changes. This reviewer defers the determination of how this data effects approval and labeling issues to the DMEDP. Of note, the Applicant's proposed label includes language regarding the contraindication of inhaled insulin in current and recent (within 6 months) smokers.

Reviewer's Comment: The clinical pharmacology studies are reviewed in detail by the Dr. Sayed Al-Habet. Refer to Dr. Al-Habet's review for details regarding the clinical pharmacology studies.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The primary sources of clinical data for this NDA are the clinical studies conducted by the Applicant and submitted with the NDA in December 2004. The Applicant also has several ongoing clinical studies, which are pertinent to the pulmonary safety analyses. Information regarding the ongoing studies was submitted by the Applicant throughout the review period including the safety update on April 26, 2005, the two-year HRCT data from Study 1029 on June 22, 2005, and the two-year PFT data for ongoing Study 1022 on July 5, 2005. Information from these submissions is included in this review.
Reviewer's Comment: The Applicant also submitted the following during the review period, which were not included in this review due to submission late in the review cycle.

- *2-year interim study report for Study 1022 submitted on July 19, 2005*
- *2-year interim study report for Study 1029 submitted on July 21, 2005*
- *Response to information request submitted on July 29, 2005.*

Clinical studies are identified with the prefix 217 followed by the study number, e.g. 217-102. Throughout this review, the prefix may be omitted and the study referred to as Study 102. Several abbreviations are commonly used throughout the review: SC – subcutaneous insulin, INH – inhaled insulin, and OA – oral agents.

The Applicant's clinical program includes 20 phase 2 and phase 3 clinical studies as well as 31 clinical pharmacology studies to support this NDA. The Applicant has completed 14 clinical studies evaluating the efficacy and safety of inhaled insulin. In addition, the Applicant has 6 ongoing clinical studies at the time of this review (1022, 1028, 1029, 1030, 1036, and 1017). The majority of the studies are controlled studies; however, two of the studies are extension studies (1036 and 111) and not controlled. Most of the studies were limited to adult subjects (≥ 18 years) with diabetes; however, one study (1009) was conducted in subjects <18 years of age. In addition, two other studies (106, 107) included subjects <18 years of age. The focus of this review is the pulmonary safety data in subjects ≥ 18 years of age.

Because of the multitude of studies, there are various logical ways to group the Applicant's studies together, e.g. diabetes type, SC comparator or OA comparator, ongoing or completed, study design, or length of study. Throughout this review, the clinical studies are usually be grouped according to diabetes type. The following tables display the Applicant's clinical studies with a focus on the relevance of each study to the pulmonary safety review. Table 3 displays the controlled clinical studies conducted in subjects with type 1 diabetes. Table 4 displays the controlled clinical studies conducted in subjects with type 2 diabetes. Table 5 displays the controlled clinical studies conducted in subjects with underlying lung disease (asthma and COPD), both of which are still ongoing. Finally, Table 6 displays the non-controlled extension studies (111, 1036), the pediatric study (1009), and an ongoing study (1017), in which the data is reported in a "blinded" fashion.

Table 3 Controlled Adult Clinical Studies in Subjects with Type 1 Diabetes NDA# 21-818

Study #	Study Purpose	Subjects	Design	Treatment Groups	Relevance to Pulmonary Safety Review
102	Efficacy, Safety	Type 1 DM Age 18-56 N = 72	P2, R, MC, OL, // 12 weeks US	-Inhaled Insulin pre-meal TID and SC HS Ultralente -SC insulin	-PFTs -BL, wk 6 (spiro), wk 12 -AEs
106*	Efficacy, Safety	Type 1 DM Age 11-64 N = 334	P3,R, MC, OL, // 24 weeks US & Canada	-Inhaled Insulin pre-meal TID and SC HS Ultralente -SC BID regular insulin and BID NPH insulin	-PFTs -BL, wk 12 (spiro), wk 24 -HRCT (subgroup) – BL & 24 wks -AEs -CXR – BL & wk 24
107*	Efficacy, Safety	Type 1 DM Age 11-65 N = 327	P3,R, MC, OL, // 24 weeks US & Canada	-Inhaled Insulin pre-meal TID and SC AM and PM NPH -SC pre-meal regular insulin and BID NPH insulin	-PFTs -BL, wk 12 (spiro), wk 24 -HRCT (subgroup) – BL & 24 wks -AEs -CXR – BL & wk 24
1026	Efficacy, Safety	Type 1 DM Age 20-50 yrs N = 74	R, SC, OL, // 24 weeks	- Inhaled insulin pre-meal and BID NPH - SC BID NPH and regular insulin	-PFTs – BL, wk 11 (spiro), wk 23 -AEs
1027	Efficacy, Safety	Type 1 DM Age 25-65 years N = 226	R, MC, OL, // 12 weeks treatment 12 weeks follow up US, Brazil Canada	-Inhaled Insulin -SC insulin	-PFTs – BL, 1, 2, 3, 4, 6, 8, and 12wks -PFTs 2, 4, 8, 12 wks after discontinuation -PFTs pre and post insulin dose – Wks 0, 4, 8, and 12 -AEs -Cough Questionnaire -CXR -BL, week 12 -BDI/TDI
1022 **Ongoing**	Efficacy, Safety	Type 1 DM Age 18-65 yrs N = 327	R, MC, OL, // 24 months Multinational	-Inhaled Insulin -SC insulin	-PFTs – BL, 12 wks, 6, 9, 12, 15, 18, 21, and 24 months -PFTs 1, 3, and 8 months after discontinuation -CXR -AEs -Cough questionnaire -BDI/TDI

DM – diabetes mellitus; P2 – phase 2; P3 – phase 3; R – randomized; MC – multicenter; OL – open label; // - parallel group; SC – subcutaneous insulin; OA – oral agents; PFTs – pulmonary function tests; AEs – adverse events; CXR – chest x-ray; HRCT – high resolution computed tomography of chest; BL – baseline; EOS – end of study

*These studies included some subjects less than 18 years of age

Table 4 Controlled Adult Clinical Studies in Subjects with Type 2 Diabetes NDA# 21-818

Study #	Study Purpose	Subjects	Design	Treatment Groups	Relevance to Pulmonary Safety Review
103	Efficacy, Safety	Type 2 DM Age 35-66 N = 56	P2, R, MC, OL, // 12 weeks US	-Inhaled Insulin pre-meal TID and SC HS Ultralente -SC insulin	-PFTs - BL, wk 6 (spiro), wk 12 -AEs
104	Efficacy, Safety	Type 2 DM Age 33-69 N = 69	P2,R, MC, OL, // 12 weeks US	-Inhaled Insulin pre-meal TID & OA -OA	-PFTs - BL, wk 6 (spiro), wk 12 -AEs
108	Efficacy, Safety	Type 2 DM Age 23-80 N = 298	P3,R, MC, OL, // 24 weeks US & Canada	-Inhaled Insulin pre-meal TID and SC HS Ultralente -SC insulin	-PFTs -BL, wk 12 (spiro), wk 24 -HRCT (subgroup) – BL & 24 wks -AEs -CXR – BL & wk 24
109	Efficacy, Safety	Type 2 DM Age 35-77 N = 309	P3,R, MC, OL, // 12 weeks US & Canada	-Inhaled Insulin pre-meal TID -Inhaled Insulin and OA -OA	-PFTs – BL & wk 12 -AEs -CXR – BL & wk 12
110	Efficacy, Safety	Type 2 DM Age 28-80 N = 145	P3,R, MC, OL, // 12 weeks US	-Inhaled Insulin pre-meal TID -Rosiglitazone	-PFTs– BL & wk 12 -AEs -CXR – BL & wk 12
1001	Efficacy, Safety	Type 2 DM Age 35-80 yrs N = 423	R, MC, OL, // originally 24 wks, then extended to 104 weeks Multinational	-Inhaled Insulin -Metformin	-PFTs –BL, Wk 24 (spiro), 36 (spiro), 52, 65, 78, 91, and wk 104 -PFTs – after 12 wk discontinuation -AEs -CXR – BL & EOS
1002	Efficacy, Safety	Type 2 DM Age 35-80 yrs N = 470	R, MC, OL, // originally 24 wks, then extended to 104 weeks Multinational	-Inhaled Insulin -Glibenclamide	-PFTs –BL, Wk 24 (spiro), 36 (spiro), 52, 65, 78, 91, and wk 104 -PFTs – after 12 wk discontinuation -AEs -CXR – BL & wk 12
1029 **Ongoing**	Efficacy, Safety	Type 2 DM Age 35-75 yrs N = 630	R, MC, OL, // 24 months Multinational	-Inhaled Insulin -SC insulin	-PFTs – BL, wk 12, month 6, 9, 12, 15, 18, 21, and 24 -PFTs – after 1, 3, and 6 m discontinuation -CXR – BL, month 12 and month 24 -AEs -HRCT - BL, 12 months, 24 months

DM – diabetes mellitus; P2 – phase 2; P3 – phase 3; R – randomized; MC – multicenter; OL – open label; // - parallel group; SC – subcutaneous insulin; OA – oral agents; PFTs – pulmonary function tests; AEs – adverse events; CXR – chest x-ray; HRCT – high resolution computed tomography of chest; BL – baseline; EOS – end of study

Table 5 Ongoing Controlled Clinical Studies in Subjects with Underlying Lung Disease NDA# 21-818

Study #	Study Purpose	Subjects	Design	Treatment Groups	Relevance to Pulmonary Safety Review
1028 **Ongoing**	Efficacy, Safety in subjects with **asthma**	Type 1 or 2 DM and Asthma Age 18-74 N =139 (interim) N=250 (planned)	R, MC, OL, // 12 month treatment 6 week follow up Multinational	Inhaled Insulin SC insulin	-PFTs – BL, 1, 2 , 3, 4, 6, 18, 26, 39, 52 wks (pre and post bronchodilator) -PFTs – 2 and 6 weeks after discontinuation -PFTs – pre and post insulin wks 0, 9, 51 -MCT -AEs -Asthma exacerbations -CXR – BL and wk 52 -BDI/TDI
1030 **Ongoing**	Efficacy, Safety in subjects with **COPD**	Type 1 or 2 DM and COPD Age 40-77 N = 67 (interim) N=250 (planned)	R, MC, OL, // 12 month treatment 6 week follow up Multinational	Inhaled Insulin SC insulin	-PFTs – BL, 1, 2 , 3, 4, 6, 18, 26, 39, 52 wks -PFTs – 2 and 6 weeks after discontinuation -MCT -COPD exacerbations -CXR – BL and wk 52 -BDI/TDI

DM – diabetes mellitus; P2 – phase 2; P3 – phase 3; R – randomized; MC – multicenter; OL – open label; // - parallel group; SC – subcutaneous insulin; OA – oral agents; PFTs – pulmonary function tests; AEs – adverse events; CXR – chest x-ray; HRCT – high resolution computed tomography of chest; BL – baseline; EOS – end of study

Table 6 Additional Clinical Studies with Inhaled Insulin

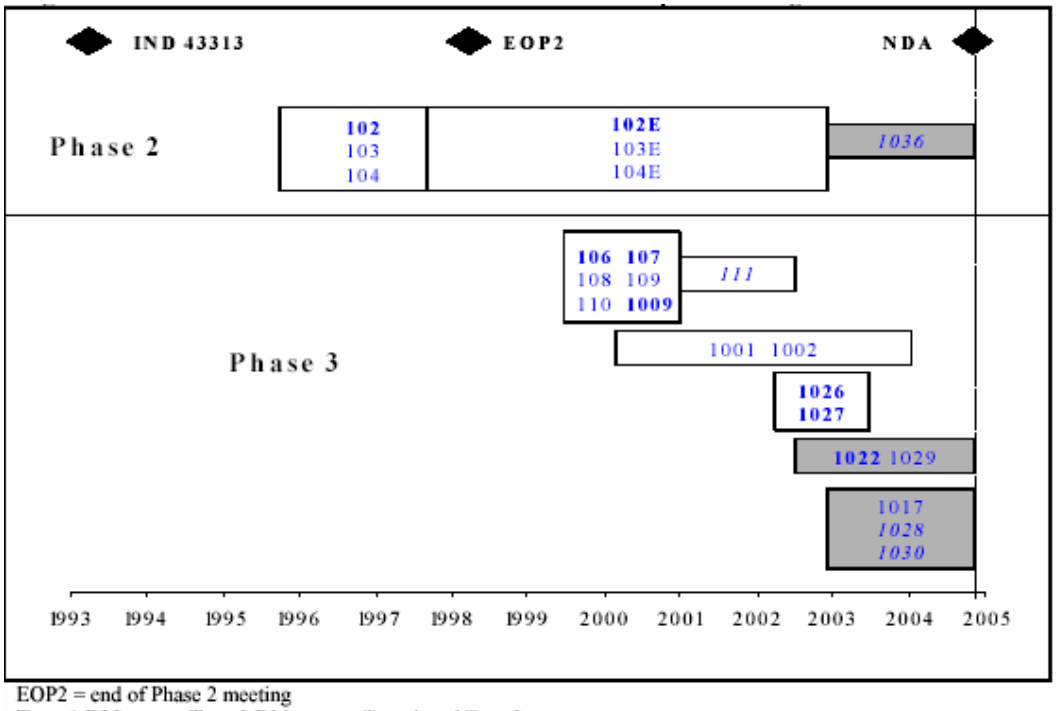
Study #	Study Purpose	Subjects	Design	Treatment Groups	Relevance to Pulmonary Safety Review
111	Safety Extension Study of 106, 107, 108, 109, 110, & 1009 And PFT trends after discontinuation	Type 1 and Type 2 DM Age 5-80 years N = 1290 n=664 Type 1 n=626 Type 2	P3, OL, MC, **extension** of 106, 107, 108, 109, 110, & 1009	-Segment 1: Inhaled Insulin (all) - Segment 2: Randomized to a) continued inhaled insulin for 6 months then discontinuation of inhaled insulin OR b) discontinuation of inhaled insulin	-PFTs – Q 6 months with spirometry every 3 months; however, extension population no "control" group -AEs
1036	Safety 4 year Extension of 102, 103, 104 **Ongoing**	Type 1 and Type 2 DM N=172 (n=62 ongoing)	P2, OL, MC, **extension** of 102, 103, 104	-Inhaled Insulin pre-meal TID (all subjects)	-PFTs –Q 6 months with spirometry every 3 months; however, no "control" group -AEs
1009	Efficacy, Safety **Pediatric**	Type 1 DM Age 6-11 N = 120	P3,R, MC, OL, // 12 weeks US	-Inhaled Insulin pre-meal TID and SC HS Ultralente/NPH or BID Ultralente/NPH -SC insulin	-PFTs – BL and wk 12 -AEs -CXR – BL and wk 12
1017	Efficacy, safety **Ongoing**	Type 2 DM N=223	P3b, R, MC, OL, // 52 weeks	- Inhaled insulin - Avandia	-PFTS – BL, wk 12, 24. 36, 52 -CXR – BL and wk 52 -AEs - Data still "blinded"

DM – diabetes mellitus; P2 – phase 2; P3 – phase 3; R – randomized; MC – multicenter; OL – open label; // - parallel group; SC – subcutaneous insulin; OA – oral agents; PFTs – pulmonary function tests; AEs – adverse events; CXR – chest x-ray; HRCT – high resolution computed tomography of chest; BL – baseline; EOS – end of study

The studies listed in Table 6 contribute less to the pulmonary safety review because of the uncontrolled design of Studies 111 and 1036. In addition, Table 6 includes a pediatric study, Study 1009. Although this NDA proposes inhaled insulin for subjects with diabetes >18 years of age, Study 1009 was reviewed for pulmonary safety in subjects <18 years of age. The limited information regarding the pulmonary safety of subjects <18 years of age is discussed separately. Finally Study 1017 is ongoing and the data in the study report is not "unblinded" and does not contribute to the pulmonary safety database in this application.

Figure 6 displays the timeline for the inhaled insulin clinical development program. The shaded boxes denote the ongoing clinical studies.

Figure 6 Timeline for Inhaled Insulin Clinical Development Program



EOP2 = end of Phase 2 meeting
Type 1 DM Type 2 DM *Type 1 and Type 2*
Shading denotes study ongoing at time of NDA submission

Source: [N21868/N_000/2004-12-27/clinstat/summary-clin-efficacy.pdf, pg 9].

As discussed in Section 6.1, Underlying Lung Disease, the phase 2 studies specified subjects with no significant pulmonary or PFT abnormalities. However, as clinical development proceeded, subjects with mild to moderate underlying lung disease were allowed with FEV_1 and DLCO as low as 70% predicted. The safety of inhaled insulin in subjects with underlying lung disease is discussed in detail in Section 6.1.

4.2 Review Strategy

The pulmonary safety data were analyzed utilizing the pooled controlled phase 2/3 studies in type 1 diabetes and type 2 diabetes. This dataset includes data from two ongoing studies, 1022 and 1029. The initial NDA submission included one year data from Study 1022 and 1029; however, the Applicant submitted additional data during the review period as discussed above in Section 4.1. The controlled phase 2/3 studies are shown below in Table 7.

Reviewer's Comment: Ideally the dataset utilized for the primary analyses includes data from completed clinical studies; however, because the ongoing studies provide information about the long term safety of inhaled insulin, the data from the ongoing studies was incorporated into this review.

Table 7 Controlled Adult Phase 2/3 Studies				
	Contributing Studies	# Subjects INH	# Subjects Comparator	Total
Adult type 1 studies	102, 106, 107, 1022*, 1026, 1027	698	705	1403
Adult type 2 studies	103, 104, 108, 109, 110, 1001, 1002, 1029*	1277	1132	2409
Total subjects		1975	1837	3812
*ongoing studies Source: N21868/N_000/2004-12-27/clinstat/summary-clin-safety.pdf, pg 131				

Reviewer's Comment: This table represents the number of subjects included in the controlled adult phase 2/3 protocol set submitted in the December 27, 2004, submission.

The Applicant also specified the all phase 2/3 protocol set for the assessment of serious adverse events. This protocol set includes data from both uncontrolled and controlled studies and thus, is not utilized in this review.

Table 8 Adult All Phase 2/3 Studies			
	Contributing Studies	# Subjects INH	# Subjects Comparator
Adult type 1 subjects	102, 102E,106, 107, 111†, 1022*, 1026, 1027, 1036*†	918	721
Adult type 2 subjects	103, 103E, 104, 104E, 108, 109, 110, 111†,1001, 1002, 1029*, 1036*†	1578	1144
All subjects		2496	1865
† Includes both type 1 and type 2 subjects *ongoing Source: N21868/N_000/2004-12-27/clinstat/summary-clin-safety.pdf, pg 131			

5 Integrated Review of Pulmonary Safety

5.1 Methods and Findings

5.1.1 Patient exposure

The number of subjects exposed to inhaled insulin and the duration of exposure to inhaled insulin are reasonable to assess the pulmonary safety in subjects without underlying lung disease. The Applicant determined the duration of exposure to study medication based upon subject month of exposure. The duration of exposure for the controlled phase 2/3 studies was calculated as the cumulative duration of treatment, excluding days during which study drug was not used. As shown below in Table 9, 214 subjects with type 1 diabetes and 375 subjects with type 2 diabetes were exposed to inhaled insulin for greater than 12 months.

**Table 9 Duration of Exposure to Study Medication
Adult Subjects in Controlled Phase 2/3 Studies** n (%)

	Number (%) of subjects*				
	Type 1		Type 2		
Exposure (months)	INH N=698	SC N=705	INH N=1277	SC N=488	OA N=644
>0-3	159 (22.8)	165 (23.4)	365 (28.6)	45 (9.2)	209 (32.5)
>3-6	264 (37.8)	249 (35.3)	288 (22.6)	141 (28.9)	137 (21.3)
>6-12	61 (8.7)	64 (9.1)	249 (19.5)	121 (24.8)	99 (15.4)
>12-18	158 (22.6)	169 (24.0)	183 (14.3)	148 (30.3)	48 (7.5)
>18-24	56 (8.0)	58 (8.2)	136 (10.6)	33 (6.8)	107 (16.6)
>24-30	0	0	56 (4.4)	0	44 (6.8)
Median exposure	5.59	5.65	5.88	9.71	5.60
Overall exposure (subjects-months)	5894	6052	12187	4868	6453

*The numbers are not cumulative. Subjects are counted only in their final treatment duration category
Source: N21868/N_000/2004-12-27/clinstat/summary-clin-safety.pdf, pg 136-137

Reviewer's Comment: The above table is based upon the original NDA submission. Due to additional information submitted during the review period, the number of subjects with exposure >12 months is greater than what is shown above.

Reviewer's Comment: If the uncontrolled extension studies are included in the patient exposure analysis, there are over 200 type 1 subjects and 500 type 2 subjects exposed to inhaled insulin for more than 2 years. However, the data from the extension studies is difficult to interpret due to the uncontrolled nature of the studies.

Reviewer's Comment: An exposure analysis based upon the dose of insulin received is also clinically meaningful since the dose of insulin varied from subject to subject. The Biometrics reviewer analyzed the change in pulmonary function tests by total daily insulin dose and total cumulative insulin dose as an exploratory analysis. Refer to Section 5.1.8.5 for details of the exploratory analysis.

5.1.2 Safety Evaluations Performed

The Applicant's monitoring for pulmonary safety in the controlled phase 2/3 studies was reasonable. Safety monitoring in the controlled phase 2/3 studies pertinent to the pulmonary safety database included adverse events, CXRs, and pulmonary function tests. In a subset of subjects in studies 106, 107, 108, and 1029, HRCTs were also performed.

Observed or volunteered adverse events reported during the study treatment period or within 1 day of the end of treatment were recorded by the investigator on the CRF regardless of treatment group or suspected causal relationship to study drug. In most studies, CXRs were performed at screening and at the end of the study. CXR were performed and read locally at radiology departments available to the clinical sites. There were no specific measures to blind the radiologist to the treatment group. In the subset of subjects who underwent HRCT evaluation, HRCT was performed at baseline and end of study. In study 1029, HRCTs were performed at baseline, 12 months, and 24 months. Study 1029 is currently ongoing. In the subset of subjects who underwent HRCTs, the HRCT scans were performed at local sites using a standardized algorithm and

subsequently interpreted at a central reading site by a third party radiologist blinded to the treatment group.

Pulmonary function tests were performed at baseline and at different time points during each individual study and at the end of each individual study. Usually, full pulmonary function tests were performed (spirometry, lung volumes, and DLCO). However, at some visits, only spirometry was obtained. PFTs were performed in the fasting state prior to dosing of study medication. In some studies, PFTs were performed pre and post insulin dose. In addition, in Studies 1028 and 1030, PFTs were performed pre and post-bronchodilator. All pulmonary function tests were performed according to ATS standards. In addition, more recent studies (1022, 1026, 1027, and 1029) utilized standard PFT equipment and centralized data analyses.

Subjects who were noted to have the following underwent further clinical evaluation: a >15% decline in FEV_1, DLCO, TLC, and or FVC; significant change in CXR or HRCT; new onset and persistent signs or symptoms of respiratory disease.

The Applicant further characterized cough AEs through the use of a cough questionnaire in Studies 1022, 1027, and 1029. In those studies, the cough questionnaire was administered to subjects who experienced cough, which was not explained by a concomitant condition. The cough questionnaire consisted of 6 questions assessing the following:

- Cough frequency at night
- Cough frequency throughout the day
- Cough severity throughout the day
- Cough timing related to short-acting insulin dosing
- Cough severity related to insulin dosing
- Sputum production.

The answers range from 0 to 4 for each question. Zero meaning none/never and 4 meaning almost constant/severe.
Reviewer's Comment: Several issues are worth noting about the Cough Questionnaire. First of all, the Cough Questionnaire was not administered to all subjects with cough AEs, but was administered to subjects with cough AEs not attributable to another condition. Allowing the investigator to determine if the cough was attributable to another condition is not ideal in this open label study. Ideally, the Applicant would have administered the cough questionnaire to every subject with report of a cough AE. Second, the cough questionnaire is confusing for some of the questions in which a grade 0 means no cough or unaware of cough. So a subject can report a cough AE, but respond no cough or unaware of cough for certain questions. Finally, the question of cough severity related to insulin dosing depends upon if the subject noted a relationship of cough to insulin dosing.

The Applicant also further characterized dyspnea through the use of the Mahler Dyspnea Indices in Studies 1022, 1027, and 1029. Dr. Mahler and colleagues developed the

Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) in 1984.[1] The Mahler Dyspnea Indices include the following components:

- Functional Impairment
  - Are there activities which make the patient breathless?
- Magnitude of Task
  - What types of activities make the patient breathless?
- Magnitude of Effort
  - What amount of effort makes the patient breathless?

Each component has one item and the focal TDI or BDI score is the sum of the three items. The Baseline Dyspnea Index is measured first to establish a baseline, whereas the TDI measures changes over time in the three components compared to the baseline state. At return visits, for the TDI the interviewer again asks a series of open-ended questions regarding changes in the three components from baseline: functional impairment, magnitude of effort, and magnitude of task. The interviewer selects a score, which is based on a -3 to +3 scale for the change in each component, as shown below:

- -3 Major Deterioration
- -2 Moderate Deterioration
- -1 Minor Deterioration
- 0 No change
- +1 Minor Improvement
- +2 Moderate Improvement
- +3 Major Improvement

The three scores are summed to determine the TDI Focal Score on a scale of -9 to +9.

All subjects were administered the Baseline Dyspnea Index at screening. The TDI was administered during studies 1022, 1027, and 1029.

5.1.3 Deaths

There were no respiratory related deaths in the controlled phase 2/phase 3 studies. No respiratory related deaths have been reported at the time of this review in the ongoing phase 3 studies (1022, 1028, 1029, and 1030).

5.1.4 Serious Respiratory Related Adverse Events (SAEs)

5.1.4.1 Methods

A serious adverse event is defined as any event that results in any of the following:

- a life-threatening adverse event
- hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity
- congenital anomaly/birth defect.

[1] Mahler DA, Weinberg DH, et. al. The measurement of dyspnea : contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; June, 85(6): 751-8.

Investigators could also consider other adverse events to be SAEs based upon clinical judgment if medical or surgical intervention was necessary to prevent an outcome listed above.

For the individual studies, the Applicant utilized COSTART preferred terms to classify the adverse events. However, for the integrated summary of safety, the Applicant utilized MedDRA to organize the SAEs by organ class/preferred term, thus the SAEs are presented using the MedDRA preferred terms. Of note, the COSTART preferred terms for the Respiratory system include terms such as bronchitis, pneumonia, and lung carcinoma; however, using the MedDRA system, these AEs are classified under Infections and Infestations and Neoplasms. Although classified in a different section using MedDRA, these AEs are relevant to the pulmonary safety analyses for inhaled insulin and therefore, are included in the discussion of SAEs. Several cases of lung neoplasm were noted in the Applicant's controlled clinical studies. These cases are discussed in greater detail in Section 5.1.7.1.

In the controlled phase 2/3 studies, there were more respiratory related SAEs in the inhaled insulin group than in the comparator groups. Interestingly, there were no respiratory related SAEs in the completed studies in subjects with type 1 diabetes. In type 2 diabetes, asthma and bronchitis SAEs were reported in more than one subject in the inhaled insulin group and were more common in the inhaled insulin group than the comparator group. Table 10 displays a summary of pulmonary SAEs in the adult controlled phase 2/3 studies in type 2 diabetes. 8

Table 10 Summary of Preferred Terms for All-Causality Respiratory Related SAEs in Adult Controlled Phase 2/3 Studies (Type 2 Diabetes)

Number of events	Inhaled Insulin n=1277	SC Insulin n=488	Oral Agents n=644
Respiratory SAEs	18	8	4
Asthma	3	0	0
Bronchial carcinoma, metastatic	1	0	0
Bronchitis	2	0	0
Bronchitis acute	1	0	0
Bronchopneumonia	1	0	0
Bronchospasm	1	0	0
Cough	1	0	0
Dyspnea	1	2	2
Epistaxis	1	0	0
Hypoxia	0	1	0
Lung adenocarcinoma	1	0	0
Lung neoplasm malignant	0	0	1
Pneumocystis carinii pneumonia	0	0	1
Pneumonia	2	3	0
Pneumothorax	1	1	0
Respiratory distress	0	1	0
Respiratory failure	1	0	0
Vocal cord polyp	1	0	0

Source: [N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 56-63, 1868, 1870-1872]

Reviewer's Comment: When this reviewer pooled the pulmonary SAEs from the individual studies, there were some discrepancies with the Applicant's All-Causality Respiratory SAEs among Subjects with Type 2 Diabetes in the Controlled Phase 2/3 Studies in the Inhaled Insulin Pulmonary Safety (pg 25). The majority of the discrepancies were due to the change to the MedRA preferred terms. Some of the respiratory related SAEs using COSTART were noted under Infections and Infestations and Neoplasms using MedRA. In addition, the Applicant's pooled SAE table includes information from interim data from the ongoing studies, which may have not been reported in the individual study reports. For example, the pooled data includes a subject with hypoxia and a subject with a pneumothorax from Study 1029. No subjects with hypoxia or pneumothorax were listed or discussed in the study report for Study 1029 submitted in the original NDA. These SAEs were noted after the interim safety report for Study 1029.

