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 and 3 Studies

	Subjects Experiencing Cough		Subjects Not Experiencing Cough	
	Exubera (N)	Comparator (N)	Exubera (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 Exubera treatment group compared to the comparator groups, but was not a common adverse event. Sixty-nine subjects (3.5%) in the Exubera 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 Exubera group, which were graded as severe. Only one dyspnea SAE was reported in the Exubera group compared to four dyspnea SAEs in the comparator groups. Eight dyspnea adverse events led to discontinuation in the Exubera 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.

7.1.5 Less Common Adverse Events

7.1.5.1 Lung Neoplasm

No definitive association between Exubera and lung neoplasm can be made based upon the five cases of lung neoplasm (4 malignant, 1 benign) that were reported in the Applicant's clinical studies. Of the four malignant cases, three were in subjects treated with Exubera. 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, Exubera
    - 75 year old female, ex-smoker diagnosed with hamartoma after 510 days treatment with Exubera

Malignant

- Adenocarcinoma – Study 1002, Subject 01336266, Exubera
    - 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 Exubera; however, Applicant advised investigator to withdraw subject when protocol violation (abnormal CXR) noted. Subject withdrawn after 98 days of treatment with Exubera. 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, which later enlarged and was found to be a carcinoma.

- Squamous cell carcinoma – Study 111, Subject 51270656, Exubera
    - 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, Exubera
    - 67 year old ex-smoker male with history of occupational asbestos exposure diagnosed with metastatic bronchial carcinoma after 663 days of treatment with Exubera.
- 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].

The Applicant calculated an expected number of lung cancer cases in the Exubera clinical program using the Northern California Kaiser Permanente Database. According to the Applicant, the number of cases of lung cancer noted in the Exubera clinical program was less than what was expected (6.99, 95% CI: 5.23-8.98) [N21868/N_000/2005-10-10/1071.pdf, pg 4].

7.1.5.2 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 Exubera 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 Exubera therapy. He was also noted to have desaturation with walking from 98% to 88%/90%. An HRCT was performed after 5 months of Exubera 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 Exubera 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 Exubera) showed no significant changes from the previous HRCT and remained consistent with pulmonary fibrosis. Follow up PFTs (6 months after discontinuation of Exubera) 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 Exubera 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 Exubera.

- Subject 50728388 – Chronic pleural parenchymal fibrosis
  - 69 year old female with type 2 diabetes enrolled in Study 108 and treated with Exubera. Subject enrolled in extension Study 111. A CXR after ~ 16 months of treatment with Exubera 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 Exubera 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.

7.1.5.3 Pleural Effusion

There have been eight cases of pleural effusion reported as an AE in the clinical studies conducted by the Applicant, primarily in the extension studies. Specifically, there have been seven cases in the extension studies (two of which occurred after discontinuation of Exubera therapy), one case in the pediatric study, Study 1009, and one case in the study in subjects with COPD, Study 1030. The following is a brief summary of the pleural effusion AEs noted in the Applicant's studies.

- Study 108/111 - Subject 50558537 –Pulmonary Edema and Pleural Effusion
    - A 63 year old male subject with type 2 diabetes who had been enrolled in study 108 and received Exubera enrolled in the extension study (Study 111). Subject developed pulmonary edema on Day 524. CXR also showed pleural effusions, which were resolved by CXR on Day 590. Subject was discontinued from the study on Day 660 due to a moderate decline in PFTs (FEV_1, FVC, TLC, and DLCO declined >15% from baseline) [N21868/N_000/2004-12-27/clinstat/diabetes/111.pdf, 784-786].

Reviewer's Comment: According to the narrative, the pulmonary edema and pleural effusion were SAEs.

- Study 109/111 - Subject 5074-0110 – Pleural effusion and pneumothorax
    - A 64 year old male with type 2 diabetes who had been enrolled in Study 109 and received Exubera in the extension Study 111 developed left chronic pyelonephritis requiring nephrectomy. Following nephrectomy, the subject developed a pneumothorax and bilateral pleural effusions. The follow up PFTs demonstrated a decline from baseline DLCO of 14%, but no decline into the abnormal range for FEV_1, FVC, or TLC [N21868/N_000/2005-08-12/07july-5_clin_responses.pdf, pg 24-25].
- Study 103/103E/1036 - Subject 5007 0056 – Pleural effusion
    - A 58 year old male with type 2 diabetes who had been enrolled in Study 103 and received Exubera in extension Study 103E was noted to have "minute" bilateral pleural effusions on treatment day 433, which spontaneously resolved by CXR on treatment day 461 [N21868/N_000/2005-08-12/07july-5_clin_responses.pdf, pg 28].
- Study 109/111 - Subject 5030 0616
    - A 58 year old male with type 2 diabetes who participated in Study 109 and received Exubera in extension Study 111 underwent CABG surgery around treatment day 589. During the hospitalization, a pleural effusion was noted [N21868/N_000/2005-08-12/07july-5_clin_responses.pdf, pg 31].

The following cases of pleural effusion were noted after discontinuation of therapy.

- Study 108/111 - Subject 5034 8462 – Pleural effusion
    - A 67 year old male with type 2 diabetes who participated in Study 108 and received Exubera in extension Study 111 underwent CABG surgery on study day 560. Exubera therapy was permanently discontinued due to the interruption of study drug administration because of surgery. Moderate pleural effusion was noted post-operatively [N21868/N_000/2005-08-12/07july-5_clin_responses.pdf, pg 30].

- Study 103/103E - Subject 50050069 – SAE Pleural Effusion
    - A 60 year old male with type 2 diabetes who had been enrolled in Study 103 and received SC insulin enrolled in the extension study for Study 103. He received Exubera in the extension study and received Exubera for ~396 days. He complained of having difficulty inhaling and the Exubera was temporarily discontinued. He complained of shortness of breath and was admitted to the hospital and diagnosed with pleural effusions and pericardial effusions (after discontinuation of Exubera therapy). Chest tubes were placed. The subject was subsequently diagnosed with acquired immunodeficiency syndrome and hepatitis B. He was discharged, but readmitted with pleural effusions requiring chest tubes again. The pleural effusions resolved [N21868/N_000/2004-12-27/clinstat/1036narr.pdf, 32-33].

The following case of pleural effusion was noted in a pediatric subject:

- Study 1009 - Subject 50826090 – SAE Pleural Effusion
    - A 13 year old male with type 1 diabetes who had been enrolled in Study 1009 and treated with Exubera in Study 111 had a routine CXR at the 12 month visit, which showed a large right pleural effusion with an infiltrate in the right lung. Previous CXRs were normal. A thoracentesis was performed, which showed an exudative effusion. The effusion re-accumulated, requiring a second thoracentesis and eventually a pleuro-peritoneal shunt. The subject underwent an extensive work-up; however, the cause of the effusion could not be identified. The pleuro-peritoneal shunt was eventually removed. The most recent HRCT revealed a small right residual pleural effusion [N21868/N_000/2004-12-27/clinstat/diabetes/111.pdf, 667-670].

The following case of pleural effusion was noted in the study in COPD subjects, Study 1030.

- Study 1030 - Subject 10151393 – Pleural effusion
    - A 72 year male with type 2 diabetes enrolled in Study 1030 being treated with Exubera experienced a severe pneumonia on treatment day 35 attributed to leg fracture. The pneumonia was associated with a pleural effusion. PFT data following the pneumonia were not available at the time of this review [N21868/N_000/2005-08-12/07july-5_clin_responses.pdf, pg 26].

Reviewer's Comment: Although all the cases of pleural effusion occurred in subjects treated with Exubera, most of the cases occurred in the extension studies, which were not controlled. In addition, many of the cases of pleural effusion had confounding factors, which could be potential causes of the pleural effusion. Thus, it is difficult to draw any definitive conclusions regarding the reports of pleural effusion with Exubera.

7.1.5.4 Sarcoidosis

There were two reports of sarcoidosis in subjects treated with Exubera in the Applicant's clinical studies. Both cases were reported in non-controlled extension studies.

- Study 106/111 - Subject 50656943 - Sarcoidosis

- A 34 year old female with type 1 diabetes received SC insulin in Study 106 and continued into extension Study 111 was diagnosed with sarcoidosis after 237 days of treatment with Exubera. Hilar adenopathy was noted on her CXR and CT scan confirmed mediastinal adenopathy and bilateral upper lobe ill-defined nodules. According to the narrative, the diagnosis was sarcoidosis. The subject continued on Exubera. The narrative did not provide information regarding any treatment for the sarcoidosis [N21868/N_000/2004-12-27/clinstat/pulm.pdf, 1232-1234].

- Study 109/111 – Subject 50420476 – Sarcoidosis
  - A 55 year old male with type 2 diabetes received Exubera in Study 109 and continued into extension study 111 was noted to have probable enlarging pulmonary arteries on CXR. A CT scan was performed which showed bilateral hilar lymphadenopathy. Sarcoidosis was diagnosed based upon a biopsy of the paratracheal lymph node. The subject discontinued from the study on Day 934 due to the sarcoidosis diagnosis. The subject had a decline in FEV_1, FVC, and DLCO of approximately 28%, 23%, and 17% from baseline to end of study (Day 935) [N21868/N_000/2004-12-27/clinstat/pulm.pdf, 1466-1468].

Reviewer's Comment: Both cases of sarcoidosis were reported in the uncontrolled extension studies and it is difficult to draw any definitive conclusions.

7.1.6 Pulmonary Function Tests (PFTs)

7.1.6.1 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 and 3 studies had some differences in design that could potentially influence the PFT results. Specifically, in the early phase 2 and 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 which established 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 specify 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 and 3 studies. However, the completed controlled phase 2 and 3 studies only provide PFT data for up to 24 weeks of Exubera exposure in subjects with type 1 diabetes. Thus, in order to assess the effects of long term administration of Exubera on pulmonary function, the data from the ongoing controlled phase 2 and 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 and 3 adult studies.

Table 17 Summary of Pulmonary Function Testing in Adult Controlled Phase 2 and 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 Exubera. A safety update was submitted on April 26, 2005, with preliminary interim 2 year PFT data for Study 1022. The 2 year PFT dataset for Study 1022 were submitted on July 5, 2005.

