Table 78 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation in Study 217-106

	Exubera			Subcutaneous Insulin		
	-10 to -15%	-15 to -20%	> -20%	-10 to -15%	-15 to -20%	> -20%
FEV_1	14 (8.4%)	4 (2.4%)	0	8 (5.1%)	1 (0.6 %)	3 (1.9%)
FVC	7 (4.2%)	3 (1.8%)	0	5 (3.2%)	1 (0.6%)	3 (1.9%)
DLCO	22 (14.7%)	16 (10.7%)	18 (12%)	18 (12.2%)	7 (4.7%)	11 (7.4%)
TLC	6 (3.9%)	4 (2.6%)	5 (3.3%)	6 (4.0%)	3 (2.0%)	1 (0.7%)

The n for the categorical analyses of each PFT parameter is the same n as listed in the change from baseline in Table 77

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 222-232]

Two subjects that did not continue into the extension study had a >15% drop in PFT parameters and a below normal value at last observation. One 34 year old male subject (106 50086666) in the Exubera group had a decline in TLC from 7.86L to 5.71L, FRC from 4.77L to 2.77L, FVC from 4.61L to 4.33L, and FEV_1 from 3.92L to 3.68L. The subject had no respiratory AEs during the study period and was enrolled in the HRCT substudy. His HRCT was within normal limits at the beginning and end of the study. The other subject (106 50146248) was a 46 year old female in the SC insulin group who had a decline in DLCO from 22.28 ml/min/mmHg to 14.41 ml/min/mmHg. However, the subject's FEV_1 and FVC actually increased from 2.33L to 2.45L and 2.95L to 3.03L, respectively. She reportedly experienced a URI during the treatment period [N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 194-196].
Reviewer's Comment: Both of these cases represent fairly dramatic changes in pulmonary function tests. It is difficult to know what to make of the first subject who lost 2L of TLC during the study without any new changes on HRCT. The Applicant attributed the decline in TLC to an improvement in air trapping and weight gain. This theory would imply significant lung disease at baseline. It is unclear what the improvement in air trapping is attributed to. For the second subject, the decline in DLCO was not accompanied by a decline in FVC.

Chest Radiography
A chest x-ray was taken at the beginning and end of the study in each of the subjects. One subject in the Exubera group had a significant change. Subject 106 50606959 had a nodule, which was noted on the end of study CXR. A CT scan was obtained and interpreted as normal [N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 198].

High Resolution Computed Tomography
An HRCT substudy was conducted at selected study sites. Seventeen Exubera subjects and 22 SC insulin subjects had HRCT scans performed at baseline and end of study. No significant changes were noted in the Exubera group. However, there were 3 subjects in the SC insulin group that had new changes noted:

- One subject had a new right basilar linear atelectasis
- One subject had a dependent posterior subpleural density
- One subject had a possible new scar or atelectasis in the lingula

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 60].

10.4.2.3 Conclusions

Study 217-106 was an open-label, 6-month, parallel group study of Exubera versus SC insulin in 334 males and females with type 1 diabetes mellitus. The results indicate that respiratory adverse events were slightly more common in the Exubera group. Increased cough, dyspnea, epistaxis, and pharyngitis were more common in the Exubera group than in the SC insulin group. A review of the mean change in pulmonary function at 24 weeks shows that both treatment groups demonstrated a slight decrease in FEV_1, FVC, and DLCO. However the decrease tended to be greater in the Exubera group, especially the DLCO. The CXR and HRCT data did not suggest any significant changes associated with Exubera use.

10.4.3 Study 217-107

Efficacy and Safety of Exubera Compared to Subcutaneous Human Insulin in an Intensive Insulin Regimen for Subjects with Type 1 Diabetes Mellitus: A Six-Month, Outpatient, Parallel Group Comparative Trial

10.4.3.1 Protocol

Study 217-107 was a phase 3, open-label, 6-month, parallel group study in 320 males and females with type 1 diabetes mellitus to compare BID SC NPH plus pre-meal Exubera to BID SC NPH plus pre-meal SC regular insulin. Subjects with the following were excluded:

- Clinically significant abnormalities on screening CXR
- Poorly-controlled asthma, clinically significant COPD, or other significant respiratory disease
- Subjects with frankly abnormal PFTs at Week -3, defined as DLCO <75%, TLC >120% or <80%, or FEV_1<70% predicted
- Any smoking within the last 6 months

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 297-300].

A screening visit was followed by a baseline lead-in period (4 weeks) during which subjects underwent pulmonary function testing. At the end of the lead-in-period, subjects were instructed on the proper use of Exubera. Eligible subjects were then randomized to either continuation of their pre-study subcutaneous insulin regimen (NPH BID, pre-meal SC regular insulin) or Exubera therapy (NPH BID, pre-meal Exubera) [N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 300-302].

Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, DLCO, and resting oxygen saturation. PFT testing was performed at baseline (week -3), week 12 (spirometry only) and week 24. PFTs were performed using ATS certified methods. If a subject had a decrease of >15% in any FEV_1, FVC, TLC, FRC, or DLCO in the absence of intercurrent illness, the PFTs were repeated. If the >15% decrease persisted, then further pulmonary evaluation, including pulmonologist consultation, CXR, or HRCT was obtained. CXRs were taken at the beginning and end of the study [N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 315, 322].

An HRCT substudy was included in Studies 217-106, 217-107, and 217-108. Approximately 100 subjects were recruited prior to randomization for the HRCT substudy at participating sites. Baseline HRCTs were obtained prior to randomization. HRCTs were performed without contrast by taking 1 mm cuts starting 2 cm above the carina and continuing inferiorly every 2cms for a total of 10 cuts. Enrollment continued until at least 50 of the subjects were randomized to Exubera. Both the baseline HRCT and 24 week HRCT were forwarded together to a central radiology site for a blinded review. A second original set of films was kept at the investigative site. Abnormalities noted on the baseline HRCT were discussed with a Pfizer clinician prior to randomization. The number and percentage of new abnormalities at the end of treatment was summarized across the 100 subjects in the substudy [N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 326].

Open-Label Extension
Subjects who completed the 24-week study were eligible for the one-year open-label extension. The details of the open-label extension will be described in the review of Study 217-111.

10.4.3.2 Results

The study commenced on May 27, 1999, and was completed on September 26, 2000. Forty centers participated in the study (United States 32, Canada 8). A total of 419 subjects were screened for the study and 328 were randomized, 163 to the Exubera and 165 to the subcutaneous arm. One subject who was randomized to receive Exubera was never treated. Subject disposition is summarized in Table 79. One subject discontinued the study due to a respiratory AE. A 52 year old female subject (107 51027141) in the Exubera group experienced cough, wheezing, SOB, chest tightness, dizziness, pulmonary obstruction, and hyperreactive airway disease. Her symptoms (except occasional dry cough) had resolved 3 weeks later at the time of pulmonary consultation. The pulmonary consultant and Applicant attributed the symptoms to underlying airway hyperreactivity subsequently provoked by exposure to Exubera. FEV_1 and FVC were higher 3 weeks after discontinuation of Exubera than at screening [N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 43, 210].

Table 79 Subject Disposition Study 217-107		
	Exubera	SC Insulin
Randomized (328)	163	165
Completed	154	152
Discontinued Study	9	13
Withdrew consent prior to treatment	1	0
Adverse Event	**1**	**1**
Pulmonary obstruction	**1**	**0**
Breast cancer	0	1
Lab abnormalities (increased AST/ALT)	1	0
Lack of efficacy	0	1
Other (includes protocol violation)	2	2
Subject defaulted (includes lost to F/U)	4	9

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 132-134]

Reviewer's Comment: Because one subject withdrew consent after randomization and before treatment the number of the subjects in the Exubera group will be 162, not 163.

The mean age of the subjects was 29 years and the majority of the subjects were Caucasian as shown in Table 80.

Table 80 Baseline Characteristics Study 217-107			
		Exubera n = 162	SC Insulin n = 165
Gender	Male	85 (52%)	89 (54%)
	Female	77 (48%)	76 (46%)
Age	Mean	29.3	29.7
	Range	12-65	11-65
Race	Caucasian	142 (88%)	152 (92%)
	Black	3 (2%)	2 (1%)
	Asian	5 (3%)	0
	Hispanic	9 (6%)	8 (5%)
	Other	3 (2%)	3 (2%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 86]

Reviewer's Comment: A review of the summary of medical history of the subjects indicates that some subjects reported a history of asthma. For example, asthma (unspecified) was reported in the past in 9 subjects and in the present in 10 subjects [N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 90].

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera group than in the SC insulin group. Increased cough, dyspnea, epistaxis, respiratory disorder, respiratory tract infection, sputum increased, and pharyngitis were more common in the Exubera group than in the SC insulin group. A detailed summary of the respiratory AEs is listed in Table 81. Most of the respiratory AEs were mild to moderate in severity. None of the SAEs were respiratory .

Table 81 Number of Subjects with Respiratory Adverse Events in Study 217-107

	Exubera n = 162	SC Insulin n = 165
Serious adverse events	7 (4.3%)	7 (4.2%)
Any adverse event	162 (100%)	164 (99.4%)
Respiratory	**128 (79%)**	**105 (64%)**
Asthma	2 (1.2%)	1 (0.6%)
Bronchitis	3 (1.9%)	4 (2.4%)
Cough increased	**41 (25.3%)**	**12 (7.3%)**
Dyspnea	**4 (2.5%)**	**1 (0.6%)**
Epistaxis	**4 (2.5%)**	**0**
Hyperventilation	0	1 (0.6%)
Laryngitis	0	1 (0.6%)
Pharyngitis	**39 (24.1%)**	**31 (18.8%)**
Pneumonia	2 (1.2%)	1 (0.6%)
Respiratory disorder	**12 (7.4%)**	**6 (3.6%)**
Respiratory tract infection	**78 (48.1%)**	**66 (40.0%)**
Rhinitis	17 (10.5%)	23 (13.9%)
Sinusitis	10 (6.2%)	15 (9.1%)
Sputum increased	**6 (3.7%)**	**1 (0.6%)**

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 166, 173-174]

Reviewer's Comment: None of the SAEs were respiratory ; therefore, a breakdown of the SAEs was not listed in the above table.