For the respiratory related SAEs, which were only noted in type 2 diabetics, the SAEs in the Respiratory, Thoracic, and Mediastinal Disorder and certain Infections and Infestations SAEs and Neoplasm SAEs were reviewed as shown in the following table.

Source System Organ Class SAEs for *Error! Reference source not found.*			
System Organ Class	***Inhaled Insulin***	***SC Insulin***	***Oral Agents***
Respiratory, Thoracic, and Mediastinal Disorders	*9*	*5*	*2*
Infections and Infestations (bronchitis, bronchopneumonia, pneumonia, pneumocystis carinii pneumonia)	*6*	*3*	*1*
Neoplasms – Lung adenocarcinoma, lung neoplasm malignant, metastatic bronchial carcinoma	*3*	*0*	*1*
Total	*18*	*8*	*4*

Source: [N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 1868, 1870-1872]

Reviewer's Comment: Although there was a fourth case of malignant lung carcinoma, squamous cell carcinoma, the fourth case was noted in Study 111, which was not a controlled study and thus, is not included in the above table.

In the safety update submitted April 26, 2005, there were two SAEs – pneumonitis (SC insulin) and mycobacterium avium complex (inhaled insulin) reported in ongoing Study 1022. These SAEs are the only respiratory related SAEs reported in subjects with type 1 diabetes.

Using the All Phase 2/3 dataset, which included the uncontrolled studies, the following additional SAEs were reported: lung disorder, pulmonary edema, respiratory distress, atelectasis, dyspnea, pleural effusion, pulmonary embolism, and pulmonary edema. Of note was the number of pneumonia SAEs. Using the All Phase 2/3 studies, 9 pneumonia SAEs were reported in the inhaled insulin group compared to 4 pneumonia SAEs in the SC insulin group. However, because these SAEs were from uncontrolled extension studies with inhaled insulin, it is difficult to draw any conclusions from the reports [N21868/N_000/2004-12-27/summary-clin-safety.pdf, 1882, 1891, 1897].

5.1.5 Dropouts and Other Significant Adverse Events

More subjects discontinued due to any AE in the inhaled insulin group than in the comparator group. More subjects discontinued due to respiratory related AEs in the inhaled insulin group than in the comparator groups as shown in Table 11.

Table 11 Number of Subjects Discontinuing Due to AEs in Adult Controlled Phase 2/3 Studies

	Type 1		Type 2		
	Inhaled Insulin n=698	SC Insulin n=705	Inhaled Insulin n=1277	SC Insulin n=488	Oral Agents n=644
Subjects discontinued due to any AE	22	6	46	6	21
Subjects discontinued due to respiratory related AE	11	0	28	0	2

Source: N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 2365, 2366, 2380, 2383

Cough was the most common respiratory AE leading to discontinuation in subjects with type 1 or type 2 diabetes. Seven subjects with type 1 diabetes discontinued due to cough and 13 subjects with type 2 diabetes discontinued due to cough in the inhaled insulin group. No subjects in the comparator groups discontinued due to cough adverse events.

In subjects with type 2 diabetes, asthma (7) and dyspnea (5) were the next most common AEs leading to discontinuation. Table 12 displays a summary of discontinuations due to respiratory related adverse events.

Table 12 Summary of Respiratory-Related Adverse Events Resulting in Discontinuation in Adult Controlled Phase 2/3 Studies

	Type 1		Type 2		
	Inhaled Insulin n=698	SC Insulin n=705	Inhaled Insulin n=1277	SC Insulin n=488	Oral Agents n=644
Number of subjects discontinuing due to adverse events	22	6	46	6	21
Number of subjects discontinuing due to respiratory related adverse events	11	0	28	0	2
Asthma	1	0	7	0	0
Bronchitis	0	0	3	0	0
Carcinoma of lung	0	0	1	0	1
Cough increased	7	0	13	0	0
Dyspnea	3	0	5	0	1
Laryngitis	1	0	0	0	0
Pharyngitis	2	0	1	0	0
Respiratory disorder	2	0	2	0	0
Respiratory tract infection	1	0	3	0	0
Sinusitis	1	0	0	0	0
Sputum increased	1	0	1	0	0

Source: [N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 2365-2366, 2380, 2382-2383]

Reviewer's Comment: For a more detailed listing of the respiratory adverse events leading to discontinuation, refer to Table 65 and Table 66 in Section 8.1.

In addition to permanent discontinuations due to respiratory AEs, there were more temporary discontinuations of therapy due to respiratory AEs in the inhaled insulin group, than in the SC insulin group.

5.1.6 Respiratory Adverse Events

The Applicant utilized preferred COSTART terms to code AEs. The data was presented by body system, preferred COSTART term, and severity. The combined data for type 1 and type 2 diabetics indicates that asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, lung disorder, pharyngitis, respiratory disorder, respiratory tract infection, rhinitis, sinusitis, sputum increased, and voice alteration were reported in more than one subject and were more common in the inhaled insulin group than in the comparator group as shown below in Table 13.

Table 13 All Causality Respiratory-Related Adverse Events in Adult Controlled Phase 2/3 Studies – Combined Type 1 and Type 2

Number of subjects (%)	Inhaled Insulin n=1975	Comparator n=1837
Any Respiratory Adverse Events	**1254 (63.5)**	**926 (50.4)**
Apnea	1 (0.05)	0
Asthma	**32 (1.6)**	**19 (1.0)**
Atelectasis	0	1 (0.05)
Bronchiectasis	0	1 (0.05)
Bronchiolitis	1 (0.05)	0
Bronchitis	**81 (4.1)**	**70 (3.8)**
Carcinoma of lung	1 (0.05)	1 (0.05)
Cough increased	**464 (23.5)**	**119 (6.5)**
Dyspnea	**69 (3.5)**	**22 (1.2)**
Edema pharynx	1 (0.05)	2 (0.1)
Emphysema	1 (0.05)	1 (0.05)
Epistaxis	**24 (1.2)**	**9 (0.5)**
Hemoptysis	1 (0.05)	0
Hyperventilation	1 (0.05)	1 (0.05)
Hypoventilation	1 (0.05)	0
Laryngitis	**15 (0.8)**	**7 (0.4)**
Lung disorder	**4 (0.2)**	**1 (0.05)**
Lung edema	1 (0.05)	2 (0.1)
Nasal polyp	1 (0.05)	1 (0.05)
Pharyngitis	**242 (12.2)**	**184 (10.0)**
Pleural disorder	1 (0.05)	1 (0.05)
Pneumonia	16 (0.8)	17 (0.9)
Respiratory disorder	**110 (5.6)**	**79 (4.3)**
Respiratory distress syndrome	0	2 (0.1)
Respiratory tract infection	**647 (32.8)**	**572 (31.1)**
Rhinitis	**199 (10.1)**	**132 (7.2)**
Sinusitis	**129 (6.5)**	**104 (5.7)**
Sputum increased	**61 (3.1)**	**15 (0.8)**
Voice alteration	**15 (0.8)**	**3 (0.2)**
Yawn	1 (0.05)	1 (0.05)

Source: [N21868/N_000/2004-12-27/pulm.pdf, pg 19]

Reviewer's Comment: Because all the clinical studies are open-label studies, assignment of causality to adverse events is subject to bias; therefore, only the all-causality adverse events are presented.

When the adverse event data is separated into adverse events in subjects with type 1 and type 2 diabetes, the data indicates that respiratory tract infection, increased cough, pharyngitis, and sinusitis were the most common respiratory related AEs reported in both treatment groups. Cough was the respiratory related AE reported at much greater incidence in the inhaled insulin group than in the comparator group.

Table 14 All Causality Respiratory-Related Adverse Events in Adult Controlled Phase 2/3 Studies

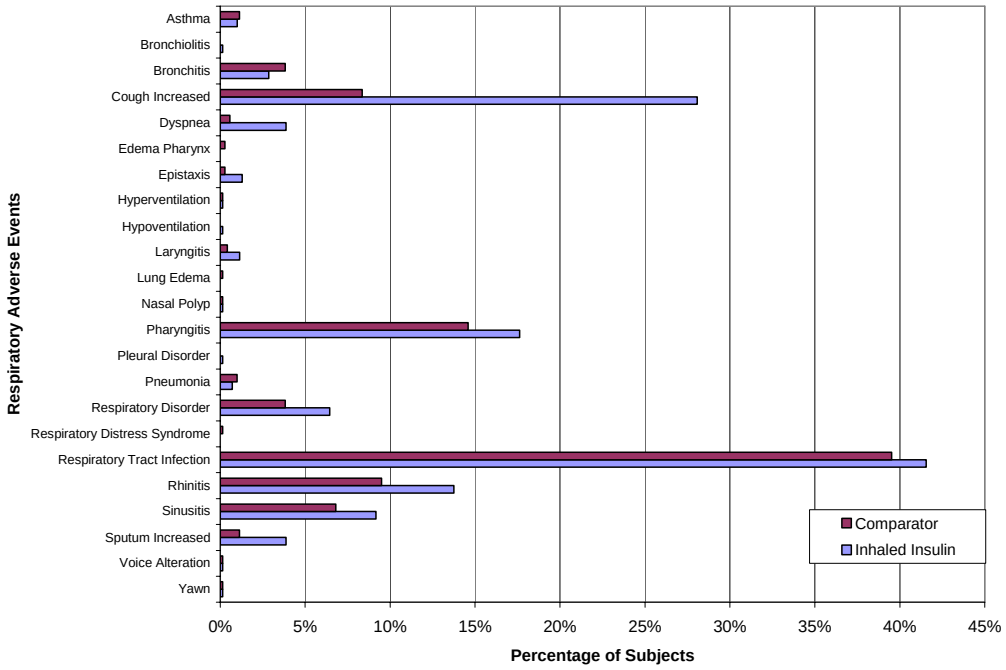
	Type 1		Type 2		
	Inhaled Insulin n=698	**SC Insulin n=705**	**Inhaled Insulin n=1277**	**SC Insulin n=488**	**Oral Agents n=644**
All Respiratory Adverse Events	**515 (73.8)**	**428 (60.5)**	**739 (57.9)**	**279 (57.2)**	**219 (34.0)**
Apnea	0	0	1 (0.1)	0	0
Asthma	7 (1.0)	8 (1.1)	25 (2.0)	8 (1.6)	3 (0.5)
Atelectasis	0	0	0	1 (0.2)	0
Bronchiectasis	0	0	0	1 (0.2)	0
Bronchiolitis	1 (0.1)	0	0	0	0
Bronchitis	20 (2.9)	27 (3.8)	61 (4.8)	17 (3.5)	26 (4.0)
Carcinoma of lung	0	0	1 (0.1)	0	1 (0.2)
Cough increased	**196 (28.1)**	**59 (8.4)**	**268 (21.0)**	**36 (7.4)**	**24 (3.7)**
Dyspnea	**27 (3.9)**	**4 (0.6)**	**42 (3.3)**	**9 (1.8)**	**9 (1.4)**
Edema pharynx	0	2 (0.3)	1 (0.1)	0	0
Emphysema	0	0	1 (0.1)	1 (0.2)	0
Epistaxis	**9 (1.3)**	**2 (0.3)**	**15 (1.2)**	**2 (0.4)**	**5 (0.8)**
Hemoptysis	0	0	1 (0.1)	0	0
Hyperventilation	1 (0.1)	1 (0.1)	0	0	0
Hypoventilation	1 (0.1)	0	0	0	0
Laryngitis	**8 (1.1)**	**3 (0.4)**	7 (0.5)	2 (0.4)	2 (0.3)
Lung disorder	0	0	4 (0.3)	1 (0.2)	0
Lung edema	0	1 (0.1)	1 (0.1)	0	1 (0.2)
Nasal polyp	1 (0.1)	1 (0.1)	0	0	0
Pharyngitis	**123 (17.6)**	**103 (14.6)**	**119 (9.3)**	**43 (8.8)**	**38 (5.9)**
Pleural disorder	1 (0.1)	0	0	1 (0.2)	0
Pneumonia	5 (0.7)	7 (1.0)	11 (0.9)	6 (1.2)	4 (0.6)
Respiratory disorder	**45 (6.4)**	**27 (3.8)**	65 (5.1)	41 (8.4)	11 (1.7)
Respiratory distress syndrome	0	1 (0.1)	0	1 (0.2)	0
Respiratory tract infection	**290 (41.5)**	**279 (39.6)**	357 (28.0)	166 (34.0)	127 (19.7)
Rhinitis	**96 (13.8)**	**67 (9.5)**	103 (8.1)	46 (9.4)	19 (3.0)
Sinusitis	**64 (9.2)**	**48 (6.8)**	65 (5.1)	41 (8.4)	15 (2.3)
Sputum increased	**27 (3.9)**	**8 (1.1)**	**34 (2.7)**	**4 (0.8)**	**3 (0.5)**
Voice alteration	1 (0.1)	1 (0.1)	**15 (1.2)**	**0**	**2 (0.3)**
Yawn	1 (0.1)	1 (0.1)	0	0	0

Source: [N21868/N_000/2004-12-27/pulm.pdf, pg 19]

Increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, respiratory disorder, respiratory tract infection, rhinitis, sinusitis, and sputum increased were more common in the inhaled insulin group than in the SC insulin group in subjects with type 1 diabetes. In subjects with type 2 diabetes increased cough, dyspnea, epistaxis, pharyngitis, sputum increased, and voice alteration were more common in the inhaled insulin group than the comparator.

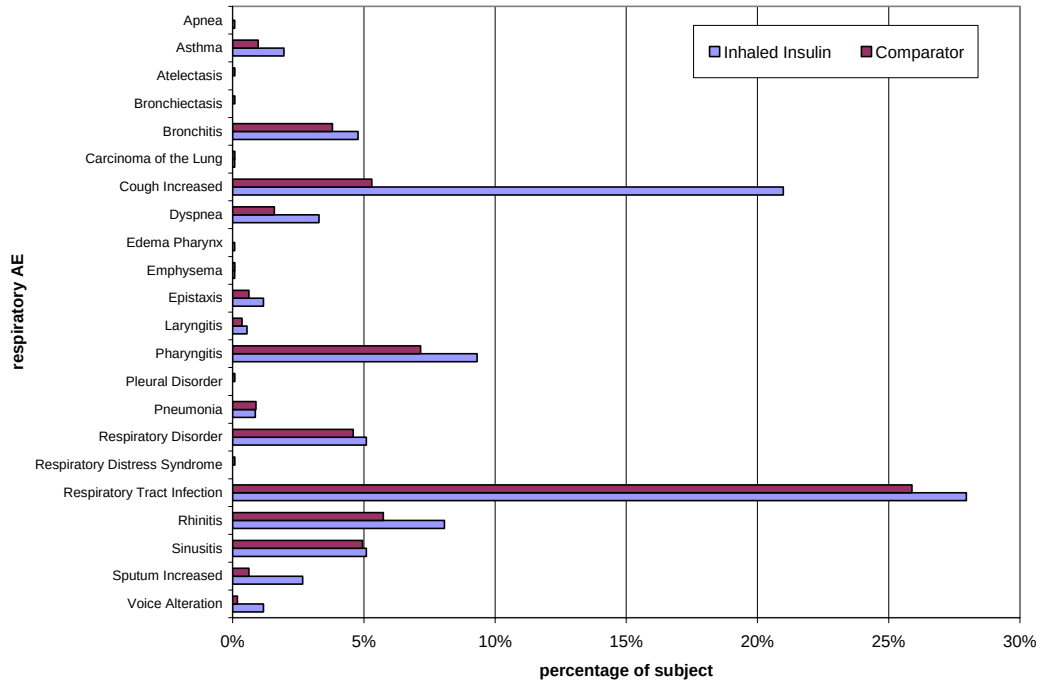
The following figures display the respiratory adverse events by treatment group in the controlled phase 2/3 studies in type 1 diabetes and type 2 diabetes, respectively.

Figure 7 Respiratory Adverse Events by Treatment Group in the Controlled Phase 2/3 Studies in Type 1 Diabetes, Adults



Source: Dr. Joan Buenconsejo's Biometrics Review

Figure 8 Respiratory Adverse Events by Treatment Group in the Controlled Phase 2/3 Studies in Type 2 Diabetes, Adults



Source: Dr. Joan Buenconsejo's Biometrics Review

5.1.6.1 Identifying common and drug-related adverse events

Cough

Cough is the respiratory adverse event, which was much more common in the inhaled insulin treatment group compared to the comparator groups. Because cough was a common respiratory adverse event in the inhaled insulin group, the Applicant attempted to further assess the cough adverse events. In the earlier phase 2/3 studies, the Applicant collected information regarding cough severity, incidence, prevalence, and duration.

In the controlled phase 2/3 adult studies with the type 1 and type 2 data combined, approximately 85% of the cough AEs were graded as mild, 13-16% were graded as moderate and 1-2% were graded as severe. Although there were more cough AEs in the inhaled insulin group, there was no significant difference in the severity of cough between the inhaled insulin group and comparator groups. The data on incidence and prevalence of cough suggested that cough incidence (onset of cough in each time interval) and prevalence (presence of cough in each interval) were more common in the first 3 months of inhaled insulin exposure. The mean duration of cough (number of weeks from reported onset of each event to the reported end of each event) was longer in the inhaled insulin group than in the comparator group by approximately 2 weeks as shown below in Table 15. The increase in cough duration appears to be primarily driven by the presence of more cough events of duration greater than 8 weeks in the inhaled insulin group [N21868/N_000/2004-12-27/pulm.pdf, pg 20. 100-107].

Table 15 Duration of Cough During the First 6 Months of Exposure in the Adult Controlled Phase 2/3 Studies

Treatment Group	# subjects reporting cough event	Total number of events	Duration -weeks mean, (SD)	Duration -weeks median
Type 1 Inhaled Insulin	179	232	5.36 (8.09)	2.29
Type 1 Comparator	49	54	3.37 (4.13)	1.93
Type 2 Inhaled Insulin	215	259	7.70 (11.85)	3.00
Type 2 Comparator	42	45	5.08 (9.15)	2.29

Source: [N21868/N_000/2004-12-27/pulm.pdf, pg 104-105]

In studies 1022, 1027, and 1029, the Applicant utilized a cough questionnaire, which consisted of 6 questions assessing the following:

- Cough frequency at night
- Cough frequency throughout the day
- Cough severity throughout the day
- Cough timing related to short-acting insulin dosing
- Cough severity related to insulin dosing
- Sputum production.

The answers range from 0 to 4 for each question. Zero meaning none/never and 4 meaning almost constant/severe. The cough questionnaire was administered to subjects who experienced cough, which was not explained by a concomitant condition.
Reviewer's Comment: In this reviewer's opinion, the cough questionnaire provides more information regarding cough adverse events, than the data from the earlier phase 2/3 studies.

The cough questionnaire data from the three individual studies that specified the use of the cough questionnaire were reviewed. The cough questionnaire data suggested that for most subjects cough was rare or occasional during the day and rare or absent at night. As with the other cough data, for most subjects the severity of cough events was primarily mild. In general, the cough was not productive. Finally, a majority of subjects reported the timing of the cough event within seconds to minutes after inhaled insulin dosing; however, some subjects did report no relationship between cough and dosing.

Although the majority of cough adverse events were mild in severity, cough adverse events led to discontinuation in 20 subjects in the inhaled insulin group and no subjects in the comparator group. Twelve of the 20 subjects, who discontinued inhaled insulin due to cough, discontinued in the first 2 months of the study [N21868/N_000/2004-12-27/pulm.pdf, pg 20. 100-101].

The Applicant performed a comparison of the change from baseline FEV_1 among subjects who experienced cough and subjects who did not experience cough. As shown below in Table 16, the Applicant's data suggests that subjects experiencing cough did not experience a greater mean decline in FEV_1 compared to subjects who did not experience cough.

Table 16 Mean Change from Baseline in FEV_1 (L) Among Subjects Who Did and Did Not Report Cough as an Adverse Event in Adult Controlled Phase 2/3 Studies

	Subjects Experiencing Cough		Subjects Not Experiencing Cough	
	Inhaled Insulin (N)	Comparator (N)	Inhaled Insulin (N)	Comparator (N)
Baseline	3.043 (429)	3.193 (107)	3.148 (1458)	3.129 (1599)
3 Months	-0.052 (352)	-0.032 (88)	-0.063 (1070)	-0.028 (1194)
6 Months	-0.065 (322)	-0.052 (90)	-0.079 (1033)	-0.050 (1217)
9 Months	-0.086(220)	-0.086 (66)	-0.080 (608)	-0.060 (729)
12 Months	-0.098 (197)	-0.124 (65)	-0.096 (577)	-0.054 (689)
24 Months	-0.131 (28)	-0.135 (6)	-0.179 (115)	-0.128 (119)

Source: [N21868/N_000/2004-12-27/pulm.pdf, pg 47]

Dyspnea

Dyspnea occurred at a greater incidence in the inhaled insulin treatment group compared to the comparator groups, but was not a common adverse event. Sixty-nine subjects (3.5%) in the inhaled insulin group and 22 subjects (1.2%) in the comparator group reported a dyspnea adverse event. The majority of the dyspnea AEs was mild; however, there were two dyspnea AEs in the inhaled insulin group, which were graded as severe. Only one dyspnea SAE was reported in the inhaled insulin group compared to four dyspnea SAEs in the comparator groups. Eight dyspnea adverse events led to discontinuation in the inhaled insulin group compared to one in the comparator groups.

The Applicant collected additional information regarding dyspnea in Studies 1022, 1027, and 1029 by using the Mahler Dyspnea Indices. The TDI data was reviewed for the three individual studies. The TDI data did not suggest any significant change in the three domains measured: functional impairment, magnitude of task, and magnitude of effort.

5.1.7 Less Common Adverse Events

5.1.7.1 Lung Neoplasm

No definitive association between inhaled insulin and lung neoplasm can be made based upon the five cases of lung neoplasm (4 malignant, 1 benign) that were reported as SAEs. Of the four malignant cases, three were in subjects treated with inhaled insulin. However, in at least one of these cases, the screening CXR demonstrated an abnormality. Two cases of lung neoplasm (1 benign, 1 malignant) were reported in Study 111, which was an uncontrolled extension study. All subjects with lung neoplasms were noted to be ex-smokers. Each of the lung neoplasm cases are briefly described below.

Benign

- Hamartoma -Study 111, Subject 51124165, Inhaled insulin
    - 75 year old female, ex-smoker diagnosed with hamartoma after 510 days treatment with inhaled insulin

Malignant

- Adenocarcinoma – Study 1002, Subject 01336266, Inhaled insulin
    - 62 year old ex-smoker male noted to have pulmonary nodule on screening. CT scan. Subject referred to thoracic surgeon, but did not want nodule investigated further. Subject randomized to inhaled insulin; however, Applicant advised investigator to withdraw subject when protocol violation (abnormal CXR) noted. Subject withdrawn after 98 days of treatment with inhaled insulin. Nodule enlargement noted and subject subsequently diagnosed with adenocarcinoma.

Reviewer's Comment: The narrative identifies the malignancy as squamous cell carcinoma. This case of lung cancer was not likely related to study medication since the subject had a nodule at screening.

- Squamous cell carcinoma – Study 111, Subject 51270656, Inhaled insulin
    - 72 year old ex-smoker male with reportedly normal screening CXR. Approximately 18 months later CXR showed right apical lung mass. Re-examination of screening CXR by radiologist suggests screening CXR might have shown a change in the right apex. Subjects diagnosed with squamous cell carcinoma.
- Bronchial carcinoma – Study 1002, Subject 01195236, Inhaled insulin
    - 67 year old ex-smoker male with history of occupational asbestos exposure diagnosed with metastatic bronchial carcinoma after 663 days of treatment with inhaled insulin.
- Bronchial carcinoma – Study 1002, Subject 00835165, Oral agent
    - 57 year old female, ex-smoker diagnosed with bronchial carcinoma on day 63 of treatment with oral agents

[N21868/N_000/2004-12-27/1001-1002.pdf, 702, 943, 956; N21868/N_000/2004-12-27/111.pdf, pg 684, 857]

5.1.7.2 Pulmonary Fibrosis

Three cases of pulmonary fibrosis were noted in the extension studies. The following is a brief summary of the cases:

- Subject 50130470 – Pulmonary Fibrosis
    - 73 year old Hispanic male with type 2 diabetes enrolled in Study 109 and treated with oral agents. Subject enrolled in extension Study 111. Screening CXR and PFTs reported as normal. After being on inhaled insulin for one month the subject complained of exertional dyspnea and cough and was noted to have a decline in TLC and DLCO from baseline after 4 months of inhaled insulin therapy. He was also noted to have desaturation with walking from 98% to 88%/90%. An HRCT was performed after 5 months of inhaled insulin therapy and on retrospective review was noted to have bilateral basilar, subpleural honeycomb cysts, mild traction bronchiectasis, and a few patches of ground glass density. The HRCT findings were noted to be consistent with pulmonary fibrosis. A retrospective review of the screening CXR was felt to be suboptimal. A retrospective review of EOS CXR for Study 109 noted scattered fibrotic scarring. He was discontinued from inhaled insulin therapy after approximately 5months of treatment. His exertional dyspnea and cough were reported to improve after discontinuation.
    - Follow up HRCT (6 months after discontinuation of inhaled insulin) showed no significant changes from the previous HRCT and remained consistent with pulmonary fibrosis. Follow up PFTs (6 months after discontinuation of inhaled insulin) were noted for normal spirometry, a reduction in TLC (76% predicted) and a reduced DLCO (57% predicted) [N21868/N_000/2004-12-27/clinstat/diabetes/111.pdf, 709-710].

Reviewer's Comment: It is unlikely that inhaled insulin was the cause of the pulmonary fibrosis since honeycomb cysts were noted on HRCT within 5 months of treatment. However, the dyspnea and cough may be treatment related, since both improved after discontinuation of inhaled insulin.

- Subject 50728388 – Chronic pleural parenchymal fibrosis
    - 69 year old female with type 2 diabetes enrolled in Study 108 and treated with inhaled insulin. Subject enrolled in extension Study 111. A CXR after ~ 16 months of treatment with inhaled insulin was noted to be changed from baseline related to chronic pleural parenchymal fibrosis. However, on follow up CXRs the pleural parenchymal fibrosis was noted to be resolved. An HRCT was not performed. She continued on inhaled insulin for approximately 3 years [N21868/N_000/2004-12-27/clinstat/diabetes/pulm.pdf, 1234-1236].

Reviewer's Comment: This case is unusual and is unclear if there was fibrosis, since fibrosis does not typically resolve. An HRCT would have provided more information regarding parenchymal changes in the lungs.

- Subject 00478322 – Mild lung fibrosis
    - 66 year old male with type 2 diabetes in Study 1002 was treated with oral agents during the study. A CXR performed on Day 361 was noted to be clinically changed from baseline. The CXR was sent to a radiologist and an AE of mild lung fibrosis was reported. FVC increased from 4.86L to 4.98L,

however, DLCO decreased from 35.85 to 28.54 mL/min/mmHg. There was no mention of an HRCT [N21868/N_000/2004-12-27/clinstat/diabetes/1001-1002.pdf, 865-866].

Reviewer's Comment: It is difficult to know what to make of this case. An HRCT would have provided more definitive information regarding parenchymal changes in the lungs. It should be noted this subject was on comparator therapy.

5.1.8 Pulmonary Function Tests (PFTs)

5.1.8.1 Methods

Pulmonary function tests were performed to assess for a change in pulmonary function associated with study medication. PFTs were performed at baseline and at different time points during each individual study and at the last observation or end of study. Usually, full pulmonary function tests were performed (spirometry – FEV_1, FVC $FEF_{25-75\%}$; lung volumes -TLC, RV; and DLCO). However, at some visits, only spirometry was obtained. PFTs were performed in the fasting state prior to dosing of study medication. However, in Study 1027, the acute effects of study medication were assessed by obtaining PFTs pre and post-insulin (10 minutes and 60 minutes) dose at Weeks 0, 1, 4, 8, and 12. Study 1027 is also unique in that PFTs were performed at more frequent intervals than in other studies.

All pulmonary function tests were performed according to ATS standards. In addition, more recent studies (1022, 1026, 1027, and 1029) utilized standard PFT equipment and centralized data analyses. It should also be noted that the earlier phase 2/3 studies had some differences in design that could potentially influence the PFT results. Specifically, in the early phase 2/3 studies (102, 103, 104, 106, 107, 108, 109, 110, 1001, and 1002), baseline PFTs were based on a single screening measurement and subjects could be retested if they failed to meet the PFT entry criteria. In contrast, in more recent studies (1022, 1026, 1027, and 1029) screening PFTs were performed separately from PFTs that established the baseline. In addition, the baseline PFT values were calculated as the mean of 2-3 separate tests. Subjects were not allowed to re-attempt to qualify if they failed to meet the PFT entry criteria.