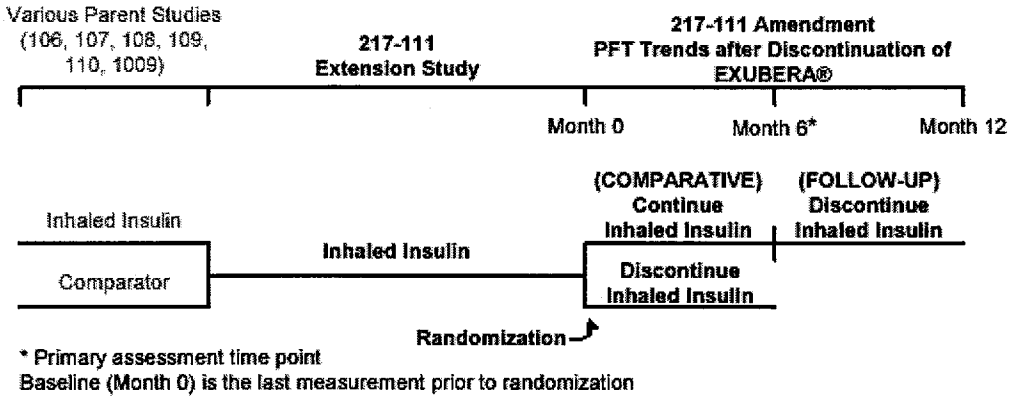
The PFT data from the adult controlled phase 2 and 3 studies will be the focus of this section of the review. The data will be reviewed separately for subjects with type 1 and type 2 diabetes as the baseline characteristics of these two groups are different. For example, the mean age of subjects with 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 Exubera. The PFT data from these extension studies provide some information on the long term exposure of Exubera. 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 Exubera on pulmonary function by amending the protocol to randomize subjects to either continuing Exubera or discontinuing Exubera 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 Exubera, this design is flawed because the randomized population was a self-selected population in that all the subjects were on Exubera and presumably tolerating Exubera. Subjects who did not tolerate Exubera may have withdrawn from the study or elected not to enter the extension study. In addition, the randomized subjects had been on Exubera 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 Exubera 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 reversal of any 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 in these studies 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 will be 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 are compared between treatment groups. The change from baseline treatment group difference is defined as the change from baseline in the Exubera group minus the change from baseline in the comparator group. The unadjusted treatment group difference will be 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 will also be 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.

7.1.6.2 Type 1 Diabetes

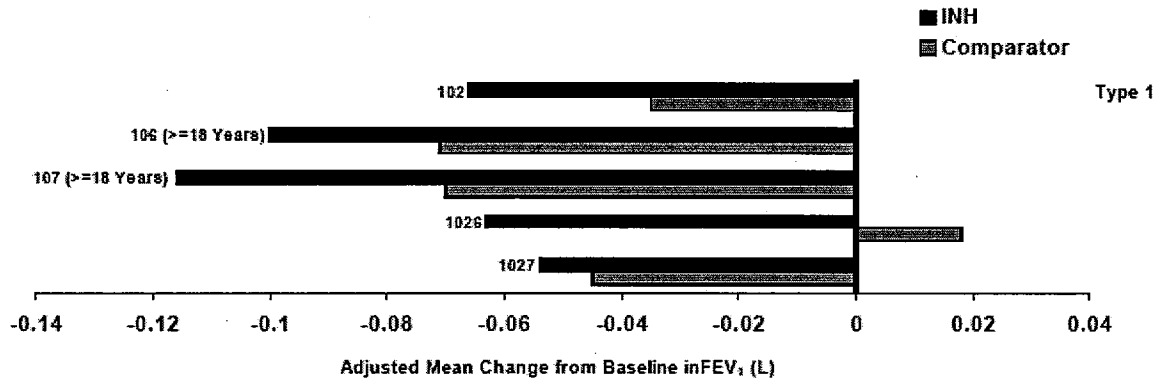
PFTs from the controlled Phase 2 and 3 studies in subjects with type 1 diabetes (102, 106, 107, 1022, 1026, and 1027) were reviewed by individual studies and as pooled data. The PFTs from the individual studies are reviewed in detail in the Appendices, Section 0. The PFT data from the pooled phase 2 and 3 studies is reviewed in this section. The results of an individual study may also be reviewed in this section to provide supportive information.

7.1.6.2.1 Forced Expiratory Volume in One Second (FEV_1)

7.1.6.2.1.1 Summary of Individual Studies

In each of the individual studies in subjects with type 1 diabetes, the Exubera 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 in FEV_1 for most of the studies in type 1 diabetes.

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



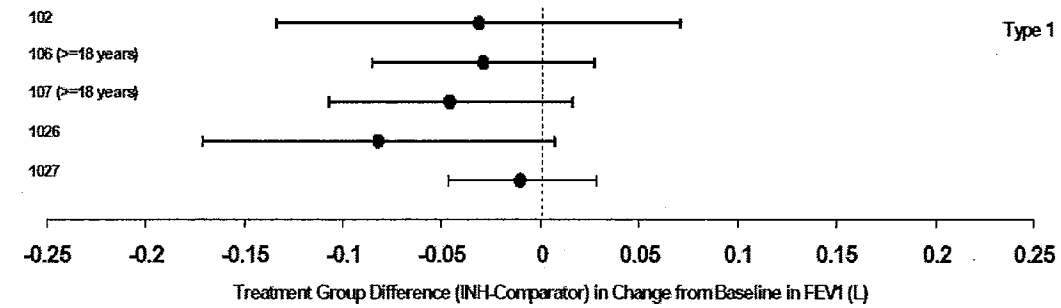
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 34

**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 Exubera 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 Exubera 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 and 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 Exubera 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.*

7.1.6.2.1.2 Pooled Controlled Phase 2 and 3 Studies in Type 1 Diabetes (Adults)

In the pooled adult controlled phase 2 and 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 Exubera 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 and 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 and 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 Exubera 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 Exubera group demonstrated an average annual decline from baseline FEV_1 of approximately 66mL/year, while the comparator group demonstrated an 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 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 and 3 studies (type 1 diabetes) conducted by the Applicant over a two year period, subjects treated with Exubera had a decline in FEV_1 (-66mL/year) similar to what would be expected in COPD patients who continue to smoke, while subjects treated with the comparator had a 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. In addition, subjects with type 1 diabetes treated with Exubera had an even greater decline from baseline FEV_1.*

The mean change from baseline in FEV_1 over time in the adult phase 2 and 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 Exubera 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, suggesting a greater treatment group difference. The treatment group difference noted at Week 48 remained fairly constant through Week 96, which is the last time point with available PFT data.

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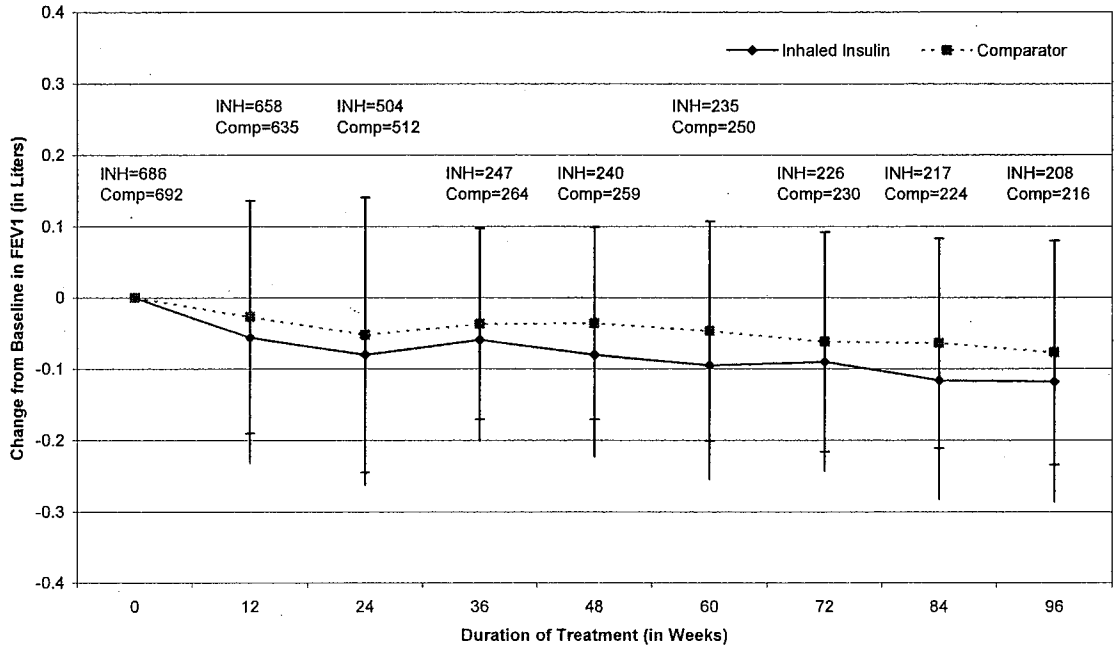
[2] Anthonisen NR, Connett JE, et al. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002; Vol 166: 675-679.
[3] Lange P, Parner J et al. A 15 year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998; 339: 1194-1200.
[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 Adults with Type 1 Diabetes

Pooled Phase 2 and 3 Controlled Studies (Mean +/-SD)



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 Exubera group – the mean change from baseline FEV_1 in the comparator group.

A 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 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 treatment group difference in mean change from baseline FEV_1 between the Exubera 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 and 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**
	Exubera	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: The 95% confidence intervals for the mean treatment group difference exclude zero at most time points. This suggests that there is a treatment group difference favoring the comparator.

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 Applicant's adjusted FEV_1 data.

Reviewer's Comment: The Applicant asserts that this data indicates the effect of Exubera on FEV_1 stabilizes and is not progressive. The data suggests that the treatment group difference is relatively stable between Week 12 and Week 36; however, an increase in the treatment group difference is noted at Week 48. This increased treatment group difference remains relatively stable through Week 96. At Week 96, there is approximately a 40mL 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. A treatment group difference of 40mL after two years of Exubera treatment of 40mL seems likely to not be clinically significant as long as the treatment group difference does not continue to increase with further Exubera treatment.

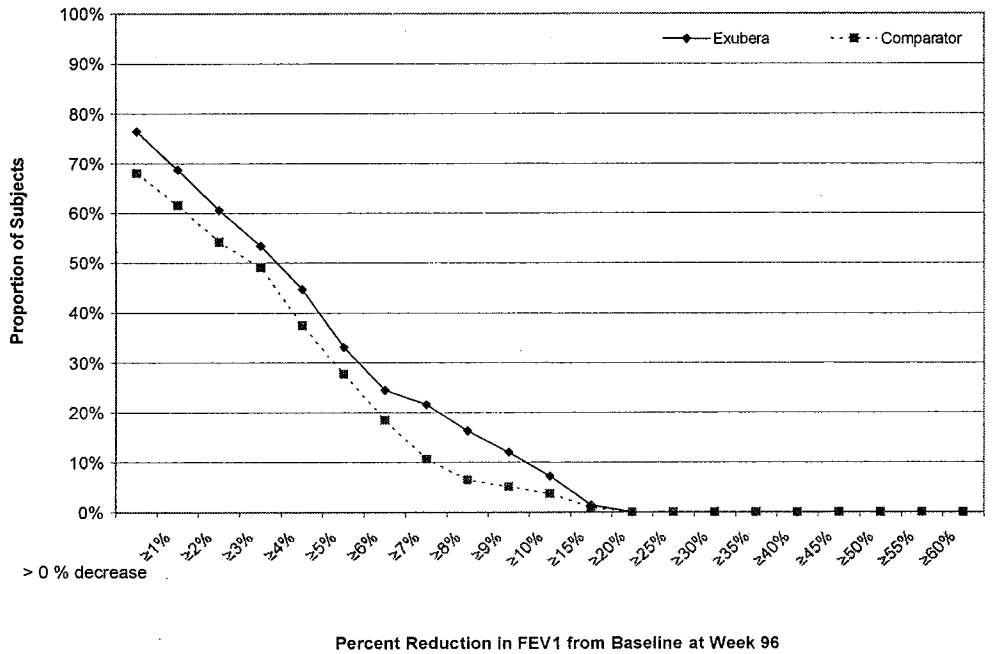
It should be noted that the Applicant has not offered a mechanism for the proposed "non-progressive" effect of Exubera on FEV_1.

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 Exubera 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 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 Exubera 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 Exubera 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 and 3 Studies in Type 1 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: The response analysis shows that approximately 70% of subjects in both treatment groups had a decline in FEV_1 at Week 96. Approximately 4% of subjects in the comparator group and 7% of subjects in the Exubera group had a decline greater than 10% from baseline.

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 and 3 studies in subjects with type 1 diabetes indicate that the Exubera group has a greater mean decline from baseline FEV_1 than the comparator group, thus, there is a treatment group difference between Exubera 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 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 Exubera 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 reversal of effect, are discussed next.

7.1.6.2.1.3 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 and 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 Exubera. Thus, the effect of discontinuation of Exubera on FEV_1 from Study 1027 is reviewed here. Finally, to assess the effect of Exubera 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: Study 1027 has limitations in that subjects are only exposed to Exubera for 12 weeks prior to discontinuation. Even if the discontinuation data suggests that there is a reversal of the effect of Exubera on FEV_1 after 12 weeks, there may not be a reversal after longer exposure.

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

Reviewer's Comment: A detailed review of Study 1027 is located in Section 0, Appendices.

The PFT data from Study 1027 suggests that a treatment group difference between Exubera 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 mean the treatment group differences.

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 Exubera on FEV_1 appears within the first couple of weeks of Exubera exposure.

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

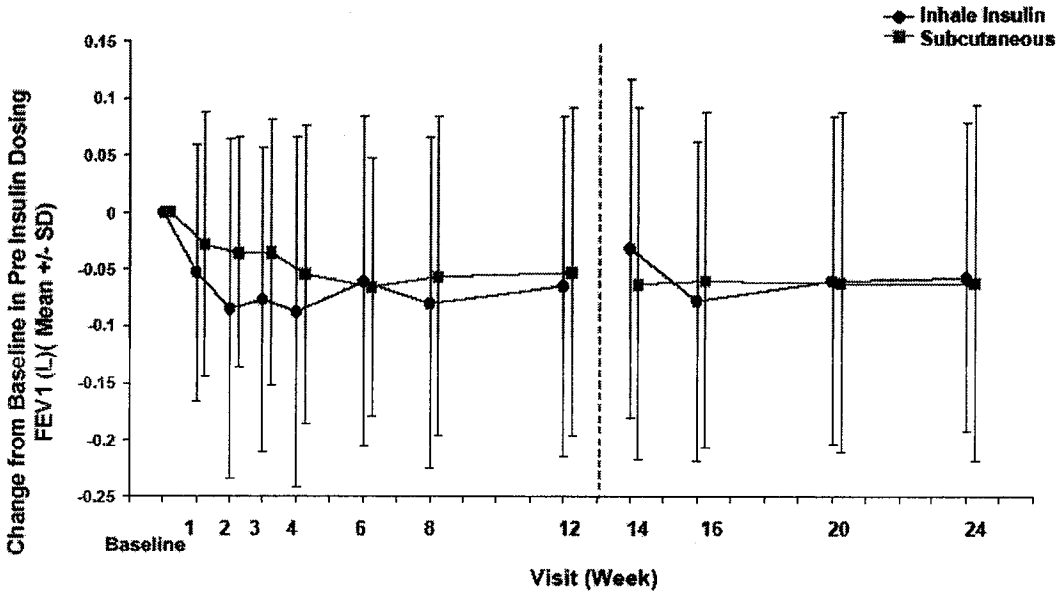
	Mean Treatment Group Difference (95% CI) Unadjusted^	Mean Treatment Group Difference (95% CI) Adjusted**
Week 1	-0.024 (-0.056, 0.007)	-0.022 (-0.053, 0.009)
Week 2	-0.046 (-0.077, -0.015)	-0.044 (-0.075, -0.013)
Week 3	-0.034 (-0.065, -0.002)	-0.032 (-0.063, -0.001)
Week 4	-0.028 (-0.059, 0.003)	-0.026 (-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 and 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 Exubera 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 reversal of the effect of Exubera on FEV_1. However, the following should be noted. First of all, it is difficult to argue reversal 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 reversal of the effect of Exubera. Also, at 2 weeks into the follow up phase, the Exubera group looks suddenly better than the comparator by about 35-41mL, which is difficult to interpret. Finally, subjects in Study 1027 were only exposed to Exubera for 12 weeks prior to discontinuation. Ideally, the Applicant should assess the effect of discontinuation of Exubera in a controlled fashion after long term exposure to Exubera. Study 1022 will provide some information regarding the effect of discontinuation of Exubera (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 Exubera is reversible, the Applicant did not propose a mechanism for reversal of the effect.

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

Table 22 Mean Observed FEV_1 Pre- and Post-Exubera 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 Exubera would not typically be expected in subjects without underlying lung disease.

7.1.6.2.1.4 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 Exubera 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 Exubera.
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 Exubera 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 and 3 studies. It should be noted that the results shown below are for both type 1 and type 2 diabetes.

Table 23 Mean Observed FEV_1 (L) and 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 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, which is contrary to the Applicant's theory that the effect of Exubera on FEV_1 stabilizes and does not progress. An annual decline in FEV_1 of 50mL is more than would be expected in subjects without underlying lung disease.

7.1.6.2.1.5 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 7.1.6.1. Like Study 1036, Study 111 provides some long term non-controlled PFT data on subjects exposed to Exubera.

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 decline in FEV_1 with time. A decline in FEV_1 is noted at 3 months and increases at each time point through Month 36 in the Exubera 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 106, 107, and 111)

Exubera			
	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-Exubera measurements
Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 960, 962

Reviewer's Comment: In Study 111, the annual rate of change from baseline based upon the 24 month data is approximately 60mL/year.

The Applicant amended Study 111 to provide additional PFT information after discontinuation of Exubera. However, as discussed in the Methods Section 7.1.6.1, the design is flawed in that the study population prior to randomization is likely enriched with subjects who responded favorably to Exubera and tolerated Exubera. Subjects who did not tolerate Exubera or had a decline in pulmonary function may have been discontinued from the study. In addition, subjects were on Exubera for various lengths of time prior to randomization into the discontinuation phase. Thus, for the effects of discontinuation of Exubera, 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].

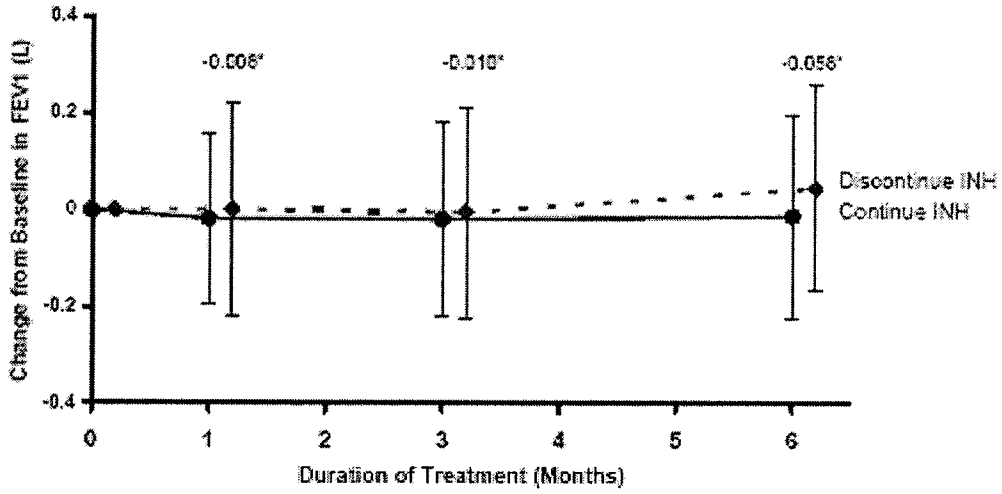
The mean observed FEV_1 and mean change in FEV_1 in the discontinuation phase are shown in Table 25 and Figure 15 below. The results show that in the 6 month discontinuation phase, subjects who discontinued Exubera demonstrated a mean increase in FEV_1, while subjects who continued on Exubera essentially 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 Exubera and is not the true baseline prior to study medication exposure. Thus, this "baseline" will be 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)**

	Exubera					
	Continued Exubera			Discontinued Exubera		
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 Exubera
**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 continue Exubera for an additional 6 months after the discontinuation phase. In this follow up phase, Exubera was discontinued. During the 6 month of follow up off Exubera, in subjects with type 1 diabetes ≥ 18 years of age, the FEV_1 increased 40 -50mL from the last FEV_1 value on Exubera [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 180].

Reviewer's Comment: The Applicant asserts that this data supports reversal of the effect of Exubera after discontinuation; however, the issues with the design of this discontinuation phase were noted above. In addition, the subjects who continued Exubera 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 reversal of the effect of Exubera on FEV_1.

7.1.6.2.1.6 Conclusions of the Effect of Exubera on FEV_1 in Type 1 Diabetes

Subjects with type 1 diabetes treated with Exubera 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 and 3 studies. A single study (1027) suggested that Exubera 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 Exubera and the comparator favoring the comparator.

The effect of Exubera 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 Exubera 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 Exubera longer than 24 months in type 1 diabetes has not been studied in controlled studies. However, non-controlled extension studies have exposed subjects to Exubera 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.

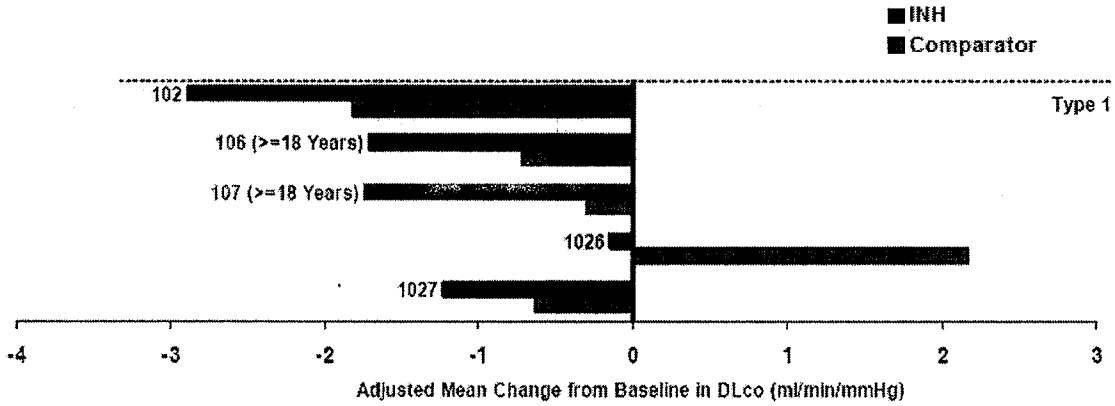
The reversal of the effect of Exubera on FEV_1 was evaluated in a controlled fashion in Study 1027. However, Study 1027 does not adequately address reversal of the effect of Exubera on FEV_1 in type 1 diabetes for two reasons. First, exposure to Exubera was only 12 weeks prior to discontinuation. Second,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

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

7.1.6.2.2.1 Summary of Individual Studies

In each of the individual studies in subjects with type 1 diabetes, the Exubera 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 and 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 Exubera 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 Exubera 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 Exubera group had a greater decline in mean change from baseline DLCO than the comparator group.