Reviewer's Comment: The more recent studies (1022, 1026, 1027, and 1029) are more rigorously designed and will likely provide more reliable PFT data because the studies utilize standard PFT equipment and centralized data analyses. In addition, the establishment of baseline pulmonary function is based upon 2-3 measurements, not just one measurement.

Because of the problems inherent with data from interim analysis from ongoing studies, the most appropriate PFT data to draw conclusions from are the completed controlled phase 2/3 studies. However, the completed controlled phase 2/3 studies only provide PFT data for up to 24 weeks of inhaled insulin exposure in subjects with type 1 diabetes. Thus, in order to assess the effects of long term administration of inhaled insulin on pulmonary function, the data from the ongoing controlled phase 2/3 studies (1022 and 1029) are included in this review of the PFT data. Table 17 displays the pulmonary function testing in the controlled phase 2/3 adult studies.

Table 17 Summary of Pulmonary Function Testing in Adult Controlled Phase 2/3 Studies		
Study Number	**Scheduled PFTs**	**Scheduled PFTs After Discontinuation of Study Medication**
Type 1 Diabetes		
102	Wks -3 (BL), 6 (spirometry only), 12	
106, 107	Wks -3 (BL), 12 (spirometry only), 24	
1026	Wks -3, -2, -1, 11 (spirometry only), 23	
1027	Wks -3, -2, -1, 0, 1, 2, 3, 4, 6, 8, 12 Pre and Post insulin dose: Wks 0, 4, 8, 12	2, 4, 8, and 12 weeks
1022*^	Wks -3, -1, -1, 12, Months 6, 9, 12, 15, 18, 21, 24	1, 3, 6 months
Type 2 Diabetes		
103, 104	Wks -3 (BL), 6 (spirometry only), 12	
108	Wks -3 (BL), 12 (spirometry only), 24	
109, 110	Wks -3 (BL) 12	
1001, 1002	Wks -4 (BL), 24, 36 (spirometry and lung volumes), 52, 65, 78, 91, 104	6 and 12 weeks
1029*	Wks -3, -1, -1, 12, Months 6, 9, 12, 15, 18, 21, 24	1, 3, 6 months
*ongoing – Data cut off at 1 year of exposure with original December 27, 2004, submission. ^ongoing – Two year PFT data from interim study results		

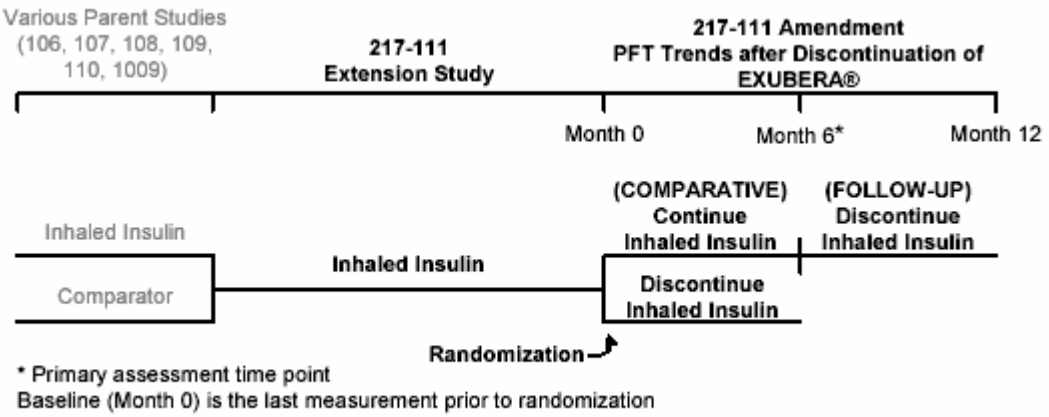
Reviewer's Comment: In the December 27, 2004, submission, Studies 1022 and 1029 include PFT data for one year exposure of inhaled insulin. A safety update was submitted on April 26, 2005, with preliminary interim 2 year PFT data for Study 1022. The 2 year PFT datasets for Study 1022 were submitted on July 5, 2005.

The PFT data from the adult controlled phase 2/3 studies is the focus of this section of the review. The data was reviewed separately for subjects with type 1 and type 2 diabetes as the baseline characteristics of these two groups are different. For example, the mean age of subjects with type 1 diabetes was 38 years, while the mean age of subjects with type 2 diabetes was 57 years.

As stated above, the PFT data that is most appropriate to draw conclusions from are the PFT data from the controlled clinical studies. It should be noted that the Applicant conducted two studies, 1036 and 111, which were extension studies of phase 2 and phase 3 studies, respectively, in which subjects received inhaled insulin. The PFT data from these extension studies provide some information on the long term exposure of inhaled insulin. However, the PFT data from the extension studies are not controlled and therefore, the interpretation of the PFT data is limited.

In extension Study 111, the Applicant attempted to assess the effects of discontinuation of inhaled insulin on pulmonary function by amending Study 111 to randomize subjects to either continuing inhaled insulin or discontinuing inhaled insulin for 6 months. The study design for Study 111 after the protocol amendment is shown below in Figure 9.

Figure 9 Study Design for Study 111 Following January 2002 Protocol Amendment



Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 59.

Although Study 111 was amended to include a comparative phase to assess the discontinuation of inhaled insulin, this design is flawed because the randomized population was a self-selected population in that all the subjects were on inhaled insulin and presumably tolerating inhaled insulin. Subjects who did not tolerate inhaled insulin may have withdrawn from the study or elected not to enter the extension study. In addition, the randomized subjects had been on inhaled insulin for varying lengths of time prior to randomization. Thus, in this reviewer's opinion, Study 111 provides limited information regarding the effects of discontinuation of inhaled insulin on pulmonary function.

That being said, the Applicant conducted several studies (1027, 1022, 1029, 1001, and 1002), which specified PFTs after discontinuation of study medication to assess the reversibility of any PFT changes noted during the treatment period in a controlled fashion. The PFTs from these studies were reviewed to assess the effect of discontinuation of study medication. Of note, Studies 1022 and 1029 are ongoing studies and PFT data following the discontinuation of study medication were not submitted in this Application.

The PFT data discussed in this review is based upon the observed PFT data. The Biometrics reviewer, Dr. Joan Buenconsejo, performed sensitivity analyses examining the effects of various methods of handling missing data. The sensitivity analyses compared the observed PFT data to the PFT data using LOCF and the PFT data using repeated measures. The conclusion from the sensitivity analyses is that the missing data does not appear to affect the overall results from the observed data. Thus, the observed data is reviewed in this section.
Reviewer's Comment: Refer to Dr. Joan Buenconsejo's Biometrics review for further details about the sensitivity analyses.

The primary focus of this review is the change from baseline in the pulmonary function tests over time. The change from baseline pulmonary function tests is compared between treatment groups. The change from baseline treatment group difference is defined as the

change from baseline in the inhaled insulin group minus the change from baseline in the comparator group. The unadjusted treatment group difference is presented using the observed change from baseline. In the later phase 3 studies, the Applicant specified using an adjustment model which includes treatment, protocol, visit, baseline measurement, age, gender, and height. The adjusted treatment group difference using the Applicant's model is also presented.
Reviewer's Comment: The model specified by the Applicant in the later phase 3 studies includes variables which are reasonable and may affect pulmonary function.

5.1.8.2 Type 1 Diabetes

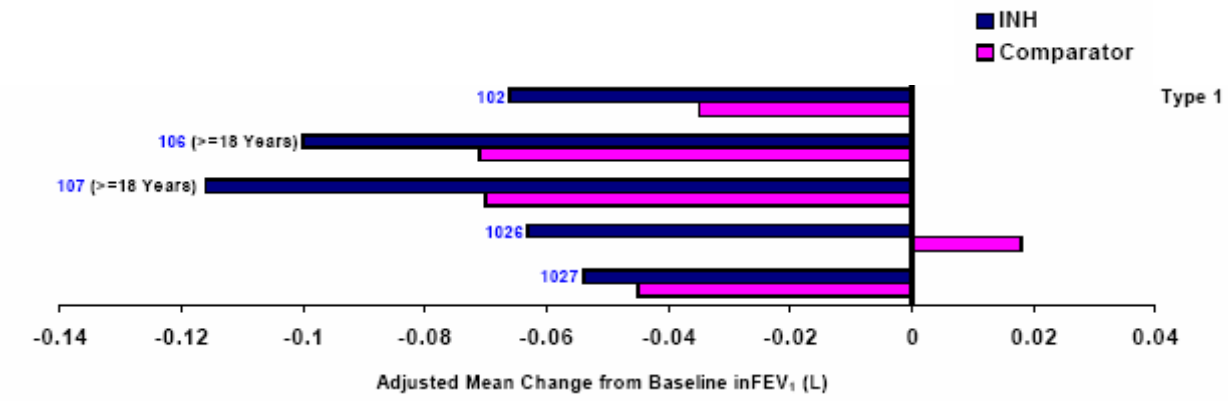
PFTs from the controlled phase 2/3 studies in subjects with type 1 diabetes (102, 106, 107, 1022, 1026, and 1027) were reviewed in each individual study and as pooled data. The PFT data from the pooled phase 2/3 studies are reviewed in this section. The results of an individual study may also be reviewed in this section to provide supportive information.

5.1.8.2.1 Forced Expiratory Volume in One Second (FEV_1)

5.1.8.2.1.1 Summary of Individual Studies

In each of the individual studies in subjects with type 1 diabetes, the inhaled insulin group demonstrated a larger mean decrease from baseline FEV_1 to the end of study FEV_1 than subjects in the SC insulin group. Figure 10 illustrates the adjusted mean change from baseline FEV_1 for most of the studies in type 1 diabetes.

Figure 10 Adjusted* Mean Change from Baseline FEV_1 (L): 3 and 6 Month Adult Controlled Phase 2/3 Studies in Type 1 Diabetes

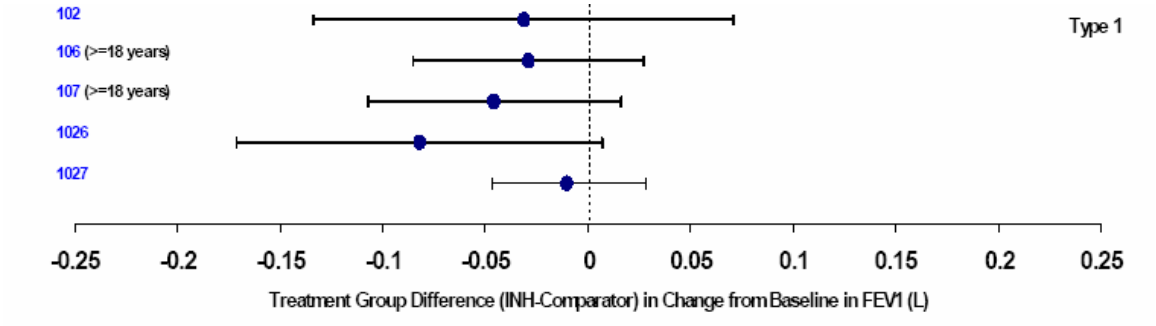


Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 34
**Reviewer's Comment: In this figure, the Applicant adjusted the mean change from baseline FEV_1 for treatment, visit, center, baseline PFT, age, height, and gender. However, when the mean change from baseline is not adjusted, a similar pattern is noted.*

Similarly, the treatment group difference, which is defined as the mean change from baseline FEV_1 in the inhaled insulin group – the mean change from baseline FEV_1 in the comparator group, favored the comparator in the individual studies as shown below in

Figure 11. A more negative treatment group difference indicates that the inhaled insulin group had a greater mean decline from baseline FEV_1 than the comparator group.

Figure 11 Adjusted* Mean Treatment Group Difference for FEV_1 Change from Baseline (L)
3 and 6 Month Adult Controlled Phase 2/3 Studies in Type 1 Diabetes



Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 35

**Reviewer's Comment: The above figure illustrates a greater decline from baseline FEV_1 in the inhaled insulin group compared to the comparator group in the individual studies. In this figure, the Applicant adjusted the mean change from baseline FEV_1 for treatment, visit, center, baseline PFT, age, height, and gender. However, when the mean change from baseline is not adjusted, a similar pattern is noted.*

5.1.8.2.1.2 Pooled Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)

In the pooled adult controlled phase 2/3 studies in subjects with type 1 diabetes, the mean baseline FEV_1 and FEV_1 percent predicted were similar between treatment groups. Subjects in both treatment groups demonstrated a decline in FEV_1 (negative change from baseline FEV_1) at each time point (Weeks 12, 24, 36, 48, 60, 72, 84, and 96). However, subjects in the inhaled insulin treatment group demonstrated a larger decline than subjects in the comparator group as shown in Table 18. The decline was noted in both groups at Week 12, which was the first on treatment measurement in some of the individual studies.

Table 18 Mean Observed FEV_1 and Change From Baseline FEV_1 (L) Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)
Studies 102, 106, 107, 1026, 1027, 1022 (ongoing)

	Inhaled Insulin			Comparator		
FEV_1 in liters	Mean Observed FEV_1 (L)	**Mean Change from Baseline FEV_1 (L)**		Mean Observed FEV_1 (L)	**Mean Change from Baseline FEV_1 (L)**	
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)
Baseline % Predicted	95.005 (12)	686		94.836 (12)	692	
Baseline	3.484 (0.8)	686		3.454 (0.8)	692	
Week 12	3.434 (0.8)	658	**-0.056 (0.2)**	3.436 (0.8)	635	**-0.027 (0.2)**
Week 24	3.442 (0.8)	504	**-0.080 (0.2)**	3.442 (0.8)	512	**-0.052 (0.2)**
Week 36*	3.473 (0.7)	247	**-0.059 (0.1)**	3.432 (0.8)	264	**-0.037 (0.1)**
Week 48*	3.465 (0.7)	240	**-0.080 (0.1)**	3.432 (0.8)	259	**-0.036 (0.1)**
Week 60*	3.450 (0.8)	235	**-0.095 (0.2)**	3.424 (0.8)	250	**-0.047 (0.2)**
Week 72*	3.457 (0.7)	226	**-0.090 (0.2)**	3.426 (0.8)	230	**-0.062 (0.2)**
Week 84*	3.446 (0.8)	217	**-0.116 (0.2)**	3.423 (0.8)	224	**-0.064 (0.1)**
Week 96*	3.465 (0.7)	208	**-0.118 (0.2)**	3.400 (0.8)	216	**-0.077 (0.2)**

Source: Dr. Joan Buenconsejo's Biometrics Review
*Interim data from Study 1022, which is ongoing

Reviewer's Comment: The FEV_1 data from the individual controlled adult phase 2/3 studies in type 1 diabetes was pooled by the Biometrics Reviewer, Dr. Joan Buenconsejo. Some of the numbers differ from the Applicant's pooled data for the following reasons. First of all, in the analyses performed by Dr. Buenconsejo, all subjects were included in the calculation of the mean baseline FEV_1. However, the Applicant only included subjects for the baseline calculation if the subject had a post-baseline FEV_1 measurement. In addition, the table above includes additional 2 year data from Study 1022 submitted during the review period. Although there are some slight differences, the change from baseline in each treatment group is consistent with the Applicant's findings.

After 96 weeks of study medication, the inhaled insulin treatment group demonstrated a mean decline from baseline FEV_1 of 118mL, while the comparator group demonstrated a mean decline from baseline FEV_1 of 77mL. Thus, over a two year period the inhaled insulin group demonstrated an average annual decline from baseline FEV_1 of approximately 59mL/year, while the comparator group demonstrated an average annual decrease from baseline FEV_1 of approximately 39mL/year.
Reviewer's Comment: To interpret the clinical significance of the change from baseline FEV_1 noted in the Applicant's studies, the following should be noted:

- *The Lung Health Study was a randomized trial of smoking cessation in middle-aged smokers who had airway obstruction. One of the main outcome variables was the annual change in lung function as measured by the FEV_1. Long term (11 year) follow up data was recently published. Subjects who continued to smoke had an annual change in FEV_1 of approximately -60mL/year. Subjects who stopped smoking had an annual change in FEV_1 of approximately -30mL/year.*[2]
- *In a longitudinal epidemiologic study, the Copenhagen City Heart Study, which was conducted between 1976 and 1994, subjects with and without self reported asthma*

[2] Anthonisen NR, Connett JE, et al. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002; Vol 166: 675-679.

were identified. The annual change in FEV_1 was determined from 15 years of data. In nonsmoking subjects without asthma, the annual change in FEV_1 was +5 to -5mL/year in subjects age 20-39 years, -17 to -24mL/year in subjects age 40-59 years and -31 to -37mL/year in subjects age 60-79 years.[3]

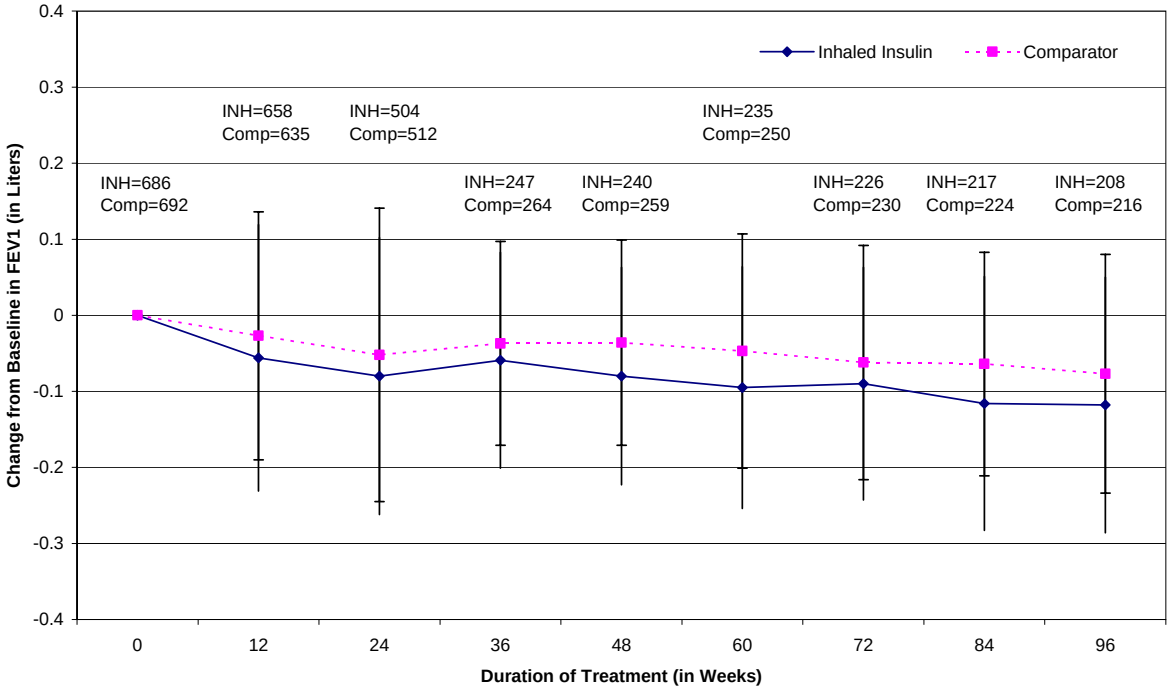
- *The Lung Health Study Research Group examined the effect of inhaled corticosteroids on pulmonary function in subjects with COPD. In a randomized, placebo-controlled trial investigating the use of inhaled triamcinolone in 1116 subjects with COPD, the rate of decline in FEV_1 in both the placebo and triamcinolone groups was approximately 45cc per year.*[4] *(The baseline FEV_1 was approximately 64% of predicted and approximately 90% of the subjects in the trial were currently smoking).*

Thus, in the controlled adult phase 2/3 studies (type 1 diabetes) conducted by the Applicant over a two year period, subjects treated with inhaled insulin had a mean decline in FEV_1 (-59mL/year) similar to what would be expected in COPD patients who continue to smoke, while subjects treated with the comparator had a mean decline in FEV_1 (-39mL/year) similar to what would be expected in COPD patients who stopped smoking.[2] *Based upon the comparator group data in the Applicant's studies, it appears as though subjects with type 1 diabetes have a greater decline in FEV_1 than what would be expected in subjects who are nonsmokers without significant underlying lung disease. The reason for this greater decline in FEV_1 is unclear. Subjects treated with inhaled insulin had an even greater mean decline from baseline FEV_1 than the comparator group.*

The mean change from baseline FEV_1over time in the adult phase 2/3 controlled studies in type 1 diabetes is shown below in Figure 12. As stated above, subjects in both treatment groups demonstrated a decline from baseline FEV_1; however, subjects in the inhaled insulin treatment group demonstrated a larger decline than subjects in the comparator group. The difference between treatment groups was noted at Week 12 and remained fairly constant until Week 48, when there is a slight further separation of the curves, indicating a greater treatment group difference. The greater treatment group difference noted at Week 48 remained fairly constant through Week 96, which is the last time point with available PFT data.

[3] Lange P, Parner J et al. A 15 year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998; 339: 1194-1200.
[4] The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000; 343:1902-9.

Figure 12 Mean Change from Baseline FEV_1 over Time in the Phase 2/3 Controlled Studies in Type 1 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: There is a significant decrease in number of subjects after 24 weeks because ongoing Study 1022 is the only source for PFT data beyond 24 weeks. A similar pattern to the above figure was noted when Study 1022 was evaluated individually.

The treatment group difference was defined as the following: the mean change from baseline FEV_1 in the inhaled insulin group – the mean change from baseline FEV_1 in the comparator group.

A mean treatment group difference was noted at Week 12 and remained constant from Week 12 through Week 36. However, at Week 48, there was an increase in the mean treatment group difference. The increased mean treatment group difference noted at Week 48 remained fairly constant until Week 96, which is the last time point with available PFT data. At Week 96, the mean treatment group difference in change from baseline FEV_1 between the inhaled insulin group and comparator group was approximately -40mL as shown below in Table 19.

Table 19 Mean Change from Baseline FEV_1 (L) and Mean Treatment Group Difference in Change from Baseline FEV_1 (L) in Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)
Studies 102, 106, 107, 1026, 1027, 1022 (ongoing)

	Mean Change from Baseline FEV_1 (N)		Mean Treatment Group Difference (95% CI) Unadjusted	Mean Treatment Group Difference (95% CI) Adjusted**
	Inhaled Insulin	Comparator		
Week 12	-0.056 (658)	-0.027 (635)	-0.029 (-0.047, -0.011)	-0.028 (-0.046, -0.011)
Week 24	-0.080 (504)	-0.052 (512)	-0.029 (-0.052, -0.006)	-0.027 (-0.046, -0.008)
Week 36*	-0.059 (247)	-0.037 (264)	-0.022 (-0.046, 0.002)	-0.021 (-0.047, 0.004)
Week 48*	-0.080 (240)	-0.036 (259)	-0.044 (-0.069, -0.020)	-0.043 (-0.071, -0.016)
Week 60*	-0.095 (235)	-0.047 (250)	-0.047 (-0.075, -0.019)	-0.046 (-0.074, -0.017)
Week 72*	-0.090 (226)	-0.062 (230)	-0.029 (-0.057, -0.0004)	-0.032 (-0.061, -0.002)
Week 84*	-0.116 (217)	-0.064 (224)	-0.052 (-0.082, -0.023)	-0.049 (-0.079, -0.019)
Week 96*	-0.118 (208)	-0.077 (216)	-0.041 (-0.072, -0.010)	-0.038 (-0.069, -0.007)

Source: Dr. Joan Buenconsejo's Biometrics Review
*Interim data from ongoing Study 1022
**Adjusted for treatment, protocol, visit, baseline measurement, age, gender, and baseline height

Reviewer's Comment: For the FEV_1 data in type 1 diabetes, the results are very similar whether using the unadjusted FEV_1 data or the Sponsor's adjusted FEV_1 data.

Reviewer's Comment: The Applicant asserts that this data indicates the effect of inhaled insulin on FEV_1 stabilizes and is not progressive. The data suggests that the mean treatment group difference is relatively stable between Week 12 and Week 36; however, an increase in the mean treatment group difference is noted at Week 48. This increased mean treatment group difference remains relatively stable through Week 96. At Week 96, there is approximately a 40mL mean treatment group difference, favoring the comparator. As discussed above, both treatment groups demonstrated a decline in FEV_1 greater than would be expected in nonsmoking subjects without significant underlying lung disease.

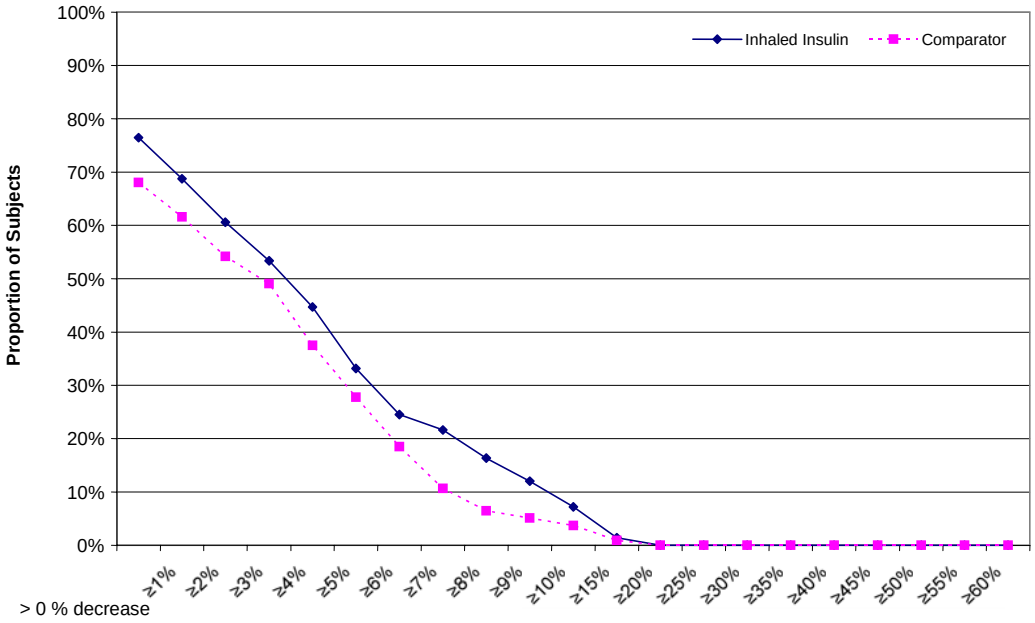
It should be noted that the Applicant has not offered a mechanism for the proposed "non-progressive" effect of inhaled insulin on FEV_1.

The Biometrics reviewer performed a categorical response analysis to assess the proportion of subjects with declines in FEV_1 of various magnitudes. The proportion of subjects with a decrease from baseline FEV_1 was analyzed at Weeks 12, 24, 36, 48, 60, 72, 84, and 96. In general, at each week analyzed, the inhaled insulin group had a higher percentage of subjects with a decline of FEV_1 than the comparator group, but the pattern of the response was similar between treatment groups. Thus, the mean difference in change from baseline FEV_1 between the treatment groups does not appear to be driven by outliers.

Reviewer's Comment: The Applicant also performed an analysis of the distributions in percent change from baseline FEV_1 over time. The Applicant's conclusion was the same. The Applicant concluded that the observed mean change from baseline FEV_1 is driven by slight shifts in the distribution curves among the broad population of subjects treated with inhaled insulin rather than by a small number of subjects with extreme values [N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 37].

The Week 96 response profile is shown in Figure 13 as an example of the response analysis. Overall, few subjects had a >15% decline from baseline FEV_1 at Week 96 as shown below. However, there were more subjects in the inhaled insulin group who had a >15% decline in FEV_1 than in the comparator group.

Figure 13 Proportion of Subjects by Percent Reduction from Baseline FEV_1 (L) at Week 96 in Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: In terms of a time relationship, the response analyses also demonstrated that there was a higher percentage of subjects in both treatment groups with a decline in FEV_1 from baseline at each additional time point through Week 96. Refer to Dr. Joan Buenconsejo's Biometrics Review for the response profile at each time point.

The controlled phase 2/3 studies in subjects with type 1 diabetes indicate that the inhaled insulin group has a greater mean decline from baseline FEV_1 than the comparator group, thus, there is a treatment group difference between inhaled insulin and the comparator favoring the comparator. The mean treatment group difference was noted at Week 12 and appeared to remain constant from Week 12 through Week 36. However, at Week 48, there was an increase in the mean treatment group difference. The increased mean treatment group difference noted at Week 48 remained fairly constant until Week 96, which is the last time point with available PFT data. At Week 96, there is approximately a 40mL mean treatment group difference, favoring the comparator.

To further explore the effects of inhaled insulin on FEV_1 in subjects with type 1 diabetes, some of the individual studies, which provide additional information about long term exposure and the potential for reversibility, are discussed next.

5.1.8.2.1.3 Study 1027

Study 1027 was a 24 week, controlled study that is worth reviewing in greater detail in this integrated summary of pulmonary safety for several reasons. First of all, Study 1027 specified more frequent pulmonary function tests (Wks -3, -2, -1, 0, 1, 2, 3, 4, 6, 8, 12) than the other phase 2/3 studies. The more frequent PFTs provide some insight as to when the treatment group difference in pulmonary function is first noticed. Second, Study 1027 specified a 12 week study medication treatment period followed by a 12 week follow up period after discontinuation of study medication. Study 1027 is the only study in type 1 diabetes to provide controlled information regarding pulmonary function tests following discontinuation of inhaled insulin. Thus, the effect of discontinuation of inhaled insulin on FEV_1 in Study 1027 is reviewed here. Finally, to assess the effect of inhaled insulin on acute airway function, Study 1027 included PFTs pre and post-insulin (10min and 60min) dose at Weeks 4, 8, and 12.
Reviewer's Comment: In terms of assessment for reversibility, Study 1027 has limitations in that subjects are only exposed to inhaled insulin for 12 weeks prior to discontinuation. Even if the discontinuation data suggests that the effects of inhaled insulin on FEV_1 are reversible after 12 weeks, the effects may not be reversible after longer exposure.

Study 1022 specifies obtaining PFTs in type 1 diabetes after discontinuation of inhaled insulin following 24 months of exposure in a controlled fashion. However, Study 1022 is an ongoing study and the data following discontinuation of inhaled insulin was not available at the time of this review.

The PFT data from Study 1027 suggests that a treatment group difference between inhaled insulin and the comparator is noted in the first two weeks of treatment. The treatment group difference fluctuated after two weeks of exposure with the maximum treatment group difference noted around Week 2 and 3. After Week 2 and 3, the treatment group difference decreases until at Week 12 when there is a small treatment group difference, favoring the comparator. Table 20 and Table 21 display the mean observed FEV_1, mean change from baseline FEV_1, and the mean treatment group differences, respectively.

Table 20 Mean Observed FEV_1 (L) and Change From Baseline FEV_1 (L)in Study 1027 Full Analysis Set**

	Inhaled Insulin				Comparator			
FEV_1 in liters	Observed FEV_1 (L)	**Change from Baseline FEV_1 (L)**		% Change from Baseline	Observed FEV_1 (L)	**Change from Baseline FEV_1 (L)**		% Change from Baseline
	Mean (SD)	N	Mean (SD)	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)
Baseline	3.333 (0.8)	109			3.303 (0.7)	116		
Week 1	3.311 (0.8)	99	**-0.059 (0.1)**	-1.837 (3.6)	3.281 (0.7)	99	**-0.034 (0.1)**	-0.936 (3.7)
Week 2	3.248 (0.8)	97	**-0.082 (0.1)**	-2.381 (4.4)	3.295 (0.7)	102	**-0.035 (0.1)**	-0.970 (3.3)
Week 3	3.258 (0.8)	93	**-0.075 (0.1)**	-2.443 (4.7)	3.302 (0.7)	97	**-0.037 (0.1)**	-1.015 (3.9)
Week 4	3.252 (0.8)	103	**-0.086 (0.2)**	-2.622 (5.1)	3.267 (0.7)	100	**-0.055 (0.1)**	-1.512 (3.9)
Week 6	3.261 (0.8)	91	**-0.062 (0.1)**	-1.918 (4.4)	3.249 (0.7)	101	**-0.066 (0.1)**	-1.852 (3.7)
Week 8	3.288 (0.8)	99	**-0.082 (0.1)**	-2.461 (4.1)	3.248 (0.7)	103	**-0.057 (0.1)**	-1.647 (4.1)
Week 12	3.309 (0.8)	96	**- 0.065(0.1)**	-1.903 (4.4)	3.252 (0.7)	97	**-0.053 (0.1)**	-1.472 (4.5)
Follow-up Phase								
Baseline*	3.367 (0.8)	93			3.305 (0.7)	101		
2 weeks	3.367 (0.8)	90	**-0.032 (0.1)**	-0.869 (4.3)	3.210 (0.7)	92	**-0.063 (0.2)**	-1.888 (5.0)
4 weeks	3.277 (0.8)	87	**-0.078 (0.1)**	-2.344 (4.4)	3.264 (0.7)	96	**-0.060 (0.1)**	-1.682 (4.7)
8 weeks	3.312 (0.8)	92	**-0.060 (0.1)**	-1.735 (4.2)	3.222 (0.7)	92	**-0.062 (0.1)**	-1.873 (4.7)
12 weeks	3.329 (0.8)	85	**-0.057 (0.1)**	-1.827 (4.2)	3.251 (0.7)	93	**-0.062 (0.2)**	-1.836 (4.8)

*Baseline for follow up phase is the baseline for only those subjects continuing into the follow up phase
**Full analysis set included subjects who had a baseline value between screening and randomization and had at least 1 post-baseline measurement in the treatment phase
Source: N21868/N_000/2004-12-27/clinstat/1027.pdf, pg 374, 375

Reviewer's Comment: The FEV_1 data from Study 1027 suggests that an effect of inhaled insulin on FEV_1 appears within the first couple of weeks of inhaled insulin use.

Table 21 Mean Treatment Group Difference (L) in Change from Baseline FEV_1 (L) in Study 1027 Full Analysis Set*

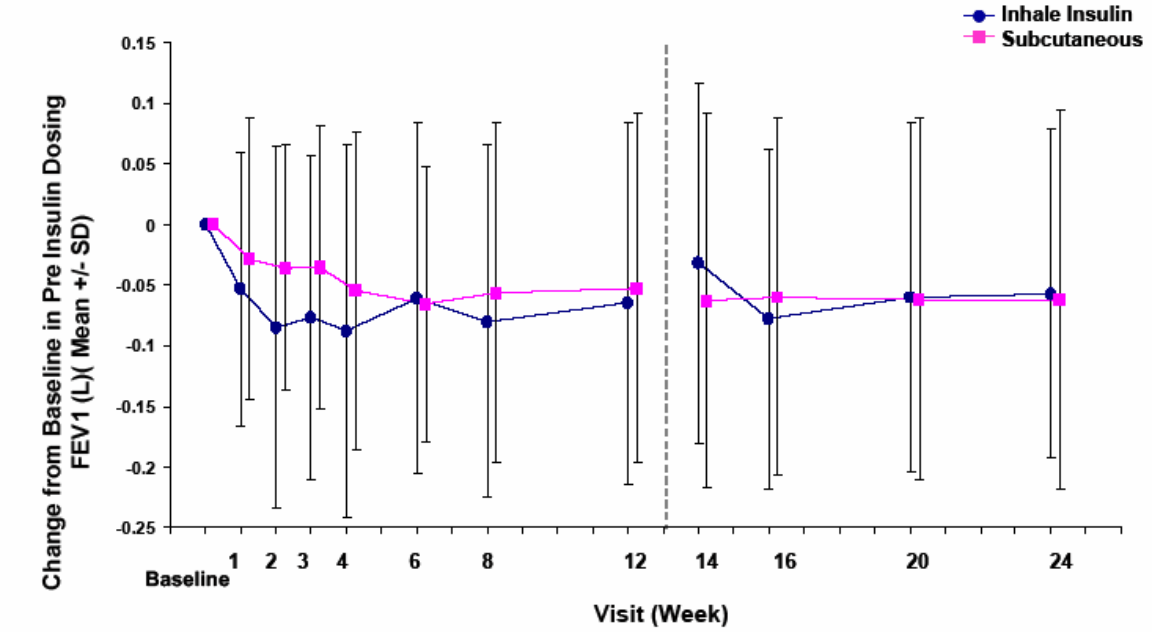
	Mean Treatment Group Difference (95% CI) Unadjusted^	Mean Treatment Group Difference (95% CI) Adjusted**
Week 1	-0.024 (-0.056, 0.007)	-0.022 (-0.053, 0.009)
Week 2	-0.046 (-0.077, -0.015)	-0.044 (-0.075, -0.013)
Week 3	-0.034 (-0.065, -0.002)	-0.032 (-0.063, -0.001)
Week 4	-0.028 (-0.059, 0.003)	-0.026 (-0.057, 0.005)
Week 6	0.001 (-0.031, 0.033)	0.004 (-0.028, 0.035)
Week 8	-0.025 (-0.056, 0.007)	-0.021 (-0.052, 0.010)
Week 12	-0.013 (-0.046, 0.019)	-0.010 (-0.041, 0.022)
Follow up phase		
2 weeks	0.035 (-0.000, 0.070)	0.041 (0.007, 0.076)
4 weeks	-0.018 (-0.053, 0.017)	-0.012 (-0.046, 0.022)
8 weeks	-0.000 (-0.036, 0.035)	0.006 (-0.029, 0.040)
12 weeks	0.006 (-0.030, 0.042)	0.014 (-0.021, 0.049)

*Full analysis set included subjects who had a baseline value between screening and randomization and had at least 1 post-baseline measurement in the treatment phase
^The unadjusted model in this table includes the terms treatment and week
**The adjusted model in this table includes the terms treatment, week, country, age, height, gender, and baseline PFT
Source: N21868/N_000/2004-12-27/clinstat/1027.pdf, pg 386, 387

Reviewer's Comment: The small treatment group difference of approximately -10mL at Week 12 in Study 1027 is not consistent with the pooled adult controlled phase 2/3 study data in type 1 diabetes, which showed a treatment group difference of approximately -30mL at Week 12.

Table 20 and Table 21 also display the follow-up phase data after discontinuation of study medication. The follow up phase data suggests that after 12 weeks of discontinuation of study medication, the treatment group difference favors the inhaled insulin group as shown above in Table 22 and below in Figure 14.

Figure 14 Mean Change from Baseline FEV_1 (L) in Study 1027 in Type 1 Diabetes
(Full Analysis Set*)



Source: N21868/N_000/2004-12-27/clinstat/1027.pdf, pg 95.
*Full analysis set included subjects who had a baseline value between screening and randomization and had at least 1 post-baseline measurement in the treatment phase

Reviewer's Comment: The Applicant asserts that this supports the reversibility of the effect of inhaled insulin on FEV_1. However, the following should be noted. First of all, it is difficult to argue the reversibility of an effect, when there was such a small treatment group difference in this study at Week 12. The Week 12 treatment difference in Study 1027 (approximately -10mL) did not show the same magnitude of treatment difference as the Week 12 data in the pooled studies (approximately -30mL). The lack of a significant treatment group difference at Week 12 limits the utility of the follow up phase data on the reversibility of the effect of inhaled insulin. Also, 2 weeks into the follow up phase, the inhaled insulin group looks suddenly better than the comparator by about 35-41mL. This seems odd and is another observation that calls the reversibility data into question. Finally, subjects in Study 1027 were only exposed to inhaled insulin for 12 weeks prior to discontinuation. Ideally, the Applicant should assess the effect of discontinuation of inhaled insulin in a controlled fashion after long term exposure to inhaled insulin. Study 1022 will provide some information regarding the effect of discontinuation of inhaled

insulin (after 24 months of treatment) on pulmonary function, but Study 1022 is still ongoing.

Reviewer's Comment: It should be noted that although the Applicant asserts the effect of inhaled insulin is reversible, the Applicant did not propose a mechanism for the reversibility.

The pre-insulin and post-insulin (10min and 60min) mean FEV_1 data was reviewed to assess the effect of inhaled insulin on acute airway function in Study 1027. The 10 and 60 minute post-inhaled insulin mean FEV_1 data did not suggest a significant acute decrease in mean FEV_1 associated with inhaled insulin as shown in Table 22.

Table 22 Mean Observed FEV_1 Pre- and Post-Inhaled Insulin Dose in Study 1027

	Inhaled Insulin		
FEV_1 in liters	Pre-Dose	10 Minutes Post-Dose	60 Minutes Pos-Dose
	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	3.333 (0.8)	3.329 (0.8)	3.332 (0.8)
Week 4	3.252 (0.8)	3.245 (0.8)	3.267 (0.8)
Week 8	3.288 (0.8)	3.276 (0.8)	3.269 (0.8)
Week 12	3.309 (0.8)	3.308 (0.8)	3.309 (0.8)
Source: N21868/N_000/2004-12-27/clinstat/1027.pdf, pg 374,389, 397			

Reviewer's Comment: Study 1027 enrolled subjects without any active lung disease, according to the protocol. Airway hyper reactivity to inhaled insulin would not typically be expected in subjects without underlying lung disease.

5.1.8.2.1.4 Study 1036

Study 1036 is an ongoing extension study of the phase 2 protocols 102 (Type 1), 103, and 104 (Type 2). Study 1036 provides some long term PFT data on subjects exposed to inhaled insulin up to 84 months. However, Study 1036 has design issues, which limit interpretation of the data. First, Study 1036 is not a controlled study from which sound conclusions can be drawn. Second, subjects who decide to stay in an open-label extension study are self-selected, which may enrich the study population with subjects who have a favorable response and tolerate inhaled insulin.
Reviewer's Comment: Study 1036 does not have a comparator group. However, the Applicant includes information on a comparator group (N=23) for Study 1036 in the Summary of Pulmonary Safety. Subjects who initially continued into the extension Studies 102E, 103E, and 104E were allowed to continue the comparator treatment. However, when Studies 102E, 103E, and 104E were combined into extension Study 1036, no subjects were allowed to continue comparator medication.

Study 1036 has at least 85 subjects who have been exposed to inhaled insulin for > 48 months and thus, provides some information regarding the change in PFTs with time. However, due to the uncontrolled nature of the study, the results should be interpreted with caution. The results for the mean observed FEV_1 and mean change from baseline FEV_1 are shown below in Table 23. The results suggest a continued decline in mean

FEV_1 over time, which is greater than what was noted in the controlled phase 2/3 studies. It should be noted that the results are for both type 1 and type 2 diabetes.

Table 23 Mean Observed FEV_1 (L) and Mean Change From Baseline FEV_1(L) (Type 1 and 2 Subjects) by Time on Treatment in Study 1036 (102, 102E, 103, 103E, 104, 104E)

	Inhaled Insulin		
	Observed	Change from Baseline FEV_1 (L)	
	Mean (SD)	N	Mean (SD)
Baseline	3.241 (.80)	156	
3 Months	3.152 (.78)	154	**-0.077 (.2)**
6 Months	3.130 (.79)	149	**-0.101 (.2)**
12 Months	3.120 (.79)	138	**-0.137 (.2)**
18 Months	3.120 (.79)	123	**-0.141 (.2)**
24 Months	3.101 (.76)	116	**-0.184 (.2)**
30 Months	3.080 (.78)	108	**-0.210 (.2)**
36 Months	3.019 (.78)	101	**-0.253 (.2)**
42 Months	3.003 (.76)	92	**-0.288 (.2)**
48 Months	2.996 (.73)	88	**-0.307 (.3)**
54 Months	3.013 (.75)	83	**-0.291 (.3)**
60 Months	3.027 (.79)	75	**-0.312 (.3)**
66 Months	3.011 (.77)	70	**-0.349 (.3)**
72 Months	3.033 (.75)	61	**-0.351 (.3)**
78 Months	2.971 (.74)	41	**-0.350 (.2)**
84 Months	3.057 (.78)	27	**-0.409 (.3)**

Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 148

The mean decline in FEV_1 in Study 1036 continues over time, roughly at a rate of about 50mL per year. After 84 months a decline of 409mL from baseline FEV_1 was noted in 27 subjects. Because Study 1036 does not have a comparator group, it is difficult to draw any firm conclusions regarding this data.
Reviewer's Comment: These data might suggest that treatment-related loss of lung function continues to accrue over time. An annual decline in FEV_1 of 50mL is more than would be expected in subjects without underlying lung disease. As discussed earlier, an annual rate of decline of 50mL per year is what would be expected in COPD patients who continue to smoke.

5.1.8.2.1.5 Study 111

Study 111 was an open-label extension study of the phase 3 Studies 106, 107 (Type 1), 108, 109, and 110 (Type 2). The design of Study 111 was discussed in the Methods Section 5.1.8.1. Like Study 1036, Study 111 provides some long term non-controlled PFT data on subjects exposed to inhaled insulin.

Study 111 included 664 subjects with type 1 diabetes and 626 subjects with type 2 diabetes. As shown in Table 24, subjects with type 1 diabetes demonstrated a mean decline in FEV_1 with time. A mean decline in FEV_1 is noted at 3 months and, in general, the decline becomes greater at each time point through Month 36 in the inhaled insulin

group. However, it should be noted that the 36 month data only includes data from 6 subjects.

Table 24 Mean Observed FEV_1 (L) and Change From Baseline* (L) in Study 111 – Adult Subjects with Type 1 Diabetes
(Studies 102, 102E, 103, 1036, 103E, 104, 104E)

Inhaled Insulin			
	Type 1		
FEV_1 in liters	Observed	**Change from Baseline***	
	Mean (SD)	N	Mean (SD)
Baseline	3.345 (0.8)	380	
3 Months	3.404 (0.8)	380	**-0.041 (0.2)**
6 Months	3.403 (0.8)	370	**-0.056 (0.3)**
12 Months	3.388 (0.8)	344	**-0.073 (0.3)**
18 Months	3.367 (0.8)	304	**-0.110 (0.3)**
24 Months	3.384 (0.8)	234	**-0.117 (0.3)**
30 Months	3.276 (0.9)	96	**-0.152 (0.3)**
36 Months	3.105 (0.9)	6	**-0.373 (0.3)**

*Baseline is based on pre-inhaled insulin measurements
Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 960, 962

Reviewer's Comment: In Study 111, based upon the 24 month data, the annual rate of decline from baseline is approximately 60mL/year, which is similar to the annual rate of change from baseline noted in Study 1036 and in the pooled controlled phase 2/3 studies in the inhaled insulin group.

The Applicant amended Study 111 to provide additional PFT information after discontinuation of inhaled insulin. However, as discussed in the Methods Section 5.1.8.1, the design is flawed in that the study population prior to randomization is likely enriched with subjects who responded favorably to inhaled insulin and tolerated inhaled insulin. Subjects who did not tolerate inhaled insulin or had a decline in pulmonary function may have been discontinued from the study. In addition, subjects were on inhaled insulin for various lengths of time prior to randomization into the discontinuation phase. Thus, for the effects of discontinuation of inhaled insulin, Study 1027 provides the most rigorous PFT data and was discussed earlier in this section.
Reviewer's Comment: The duration of treatment prior to the discontinuation phase was variable among subjects and ranged from >12 months to >30 months [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 1099].

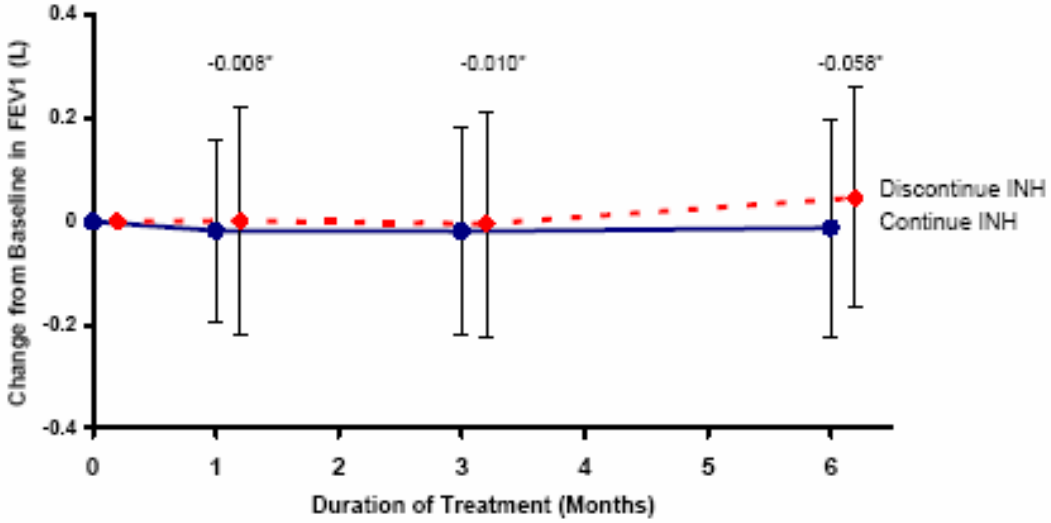
The mean observed FEV_1 and mean change in FEV_1 in the discontinuation phase are shown in Table 25 and Figure 15 below. The results show that in the 6 months discontinuation phase, subjects who discontinued inhaled insulin demonstrated a mean increase in FEV_1, while subjects who continued on inhaled insulin essentially had no further mean change in FEV_1.
Reviewer's Comment: The "baseline" for the discontinuation phase was the last value prior to or within 7 days after being randomized to continuation or discontinuation of inhaled insulin and is not the true baseline prior to study medication exposure. Thus, this "baseline" is in quotes to distinguish it from the true pre-study medication baseline.

Table 25 Mean Observed FEV_1 and Change in FEV_1 in Discontinuation Phase of Study 111 – Adult Subjects with Type 1 Diabetes (Primary Analysis Set)**

Inhaled Insulin						
	Continued Inhaled Insulin			Discontinued Inhaled Insulin		
FEV_1 in liters	Observed	**Change from "Baseline"***		Observed	**Change from "Baseline"***	
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)
"Baseline"*	3.489 (0.8)	115		3.429 (0.8)	122	
1 Month	3.469 (0.8)	104	**-0.018 (0.2)**	3.435 (0.8)	118	**0.001 (0.2)**
3 Months	3.464 (0.8)	113	**-0.019 (0.2)**	3.450 (0.9)	119	**-0.005 (0.2)**
6 Months	3.474 (0.8)	109	**-0.013 (0.2)**	3.477 (0.9)	116	**0.046 (0.2)**

* "Baseline" for the discontinuation phase was the last value prior to or within 7 days after being randomized to continuation or discontinuation of inhaled insulin
**Primary analysis set includes all randomized subjects who had a baseline FEV_1 measurement and a post-baseline measurements and received study drug for at least 50% of the duration of the controlled segment
Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 1729

Figure 15 Mean Change in FEV_1 from "Baseline" in the Discontinuation Phase of Study 111 in Adults Type 1 Subjects



Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 46.

Reviewer's Comment: The Applicant also followed the group who was randomized to continued inhaled insulin for an additional 6 months after the discontinuation phase. In this follow up phase inhaled insulin was discontinued. During the 6 month of follow up off inhaled insulin, in subjects with type 1 diabetes ≥ 18 years of age, the FEV_1 increased 40 -50mL from the last FEV_1 value on inhaled insulin [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 180].

Reviewer's Comment: The Applicant asserts that this data supports the reversibility of the effect of inhaled insulin after discontinuation; however, the issues with the design of this discontinuation phase were noted above. In addition, the subjects who continued inhaled insulin had essentially no decline in FEV_1 between one and six months, which is

not consistent with the earlier phase of Study 111 or Study 1036. Thus, the results should be interpreted with caution and do not adequately address the potential reversibility of the effect of inhaled insulin on FEV1.

5.1.8.2.1.6 Conclusions of the Effect of Inhaled Insulin on FEV_1 in Type 1 Diabetes

Subjects with type 1 diabetes treated with inhaled insulin consistently showed a greater mean decline in FEV_1 from baseline over time compared to the comparator group in each individual study as well as in the pooled adult controlled phase 2/3 studies. A single study (1027) suggested that inhaled insulin has an affect on the FEV_1 within the first few weeks of exposure. The pooled controlled studies indicate that there is a treatment group difference between inhaled insulin and the comparator favoring the comparator.

The effect of inhaled insulin on FEV_1 progressed during the first year of exposure then stabilized between the first and second year as evidenced by a fairly constant mean treatment group difference of approximately -20mL from Week 12 through Week 36 followed by an increase in the mean treatment group difference to approximately -40mL at Week 48. The increased mean treatment group difference noted at Week 48 remained fairly constant until Week 96, which is the last time point with available PFT data.

After 2 years of treatment, subjects in the inhaled insulin group had a mean decline from baseline FEV_1 of 118mL while subjects in the comparator group had a mean decline from baseline FEV_1 of 77mL. Both treatment groups demonstrated a larger FEV_1 decline than what would be expected in non-smoking subjects without significant lung disease. At Week 96, there is approximately a 40mL treatment group difference, favoring the comparator.

Exposure to inhaled insulin longer than 24 months in type 1 diabetes has not been studied in controlled studies. However, non-controlled extension studies have exposed subjects to inhaled insulin up to 84 months. The non-controlled PFT data from two extension studies (1036 and 111) suggest that the mean decline from baseline FEV_1 continues with continued exposure. However, without a comparator group, it is unclear if this further decline is treatment related.

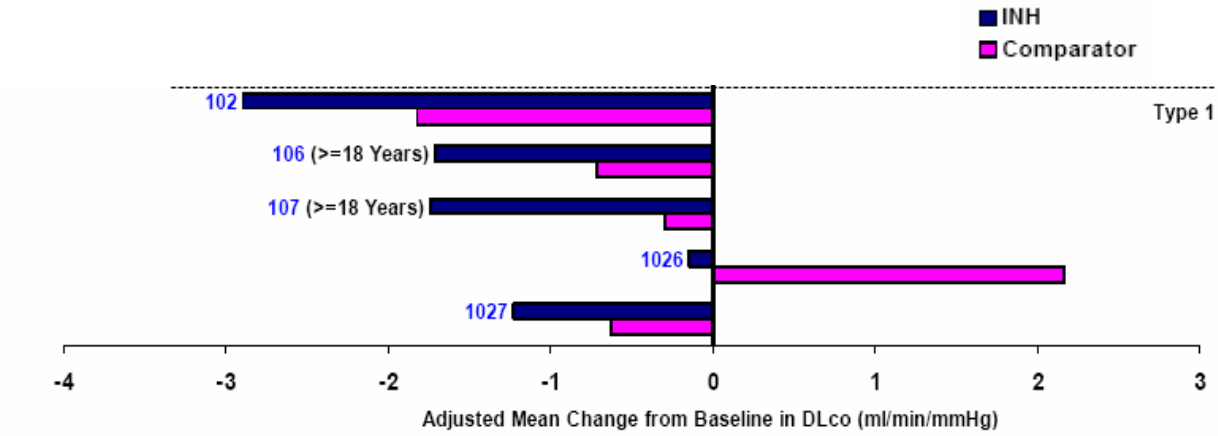
The reversibility of the effect of inhaled insulin on FEV_1 was evaluated in a controlled fashion in Study 1027. However, Study 1027 does not adequately address the effect of the reversibility in type 1 diabetes for two reasons. First, exposure to inhaled insulin was only 12 weeks prior to discontinuation. Second, prior to entering the discontinuation phase, there was essentially no treatment group difference (-9mL). Thus, there was no significant treatment effect to reverse. Reversibility of the effect of long term inhaled insulin use was also assessed in the extension Study 111. However, the study design and results have issues which limit the interpretability of the reversibility data. Thus, there is not adequate controlled data to support that the mean change from baseline FEV_1 treatment group difference noted with inhaled insulin (short term or long term) in type 1 diabetes is reversible.

5.1.8.2.2 Single Breath Carbon Monoxide Diffusion Capacity (DLCO) in Type 1 Diabetes

5.1.8.2.2.1 Summary of Individual Studies

In each of the individual studies in subjects with type 1 diabetes, the inhaled insulin group demonstrated a larger adjusted mean decrease from baseline DLCO to the end of study DLCO than subjects in the comparator group as shown below in Figure 16.

Figure 16 Adjusted* Mean Change from Baseline DLCO (mL/min/mmHg) 3 and 6 Month Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)

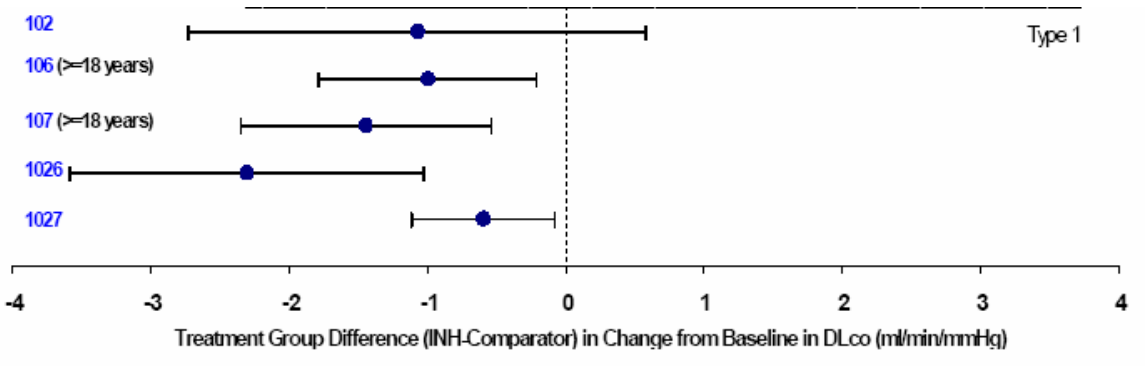


Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 48

**Reviewer's Comment: The above figure illustrates a greater mean decline from baseline DLCO in the inhaled insulin group compared to the comparator group in the individual studies. In this figure, the Applicant adjusted the mean change from baseline DLCO for treatment, visit, center, baseline PFT, age, height, and gender.*
Reviewer's Comment: The above figure does not include the ongoing Study 1022.

Similarly, the mean treatment group difference, which is defined as the mean change from baseline DLCO in the inhaled insulin group – the mean change from baseline DLCO in the comparator group, favored the comparator in the individual studies as shown below in Figure 17. A more negative treatment group difference indicates that the inhaled insulin group had a greater decline in mean change from baseline DLCO than the comparator group.