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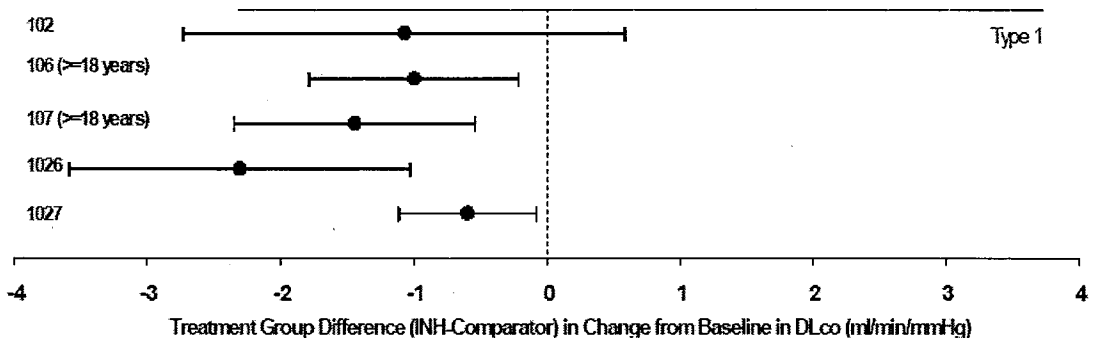
Figure 17 Adjusted* Mean Treatment Group Difference for DLCO Change from Baseline (mL/min/mmHg)
3 and 6 Month Controlled Phase 2 and 3 Studies in Type 1 Diabetes (Adults)



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 Exubera 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.*

7.1.6.2.2.2 Pooled Controlled Adult Phase 2 and 3 Studies in Type 1 Diabetes

In the pooled adult controlled phase 2 and 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 Exubera 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 and 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

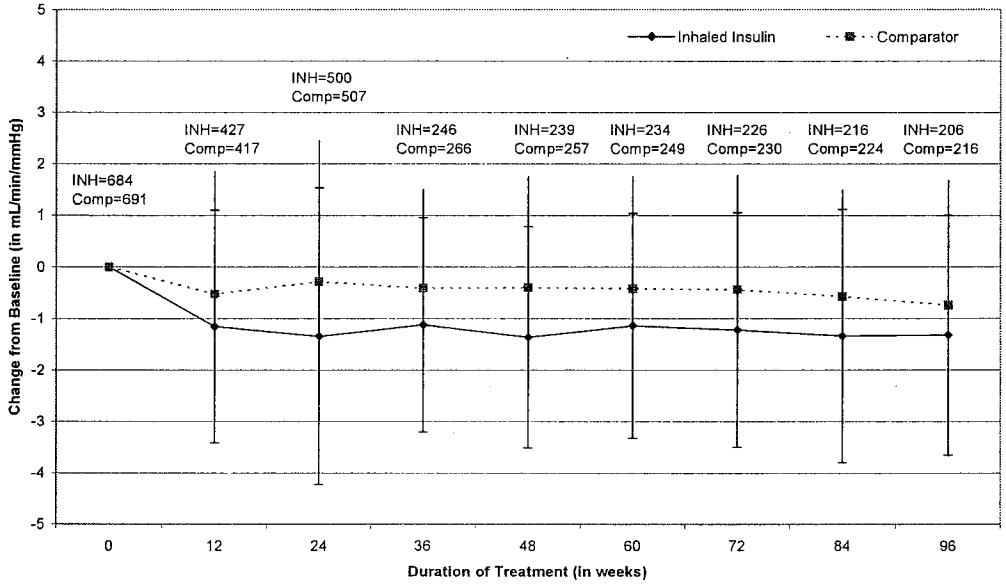
Reviewer's Comment: The DLCO data from the individual controlled adult phase 2 and 3 studies in type 1 diabetes was pooled by the Biometrics Reviewer, Dr. Joan Buenconsejo. Some of the numbers differ from the Applicant's pooled data because in the analyses performed by Dr. Buenconsejo, all subjects were 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 Exubera group had approximately twice the decline in DLCO as the comparator group. After 96 weeks of study medication, the Exubera 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.

The mean change from baseline DLCO over time in the adult phase 2 and 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 Exubera treatment group demonstrated a larger decline than subjects in the comparator group.

Figure 18 Mean Change from Baseline DLCO over Time in Type 1 Diabetes (Adults)

Pooled Phase 2 and 3 Controlled Studies (Mean +/-SD)



Source: Dr. Joan Buenconsejo's Biometrics Review

The mean treatment group difference was defined as the following: the mean change from baseline DLCO in the Exubera 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 and 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**
	Exubera	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 95% confidence intervals for the mean treatment group difference exclude zero at each time point. This suggests that there is a treatment group difference favoring the comparator.

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 Exubera 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.

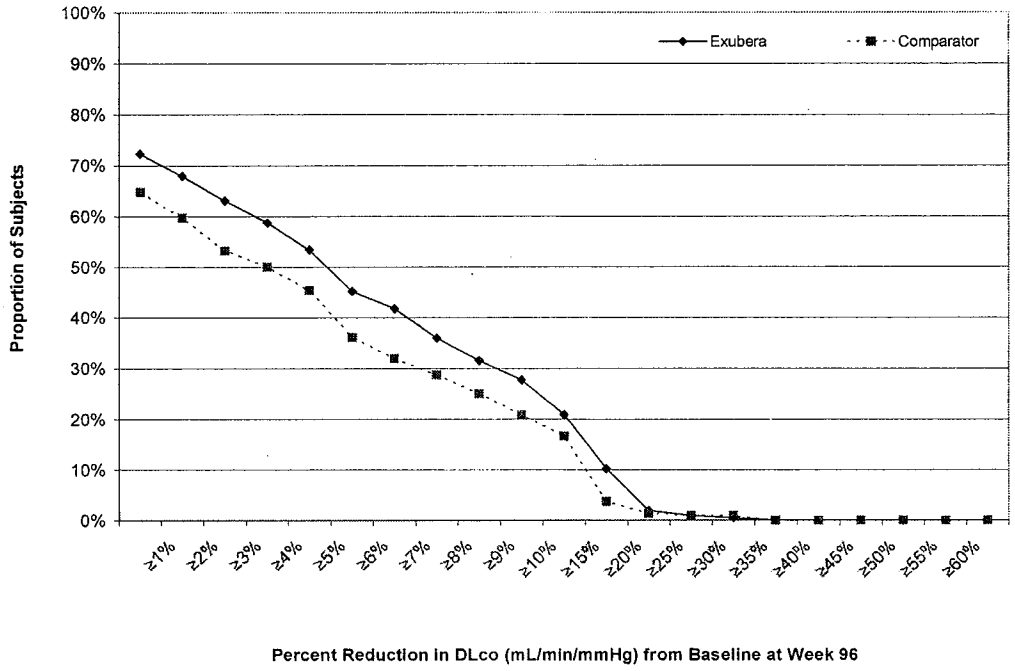
It should be noted that the Applicant has not offered a mechanism for the proposed "non-progressive" effect of Exubera on DLCO.

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 Exubera 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 Exubera 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 and 3 Studies in Type 1 Diabetes (Adults)



Source: Dr. Joan Buenconsejo's Biometrics Review

The controlled phase 2 and 3 studies in subjects with type 1 diabetes indicate that the Exubera group had a greater decline in DLCO than the comparator group, thus, there is a treatment group difference between Exubera 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 unadjusted treatment group difference was -0.5 to -0.6mL/min/mmHg.

To further explore the effects of Exubera 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 reversal of the effect of Exubera, are reviewed next.

7.1.6.2.2.3 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 and 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 Exubera. Thus, the effect of discontinuation of Exubera on DLCO from Study 1027 is reviewed here.
Reviewer's Comment: Study 1027 has limitations in that subjects are only exposed to Exubera for 12 weeks prior to discontinuation. Even if the discontinuation data suggest a reversal of the effect of Exubera on DLCO, reversal of effect after longer Exubera exposure remains unknown.

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

The PFT data from Study 1027 suggests that the treatment group difference between Exubera 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.

Table 28 Mean Observed DLCO and 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 Exubera on DLCO appears within the first couple of weeks of Exubera exposure.

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

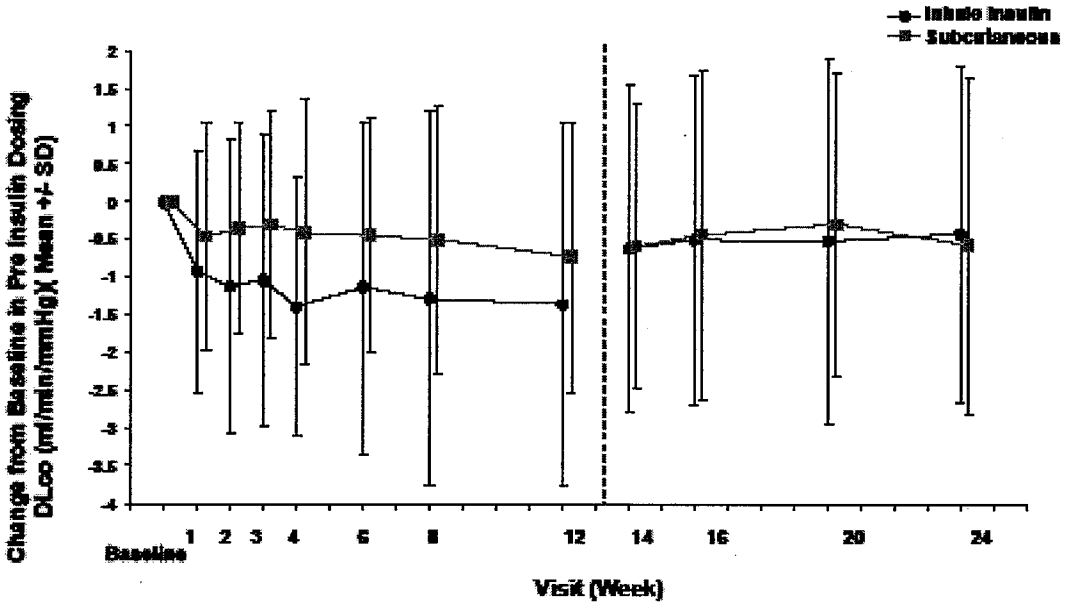
	Mean Treatment Group Difference (95% CI) Unadjusted***	Mean Treatment Group Difference (95% CI) Adjusted*
Week 1	-0.400 (-0.843, 0.043)	-0.385 (-0.809, 0.039)
Week 2	-0.739 (-1.177, -0.301)	-0.740 (-1.159, -0.321)
Week 3	-0.684 (-1.126, -0.241)	-0.683 (-1.107, -0.259)
Week 4	-0.903 (-1.341, -0.465)	-0.898 (-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 and 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 Exubera 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 Exubera for 2 weeks, the treatment group difference decreases.