Figure 17 Adjusted* Mean Treatment Group Difference for DLCO Change from Baseline (mL/min/mmHg)
3 and 6 Month Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)



Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 49

**Reviewer's Comment: The above figure illustrates a greater mean decrease from baseline DLCO in the inhaled insulin group compared to the comparator group in the individual studies. In this figure, the Applicant adjusted the mean change from baseline DLCO for treatment, visit, center, baseline PFT, age, height, and gender. The above figure does not include the ongoing Study 1022.*

5.1.8.2.2.2 Pooled Controlled Adult Phase 2/3 Studies in Type 1 Diabetes

In the pooled adult controlled phase 2/3 studies in subjects with type 1 diabetes, the mean baseline DLCO and mean percent predicted DLCO were similar between treatment groups. Subjects in both treatment groups demonstrated a decline from baseline DLCO at Weeks 12, 24, 36, 48, 60, 72, and 96. However, subjects in the inhaled insulin treatment group demonstrated a larger mean decline from baseline DLCO than subjects in the comparator group at each time point as shown below in Table 26. The decline was noted in both groups at Week 12, which was the first on treatment measurement in some of the individual studies.

Table 26 Mean Observed DLCO and Change From Baseline DLCO (mL/min/mmHg)
Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)
Studies 102, 106, 107, 1026, 1027, 1022 (ongoing)

	Inhaled Insulin			Comparator		
DLCO in ml/min/mmHg	Observed	Change from Baseline		Observed	Change from Baseline	
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)
Baseline % Predicted	95.401 (14.4)	684		95.074 (15.0)	691	
Baseline	27.872 (6.6)	684		27.521 (6.6)	691	
Week 12	26.738 (6.3)	427	-1.157 (2.3)	26.851 (6.3)	417	-0.523 (2.4)
Week 24	26.898 (6.3)	500	-1.348 (2.9)	27.314 (6.4)	507	-0.286 (2.7)
Week 36*	26.998 (6.1)	246	-1.125 (2.1)	26.761 (6.4)	266	-0.411 (1.9)
Week 48*	27.931 (6.0)	239	-1.368 (2.1)	26.753 (6.1)	257	-0.404 (2.2)
Week 60*	27.170 (6.0)	234	-1.145 (2.2)	26.757 (6.1)	249	-0.422 (2.2)
Week 72*	27.070 (6.0)	226	-1.223 (2.3)	25.702 (6.4)	230	-0.439 (2.2)
Week 84*	27.083 (6.0)	216	-1.340 (2.5)	26.725 (6.2)	224	-0.575 (2.1)
Week 96*	27.089 (6.0)	206	-1.324 (2.3)	26.475 (6.0)	216	-0.742 (2.4)

Source: Dr. Joan Buenconsejo's Biometrics Review

*Week 36, 48, 60, 72, 84, and 96 data from ongoing Study 1022

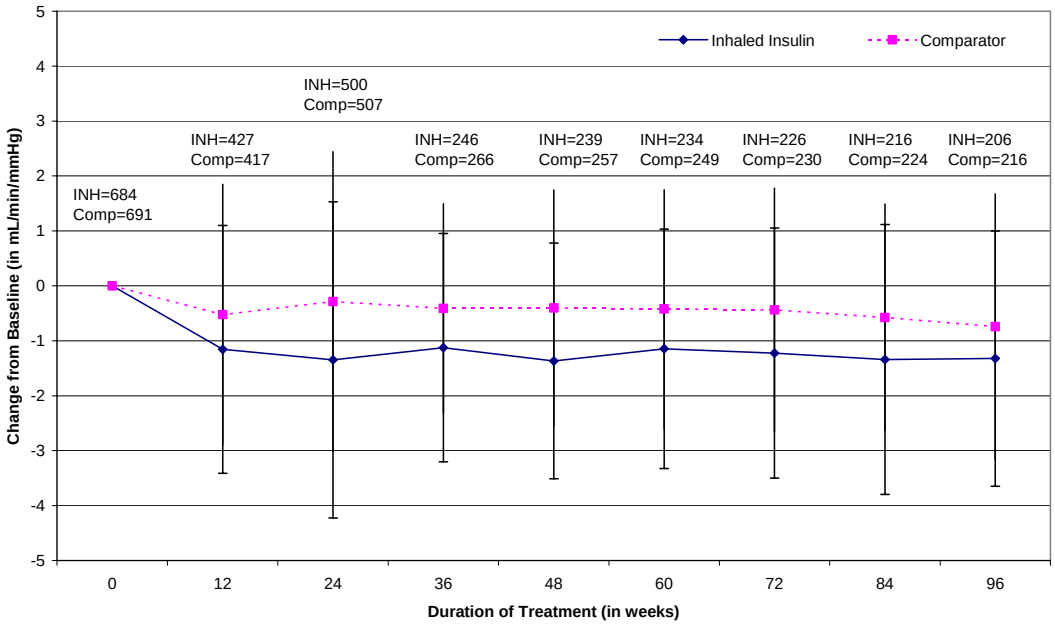
Reviewer's Comment: The DLCO data from the individual controlled adult phase 2/3 studies in type 1 diabetes was pooled by the Biometrics Reviewer, Dr. Joan Buenconsejo. Some of the numbers differ from the Applicant's pooled data because in the analyses performed by Dr. Buenconsejo, all subjects were included in the calculation of the mean baseline DLCO. However, the Applicant only included subjects for the baseline calculation if the subject had a post-baseline DLCO measurement. In addition, the above table contains PFT data from ongoing Study 1022 submitted during the review period. Although there are some slight differences in the baseline, the change from baseline in each treatment group is consistent with the Applicant's findings.

At Week 96, subjects in the inhaled insulin group had approximately twice the decline in DLCO as the comparator group. After 96 weeks of study medication, the inhaled insulin treatment group demonstrated a mean decline from baseline of 1.324 mL/min/mmHg and the comparator treatment group demonstrated a mean decline from baseline of 0.742mL/min/mmHg.

Reviewer's Comment: Unlike with the pulmonary function test, FEV_1, there is less epidemiologic data to put the decline in DLCO noted in the clinical studies into perspective. However, a decline of 1.324mL/min/mmHg from a baseline of 28.872mL/min/mmHg is a decline of approximately 4% over two years.

The mean change from baseline DLCO over time in the adult phase 2/3 controlled studies in type 1 diabetes is shown below in Figure 18. Subjects in both treatment groups demonstrated a decline from baseline DLCO at all time points. However, subjects in the inhaled insulin treatment group demonstrated a larger decline than subjects in the comparator group.

Figure 18 Mean Change from Baseline DLCO over Time in the Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

The mean <u>treatment group difference</u> was defined as the following: the mean change from baseline DLCO in the inhaled insulin group – the mean change from baseline DLCO in the comparator group. A difference between treatment groups was noted at Week 12 and fluctuated throughout the treatment period; however, the Week 96 DLCO data and Week 12 data showed a similar mean treatment group difference as shown below in Table 27. At Week 96, the mean treatment group difference was approximately -0.5 to -0.6mL/min/mmHg.

Table 27 Mean Change from Baseline DLCO (mL/min/mmHg) and Mean Treatment Group Difference (mL/min/mmHg) in Change from Baseline DLCO in Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)

	Mean Change from Baseline DLCO (N)		Mean Treatment Group Difference (95% CI) Unadjusted	Mean Treatment Group Difference (95% CI) Adjusted**
	Inhaled Insulin	Comparator		
Week 12	-1.157 (427)	-0.523 (417)	-0.634 (-0.946, -0.321)	-0.680 (-0.976, -0.384)
Week 24	-1.348 (500)	-0.286 (507)	-1.061 (-1.408, -0.715)	-0.955 (-1.233, -0.677)
Week 36*	-1.125 (246)	-0.411 (266)	-0.714 (-1.060, -0.368)	-0.716 (-1.074, -0.359)
Week 48*	-1.368 (239)	-0.404 (257)	-0.964 (-1.343, -0.584)	-0.893 (-1.283, -0.502)
Week 60*	-1.145 (234)	-0.422 (249)	-0.723 (-1.112, -0.334)	-0.653 (-1.060, -0.246)
Week 72*	-1.223 (226)	-0.439 (230)	-0.783 (-1.197, -0.370)	-0.585 (-1.005, -0.165)
Week 84*	-1.340 (216)	-0.575 (224)	-0.765 (-1.189, -0.341)	-0.646 (-1.075, -0.216)
Week 96*	-1.324 (206)	-0.742 (216)	-0.582 (-1.036, -0.128)	-0.513 (-0.953, -0.072)

Source: Dr. Joan Buenconsejo's Biometrics Review
*Interim data from Study 1022, which is ongoing
**Adjusted for treatment, protocol, visit, baseline measurement, age, gender, and baseline height;

Reviewer's Comment: The unadjusted and adjusted mean treatment group differences were fairly similar.

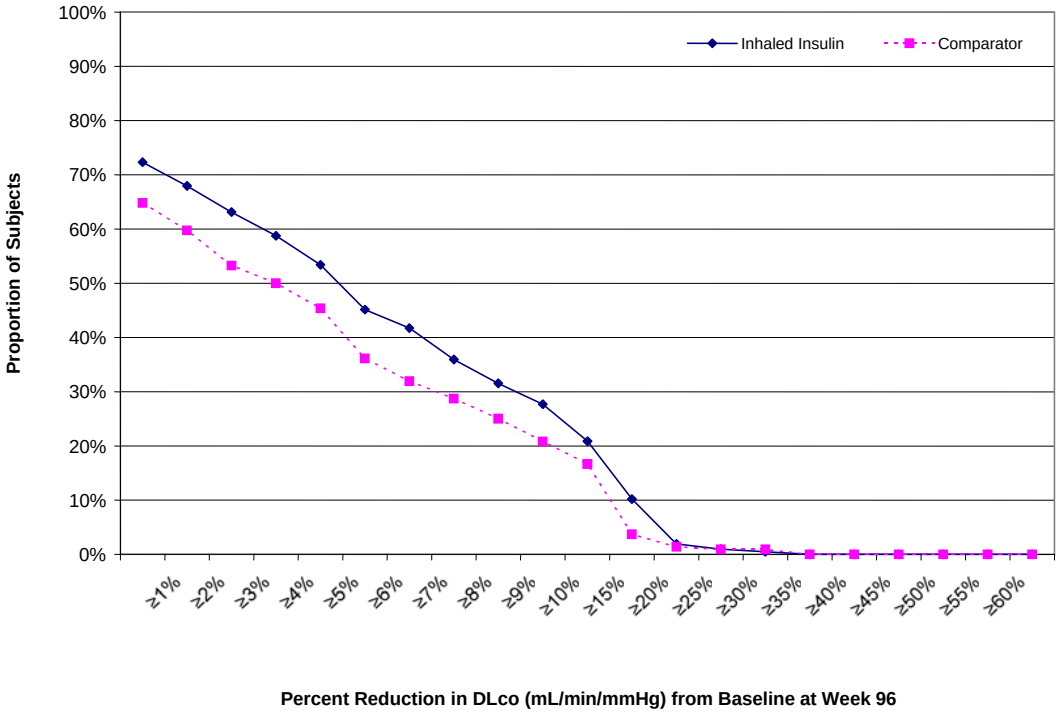
Reviewer's Comment: The Applicant asserts that this data indicates the effect of inhaled insulin on DLCO stabilizes and is not progressive. The data does suggest that the treatment group difference fluctuated during the treatment period; however, the treatment group difference at Week 12 and Week 96 were quite similar. Unlike FEV_1, there is little epidemiologic data to put the DLCO treatment group difference of -0.5 to -0.6mL/min/mmHg noted in the clinical studies into perspective.

It should be noted that the Applicant has not offered a mechanism for the proposed "non-progressive" effect of inhaled insulin on DLCO.

The Biometrics reviewer performed a categorical response analysis to assess the proportion of subjects with declines in DLCO of various magnitudes. The proportion of subjects with a decline from baseline DLCO was analyzed at Weeks 12, 24, 36, 48, 60, 72, 84 and 96. In general, at each week analyzed the inhaled insulin group had a higher percentage of subjects with a decline from baseline DLCO than the comparator group, but the pattern of the response is similar between treatment groups. Thus, the difference in mean DLCO between the treatment groups does not appear to be driven by outliers.

The Week 96 response profile is shown in Figure 19 as an example of the response analysis. Overall, approximately 10% of subjects in the inhaled insulin group with DLCO measurements at Week 96 had a >15% decline from baseline DLCO compared to approximately 3% in the comparator group.

Figure 19 Proportion of Subjects by Percent Reduction from Baseline DLCO (ml/min/mmHg) at Week 96 in the Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

The controlled phase 2/3 studies in subjects with type 1 diabetes indicate that the inhaled insulin group had a greater mean decline in DLCO than the comparator group, thus, there is a treatment group difference between inhaled insulin and the comparator favoring the comparator. A difference between treatment groups was noted at Week 12 and although fluctuated throughout the treatment period, the Week 96 DLCO data and Week 12 DLCO data showed a similar treatment group difference. At Week 96, the treatment group difference was between -0.5 to -0.6mL/min/mmHg.

To further explore the effects of inhaled insulin on DLCO in subjects with type 1 diabetes, some of the individual studies, which provide additional information about long term exposure and the potential for reversibility, are reviewed next.

5.1.8.2.2.3 Study 1027

Study 1027 was a 24 week, controlled study that is worth reviewing in greater detail in this integrated summary of pulmonary safety for several reasons. First of all, Study 1027 specified more frequent pulmonary function tests (Wks -3, -2, -1, 0, 1, 2, 3, 4, 6, 8, 12) than the other phase 2/3 studies. The more frequent PFTs provide some insight as to when the treatment group difference in pulmonary function is first noticed. Second, Study 1027 specified a 12 week study medication treatment period followed by a 12 week follow up period after discontinuation of study medication. Study 1027 is the only

study in type 1 diabetics to provide controlled information regarding pulmonary function tests following discontinuation of inhaled insulin. Thus, the effect of discontinuation of inhaled insulin on DLCO from Study 1027 is reviewed here.
Reviewer's Comment: Study 1027 has limitations in that subjects are only exposed to inhaled insulin for 12 weeks prior to discontinuation. Even if the discontinuation data suggests that the effects of inhaled insulin on DLCO are reversible after 12 weeks of inhaled insulin exposure, the effects may not be reversible after longer inhaled insulin exposure.

Reviewer's Comment: Study 1022 also specifies obtaining PFTs in type 1 diabetics after discontinuation of inhaled insulin following 24 months of exposure in a controlled fashion. However, Study 1022 is an ongoing study and the data following discontinuation of inhaled insulin was not available at the time of this review.

The PFT data from Study 1027 suggests that a treatment group difference between inhaled insulin and the comparator is noted in the first two weeks of treatment. The mean treatment group difference fluctuated some after two weeks and the maximum treatment group difference was noted at Week 4. After Week 4, the treatment group difference fluctuated, but in general decreased. At Week 12 there was a treatment group difference around -0.6 ml/min/mmHg, favoring the comparator. Table 28 and Table 29 display the mean observed DLCO, mean change from baseline DLCO, and the mean treatment group differences, respectively.

Table 28 Mean Observed DLCO and Mean Change From Baseline DLCO (mL/min/mmHg) in Study 1027 -Full Analysis Set**

	Inhaled Insulin				Comparator			
DLCO in ml/min/mmHg	Observed	**Change from Baseline**		% Change from Baseline	Observed	**Change from Baseline**		% Change from Baseline
	Mean (SD)	N	Mean (SD)	Mean (SD)	Mean (SD)	N	Mean (SD)	Mean (SD)
Baseline	26.91 (6.7)	109			27.05 (5.7)	116		
Week 1	26.39 (6.4)	96	**-0.905 (1.6)**	-3.048 (5.5)	26.36 (5.1)	98	**-0.444 (1.5)**	-1.421 (5.5)
Week 2	25.75 (6.2)	97	**-1.122 (1.9)**	-3.812 (6.6)	26.82 (6.0)	102	**-0.349 (1.4)**	-1.206 (5.4)
Week 3	25.92 (6.5)	93	**-1.108 (1.9)**	-4.011 (6.9)	26.97 (5.9)	97	**-0.345 (1.6)**	-1.135 (5.8)
Week 4	25.53 (6.5)	103	**-1.400 (1.7)**	-5.107 (6.6)	26.72 (5.6)	100	**-0.461 (1.8)**	-1.433 (6.4)
Week 6	25.98 (6.3)	92	**-1.134 (2.2)**	-3.906 (7.8)	26.64 (5.9)	101	**-0.487 (1.6)**	-1.612 (6.0)
Week 8	25.95 (6.3)	99	**-1.317 (2.5)**	-4.425 (9.7)	26.49 (5.5)	102	**-0.490 (1.8)**	-1.480 (6.4)
Week 12	25.78 (6.6)	95	**-1.359 (2.4)**	-4.944 (2.4)	26.20 (5.8)	97	**-0.740 (1.8)**	-2.564 (6.6)
Follow-up Phase								
Baseline*	27.07 (6.7)	93			26.95 (5.9)	101		
2 weeks	26.77 (6.5)	90	**-0.626 (2.2)**	-2.090 (8.1)	26.25 (5.9)	92	**-0.592 (1.9)**	-2.024 (6.8)
4 weeks	26.55 (6.7)	87	**-0.506 (2.2)**	-1.661 (8.1)	26.67 (6.0)	96	**-0.440 (2.2)**	-1.524 (7.9)
8 weeks	26.52 (6.6)	91	**-0.529 (2.4)**	-1.766 (8.7)	26.41 (5.9)	92	**-0.301 (2.0)**	-1.120 (7.3)
12 weeks	26.66 (7.1)	85	**-0.426 (2.2)**	-1.781(8.0)	26.51 (6.0)	93	**-0.585 (2.2)**	-1.948 (8.2)

*Baseline for follow up phase is the baseline for only those subjects continuing into the follow up phase
**Full analysis set included subjects who had a baseline value between screening and randomization and had at least 1 post-baseline measurement in the treatment phase
Source: N21868/N_000/2004-12-27/clinstat/1027.pdf, pg 408-409

Reviewer's Comment: The DLCO data from Study 1027 suggests than an effect of inhaled insulin on DLCO appears within the first couple of weeks of inhaled insulin exposure.

Table 29 Mean Treatment Group Difference in Change from Baseline DLCO (mL/min/mmHg) in Study 1027 - Full Analysis Set**

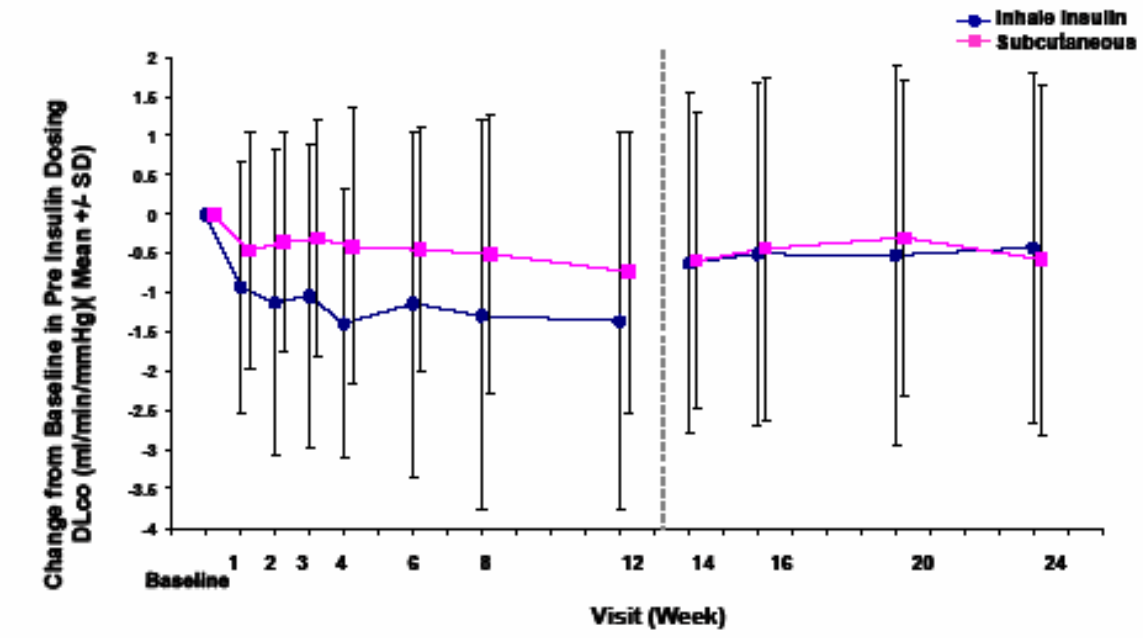
	Mean Treatment Group Difference (95% CI) Unadjusted***	Mean Treatment Group Difference (95% CI) Adjusted*
Week 1	-0.400 (-0.843, 0.043)	-0.385 (-0.809, 0.039)
Week 2	-0.739 (-1.177, -0.301)	-0.740 (-1.159, -0.321)
Week 3	-0.684 (-1.126, -0.241)	-0.683 (-1.107, -0.259)
Week 4	-0.903 (-1.341, -0.465)	-0.898 (-1.317, -0.479)
Week 6	-0.669 (-1.119, -0.219)	-0.652 (-1.083, -0.221)
Week 8	-0.798 (-1.243, -0.354)	-0.768 (-1.193, -0.344)
Week 12	-0.637 (-1.093, -0.181)	-0.597 (-1.033, -0.162)
Follow up phase		
2 weeks	-0.059 (-0.584, 0.467)	-0.043 (-0.559, 0.473)
4 weeks	-0.066 (-0.590, 0.459)	-0.052 (-0.566, 0.463)
8 weeks	-0.167 (-0.694, 0.359)	-0.149 (-0.665, 0.367)
12 weeks	0.182 (-0.354, 0.717)	0.204 (-0.321, 0.729)

Baseline for follow up phase is the baseline for only those subjects continuing into the follow up phase
*Adjustment model includes terms of treatment, week, country, age, height, gender, and baseline PFT
**Full analysis set included subjects who had a baseline value between screening and randomization and had at least 1 post-baseline measurement in the treatment phase
***Unadjusted model included terms of treatment and week
Source: N21868/N_000/2004-12-27/clinstat/1027.pdf, pg 420, 421

Reviewer's Comment: The treatment group difference noted at Week 12 in Study 1027 is similar to the Week 12 data in the pooled controlled phase 2/3 studies.

Table 28 and Table 29 also display the follow-up phase data after discontinuation of study medication. The follow up phase data suggests that after discontinuation of study medication, the treatment group difference decreases. At Week 12 of the follow up phase, the treatment group difference favors the inhaled insulin group as shown below in Figure 20.

Figure 20 Mean Change from Baseline in DLCO in Study 1027 in Type 1 Diabetes
(Full Analysis Set*)



Source: N21868/N_000/2004-12-27/clinstat/1027.pdf, pg 99.
**Full analysis set included subjects who had a baseline value between screening and randomization and had at least 1 post-baseline measurement in the treatment phase

Reviewer's Comment: It is interesting that after discontinuation of inhaled insulin for 2 weeks, the treatment group difference decreases.

Reviewer's Comment: The Applicant asserts that this supports the reversibility of the effect of inhaled insulin on DLCO. However, it should be noted that subjects in Study 1027 were only exposed to inhaled insulin for 12 weeks prior to discontinuation. Even if the discontinuation data suggests that the effects of inhaled insulin on DLCO are reversible after 12 weeks of inhaled insulin exposure, the effects may not be reversible after longer inhaled insulin exposure. Ideally, the Applicant should assess the effect of discontinuation of inhaled insulin in a controlled fashion after long term exposure to inhaled insulin.

5.1.8.2.2.4 Study 1036

Study 1036 is an ongoing extension study of the phase 2 protocols 102 (Type 1), 103 (Type 2), and 104 (Type 2). Study 1036 provides some long term data on subjects exposed to inhaled insulin up to 84 months (n=38 subjects). However, Study 1036 has design issues, which limit interpretation of the data. First of all, Study 1036 is not a controlled study from which sound conclusions can be drawn. Second, subjects who decide to stay in an open-label extension study are self-selected, which may enrich the study population with subjects who have a favorable response and tolerate inhaled insulin.

Reviewer's Comment: Study 1036 does not have a comparator group. However, the Applicant includes information on a comparator group (n=23) for Study 1036 in the Summary of Pulmonary Safety. Subjects who initially continued into the extension Studies 102E, 103E, and 104E were allowed to continue the comparator treatment. However, when Studies 102E, 103E, and 104E were combined into extension Study 1036, no subjects were allowed to continue comparator medication.

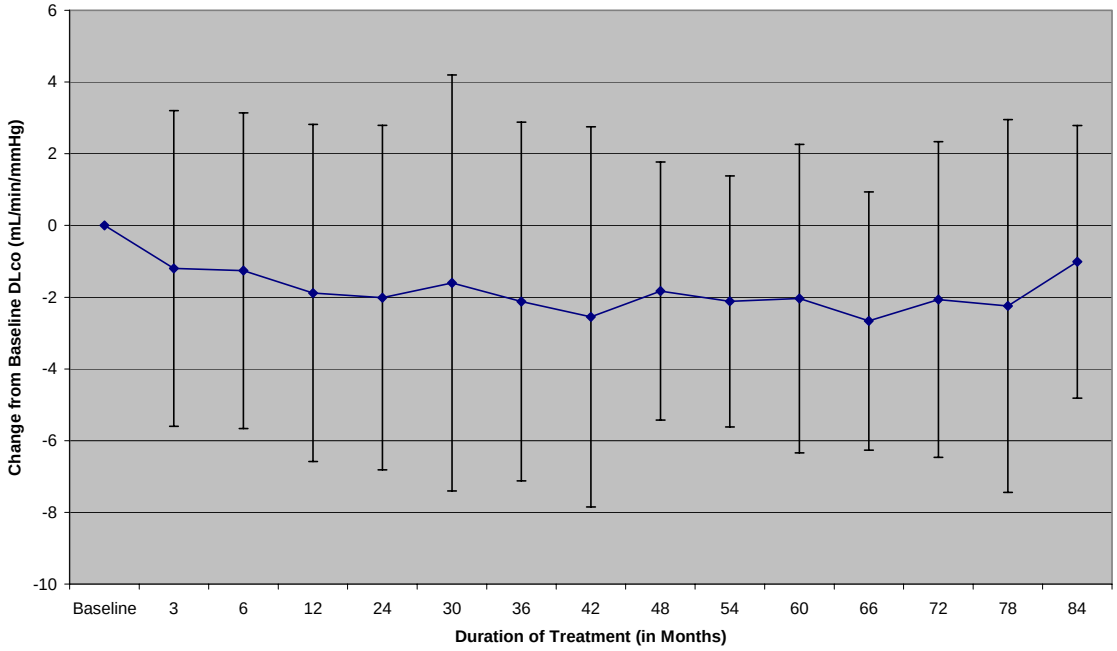
That being said, Study 1036 has at least 85 subjects who have been exposed to inhaled insulin for > 48 months and thus, provides some information regarding the change in PFTs with time. However, due to the uncontrolled nature of the study, the results should be interpreted with caution. The results for the mean observed DLCO and mean change from baseline DLCO are shown below in Table 30 and Figure 21.

Table 30 Mean Observed DLCO (mL/min/mmHg) and Change From Baseline DLCO (mL/min/mmHg) (Type 1 and 2 Subjects) by Time on Treatment in Study 1036
(Studies 102, 102E, 103, 103E, 104, 104E)

	Inhaled Insulin		
DLCO mL/min/mmHg	Observed	**Change from Baseline (mL/min/mmHg)**	
	Mean (SD)	N	Mean (SD)
Baseline	25.768 (6.7)	152	
3 months	24.597 (6.7)	149	**-1.200 (4.4)**
6 months	24.491 (6.3)	130	**-1.262 (4.4)**
12 months	24.448 (6.5)	115	**-1.883 (4.7)**
24 months	24.427 (6.2)	113	**-2.012 (4.8)**
30 months	24.827 (6.9)	100	**-1.601 (5.8)**
36 months	23.942 (6.5)	95	**-2.122 (5.0)**
42 months	23.824 (6.3)	86	**-2.550 (5.3)**
48 months	24.164 (6.1)	82	**-1.827 (3.6)**
54 months	24.044 (6.2)	80	**-2.118 (3.5)**
60 months	24.136 (5.9)	70	**-2.037 (4.3)**
66 months	24.167 (6.3)	62	**-2.664 (3.6)**
72 months	23.937 (6.5)	54	**-2.066 (4.4)**
78 months	22.885 (6.0)	39	**-2.245 (5.2)**
84 months	24.187 (6.2)	26	**-1.014 (3.8)**

Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 152

Figure 21 Mean Change from Baseline DLCO (mL/min/mmHg) over Time in Type 1 and Type 2 Subjects on Inhaled Insulin in Study 1036
(Studies 102, 102E, 103, 103E, 104, 104E)



As shown above, the mean decline in DLCO fluctuates over time. Towards the end of the 84 month period, the number of subjects decreases. After 84 months a mean decline of 1.104 mL/min/mmHg from baseline DLCO was noted in 26 subjects; however, this change from baseline is inconsistent with earlier measures and is based upon only 26 subjects. The change from baseline DLCO noted from Week 12-78 is fairly consistent between approximately -1.8 to -2.7mL/min/mmHg. Over a 78 week treatment period, a change from baseline DLCO of -2mL/min/mmHg is an average annual rate of decline of approximately 0.3mL/min/mmHg per year. However, because Study 1036 does not have a comparator group, it is difficult to draw any firm conclusions regarding this data. *Reviewer's Comment: The data from Study 1036 suggests that between 1 and 7 years of exposure to inhaled insulin, the change from baseline DLCO stabilizes.*

5.1.8.2.2.5 Study 111

Study 111 was an open-label extension study of the phase 3 protocols 106 and 107 (Type 1) and 108, 109, 110 (Type 2). The design of Study 111 was discussed in the Methods Section 5.1.8.1. Like Study 1036, Study 111 provides some long term non-controlled PFT data on subjects exposed to inhaled insulin.

Study 111 included 664 subjects with type 1 diabetes and 626 subjects with type 2 diabetes. As shown in Table 31, subjects with type 1 diabetes demonstrated a mean decline in DLCO at 6 months which fluctuated slightly through 24 months. At 30 months, the number of subjects decreased and the mean decline from baseline DLCO became larger. In contrast, at 36 months with data on 6 subjects, there was an increase from baseline DLCO.

Reviewer's Comment: The results for the mean change from baseline DLCO between 24 and 30 months are in the same vicinity as the results for the mean change from baseline DLCO in Study 1036. However, the 36 months data (based on 6 subjects) is clearly not consistent with the other extension study, Study 1036, in which the mean change from baseline DLCO was -2.122 mL/min/mmHg.

Table 31 Mean Observed DLCO (mL/min/mmHg) and Mean Change From Baseline DLCO (mL/min/mmHg) in Study 111 – Type 1 Diabetes (Adults)
(Studies 108, 109, 110, 111)

Inhaled Insulin			
	Type 1		
DLCO in mL/min/mmHg	Observed	**Change from Baseline DLCO**	
	Mean (SD)	N	Mean (SD)
Baseline	27.920 (6.7)	379	
6 months	26.311 (6.3)	375	**-1.528 (3.6)**
12 months	26.061 (6.3)	334	**-1.943 (3.9)**
18 months	26.126 (6.4)	302	**-1.826 (3.9)**
24 months	26.158 (6.3)	228	**-1.782 (3.9)**
30 months	25.183 (6.3)	94	**-2.197 (4.1)**
36 months	25.854 (8.2)	6	**0.388 (4.7)**

*Baseline is based on pre-inhaled insulin measurements
Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 978

Study 111was amended to provide additional PFT information after discontinuation of inhaled insulin. However, as discussed in the Methods Section 5.1.8.1, the design is flawed in that the study population prior to randomization is likely enriched with subjects who responded favorably to inhaled insulin and tolerated inhaled insulin. Subjects who did not tolerate inhaled insulin or had a decline in pulmonary function may have been discontinued from the study. In addition, subjects were on inhaled insulin for various lengths of time prior to randomization into the discontinuation phase. Thus, for the effects of discontinuation of inhaled insulin, Study 1027 provides the most rigorous PFT data. Study 1027 was discussed earlier in this section.

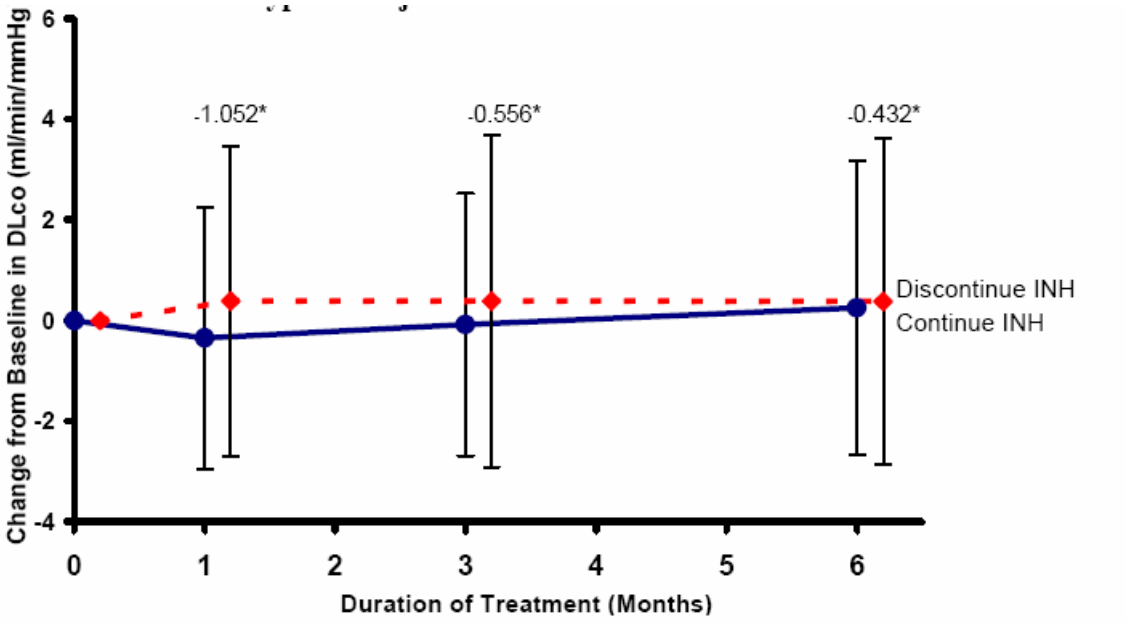
The mean observed DLCO and mean change from "baseline" DLCO in the discontinuation phase are shown in Table 32 and
Figure 22 below. The results show that in the discontinuation phase, subjects who discontinued inhaled insulin had a mean increase in DLCO. By Month 6 of the discontinuation phase, the mean change from "baseline" DLCO was similar between treatment groups.
Reviewer's Comment: The "baseline" for the discontinuation phase was the last value prior to or within 7 days after being randomized to continuation or discontinuation of inhaled insulin and is not the true baseline prior to study medication exposure. Thus, this "baseline" is in quotes to distinguish it from the true pre-study medication baseline.

Table 32 Mean Observed DLCO (mL/min/mmHg) and Mean Change in DLCO (mL/min/mmHg) in Discontinuation Phase of Study 111 – Adult Subjects with Type 1 Diabetes (Primary Analysis Set)**

Inhaled Insulin						
	Continued Inhaled Insulin			Discontinued Inhaled Insulin		
DLCO (mL/min/mmHg)	Observed	Change from Baseline		Observed	Change from Baseline	
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)
"Baseline"*	26.494 (6.6)	115		26.821 (6.4)	120	
Month 1	25.909 (6.5)	103	**-0.347 (2.6)**	27.413 (6.6)	114	**0.389 (3.1)**
Month 3	26.341 (6.5)	113	**-0.079 (2.6)**	27.271 (6.2)	117	**0.386 (3.3)**
Month 6	26.631 (6.5)	107	**0.254 (2.9)**	27.268 (6.8)	113	**0.383 (3.2)**

*Baseline for the discontinuation phase was the last value prior to or within 7 days after being randomized to discontinuation or continuation of inhaled insulin
**Primary analysis set includes all randomized subjects who had a baseline FEV_1 measurement and a post-baseline measurements and received study drug for at least 50% of the duration of the controlled segment
Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 1753

Figure 22 Mean Change in DLCO from "Baseline" in the Discontinuation Phase of Study 111 in Adults Type 1 Subjects



Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 59.

Reviewer's Comment: The Applicant also followed the group who was randomized to continued inhaled insulin for an additional 6 months after the discontinuation phase. In this follow up phase inhaled insulin was discontinued. In subjects with type 1 diabetes ≥ 18 years of age, the mean increase in DLCO was 0.45mL/min/mmHg from the last DLCO value on inhaled insulin [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 181].

Reviewer's Comment: The Applicant asserts that this data supports the reversibility of the effect of inhaled insulin after discontinuation; however, the following should be noted. First, as mentioned above, there are design issues with this discontinuation phase, such as a potentially enriched population and varying lengths of inhaled insulin exposure. Second, in order to assess reversibility, a treatment effect should be established first. It is unclear what the mean change from baseline DLCO was for the group entering the discontinuation phase.

5.1.8.2.2.6 Conclusions of the Effect of Inhaled Insulin on DLCO in Type 1 Diabetes

Subjects with type 1 diabetes treated with inhaled insulin consistently showed a greater mean decline from baseline DLCO over time compared to the comparator group in most of the individual studies as well as in the pooled adult controlled phase 2/3 studies in type 1 diabetes. A single study (1027) suggested that inhaled insulin affects the DLCO within the first two weeks of exposure. In the pooled phase 2/3 controlled studies in type 1 diabetes, the inhaled insulin group had a greater mean decline in DLCO than the comparator group, thus, there is a treatment group difference favoring the comparator.

The effect of inhaled insulin on DLCO fluctuated during the treatment period. At Week 96, the mean treatment group difference was approximately -0.5 to -0.6mL/min/mmHg, favoring the comparator. The maximum mean treatment group difference was noted at Week 24 and was -1 mL/min/mmHg, favoring the comparator. However, the Week 96 data and Week 12 DLCO data showed a similar treatment group difference. Thus, the effect of inhaled insulin on DLCO did not appear to progress over two years of treatment.

Exposure to inhaled insulin longer than 24 months in type 1 diabetes has not been studied in controlled studies. One non-controlled extension study (Study 1036) has exposed subjects to inhaled insulin up to 84 months. The data suggest that after a mean decline from baseline DLCO in the first 12 months, the mean change from baseline DLCO does not continue to progress through 84 months of exposure.

The reversibility of the effect of inhaled insulin on DLCO was evaluated in a controlled fashion in Study 1027. The data from Study 1027 does suggest that after 12 weeks of inhaled insulin treatment followed by discontinuation of inhaled insulin, the treatment group difference decreases and in fact, favors the inhaled insulin group (after 12 weeks of discontinuation) However, Study 1027 does not adequately address the effect of the reversibility of the effect of inhaled insulin. Even if the discontinuation data suggests the effects of inhaled insulin on DLCO are reversible after 12 weeks of inhaled insulin exposure, the effects may not be reversible after longer inhaled insulin exposure.

Reversibility of the effect of long term inhaled insulin use was also assessed in the extension Study 111. However, the study design and results have issues which limit the interpretability of the reversibility data. Thus, there is not adequate controlled data to determine if the long term effects on DLCO from exposure to inhaled insulin are reversible.

5.1.8.2.3 Additional Pulmonary Function Tests

Additional pulmonary function tests were measured in the clinical studies. A review of the other pulmonary function tests suggests the results do not add much additional information regarding the effects of inhaled insulin on pulmonary function.

The Division reviewed the forced vital capacity (FVC), total lung capacity (TLC), and functional residual capacity (FRC) data for the controlled adult phase 2/3 study dataset. The Biometrics reviewer determined the mean treatment group difference for these pulmonary function tests using the observed change from baseline data to determine the unadjusted treatment group difference. In addition, the Biometrics reviewer adjusted the treatment group difference for treatment, protocol, visit, baseline measurement, age, gender, and baseline height (per the Applicant).

In general, in the pooled controlled phase 2/3 studies in type 1 diabetes, there was no significant change from baseline in FVC and TLC during the 96 week treatment period. There was a mean treatment group difference in change from baseline FRC at Week 96 of approximately -40 to -60mL. This mean treatment group difference was relatively stable throughout the two year treatment period as shown below in Table 33.

Table 33 Mean Change from Baseline and Mean Treatment Group Difference for Additional Pulmonary Function Tests in Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)

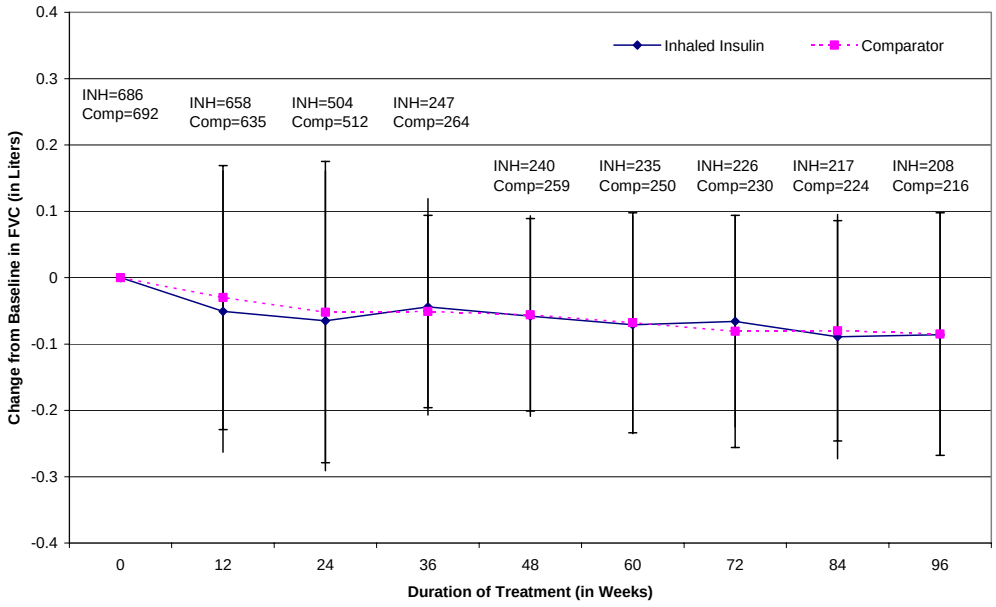
	Mean Observed Change from Baseline (N)		Mean Treatment Group Difference	
	Inhaled Insulin	Comparator	Treatment Group Difference Unadjusted (95% CI)	Treatment Group Difference Adjusted* (95% CI)
FVC				
Week 12	-0.051 (658)	-0.030 (635)	-0.020 (-0.043, 0.002)	-0.021 (-0.042, 0.000)
Week 24	-0.065 (504)	-0.052 (512)	-0.013 (-0.041, 0.014)	-0.012 (-0.035, 0.010)
Week 36	-0.044 (247)	-0.051 (264)	0.007 (-0.019, 0.034)	0.004 (-0.026, 0.033)
Week 48	-0.058 (240)	-0.056 (259)	-0.002 (-0.028, 0.024)	-0.003 (-0.035, 0.029)
Week 60	-0.071 (235)	-0.068 (250)	-0.003 (-0.032, 0.027)	-0.003 (-0.036, 0.030)
Week 72	-0.066 (226)	-0.081 (230)	0.014 (-0.016, 0.045)	0.015 (-0.019, 0.050)
Week 84	-0.089 (217)	-0.080 (224)	-0.008 (-0.041, 0.025)	-0.004 (-0.040, 0.031)
Week 96	-0.086 (208)	-0.085 (216)	-0.001 (-0.036, 0.034)	-0.001 (-0.037, 0.035)
TLC				
Week 12	0.004 (427)	-0.027 (412)	0.031 (-0.017, 0.079)	0.008 (-0.042, 0.057)
Week 24	-0.007 (501)	0.012 (506)	-0.019 (-0.076, 0.037)	-0.029 (-0.074, 0.018)
Week 36	0.016 (246)	-0.005 (265)	0.021 (-0.038, 0.079)	-0.016 (-0.077, 0.044)
Week 48	-0.0006 (240)	-0.010 (257)	0.011 (-0.050, 0.072)	-0.013 (-0.078, 0.053)
Week 60	-0.005 (232)	-0.033 (249)	0.028 (-0.039, 0.095)	0.016 (-0.052, 0.083)
Week 72	-0.002 (225)	-0.007 (229)	0.006 (-0.063, 0.075)	-0.004 (-0.073, 0.066)
Week 84	-0.035 (213)	-0.039 (223)	0.004 (-0.063, 0.070)	-0.011 (-0.083, 0.060)
Week 96	-0.012 (204)	-0.006 (216)	0.018 (-0.057, 0.092)	0.006 (-0.067, 0.079)
FRC				
Week 12	-0.066 (426)	-0.099 (411)	0.033 (-0.019, 0.086)	0.002 (-0.051, 0.055)
Week 24	-0.044 (500)	-0.013 (502)	-0.031 (-0.091, 0.029)	-0.046 (-0.095, 0.004)
Week 36	-0.070 (247)	-0.070 (265)	0.00003 (-0.067, 0.067)	-0.032 (-0.096, 0.032)
Week 48	-0.120 (240)	-0.107 (257)	-0.012 (-0.085, 0.060)	-0.045 (-0.115, 0.025)
Week 60	-0.147 (233)	-0.121 (249)	-0.026 (-0.101, 0.049)	-0.048 (-0.121, 0.024)
Week 72	-0.156 (226)	-0.119 (230)	-0.037 (-0.111, 0.037)	-0.055 (-0.129, 0.019)
Week 84	-0.186 (213)	-0.151 (223)	-0.035 (-0.118, 0.048)	-0.061 (-0.137, 0.015)
Week 96	-0.143 (204)	-0.107 (216)	-0.037 (-0.122, 0.048)	-0.058 (-0.136, 0.020)

*Adjusted model includes treatment, protocol, visit, baseline measurement, age, gender, and baseline height
Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: In general, the adjusted and unadjusted treatment group differences showed similar trends.

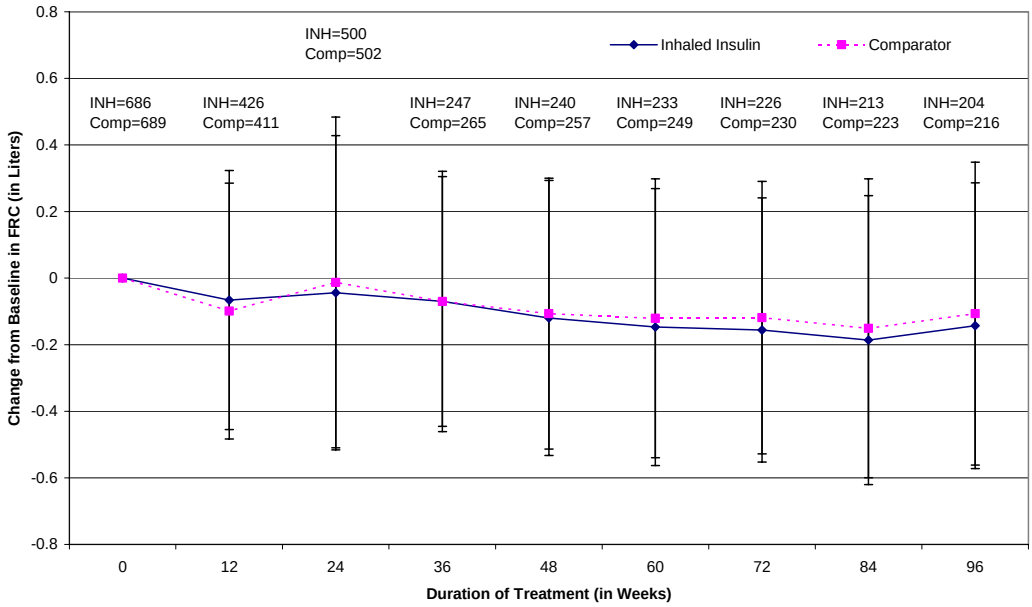
The following figures graphically display the mean change from baseline FVC, FRC, and TLC in type 1 diabetes.

Figure 23 Mean Change from Baseline FVC (L) by Time in Adult Phase 2/3 Controlled Studies in Type 1 Diabetes



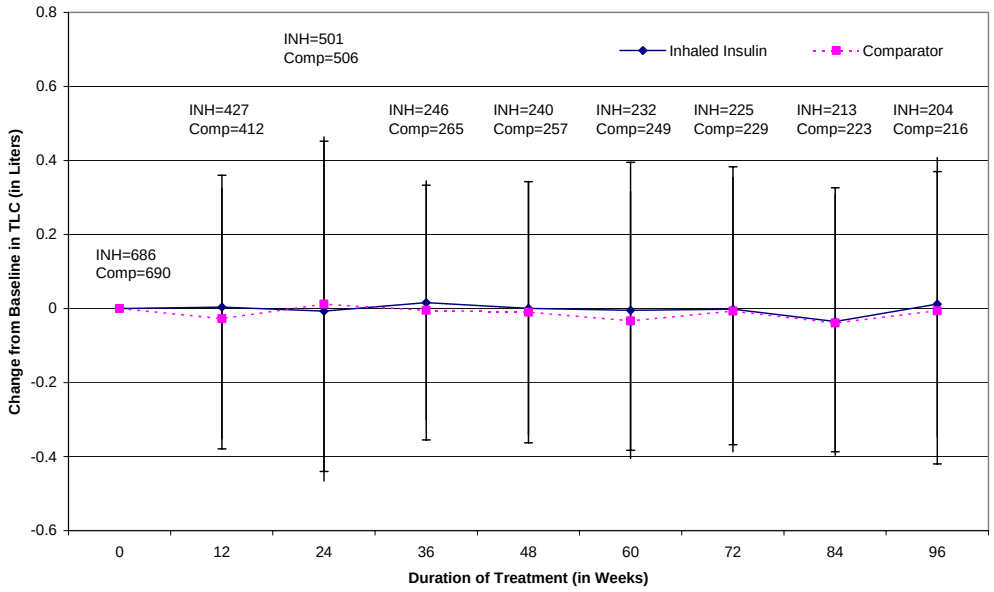
Source: Dr. Joan Buenconsejo's Biometrics Review

Figure 24 Mean Change from Baseline FRC (L) by Time in Adult Phase 2/3 Controlled Studies in Type 1 Diabetes



Source: Dr. Joan Buenconsejo's Biometrics Review

Figure 25 Mean Change from Baseline TLC (L) by Time in Adult Phase 2/3 Controlled Studies in Type 1 Diabetes



Source: Dr. Joan Buenconsejo's Biometrics Review

The Applicant determined the treatment group difference for FEV_1/FVC%, residual volume (RV), and forced expiratory flow 25-75% ($FEF_{25-75\%}$) at 12 months. A mean treatment group difference (-46mL) was noted for change from baseline RV at Month 12, favoring the comparator. A mean treatment group difference (-0.9%) for decline from baseline FEV_1/FVC% was noted at Month 12, favoring the comparator. This is consistent with a decline from baseline FEV_1 coupled with no significant change from baseline FVC in the pooled controlled phase 2/3 dataset. A mean treatment group difference of decline from baseline $FEF_{25-75\%}$ of -0.115L/s was noted at Month 12, favoring the comparator. However, the clinical significance of this is unclear, since $FEF_{25-75\%}$ is less reproducible than FEV_1. The results for these additional PFTs are shown below in Table 34.

Table 34 Mean Change from Baseline and Treatment Group Difference for Additional Pulmonary Function Tests in Controlled Phase 2/3 Studies in Type 1 Diabetes (Adults)

	Mean Observed Change from Baseline (N)		Mean Treatment Group Difference
	Inhaled Insulin	Comparator	Treatment Group Difference (95% CI) Adjusted by Applicant+
FEV_1/FVC (%)			
Month 3	-0.420 (659)	-0.0140 (634)	-0.254 (-0.536, 0.028)
Month 6	-0.708 (507)	-0.278 (512)	-0.421 (-0.724, -0.118)
Month 9	-0.589 (251)	0.047 (263)	-0.593 (-0.987, -0.199)
Month 12	-0.776 (238)	0.173 (258)	-0.901 (-1.332, -0.470)
RV (L)			
Month 3	0.003 (428)	-0.034 (410)	0.002 (-0.043, 0.047)
Month 6	0.023 (502)	0.036 (503)	-0.045 (-0.086, -0.004)
Month 9	0.021 (250)	0.007 (265)	-0.032 (-0.088, 0.024)
Month 12	-0.009 (237)	0.001 (256)	-0.046 (-0.105, 0.013)
FEF 25-75% (L/s)			
Month 3	-0.103 (658)	-0.027 (634)	-0.073 (-0.117, -0.030)
Month 6	-0.133 (507)	-0.078 (512)	-0.050 (-0.097, -0.003)
Month 9	-0.090 (251)	-0.013 (263)	-0.065 (-0.128, -0.003)
Month 12	-0.137 (238)	-0.015 (258)	-0.115 (-0.183, -0.048)

+Applicant adjustment includes: Treatment, protocol, visit, baseline measurement, age, gender, and baseline height
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg. 128, 129, 132, 133, 136, 137

5.1.8.3 Type 2 Diabetes

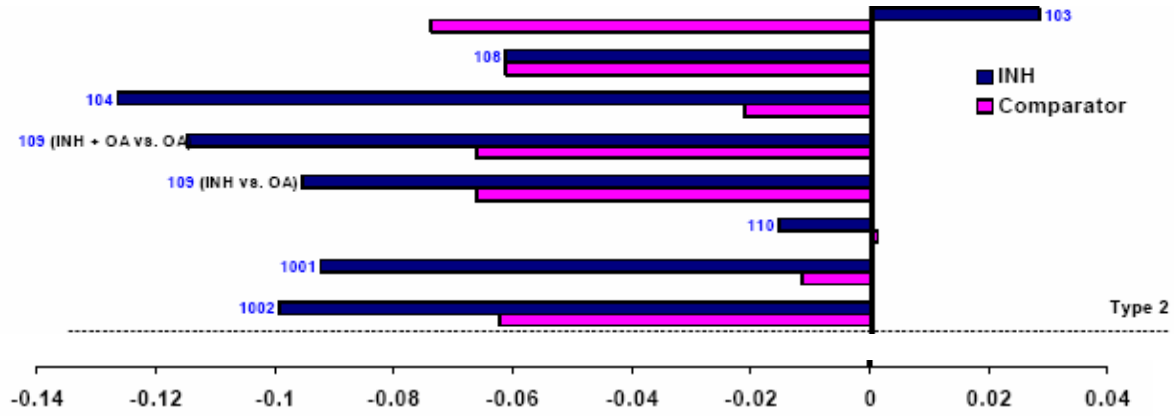
PFTs from the controlled Phase 2/3 studies in subjects with type 2 diabetes (102, 103, 104, 108. 109, 110, 1001, 1002, and 1029) were reviewed by individual studies and as pooled data. The PFT data from the pooled phase 2/3 studies in type 2 diabetes are reviewed in this section. The results of an individual study may also be reviewed in this section to provide supportive information.

5.1.8.3.1 Forced Expiratory Volume in One Second (FEV_1)

5.1.8.3.1.1 Summary of Individual Studies

In most of the individual studies in subjects with type 2 diabetes, the inhaled insulin group demonstrated a larger mean decrease from baseline FEV_1 to the end of study FEV_1 than subjects in the comparator treatment groups. Figure 26 illustrates the adjusted mean change from baseline in FEV_1 for most of the studies in type 2 diabetes.

Figure 26 Adjusted* Mean Change from Baseline in FEV_1 (L): 3 and 6 Month Adult Controlled Phase 2/3 Studies in Type 2 Diabetes

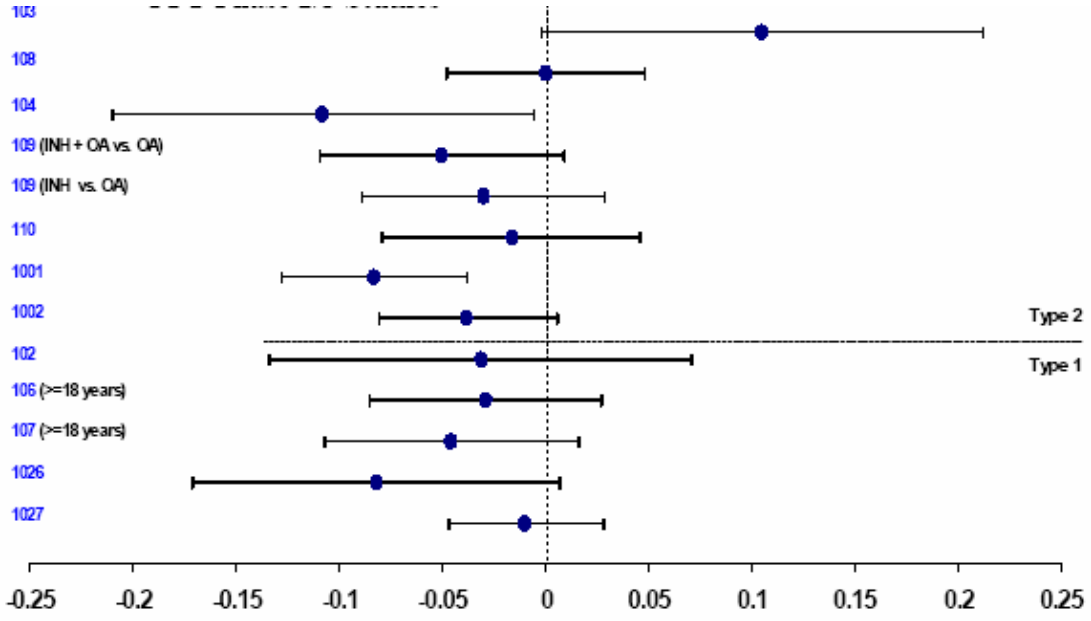


Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 34

**Reviewer's Comment: In this figure, the Applicant adjusted the mean change from baseline FEV_1 for treatment, visit, center, baseline PFT, age, height, and gender.*

Similarly, the mean treatment group difference, which is defined as the mean change in FEV_1 from baseline in the inhaled insulin group – the mean change from baseline FEV_1 in the comparator group, favored the comparator in most of the individual studies as shown below in the top half (type 2) of Figure 27. A more negative treatment group difference indicates that the inhaled insulin group had a greater mean decrease from baseline FEV_1 than the comparator group.