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

7.1.6.2.2.4 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 Exubera 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 Exubera.
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.

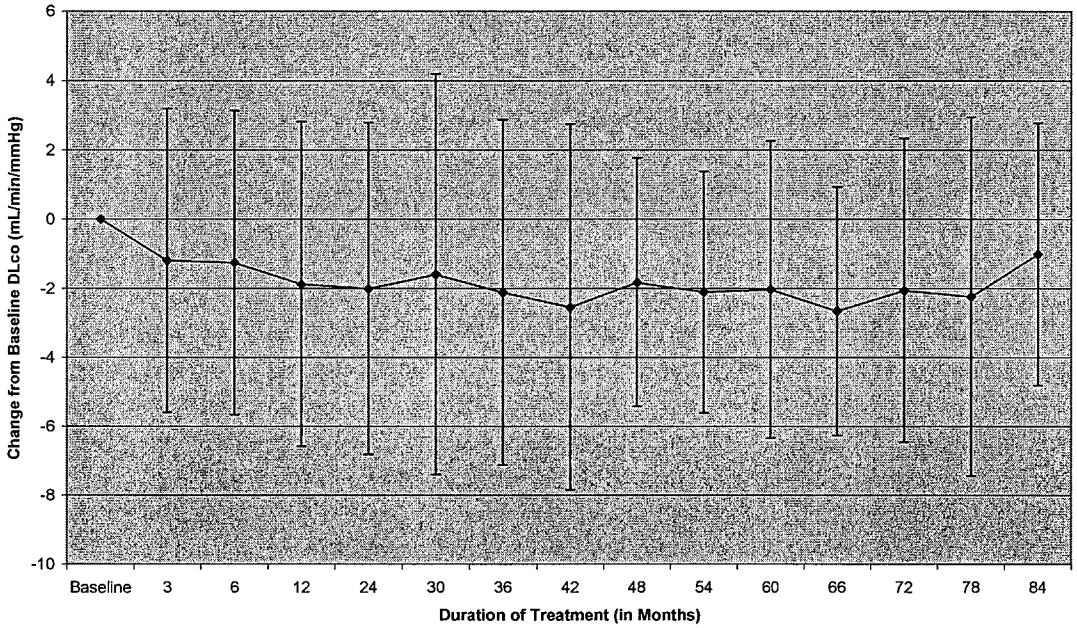
That being said, Study 1036 has at least 85 subjects who have been exposed to Exubera for > 48 months and thus, provides some information regarding the change in PFTs with time. However, due to the uncontrolled nature of the study, the results should be interpreted with caution. The results for the observed DLCO and 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 Change from Baseline DLCO (mL/min/mmHg) over Time in Type 1 and Type 2 Subjects on Exubera 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 Exubera, the change from baseline DLCO stabilizes.*

7.1.6.2.2.5 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 7.1.6.1. Like Study 1036, Study 111 provides some long term non-controlled PFT data on subjects exposed to Exubera.

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 Study 1036, in which the mean change from baseline DLCO at 36 months was -2.122 mL/min/mmHg.

Table 31 Mean Observed DLCO (mL/min/mmHg) and Change From Baseline DLCO (mL/min/mmHg) in Study 111 – Type 1 Diabetes (Adults)
(Studies 106, 107, and 111)

	Exubera		
	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-Exubera measurements
Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 978

Study 111was amended to provide additional PFT information after discontinuation of Exubera. However, as discussed in the Methods Section 7.1.6.1, the design is flawed in that the study population prior to randomization is likely enriched with subjects who responded favorably to Exubera and tolerated Exubera. Subjects who did not tolerate Exubera or had a decline in pulmonary function may have been discontinued from the study. In addition, subjects were on Exubera for various lengths of time prior to randomization into the discontinuation phase. Thus, for the effects of discontinuation of Exubera, Study 1027 provides the most rigorous PFT data. Study 1027 was discussed earlier in this section.

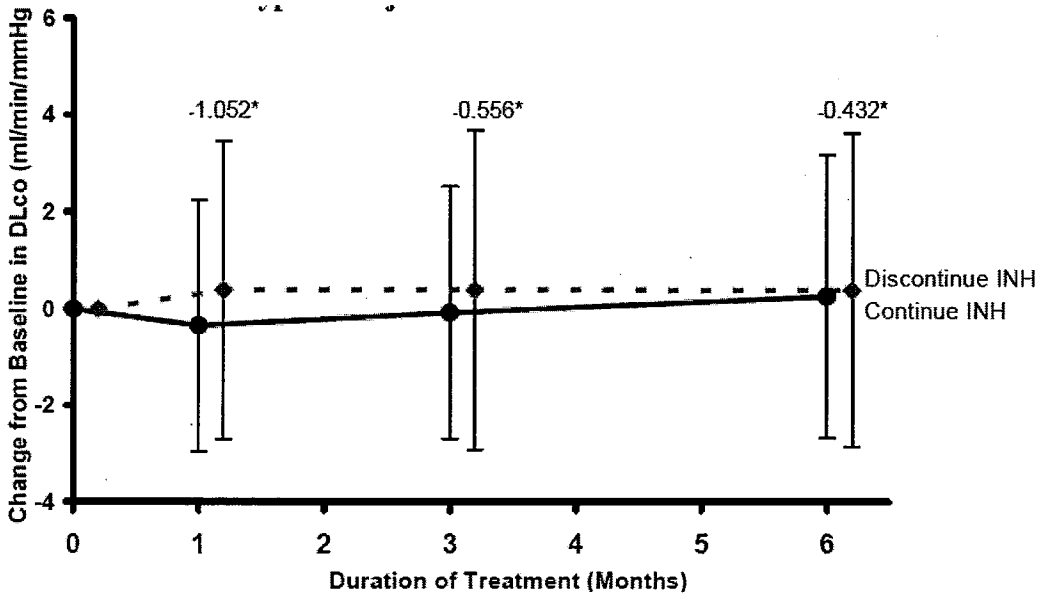
The mean observed DLCO and change from "baseline" DLCO in the discontinuation phase are shown in Table 32 and
Figure 22 below. The results show that in the discontinuation phase, subjects who discontinued Exubera had an increase in DLCO. By Month 6 of the discontinuation phase, the mean change from "baseline" 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 Exubera 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 Change in DLCO (mL/min/mmHg) in Discontinuation Phase of Study 111 – Adult Subjects with Type 1 Diabetes (Primary Analysis Set)**

Exubera						
	Continued Exubera			Discontinued Exubera		
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 Exubera
**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 Exubera for an additional 6 months after the discontinuation phase. In this follow up phase Exubera was discontinued. In subjects with type 1 diabetes ≥ 18 years of age, the mean DLCO increased 0.45mL/min/mmHg from the last DLCO value on Exubera [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 181].

Reviewer's Comment: The Applicant asserts that this data supports reversal of the effect of Exubera 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 Exubera exposure. Second, in order to assess reversal of the effect of Exubera, 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.

7.1.6.2.2.6 Conclusions of the Effect of Exubera on DLCO in Type 1 Diabetes

Subjects with type 1 diabetes treated with Exubera 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 and 3 studies in type 1 diabetes. A single study (1027) suggested that Exubera affects the DLCO within the first two weeks of exposure. In the pooled phase 2 and 3 controlled studies in type 1 diabetes, the Exubera 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 Exubera 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 Exubera on DLCO did not appear to progress over two years of treatment.

Exposure to Exubera 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 Exubera 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.

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

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

7.1.6.2.3 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 Exubera 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 and 3 study dataset. The Biometrics reviewer determined the treatment group difference for each pulmonary function test using the observed change from baseline to determine the unadjusted treatment group difference. In addition, the Biometrics reviewer adjusted the treatment group difference for protocol and adjusted for treatment, protocol, visit, baseline measurement, age, gender, and baseline height (per the Applicant).

In general, in type 1 diabetes, there was no significant change from baseline in FVC and TLC during the 96 week treatment period. There was a small treatment group difference in FRC at Week 96 of approximately -40 to -60mL. This 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 Treatment Group Difference for Additional Pulmonary Function Tests in Controlled Phase 2 and 3 Studies in Type 1 Diabetes (Adults)

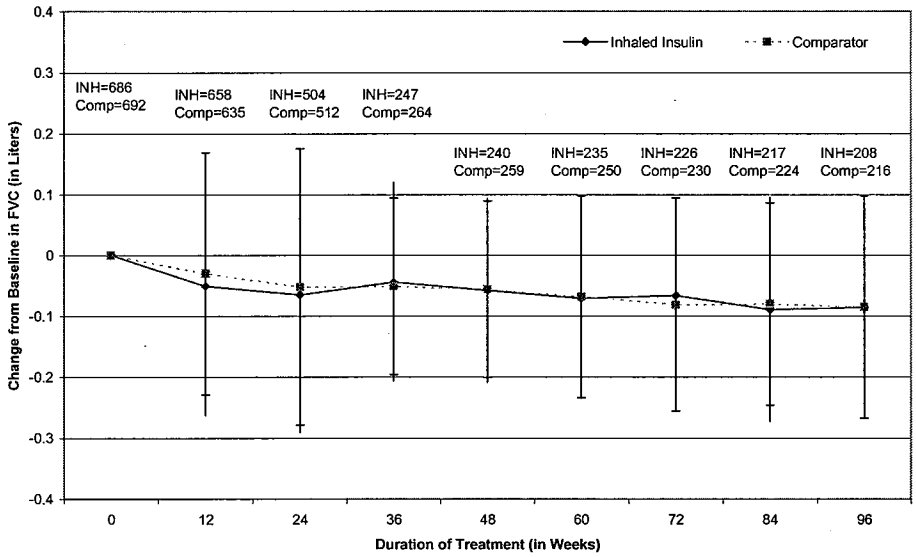
	Mean Observed Change from Baseline (N)		Mean Treatment Group Difference	
	Exubera	Comparator	Treatment Group Difference Unadjusted (95% CI)	Treatment Group Difference Adjusted* (95% CI)
FVC				
Week 12	-0.051 (658)	-0.030 (635)	-0.020 (-0.043, 0.002)	-0.021 (-0.042, 0.000)
Week 24	-0.065 (504)	-0.052 (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.

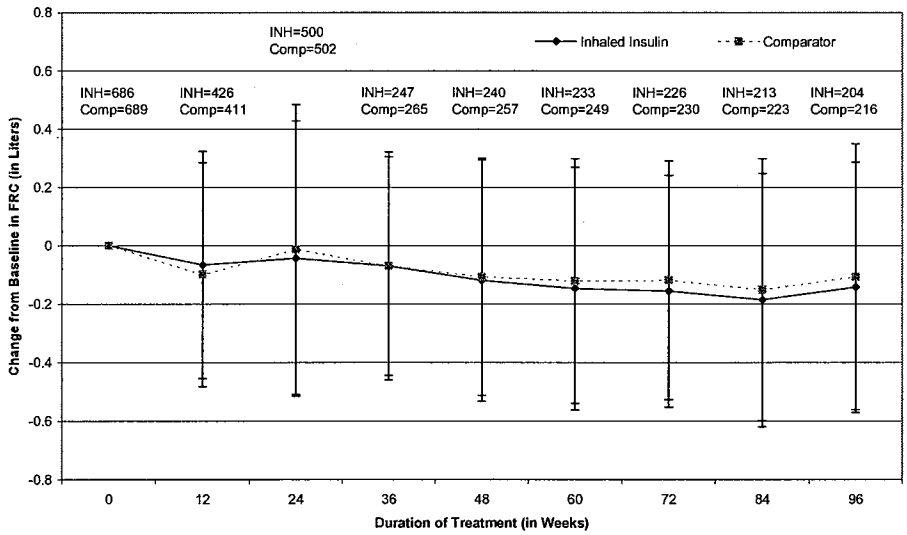
The following figures graphically display the mean change from baseline FVC, FRC, and TLC in type 1 diabetes.

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



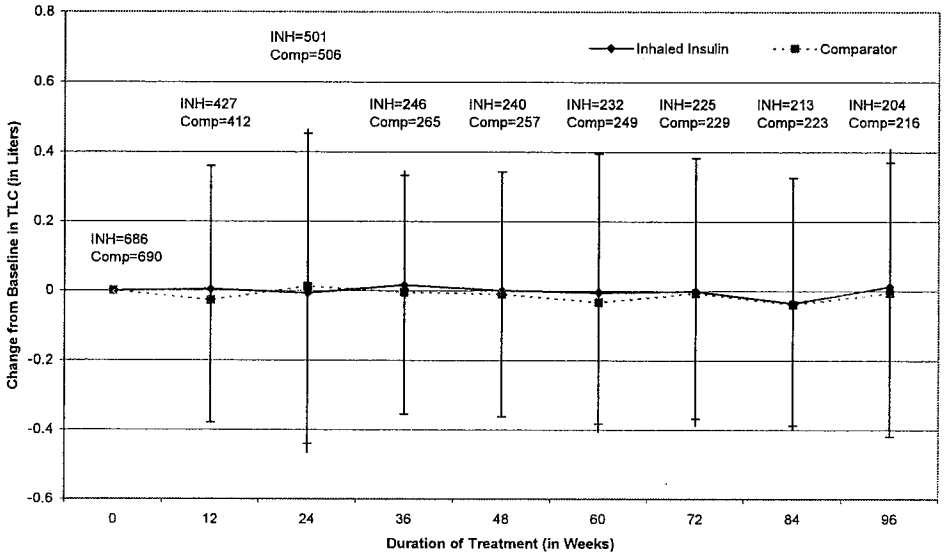
Source: Dr. Joan Buenconsejo's Biometrics Review

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



Source: Dr. Joan Buenconsejo's Biometrics Review

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



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 and 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 and 3 Studies in Type 1 Diabetes (Adults)

	Mean Observed Change from Baseline (N)		Mean Treatment Group Difference
	Exubera	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

7.1.6.3 Type 2 Diabetes

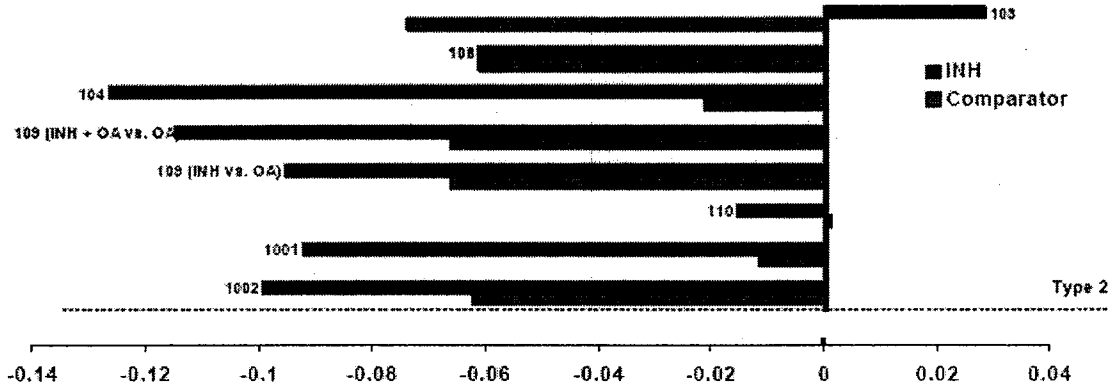
PFTs from the controlled Phase 2 and 3 studies in subjects with type 2 diabetes (103, 104, 108. 109, 110, 1001, 1002, and 1029) were reviewed by individual studies and as pooled data. The PFT data from the individual studies are reviewed in the Appendices, Section 0. The PFT data from the pooled phase 2 and 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.

7.1.6.3.1 Forced Expiratory Volume in One Second (FEV_1)

7.1.6.3.1.1 Summary of Individual Studies

In most of the individual studies in subjects with type 2 diabetes, the Exubera 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 and 3 Studies in Type 2 Diabetes

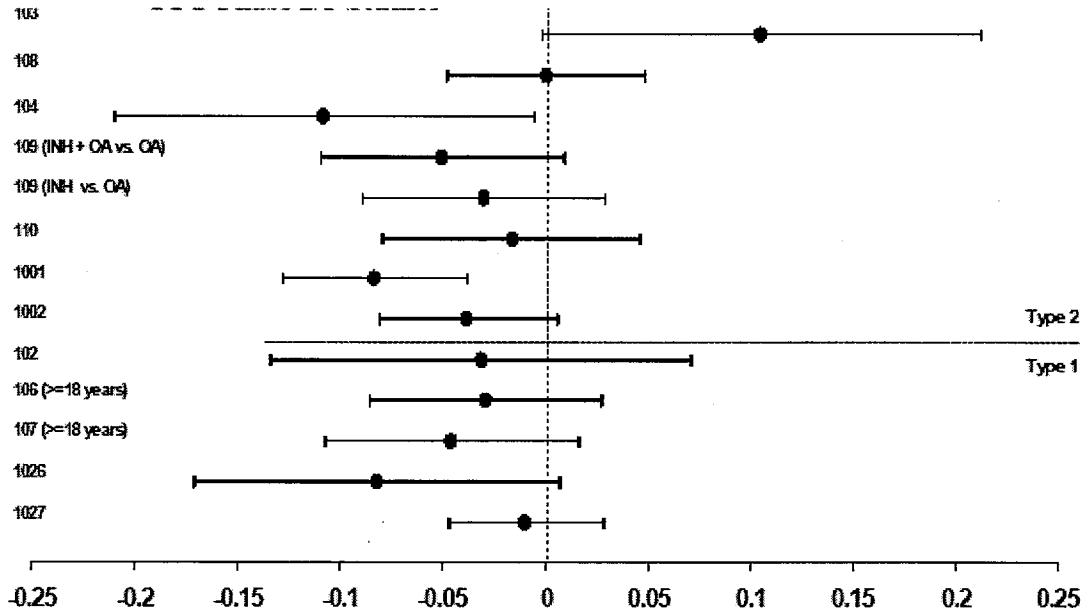


Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 34

**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 Exubera 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 Exubera 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 and 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.*

7.1.6.3.1.2 Pooled Controlled Adult Phase 2 and 3 Studies in Type 2 Diabetes

In the pooled adult controlled phase 2 and 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 Exubera treatment group demonstrated a larger 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 Change From Baseline Controlled Phase 2 and 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 and 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.

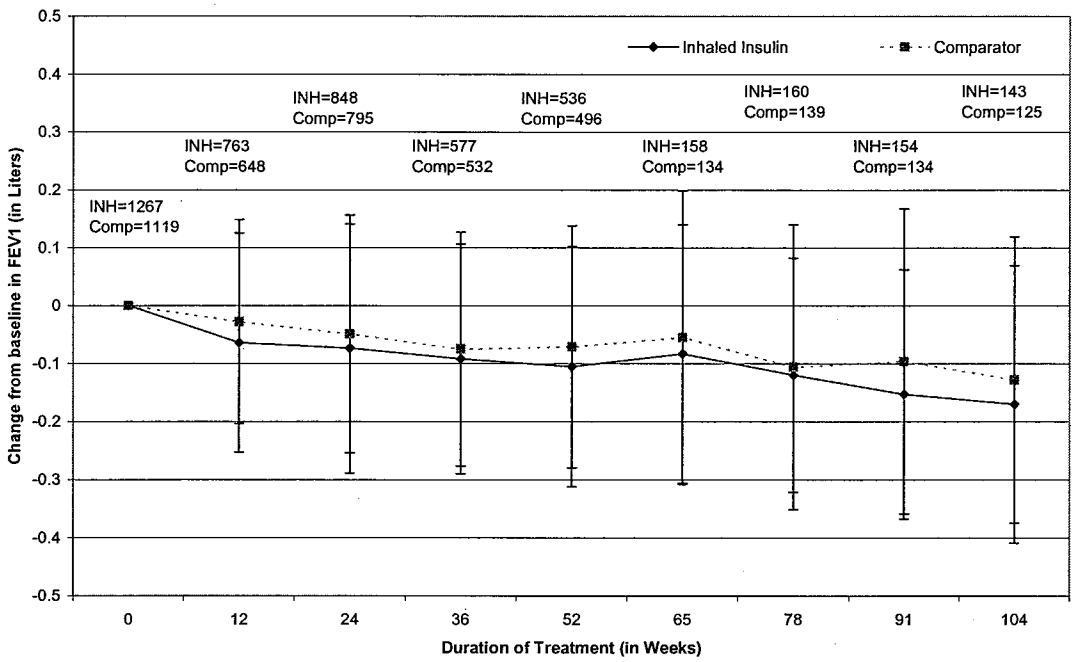
Reviewer's Comment: It should be noted that the PFT data after Week 52 is from the combined Study 1001-1002.

After 104 weeks of study medication, the Exubera 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 Exubera 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 Exubera group had an even greater decline in FEV_1 than the comparator group. Second, based upon the controlled phase 2 and 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 Exubera 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 and 3 controlled studies in type 2 diabetes is shown below in Figure 28, which shows that subjects in the Exubera treatment group demonstrated a greater 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 appears to be similar to the difference between treatment groups at Week 12.