Figure 27 Adjusted* Mean Treatment Group Difference for FEV_1 Change from Baseline (L)
3 and 6 Month Adult Controlled Phase 2/3 Studies in Type 2 Diabetes



Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 35

**Reviewer's Comment: In this figure, the Applicant adjusted the mean change from baseline FEV_1 for treatment, visit, center, baseline PFT, age, height, and gender.*

5.1.8.3.1.2 Pooled Controlled Adult Phase 2/3 Studies in Type 2 Diabetes

In the pooled adult controlled phase 2/3 studies in subjects with type 2 diabetes, the mean baseline FEV_1 and mean FEV_1 percent predicted were similar between treatment groups. Subjects in both treatment groups demonstrated a decline from baseline FEV_1 at each time point as shown below in Table 35. However, subjects in the inhaled insulin treatment group demonstrated a larger mean decline than subjects in the comparator group at each time point. The decline was noted in both groups at Week 12, which was the first on treatment measurement in some of the individual studies.

Table 35 Mean Observed FEV_1 and Mean Change From Baseline Controlled Phase 2/3 Studies in Type 2 Diabetes (Adults)
Studies 103, 104, 108, 109, 110, 1001, 1002, 1029 (ongoing)

	Inhaled Insulin			Comparator		
FEV_1 (L)	Observed	**Change from Baseline**		Observed	**Change from Baseline**	
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)
Baseline % Predicted	96.05 (14)	1266		96.21 (15)	1117	
Baseline	2.924 (.70)	1267		2.928 (.73)	1119	
Week 12	2.866 (.68)	763	-0.064 (.19)	2.926 (.71)	648	-0.028 (.18)
Week 24	2.831 (.70)	848	-0.074 (.21)	2.873 (.71)	795	-0.049 (.21)
Week 36	2.839 (.69)	577	-0.092 (.20)	2.835 (.70)	532	-0.075 (.20)
Week 48/52	2.819 (.69)	536	-0.105 (.21)	2.851 (.71)	496	-0.071 (.21)
Week 65	2.784 (.69)	158	-0.083 (.22)	2.718 (.66)	134	-0.055 (.25)
Week 78	2.736 (.69)	160	-0.120 (.20)	2.717 (.67)	139	-0.106 (.25)
Week 91	2.706 (.67)	154	-0.153 (.22)	2.699 (.63)	134	-0.096 (.26)
Week 104	2.663 (.68)	143	-0.170 (.24)	2.708 (.67)	125	-0.128 (.25)

Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: The FEV_1 data from the individual controlled adult phase 2/3 studies in type 2 diabetes was pooled by the Biometrics Reviewer, Dr. Joan Buenconsejo. Some of the numbers differ slightly from the Applicant's pooled data due to small differences in the number of subjects. The difference is because in the analyses performed by Dr. Buenconsejo, all subjects were included in the calculation of the mean baseline FEV_1. However, the Applicant only included subjects for the baseline calculation if the subject had a post-baseline FEV_1 measurement. Although there are some slight differences in the baseline values, the change from baseline in each treatment group is consistent with the Applicant's findings.

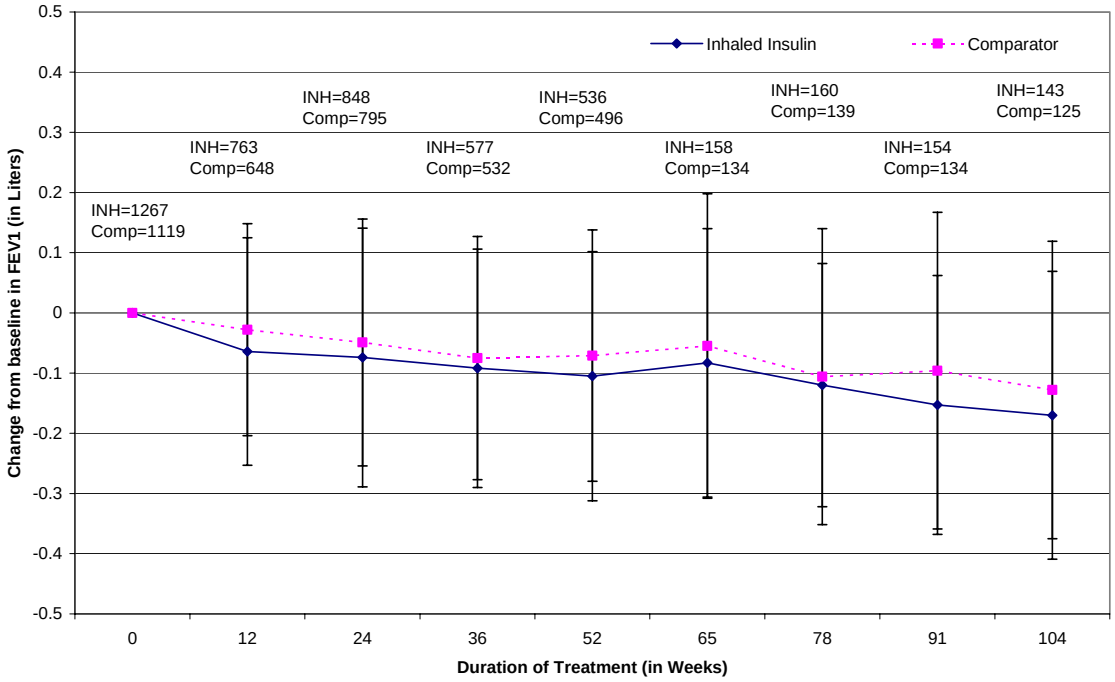
Reviewer's Comment: It should be noted that the PFT data after Week 52 is from the combined Study 1001-1002.

After 104 weeks of study medication, the inhaled insulin treatment group demonstrated a mean decline from baseline FEV_1 of 170mL, while the comparator group demonstrated a mean decline of 128mL from baseline FEV_1. Averaged over a two year period, the inhaled insulin group demonstrated an annual decline from baseline FEV_1 of approximately 85mL/year, while the comparator group demonstrated an annual decline from baseline FEV_1 of approximately 65mL/year.

Reviewer's Comment: Several points are worth noting. First, similar to the studies in subjects with type 1 diabetes, the decline in lung function is higher in both groups than what would be expected in nonsmoking subjects without underlying lung disease. The comparator group in type 2 diabetes had a decline in FEV_1 similar to what would be expected in COPD patients who smoke.[2] The inhaled insulin group had an even greater decline in FEV_1 than the comparator group. Second, based upon the controlled phase 2/3 studies, the approximate annual decline from baseline FEV_1 is greater in subjects with type 2 diabetes than subjects with type 1 diabetes (-66mL/year in inhaled insulin group and -39mL/year in comparator group). The reason for the greater decline in FEV_1 in subjects with type 2 diabetes is not clear.

The mean change from baseline FEV_1 over time in the adult phase 2/3 controlled studies in type 2 diabetes is shown below in Figure 28, which shows that subjects in the inhaled insulin treatment group demonstrated a greater mean decline in FEV_1 than subjects in the comparator group. The difference between treatment groups was noted at Week 12 and fluctuated slightly until Week 104. At Week 104, the difference between treatment groups is similar to the difference between treatment groups at Week 12.

Figure 28 Mean Change from Baseline FEV_1 over Time in the Phase 2/3 Controlled Studies in Type 2 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

The treatment group difference was defined above as the following: the mean change from baseline FEV_1 in the inhaled insulin group – the mean change from baseline FEV_1 in the comparator group.

A treatment group difference was noted at Week 12 and fluctuated during the treatment period from a maximum at Week 91 (~ -50mL) to a minimum at Week 78 (~ -10mL). No consistent pattern was noted other than the mean treatment group difference always favored the comparator. At Week 104, the mean treatment group difference was similar to the mean treatment group difference at Week 12. At Week 104, the treatment group difference was approximately -30 to -40mL as shown below in Table 36. The controlled data in subjects with type 2 diabetes exposed to inhaled insulin for up to 2 years suggests that the treatment group difference does not progress between Week 12 and Week 104.

Table 36 Mean Change from Baseline FEV_1 (L) and Mean Treatment Group Difference (L) in Change from Baseline FEV_1 in Controlled Phase 2/3 Studies in Type 2 Diabetes (Adults)

	Mean Change from Baseline FEV_1 (N)		Mean Treatment Group Difference (95% CI) Unadjusted	Mean Treatment Group Difference (95% CI) Adjusted**
	Inhaled Insulin	Comparator		
Week 12	-0.064 (763)	-0.028 (648)	-0.036 (-0.055, -0.017)	-0.043 (-0.063, -0.022)
Week 24	-0.074 (848)	-0.049 (795)	-0.025 (-0.045, -0.005)	-0.024 (-0.043, -0.005)
Week 36	-0.092 (577)	-0.075 (532)	-0.017 (-0.041, 0.006)	-0.009 (-0.032, 0.013)
Week 48/52	-0.105 (536)	-0.071 (496)	-0.034 (-0.059, -0.009)	-0.028 (-0.052, -0.005)
Week 65	-0.083 (158)	-0.055 (134)	-0.028 (-0.083, 0.027)	-0.027 (-0.067, 0.013)
Week 78	-0.120(160)	-0.106 (139)	-0.013 (-0.064, 0.038)	-0.010 (-0.054, 0.033)
Week 91	-0.153 (154)	-0.096 (134)	-0.057 (-0.112, -0.001)	-0.053 (-0.099, -0.008)
Week 104	-0.170 (143)	-0.128 (125)	-0.042 (-0.100, 0.017)	-0.031 (-0.078, 0.017)

Source: Dr. Joan Buenconsejo's Biometrics Review; Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 117
**Adjusted for treatment, protocol, visit, baseline measurement, age, gender, and baseline height

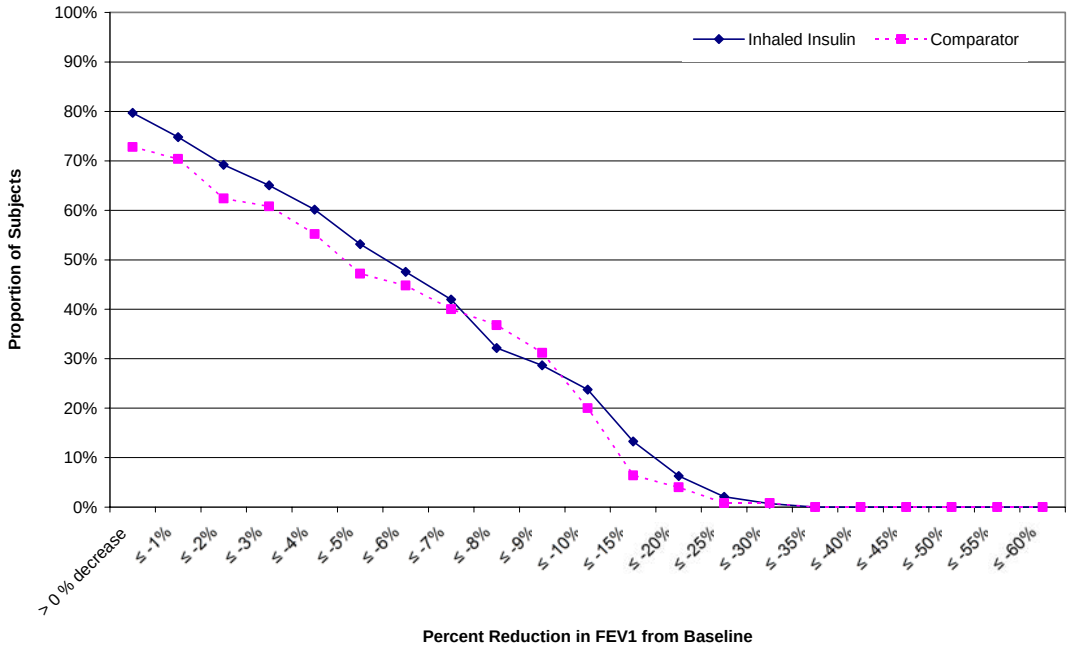
Reviewer's Comment: The Applicant asserts that this data indicates the effect of inhaled insulin on FEV_1 stabilizes and is not progressive.

Reviewer's Comment: The -30 to -40mL mean treatment group difference at 2 years is similar to the -40mL mean treatment group difference noted in subjects with type 1 diabetes.

The Biometrics reviewer performed a categorical response analysis to assess the proportion of subjects with declines in FEV_1 of various magnitudes. The proportion of subjects with a decrease in FEV_1 was analyzed at Weeks 12, 24, 36, 48, 65, 78, 91, and 104. In general, at most time points the inhaled insulin group had a higher percentage of subjects with a decline from baseline FEV_1 than the comparator group, but the pattern of the response was similar between treatment groups. Thus, the difference in mean FEV_1 between the treatment groups does not appear to be driven by outliers.
Reviewer's Comment: The Applicant also performed an analysis of the distributions in percent change from baseline FEV_1 over time. The Applicant's conclusion was that the observed mean change from baseline FEV_1 is driven by slight shifts in the distribution curves among the broad population of subjects treated with inhaled insulin rather than by a small number of subjects with extreme values N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 37].

The Week 104 response profile is shown in Figure 29 as an example of the response analysis. In general, there were more subjects with decline in FEV_1 in the inhaled insulin group than in the comparator group. At Week 104, 13% of inhaled insulin subjects and 6% of comparator group subjects had a $\geq$ 15% decline from baseline FEV_1.

Figure 29 Proportion of Subjects by Percent Reduction from Baseline FEV_1 (L) at Week 104 in Controlled Phase 2/3 Studies in Type 2 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

The controlled phase 2/3 studies in subjects with type 1 diabetes indicate that the inhaled insulin group has a greater decline in FEV_1 than the comparator group, thus, there is a treatment group difference between inhaled insulin and the comparator favoring the comparator. A mean treatment group difference of approximately -40mL was noted at Week 12 and fluctuated throughout the treatment period. However, at Week 104, a similar treatment group difference of approximately -30 to -40mL was noted. The controlled data in subjects with type 2 diabetes suggest that the treatment group difference does not significantly change over a 2 year period.

To further explore the effects of inhaled insulin on FEV_1 in subjects with type 2 diabetes, some of the individual studies, which provide additional information about long term exposure and the potential for reversibility, are reviewed next.

5.1.8.3.1.3 Study 1001-1002

Studies 1001 and 1002 were originally 24 week open-label, randomized, parallel group studies comparing inhaled insulin as adjunctive therapy versus oral agent adjunctive therapy in subjects with type 2 diabetes. Both studies were amended twice to extend the treatment period (first to 52 weeks, then to 104 weeks) and the Applicant combined the extended studies. The objective of the first 24 weeks was to compare the efficacy of the two treatments groups. The objective for the additional 80 weeks treatment and 12 week washout period was to evaluate safety. PFTs were obtained at Weeks 24, 36, 52, 65, 78, 91, and 104. Following the treatment period, subjects underwent a 12 week follow up phase during which inhaled insulin was discontinued. However, due to the protocol

amendments extending the study, the PFT data following discontinuation could be after 52 weeks of inhaled insulin exposure or 104 weeks of inhaled insulin exposure. The rationale for discussing Study 1001-1002 in the integrated safety summary is that Study 1001-1002 provides some controlled data on the long term effects of inhaled insulin on PFTs in subjects with Type 2 diabetes. In addition, Study 1001-1002 provides some controlled PFT data following discontinuation of inhaled insulin in subjects with type 2 diabetes.

Reviewer's Comment: Study 1029 also specifies obtaining PFTs in subjects with type 2 diabetes after discontinuation of inhaled insulin following 24 months of exposure in a controlled fashion. However, Study 1029 is an ongoing study and the data following discontinuation of inhaled insulin was not available at the time of this review.

The FEV_1 data from combined Study 1001-1002 suggest that the treatment group difference between inhaled insulin and the comparator was greatest at Weeks 24 and 91 and fluctuated throughout the rest of the treatment period. The treatment group difference did not significantly increase from Week 24 to Week 104. Table 37 displays the mean observed FEV_1, mean change from baseline FEV_1 and the mean unadjusted treatment group difference.

Reviewer's Comment: The Applicant asserts that this supports that the effect of inhaled insulin on FEV_1 is not progressive. However, the Applicant did not provide a proposed mechanism for an effect on FEV_1 that is not progressive.

Table 37 Mean Observed FEV_1 (L), Mean Change From Baseline FEV_1 (L) and Mean Treatment Group Difference (L) in Combined Study 1001-1002 All Subjects

	Inhaled Insulin			Comparator			
FEV_1 in liters	Observed	**Change from Baseline**		Observed		**Change from Baseline**	Treatment Group Difference (95% CI) Unadjusted
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)	
Baseline	2.901 (0.7)	471		2.892 (0.7)	437		
Week 24	2.807 (0.7)	430	-0.092 (0.2)	2.837 (0.7)	372	-0.042 (0.2)	-0.051 (-0.083, -0.018)
Week 36	2.821 (0.7)	312	-0.103 (0.2)	2.792 (0.7)	257	-0.081 (0.2)	-0.022 (-0.060, 0.015)
Week 48/52	2.795 (0.7)	309	-0.115 (0.2)	2.822 (0.7)	261	-0.068 (0.2)	-0.047 (-0.086, -0.008)
Week 65	2.784 (0.7)	158	-0.083 (0.2)	2.718 (0.7)	134	-0.055 (0.3)	-0.028 (-0.083, 0.027)
Week 78	2.736 (0.7)	160	-0.120 (0.2)	2.717 (0.7)	139	-0.106 (0.2)	-0.013 (-0.064, 0.038)
Week 91	2.706 (0.7)	154	-0.153 (0.2)	2.699 (0.6)	134	-0.096 (0.3)	-0.057 (-0.112, -0.001)
Week 104	2.663 (0.7)	143	-0.170 (0.2)	2.708 (0.6)	125	-0.128 (0.2)	-0.042 (-0.100, 0.017)
Follow-up Phase							
6 weeks	2.703 (0.7)	149	-0.139 (0.2)	2.707 (0.7)	138	-0.147 (0.3)	0.008 (-0.049, 0.065)
12 weeks	2.689 (0.7)	132	-0.164 (0.2)	2.689 (0.7)	128	-0.150 (0.2)	-0.014 (-0.073, 0.044)

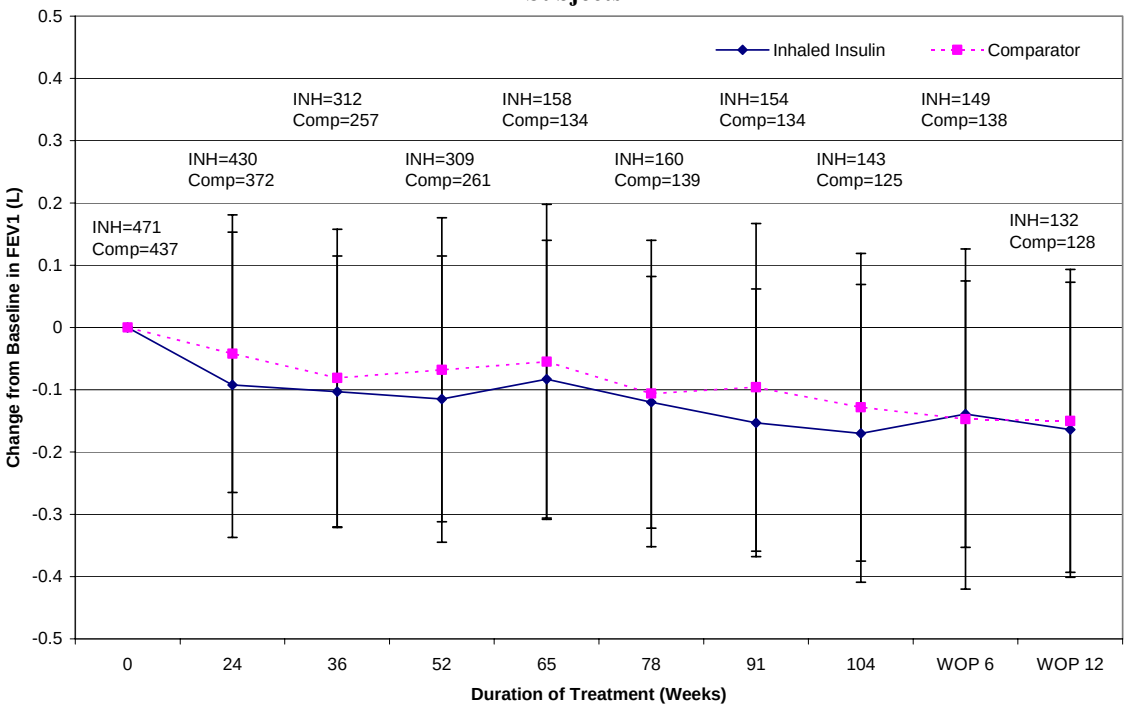
Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: This table contains the results for all subjects. A fair number of subjects (~300) did not continue into the second year extension mostly because ethics committee and/or regulatory approval were not available when the subjects completed the 52 week study, according to the Applicant. The majority of the follow up phase data is from subjects who completed 104 weeks of treatment; however, the follow up phase data also contains data from 19 subjects who only completed the 52 week treatment phase and did not enter the second year extension.

Reviewer's Comment: The Applicant also adjusted the treatment group difference (all subjects) for protocol, country, PFT at baseline, age, gender, and baseline height. The results are not shown in the table above, but are consistent with the unadjusted treatment group difference [N21868/N_000/2004-12-27/clinstat/1001-1002.pdf, pg 348].

Table 37 also displays the follow-up phase data after discontinuation of study medication. The majority of subjects in the follow up phase completed 104 weeks of treatment. The follow up phase data suggest that after discontinuation of study medication, the treatment group difference decreases as shown below in Figure 30, in which WOP 6 and WOP 12 indicate 6 weeks and 12 weeks following discontinuation of inhaled insulin. In those subjects who underwent the follow up phase, after 12 weeks of discontinuation of study medication, there was very little treatment group difference.
Reviewer's Comment: The Applicant asserts that this supports the reversibility of the effect of inhaled insulin on FEV_1. It should be noted that the Applicant did not propose a mechanism for the reversibility.

Figure 30 Mean Change from Baseline FEV_1 (L) in Combined Study 1001-1002 in Type 2 Diabetes



Source: Dr. Joan Buenconsejo's Biometrics Review

5.1.8.3.1.4 Study 1036

Study 1036 is an ongoing uncontrolled extension study of the phase 2 protocols 102 (Type 1), 103 (Type 2), and 104 (Type 2). Study 1036 provides some long term PFT data on subjects with both type 1 and type 2 diabetes exposed to inhaled insulin up to 84 months. Study 1036 was discussed in Section 5.1.8.2.1.4 and will not be discussed in

detail here. The results for Study 1036 suggest the average rate of decline from baseline FEV_1 in the inhaled insulin group over a 6-7 year period is approximately 50-60mL/year. However, due to the uncontrolled nature of the study, the results should be interpreted with caution.

5.1.8.3.1.5 Study 111

Study 111 was an open-label extension study of the phase 3 protocols 106 and 107 (Type 1) and 108, 109, 110 (Type 2). The design of Study 111 was discussed in the Methods Section 5.1.8.1. Like Study 1036, Study 111 provides some long term non-controlled PFT data on subjects exposed to inhaled insulin.

Study 111 included 664 subjects with type 1 diabetes and 626 subjects with type 2 diabetes. As shown in Table 38, subjects with type 2 diabetes demonstrated a mean decline from baseline FEV_1 over time. A decline in FEV_1 is noted at 3 months and the decline increases at each time point through Month 30 in the inhaled insulin group. There is less of a decline noted at 36 months, but data is only available for 4 subjects.

Table 38 Mean Observed FEV_1 (L) and Change From Baseline FEV_1 (L) in Study 111 – Adult Subjects with Type 2 Diabetes
(Studies 102, 102E, 103, 1036, 103E, 104, 104E)

Inhaled Insulin			
	Type 2		
FEV_1 in liters	Observed	**Change from Baseline**	
	Mean (SD)	N	Mean (SD)
Baseline	2.943 (0.7)	613	
3 Months	2.879 (0.7)	612	**-0.064 (0.2)**
6 Months	2.871 (0.7)	584	**-0.073 (0.2)**
12 Months	2.841 (0.7)	546	**-0.106 (0.2)**
18 Months	2.803 (0.7)	499	**-0.148 (0.2)**
24 Months	2.826 (0.7)	381	**-0.172 (0.2)**
30 Months	2.867 (0.6)	142	**-0.216 (0.3)**
36 Months	3.727 (0.5)	4	**-0.100 (0.1)**

*Baseline is based on pre-inhaled insulin measurements Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 960, 962

Study 111was amended to provide additional PFT information after discontinuation of inhaled insulin. However, as discussed in the Methods Section 5.1.8.1, the design is flawed in that the study population prior to randomization is likely enriched with subjects who responded favorably to inhaled insulin and tolerated inhaled insulin. Subjects who did not tolerate inhaled insulin or had a decline in pulmonary function may have been discontinued from the study. In addition, subjects were on inhaled insulin for various lengths of time prior to randomization into the discontinuation phase.
Reviewer's Comment: The duration of treatment prior to the discontinuation phase was variable among subjects and ranged from >12 months to >30 months [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 1099].

The mean observed FEV_1 and mean change in FEV_1 in the discontinuation phase are shown in Table 39 and Figure 31 below. The results show that in the discontinuation phase, subjects who continued on inhaled insulin initially demonstrated a decline in FEV_1

at Months 1 and 3, but by Month 6 there was no significant decline in FEV_1. On the other hand, subjects who discontinued inhaled insulin demonstrated an increase in FEV_1 in one month. The increase in FEV_1 did not significantly change from one month to six months following discontinuation.

Reviewer's Comment: Subjects who were treated with inhaled insulin did not continue to demonstrate a decline in FEV_1 at 6 months, which is inconsistent with the pooled phase 2/3 studies, Study 1036, and the earlier phase of Study 111, in which subjects had a continual decline in FEV_1 over time with inhaled insulin exposure.

Table 39 Mean Observed FEV_1 (L) and Change in FEV_1 in Discontinuation Phase of Study 111 – Adult Subjects with Type 2 Diabetes (Primary Analysis Set)**

Inhaled Insulin						
	Continued Inhaled Insulin			Discontinued Inhaled Insulin		
FEV_1 in liters	Observed	**Change from "Baseline"**		Observed	**Change from "Baseline"**	
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)
"Baseline"*	2.761 (0.7)	198		2.822 (0.7)	203	
1 Month	2.744 (0.7)	191	**-0.018 (0.2)**	2.853 (0.7)	201	**0.029 (0.2)**
3 Months	2.726 (0.7)	195	**-0.028 (0.2)**	2.851 (0.7)	199	**0.027 (0.2)**
6 Months	2.750 (0.7)	192	**-0.002 (0.2)**	2.849 (0.7)	197	**0.030 (0.2)**

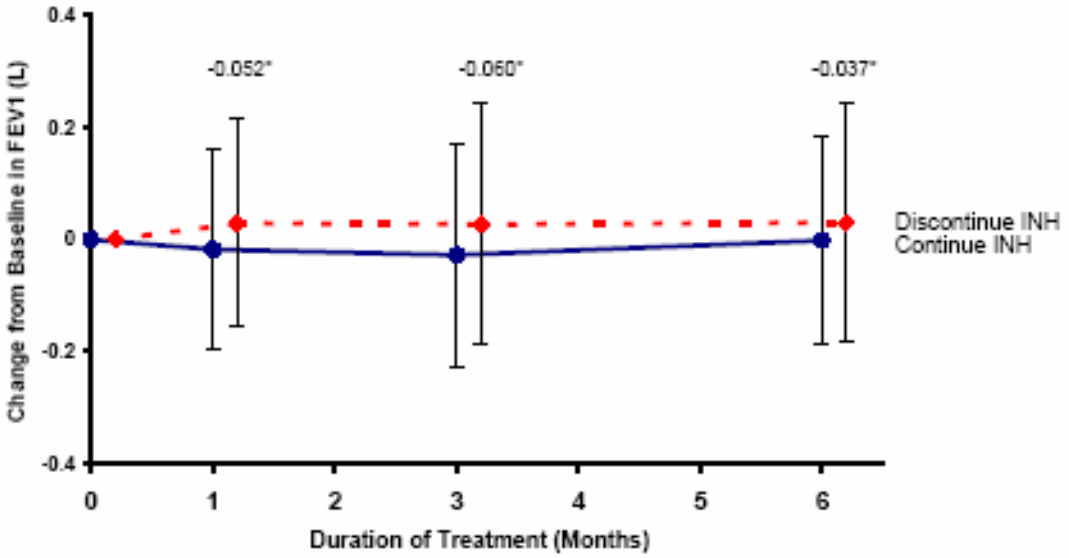
* "Baseline" for the discontinuation phase was the last value prior to or within 7 days after being randomized to discontinuation or continuation of inhaled insulin

**Primary analysis set includes all randomized subjects who had a baseline FEV_1 measurement and a post-baseline measurements and received study drug for at least 50% of the duration of the controlled segment

Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 1730

Reviewer's Comment: It should be noted that the baseline for the discontinuation phase was the last value prior to or within 7 days after being randomized to discontinuation or continuation of inhaled insulin and is not the true baseline prior to study medication exposure. Thus, this "baseline" is in quotes to distinguish it from the true pre-study medication baseline.