Figure 28 Mean Change from Baseline FEV_1 over Time in Type 2 Diabetes
Pooled Phase 2 and 3 Controlled Studies (Mean +/-SD)



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 Exubera 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 treatment group difference always favored the comparator. At Week 104, the mean treatment group difference was similar to the 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 Exubera 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 and 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**
	Exubera	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

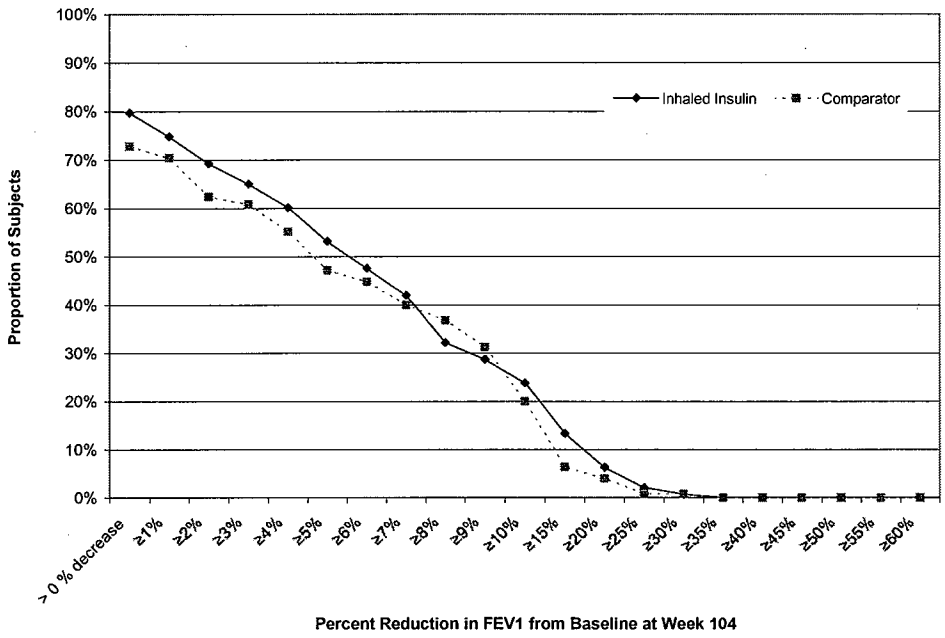
Reviewer's Comment: The 95% confidence intervals for the mean treatment group difference exclude zero at half of the time points. A treatment group difference of -30 to -40mL seems likely to not be clinically significant as long as the treatment group difference remains stable over time and is not progressive. The -30 to -40mL treatment group difference at 2 years is similar to the -40mL treatment group difference noted in subjects with type 1 diabetes.

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

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 Exubera 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 Exubera 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 Exubera group than in the comparator group. At Week 104, 13% of Exubera 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 and 3 Studies in Adults with Type 2 Diabetes



Source: Dr. Joan Buenconsejo's Biometrics Review

The controlled phase 2 and 3 studies in subjects with type 1 diabetes indicate that the Exubera group has a greater decline in FEV1 than the comparator group, thus, there is a treatment group difference between Exubera and the comparator favoring the comparator. A 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 suggests that the treatment group difference does not progress over a 2 year period.
Reviewer's Comment: A treatment group difference of 40mL seems likely to not be clinically significant as long as the treatment group difference remains stable over time and is not progressive.

To further explore the effects of Exubera 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 reversal of the effects of Exubera, will be reviewed next.

7.1.6.3.1.3 Study 1001-1002

Studies 1001 and 1002 were originally 24 week open-label, randomized, parallel group studies comparing Exubera 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 Exubera was discontinued. However, due to the protocol amendments extending the study, the PFT data following discontinuation could be after 52 weeks of Exubera exposure or 104 weeks of Exubera 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 Exubera on PFTs in subjects with Type 2 diabetes. In addition, Study 1001-1002 provides some controlled PFT data following discontinuation of Exubera in subjects with type 2 diabetes.
Reviewer's comment: For a detailed review of the individual 24 week Studies 1001 and 1002 as well as the combined Study 1001-1002, refer to Section 0, Appendices.

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

The FEV_1 data from combined Study 1001-1002 suggests that the treatment group difference between Exubera and the comparator was greatest at Weeks 24 and 91 and fluctuated throughout the rest of the treatment period. The treatment group difference does 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 Exubera on FEV1 is not progressive. However, the Applicant did not provide a proposed mechanism for an early effect 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

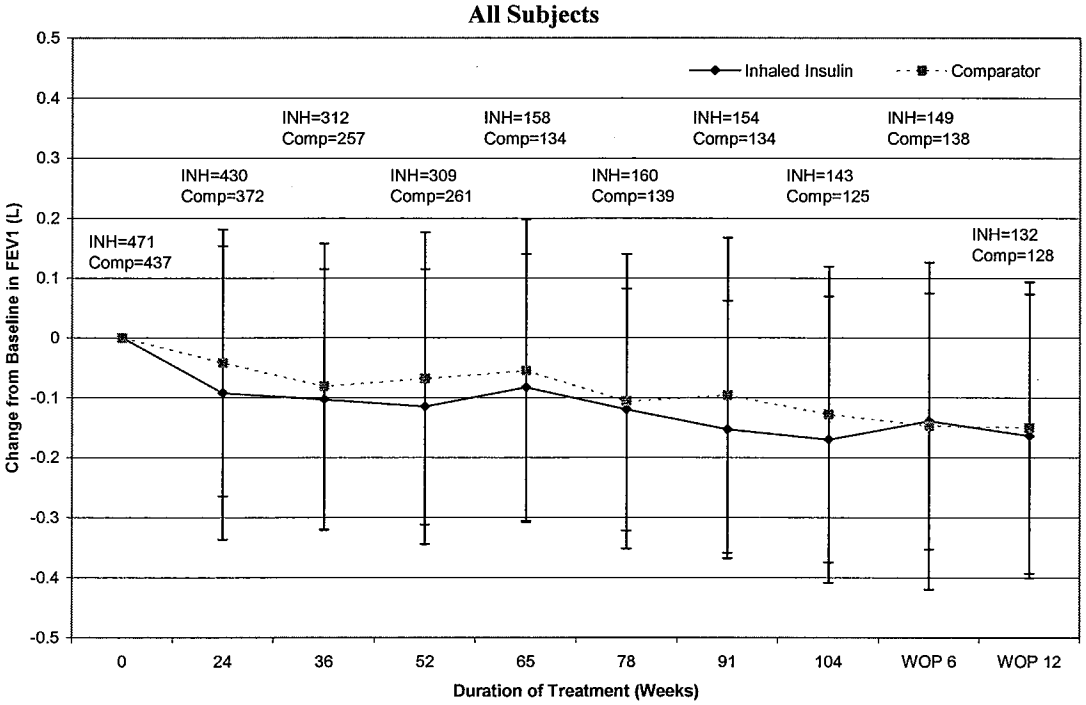
Reviewer's Comment: This table contains the results for all subjects. A fair number of subjects (300) did not continue into the second year extension mostly because ethics committee and/or regulatory approval were not available when the subjects completed

the 52 week study, according to the Applicant. The majority of the follow up phase data are from subjects who completed 104 weeks of treatment; however, the follow up phase data also contain data from 19 subjects who only completed the 52 week treatment phase and did not enter the two 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 Exubera. 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 reversal of the effect of Exubera on FEV_1. It should be noted that the Applicant did not propose a mechanism for reversal of the effect of Exubera.

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



Source: Dr. Joan Buenconsejo's Biometrics Review

7.1.6.3.1.4 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 Exubera up to 84 months. Study 1036 was discussed in Section 7.1.6.2.1.4 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 Exubera 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.

7.1.6.3.1.5 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 7.1.6.1. Like Study 1036, Study 111 provides some long term non-controlled PFT data on subjects exposed to Exubera.

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 Exubera 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 108, 109, 110, and 111)

Exubera			
	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-Exubera 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 Exubera. However, as discussed in the Methods Section 7.1.6.1, the design is flawed in that the study population prior to randomization is likely enriched with subjects who responded favorably to Exubera and tolerated Exubera. Subjects who did not tolerate Exubera or had a decline in pulmonary function may have been discontinued from the study. In addition, subjects were on Exubera 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 Exubera 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 Exubera 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: One issue with the discontinuation phase data is that subjects who were treated with Exubera did not continue to demonstrate a decline in FEV_1 at 6 months, which is inconsistent with the pooled phase 2 and 3 studies, Study 1036, and the earlier phase of Study 111, in which subjects had a continual decline in FEV_1 over time with Exubera 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)**

Exubera						
	Continued Exubera			Discontinued Exubera		
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 Exubera
**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 Exubera and is not the true baseline prior to study medication exposure. Thus, this "baseline" will be in quotes to distinguish it from the true pre-study medication baseline.

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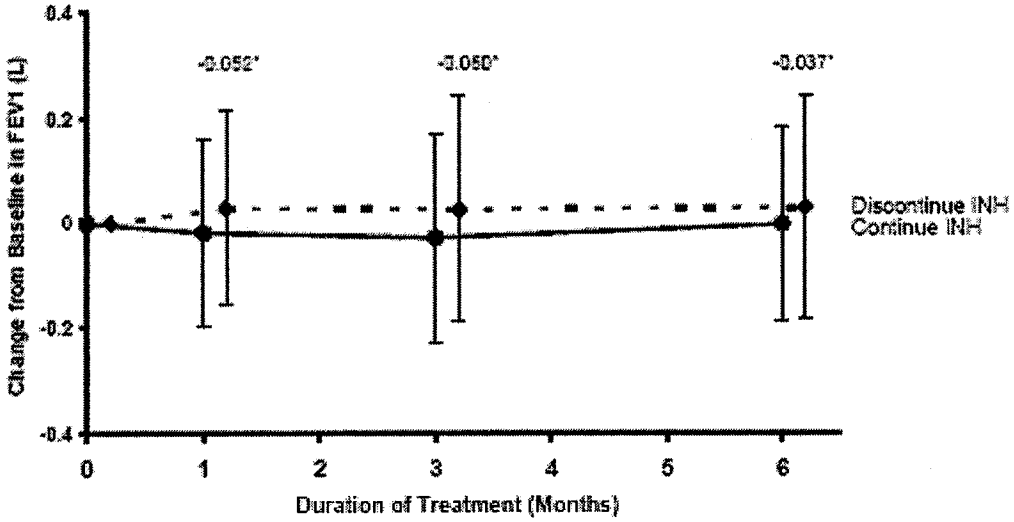
Figure 31 Mean Change in FEV_1 in the Discontinuation Phase of Study 111 in Type 2 Subjects (Adults)



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 Exubera for an additional 6 months after the discontinuation phase. In this follow up phase Exubera was discontinued. In subjects with type 2 diabetes ≥ 18 years of age, the FEV_1 decreased 30mL from the last FEV_1 value on Exubera [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 180].

Reviewer's Comment: The Applicant asserts that these data support reversal of the effect of Exubera after discontinuation; however, the issues with the design of this discontinuation phase were noted above. In addition, the subjects who continued Exubera 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 reversal of effect of Exubera on FEV_1.

7.1.6.3.1.6 Conclusions of the Effect of Exubera on FEV_1 in Type 2 Diabetes

Subjects with type 2 diabetes treated with Exubera 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 and 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 Exubera 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 Exubera longer than 24 months in type 2 diabetes has not been studied in controlled studies. However, non-controlled extension studies have exposed subjects to Exubera 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.

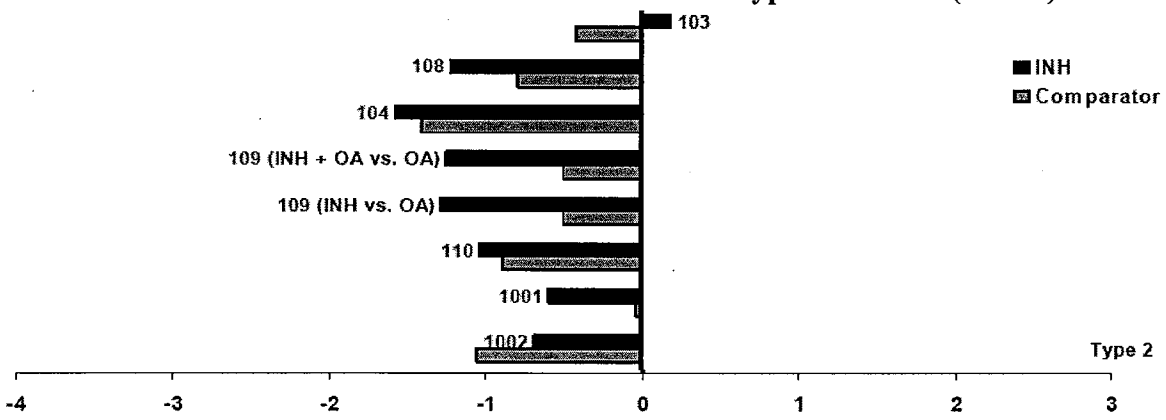
Reversal of the effect of Exubera on FEV_1 was evaluated in combined Study 1001-1002. The results of combined Study 1001-1002 suggest that the treatment group difference after Exubera treatment for 104 weeks was -40mL. However, after discontinuation of Exubera for 6-12 weeks, there was minimal treatment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

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

7.1.6.3.2.1 Summary of Individual Studies

In most of the individual studies in subjects with type 2 diabetes, the Exubera 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 and 3 Studies in Type 2 Diabetes (Adults)



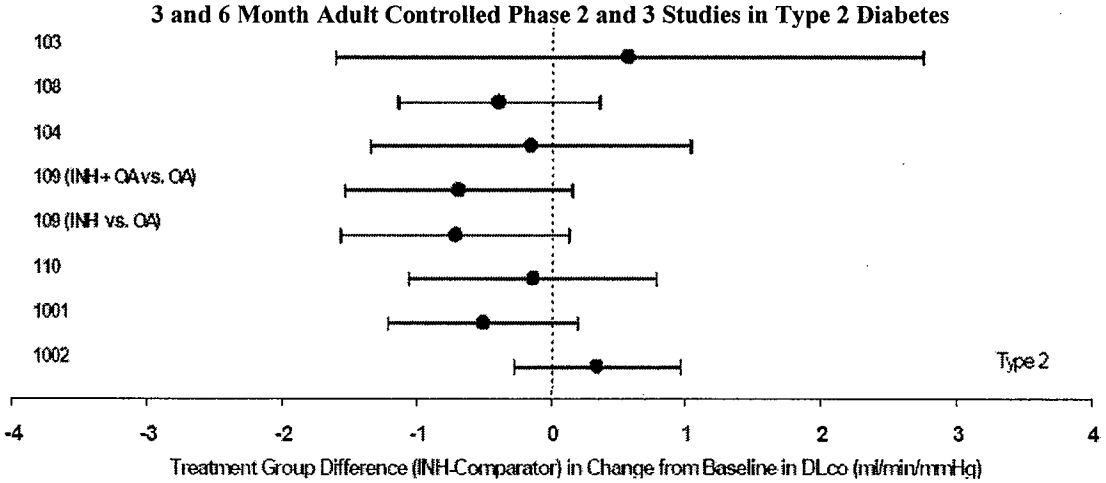
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 48

**Reviewer's Comment: The above figure illustrates a greater mean decline from baseline DLCO in the Exubera 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 treatment group difference, which is defined as the mean change from baseline DLCO in the Exubera 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 Exubera group had a greater decline in mean change 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 and 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 Exubera 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.*

7.1.6.3.2.2 Pooled Controlled Adult Phase 2 and 3 Studies in Type 2 Diabetes

In the pooled adult controlled phase 2 and 3 studies in subjects with type 2 diabetes, the mean baseline DLCO and 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 Exubera treatment group demonstrated a larger 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 and 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

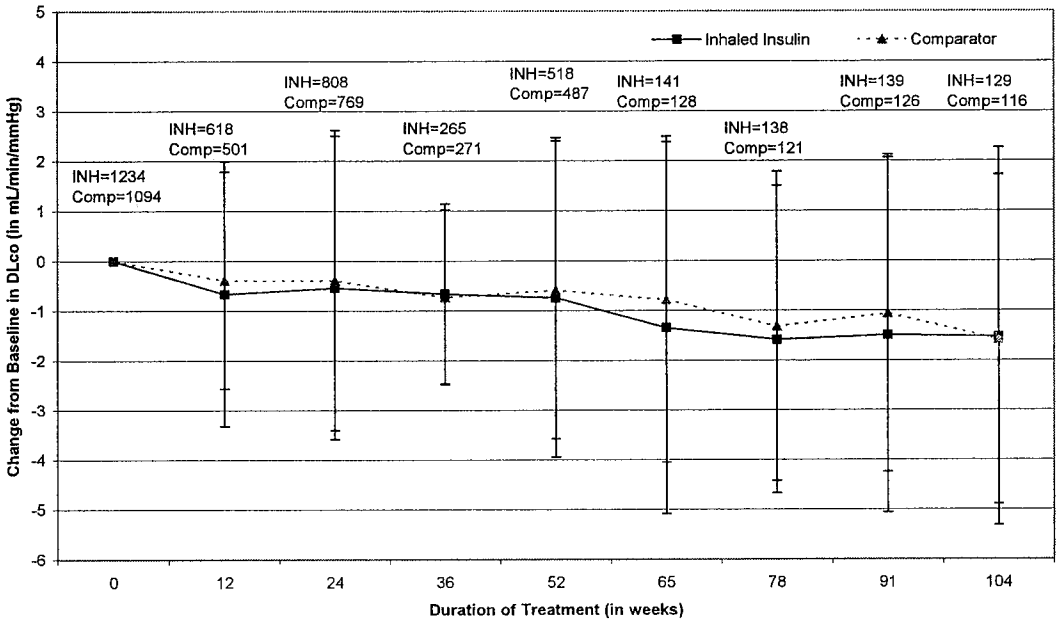
Reviewer's Comment: The DLCO data from the individual controlled adult phase 2 and 3 studies in type 1 diabetes was pooled by the Biometrics Reviewer, Dr. Joan Buenconsejo. Some of the numbers differ from the Applicant's pooled data due to small differences in the number of subjects. The difference is 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 Exubera 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 and 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 Exubera treatment group demonstrated a larger 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 treatment group difference.

Figure 34 Mean Change from Baseline DLCO vs. Time in Type 2 Diabetes

Pooled Phase 2 and 3 Controlled Studies (Mean +/-SD)



Source: Dr. Joan Buenconsejo's Biometrics Review

The treatment group difference was defined as the following: the mean change from baseline DLCO in the Exubera 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 Exubera group.

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Table 41 Mean Change from Baseline DLCO and Mean Treatment Group Difference in Change from Baseline DLCO in Controlled Phase 2 and 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*
	Exubera	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

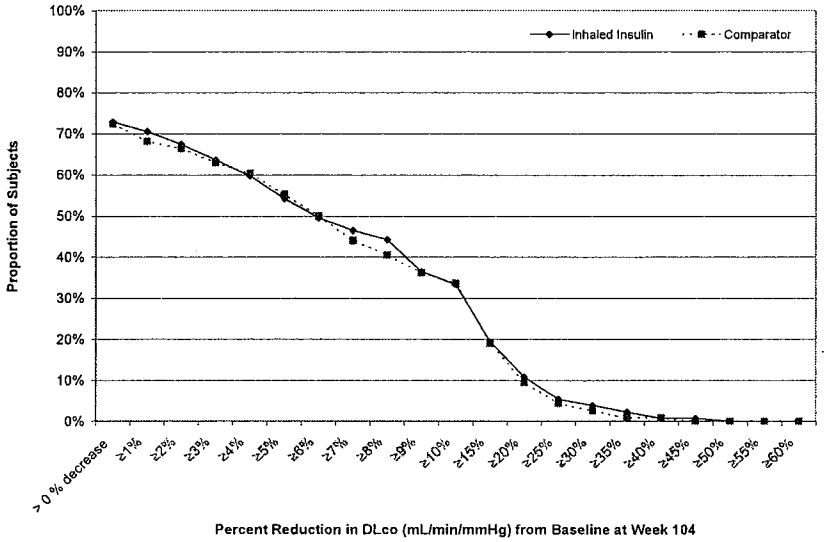
Reviewer's Comment: The unadjusted and adjusted treatment group difference provide somewhat different values towards the end of the study. The reason for the difference is unclear. The treatment group difference at Week 104 favors the Exubera group and is not consistent with earlier data.

Reviewer's Comment: The Applicant asserts that this data indicates the effect of Exubera 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 Exubera 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 and 3 Studies in Adults with Type 2 Diabetes



Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: The response analysis at Week 104 indicates a similar proportion of subjects in each treatment group with decline in DLCO. However, the response analyses at earlier time points indicated that the Exubera group had a greater decline in DLCO than the comparator group.

To further explore the effects of Exubera 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 reversal of the effect of Exubera, are reviewed next.

7.1.6.3.2.3 Study 1001-1002

Studies 1001 and 1002 were originally 24 week open-label, randomized, parallel group studies comparing Exubera 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 Exubera 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 Exubera in subjects with Type 2 diabetes. In addition, Study 1001-1002 provides some controlled PFT data following discontinuation of Exubera in subjects with type 2 diabetes.

Reviewer's comment: For a detailed review of the individual 24 week Studies 1001 and 1002 as well as the combined Study 1001-1002, refer to Section 0, Appendices.
Reviewer's Comment: Study 1029 also specifies obtaining PFTs after discontinuation of Exubera following 24 months of exposure in subjects with type 2 diabetes. However, Study 1029 is an ongoing study and the data following discontinuation of Exubera was not available at the time of this review.

The DLCO data from combined Study 1001-1002 suggests that the treatment group difference between Exubera 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 the two 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.