Figure 31 Mean Change in FEV_1 in the Discontinuation Phase of Study 111 in Type 2 Subjects (Adults)



Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 47.

Reviewer's Comment: The Applicant also followed the group who was randomized to continued inhaled insulin for an additional 6 months after the discontinuation phase. In this follow up phase inhaled insulin was discontinued. In subjects with type 2 diabetes ≥ 18 years of age, the FEV_1 decreased 30mL from the last FEV_1 value on inhaled insulin [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 180].

Reviewer's Comment: The Applicant asserts that these data support the reversibility of the effect of inhaled insulin after discontinuation; however, the issues with the design of this discontinuation phase were noted above. In addition, the subjects who continued inhaled insulin had essentially no change in FEV_1 at 6 months, which is not consistent with other FEV_1 data in type 2 diabetes. Thus, the results should be interpreted with caution and do not adequately address the potential reversibility of the effect of inhaled insulin on FEV_1.

5.1.8.3.1.6 Conclusions of the Effect of Inhaled Insulin on FEV_1 in Type 2 Diabetes

Subjects with type 2 diabetes treated with inhaled insulin showed a greater decline in FEV_1 from baseline over time compared to the comparator group in most of the individual studies as well as in the pooled adult controlled phase 2/3 studies. The pooled controlled studies indicate that there is treatment group difference favoring the comparator within 3 months of exposure. The treatment group difference fluctuates during the 104 week treatment period; however, the treatment group difference at Week 12 and Week 104 are similar.

After two years of treatment, the inhaled insulin group demonstrated a mean decline from baseline FEV_1 of 170mL, while subjects in the comparator group demonstrated a mean decline from baseline FEV_1 of 128mL. Both treatment groups demonstrated a larger mean decline from baseline FEV_1 than would be expected in non-smoking subjects

without significant lung disease. At Week 104, the mean treatment group difference is approximately -40mL, which is similar to the mean treatment group difference for change from baseline FEV_1 in subjects with type 1 diabetes.

Exposure to inhaled insulin longer than 24 months in type 2 diabetes has not been studied in controlled studies. However, non-controlled extension studies have exposed subjects to inhaled insulin up to 84 months. The non-controlled PFT data from two extension studies (1036 and 111) suggest that the decline from baseline FEV_1 continues with continued exposure. However, without a comparator group, it is unclear if the mean treatment group difference changes further with time.

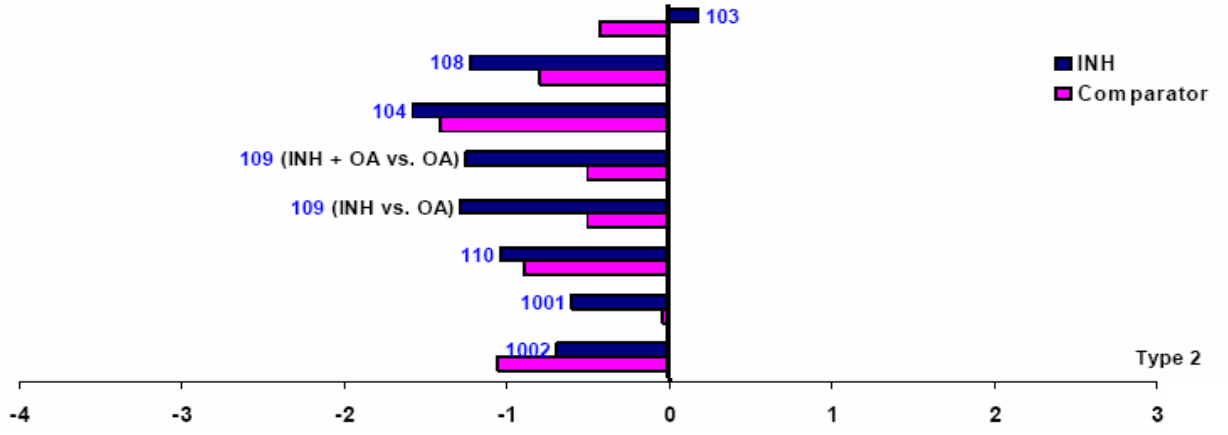
The reversibility of the effect of inhaled insulin on FEV_1 was evaluated in combined Study 1001-1002. The results of combined Study 1001-1002 suggest that the treatment group difference after inhaled insulin treatment for 104 weeks was -40mL. However, after discontinuation of inhaled insulin for 6-12 weeks, there was minimal treatment group difference, which suggests the effects of inhaled insulin treatment (up to 104 weeks) on FEV_1 may be reversible.

5.1.8.3.2 Single Breath Carbon Monoxide Diffusion Capacity (DLCO) in Type 2 Diabetes

5.1.8.3.2.1 Summary of Individual Studies

In most of the individual studies in subjects with type 2 diabetes, the inhaled insulin group demonstrated a greater mean decrease from baseline DLCO than subjects in the comparator group. Figure 32 illustrates the adjusted mean change from baseline in DLCO for all of the studies in type 2 diabetes except Study 1029.

Figure 32 Adjusted* Mean Change from Baseline in DLCO (mL/min/mmHg) 3 and 6 Month Controlled Phase 2/3 Studies in Type 2 Diabetes (Adults)



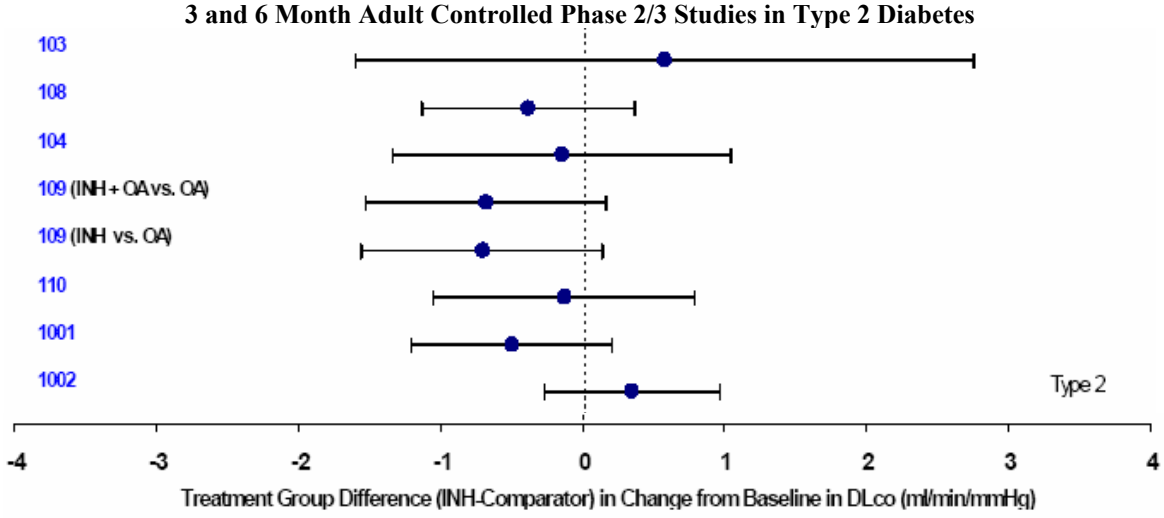
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 48

**Reviewer's Comment: The above figure illustrates a greater mean decline from baseline DLCO in the inhaled insulin group compared to the comparator group in most of the individual studies. In this figure, the Applicant adjusted the mean change from baseline DLCO for treatment, visit, center, baseline PFT, age, height, and gender.*

Similarly, the mean treatment group difference, which is defined as the mean change from baseline DLCO in the inhaled insulin group – the mean change from baseline DLCO in the comparator group, favored the comparator in most of the individual studies as shown below in Figure 33. A more negative treatment group difference indicates that the inhaled insulin group had a greater mean decline from baseline DLCO than the comparator group.

Figure 33 Adjusted* Mean Treatment Group Difference for DLCO Change from Baseline (mL/min/mmHg)

3 and 6 Month Adult Controlled Phase 2/3 Studies in Type 2 Diabetes



Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 49

**Reviewer's Comment: The above figure illustrates a greater mean decrease from baseline DLCO in the inhaled insulin group compared to the comparator group in most of the individual studies. In this figure, the Applicant adjusted the mean change from baseline DLCO for treatment, visit, center, baseline PFT, age, height, and gender.*

5.1.8.3.2.2 Pooled Controlled Adult Phase 2/3 Studies in Type 2 Diabetes

In the pooled adult controlled phase 2/3 studies in subjects with type 2 diabetes, the mean baseline DLCO and mean DLCO percent predicted were similar between treatment groups. Subjects in both treatment groups demonstrated a decline from baseline DLCO as shown below in Table 40. However, subjects in the inhaled insulin treatment group demonstrated a larger mean decline from baseline DLCO than subjects in the comparator group at most time points. The decline was noted in both groups at Week 12, which was the first on treatment measurement in some of the individual studies.

Table 40 Mean Observed DLCO and Change From Baseline Controlled Phase 2/3 Studies in Type 2 Diabetes (Adult)
Studies 103, 104, 108, 109, 110, 1001, 1002, 1029 (ongoing)

DLCO mL/min/mm Hg	Inhaled Insulin			Comparator		
	Observed	Change from Baseline		Observed	Change from Baseline	
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)
Baseline % Predicted	97.41 (38)	1232		96.22 (17)	1091	
Baseline	25.091 (6.2)	1234		24.892 (6.2)	1094	
Week 12	24.091 (6.0)	618	-0.666 (2.7)	24.135 (5.9)	501	-0.388 (2.2)
Week 24	24.516 (6.2)	808	-0.540 (3.0)	24.411 (6.1)	769	-0.395 (3.0)
Week 36	23.728 (5.4)	265	-0.660 (1.8)	23.239 (5.6)	271	-0.731 (1.8)
Week 48/52	24.559 (6.3)	518	-0.742 (3.2)	24.195 (6.0)	487	-0.591 (3.0)
Week 65	24.550 (5.7)	141	-1.352 (3.7)	24.288 (5.8)	128	-0.782 (3.3)
Week 78	24.200 (5.9)	138	-1.588 (3.1)	24.243 (5.7)	121	-1.318 (3.1)
Week 91	24.251 (5.8)	139	-1.495 (3.6)	24.135 (5.6)	126	-1.063 (3.2)
Week 104	24.017 (5.7)	129	-1.529 (3.8)	24.056 (5.7)	116	-1.583 (3.3)

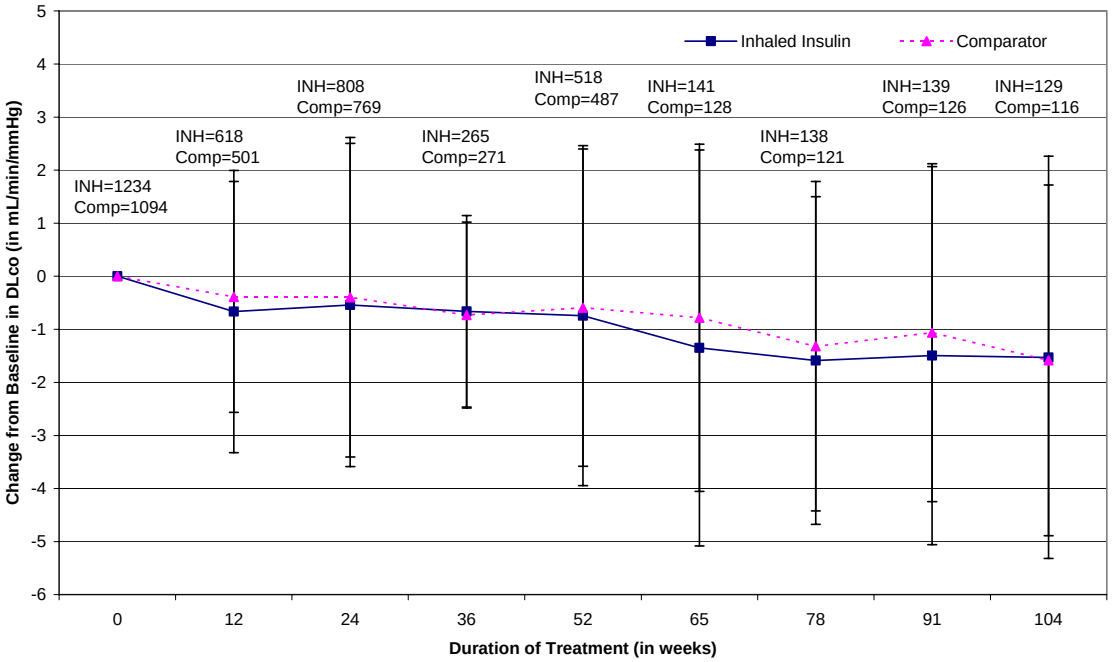
Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: The DLCO data from the individual controlled adult phase 2/3 studies in type 1 diabetes was pooled by the Biometrics Reviewer, Dr. Joan Buenconsejo. Some of the numbers differ from the Applicant's pooled data due to small differences in the number of subjects. The difference is because in the analyses performed by Dr. Buenconsejo, all subjects were included in the calculation of the mean baseline DLCO. However, the Applicant only included subjects for the baseline calculation if the subject had a post-baseline DLCO measurement. Although there are some slight differences in the baseline, the change from baseline in each treatment group is consistent with the Applicant's findings.

After 104 weeks of study medication, the inhaled insulin treatment group demonstrated a mean decrease from baseline DLCO of 1.529mL/min/mmHg, while the comparator group demonstrated a mean decline from baseline DLCO of 1.583mL/min/mmHg. Thus, over a two year period, both treatment groups demonstrated an average annual rate of decline from baseline DLCO of 0.75mL/min/mmHg per year.

The mean change from baseline DLCO over time in the adult phase 2/3 controlled studies in type 2 diabetes is shown below in Figure 34. Subjects in both treatment groups demonstrated a decline from baseline DLCO at all time points, although subjects in the inhaled insulin treatment group demonstrated a larger mean decline than subjects in the comparator group at many time points. The difference between treatment groups was noted at Week 12, but was not consistent over time. The treatment group difference was the greatest at Week 65 and subsequently decreased until Week 104 when there was essentially no mean treatment group difference.

Figure 34 Mean Change from Baseline DLCO vs. Time in Adult Phase 2/3 Controlled Studies in Type 2 Diabetes



Source: Dr. Joan Buenconsejo's Biometrics Review

The treatment group difference was defined as the following: the mean change from baseline DLCO in the inhaled insulin group – the mean change from baseline DLCO in the comparator group. The mean treatment group difference for change from baseline DLCO (unadjusted and adjusted) is shown below in Table 41. At Week 104 both the adjusted and unadjusted treatment group difference are positive, favoring the inhaled insulin group.

Table 41 Mean Change from Baseline DLCO and Mean Treatment Group Difference in Change from Baseline DLCO in Controlled Phase 2/3 Studies in Type 2 Diabetes (Adults)

DLCO mL/min/mmHg	Mean Change from Baseline DLCO (N)		Mean Treatment Group Difference (95% CI) Unadjusted	Mean Treatment Group Difference (95% CI) Adjusted*
	Inhaled Insulin	Comparator		
Week 12	-0.666 (618)	-0.388 (501)	-0.278 (-0.568, 0.011)	-0.230 (-0.540, 0.079)
Week 24	-0.540 (808)	-0.395 (769)	-0.145 (-0.445, 0.154)	-0.163 (-0.429, 0.104)
Week 36	-0.660 (265)	-0.731 (271)	0.071 (-0.230, 0.373)	0.107 (-0.277, 0.490)
Week 48/52	-0.742 (518)	-0.591 (487)	-0.151 (-0.535, 0.233)	-0.122 (-0.455, 0.210)
Week 65	-1.352 (141)	-0.782 (128)	-0.570 (-1.416, 0.276)	-0.180 (-0.737, 0.376)
Week 78	-1.588 (138)	-1.318 (121)	-0.270 (-1.029, 0.489)	-0.075 (-0.696, 0.546)
Week 91	-1.495 (139)	-1.063 (126)	-0.431 (-1.252, 0.390)	-0.173 (-0.814, 0.468)
Week 104	-1.529 (129)	-1.583 (116)	0.054 (-0.846, 0.954)	0.194 (-0.481, 0.869)

Source: Dr. Joan Buenconsejo's Biometrics Review
*Adjusted for treatment, protocol, visit, baseline measurement, age, gender, and baseline height

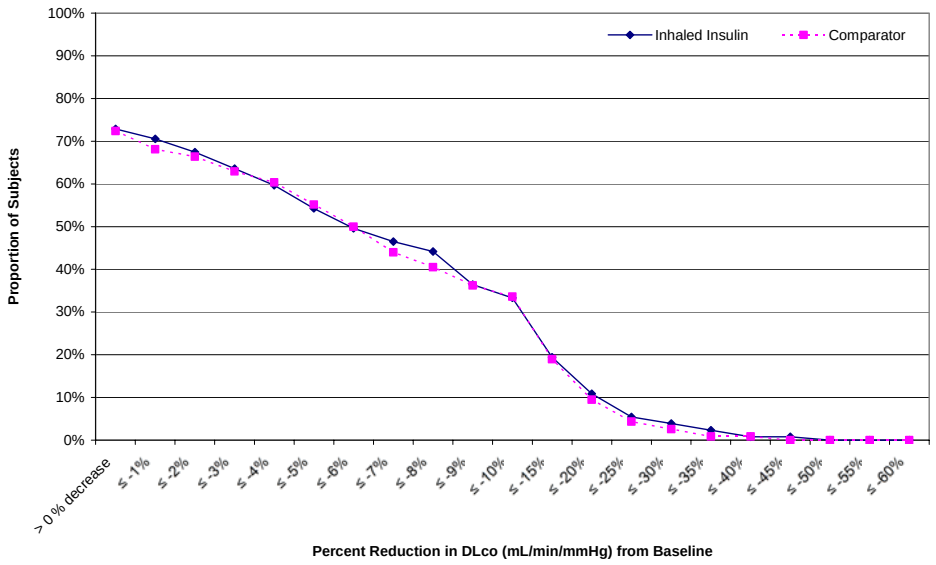
Reviewer's Comment: The following should be noted in the above table. The unadjusted and adjusted treatment group difference provide somewhat different values towards the end of the study. The reason for the difference is unclear but could be explained by an imbalance in the treatment groups. In addition, the treatment group difference at Week 104 favors the inhaled insulin group and is not consistent with earlier data.

Reviewer's Comment: The Applicant asserts that this data indicates the effect of inhaled insulin on DLCO stabilizes after the first post-baseline measurement and is not progressive. The Applicant did not provide a proposed mechanism for an early effect on DLCO that is not progressive.

The Biometrics reviewer performed a categorical response analysis to assess the proportion of subjects with declines in DLCO of various magnitudes. The proportion of subjects with a decrease in DLCO was analyzed at Weeks 12, 24, 36, 48/52, 65, 78, 91, and 104. In general, at most time points the inhaled insulin group had a higher percentage of subjects with a decline from baseline DLCO than the comparator group, but the pattern of the response is similar between treatment groups. Thus, the difference in mean DLCO between the treatment groups does not appear to be driven by outliers.

The Week 104 response profile is shown in Figure 35 as an example of the response analysis. In general, at Week 104, the response profile was similar between treatment groups. A similar percentage of subjects demonstrated a $\geq$ 15% decrease from baseline DLCO in each treatment group.

Figure 35 Proportion of Subjects by Percent Reduction from Baseline DLCO (mL/min/mmHg) at Week 104 in the Controlled Phase 2/3 Studies in Type 2 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: The controlled phase 2/3 studies in subjects with type 2 diabetes indicate that the inhaled insulin group had a greater decline in DLCO than the comparator group for most time points except Week 104, in which the decline from baseline DLCO was greater in the comparator group. At Week 104 the treatment group difference favored inhaled insulin.

To further explore the effects of inhaled insulin on DLCO in subjects with type 2 diabetes, some of the individual studies, which provide additional information about long term exposure and the potential for reversibility, are reviewed next.

5.1.8.3.2.3 Study 1001-1002

Studies 1001 and 1002 were originally 24 week open-label, randomized, parallel group studies comparing inhaled insulin as adjunctive therapy versus oral agent adjunctive therapy in subjects with type 2 diabetes. However, both studies were amended twice to extend the treatment period (first to 52 weeks, then to 104 weeks) and the Applicant combined the extended studies. The objective of the first 24 weeks was to compare the efficacy of the two treatments groups. The objective for the additional 80 weeks treatment and 12 week washout period was to evaluate safety. PFTs were obtained at Weeks 24, 36, 52, 65, 78, 91, and 104. Following the treatment period, subjects underwent a 12 week follow up phase during which inhaled insulin was discontinued. However, due to the protocol amendments extending the study, the PFT data following discontinuation could be after 52 weeks of exposure or 104 weeks of exposure. The rationale for discussing Study 1001-1002 in the integrated safety summary is that Study 1001-1002 provides some controlled data on the long term effects of inhaled insulin in subjects with Type 2 diabetes. In addition, Study 1001-1002 provides some controlled PFT data following discontinuation of inhaled insulin in subjects with type 2 diabetes.

Reviewer's Comment: Study 1029 also specifies obtaining PFTs after discontinuation of inhaled insulin following 24 months of exposure in subjects with type 2 diabetes. However, Study 1029 is an ongoing study and the data following discontinuation of inhaled insulin was not available at the time of this review.

The DLCO data from combined Study 1001-1002 suggest that the treatment group difference between inhaled insulin and the comparator was greatest at Weeks 65 then decreased until Week 104 when there was essentially no treatment group difference.

Table 42 Mean Observed DLCO, Change From Baseline DLCO, and Treatment Group Difference in Combined Study 1001-1002 All Subjects

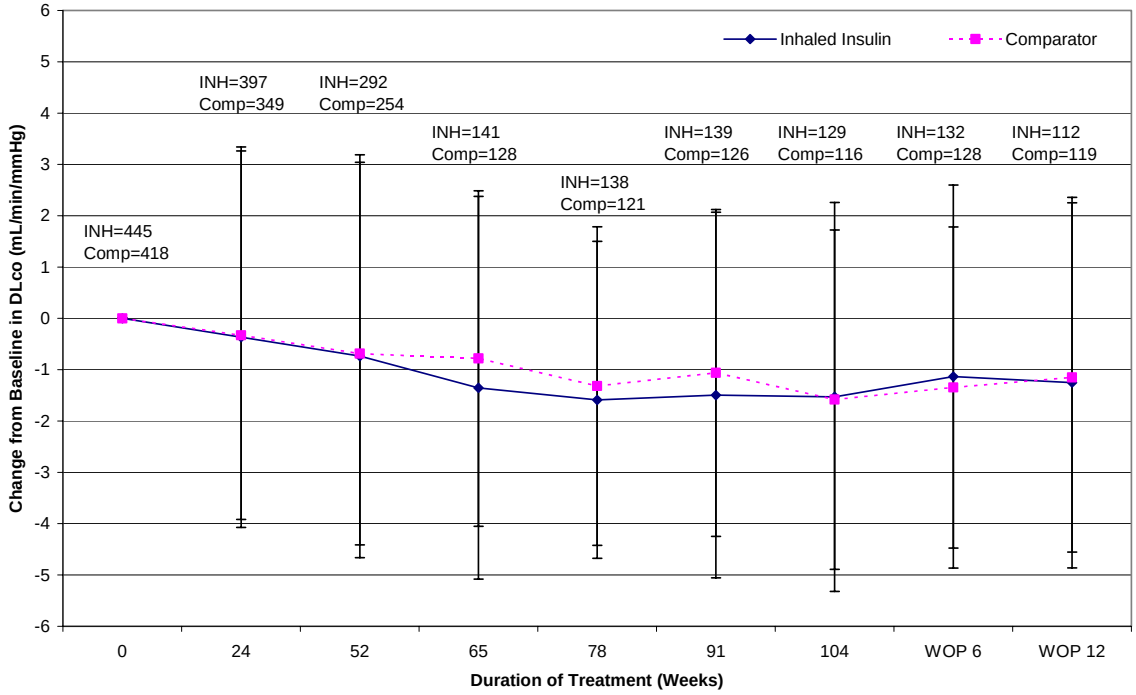
	Inhaled Insulin			Comparator			
DLCO (mL/min/ mmHg)	Observed	**Change from Baseline**		Observed		**Change from Baseline**	Treatment Group Difference (95% CI) Unadjusted
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)	
Baseline	25.972 (6.4)	445		25.742 (6.3)	418		
Week 24	25.659 (6.7)	397	-0.366 (3.7)	25.443 (6.4)	349	-0.328 (3.6)	-0.038 (-0.564, 0.489)
Week 48/52	25.136 (7.0)	292	-0.737 (3.9)	24.870 (6.1)	254	-0.688 (3.7)	-0.049 (0.695, 0.597)
Week 65	24.550 (5.7)	141	-1.352 (3.7)	24.288 (5.8)	128	-0.782 (3.3)	-0.570 (-1.416, 0.276)
Week 78	24.200 (5.9)	138	-1.588 (3.1)	24.243 (5.7)	121	-1.318 (3.1)	-0.270 (-1.029, 0.489)
Week 91	24.251 (5.8)	139	-1.495 (3.6)	24.135 (5.6)	126	-1.063 (3.2)	-0.431 (-1.252, 0.390)
Week 104	24.017 (5.7)	129	-1.529 (3.8)	24.056 (6.2)	116	-1.583 (3.3)	0.054 (-0.846, 0.954)
Follow-up Phase							
6 weeks	24.114 (6.0)	132	-1.133 (3.7)	24.364 (5.8)	128	-1.347 (3.1)	0.214 (-0.628, 1.056)
12 weeks	24.218 (5.7)	112	-1.253 (3.6)	24.569 (5.8)	119	-1.149 (3.4)	-0.103 (-1.013, 0.806)

Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: This table contains the results for all subjects. A fair number of subjects (~300) did not continue into the second year extension mostly because ethics committee and/or regulatory approval were not available when the subjects completed the 52 week study (according to the Applicant). The majority of the follow up phase data is on subjects who completed 104 weeks of treatment; however, the follow up phase data also contains data on 19 subjects who completed the 52 week treatment phase, but did not enter into the second year extension.
Reviewer's Comment: The Applicant also adjusted the treatment group difference (all subjects) for protocol, country, PFT at baseline, age, gender, and baseline height. The results are not shown in the table above. The values for the adjusted treatment group difference as determined by the Applicant are not the same as the unadjusted treatment group difference. However, the general pattern of the treatment group difference is the same [N21868/N_000/2004-12-27/clinstat/1001-1002.pdf, pg 366].

Table 37 also displays the follow-up phase data after discontinuation of study medication. The majority of subjects in the follow up phase completed 104 weeks of treatment. The follow up phase data suggests that after discontinuation of study medication, the lack of significant treatment group difference continues as shown below in Figure 36.

Figure 36 Mean Change from Baseline DLCO by Time in Combined Study 1001-1002 in Type 2 Diabetes (All Subjects)



Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: The Applicant asserts that this supports the reversibility of the effect of inhaled insulin on FEV_1. However, because there was no significant treatment group difference at Week 104, it is difficult to demonstrate reversibility.

5.1.8.3.2.4 Study 1036

Study 1036 is an ongoing uncontrolled extension study of the phase 2 protocols 102 (Type 1), 103, and 104 (Type 2). Study 1036 provides some long term PFT data on subjects with both type 1 and type 2 diabetes exposed to inhaled insulin up to 84 months. Study 1036 was discussed in Section 5.1.8.2.1.4 and is not discussed in detail here. The results for Study 1036 suggests that the decline in DLCO over a 78 month treatment period is -2mL/min/mmHg, which is approximately an annual rate of decline from baseline DLCO of 0.3mL/min/mmHg. However, due to the uncontrolled nature of the study, the results should be interpreted with caution.
Reviewer's Comment: The data from Study 1036 suggests that between 1 and 7 years of exposure to inhaled insulin, the change from baseline DLCO stabilizes.

5.1.8.3.2.5 Study 111

Study 111 was an open-label extension study of the phase 3 protocols 106 and 107 (Type 1) and 108, 109, 110 (Type 2). The design of Study 111 was discussed in the Methods Section 5.1.8.1. Like Study 1036, Study 111 provides some long term non-controlled PFT data on subjects exposed to inhaled insulin.