Reviewer's Comment: Hypoglycemia was the most common AE in both treatment groups.

Cough was more common in the Exubera group than in the SC insulin group. Forty-one subjects in the Exubera group reported 51 cough events, while 12 subjects in the SC insulin group reported 12 cough events. In the Exubera group, about half of the cough AEs were reported in the first 4 weeks and the majority of cough AEs were reported in the first 12 weeks. Most of the cough AEs were mild to moderate in severity. One event in the Exubera group was graded as severe. The Applicant determined the mean duration of cough based upon the reported onset to the reported end of each event. The Applicant determined the duration of cough was 4.50 weeks and 1.35 weeks for the Exubera group and SC insulin group, respectively [N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 223-225].

Pulmonary Function Tests

Baseline PFTs were well-matched between the treatment groups. A review of the mean change in pulmonary function at 24 weeks shows that the FEV_1, FVC, and TLC were essentially unchanged in the Exubera group. A greater decrease in DLCO was noted in the Exubera group compared to the SC insulin group. A summary of the mean change in pulmonary function tests is shown in Table 82.

Table 82 Pulmonary Function Tests for Study 217-107 – Summary of Mean Change

	Exubera			Subcutaneous Insulin		
PFT	BL	Week 24 (LOCF)	Change from BL	BL	Week 24 (LOCF)	Change from BL
FEV_1	N=162	N=162	N=162	N=165	N=160	N=160
Mean (L)	3.23	3.27	-0.016	3.38	3.38	0.008
SD	0.78	0.77	0.26	0.78	0.79	0.24
FVC	N=162	N=162	N=162	N=165	N=160	N=160
Mean (L)	4.02	4.04	0.03	4.10	4.10	0.022
SD	1.01	0.95	0.31	1.03	1.01	0.27
DLCO	N=159	N=157	N=157	N=164	N=150	N=149
Mean (ml/min/mmHg)	26.40	25.66	-0.75	27.07	26.80	-0.23
SD	6.89	6.22	3.88	6.89	6.41	3.34
TLC	N=162	N=157	N=157	N=165	N=152	N=152
Mean (L)	5.52	5.57	0.05	5.61	5.71	0.08
SD	1.36	1.27	0.52	1.40	1.31	0.54

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 74]

Reviewer's Comment: The Applicant used the last observation carried forward (LOCF) for missing data, which is displayed in Table 82. The results for the mean change from baseline for FEV_1, FVC, TLC, and DLCO were similar for the Week 24 observed data and the Week 24 (LOCF) data [N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 237-246]

A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group who had a decline in PFT parameters of more than 10%. Table 83 displays the results for the categorical analyses of the PFT data. More subjects had a decline in DLCO than any other PFT parameter. All subjects who had a >15% drop from baseline in FEV_1, FVC, TLC, or DLCO and had a below normal value (<80%) at last observation continued into the extension study (Study 217-111). The results will be discussed further in Study 217-111.

Table 83 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation in Study 217-107

	Exubera			Subcutaneous Insulin		
	-10 to -15%	**-15 to -20%**	**> -20%**	**-10 to -15%**	**-15 to -20%**	**> -20%**
FEV_1	11 (6.8%)	4 (2.5%)	1 (0.6%)	8 (5.0%)	1 (0.6%)	2 (1.3%)
FVC	4 (2.5%)	3 (1.9%)	1 (0.6%)	4 (2.5%)	0	0
DLCO	25 (16.2%)	10 (6.5%)	10 (6.5%)	18 (12.1%)	6 (4.0%)	7 (4.7%)
TLC	7 (4.5%)	3 (1.9%)	2 (1.3%)	5 (3.3%)	0	5 (3.3%)

The n for the categorical analyses of each PFT parameter is the same n as listed in the change from baseline in Table 82
[N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 237-246]

Chest Radiography

A chest x-ray was taken at the beginning and end of the study in each of the subjects. One subject in the Exubera group had a significant change. One subject had a nodular density, which was noted on the end of study CXR and was felt to be a nipple shadow. Five subjects in the SC insulin group had significant changes in CXR from screening (nodular density, not noted on F/U CXR; focal opacity RUL; patch of infiltrate LLL; osteopenic vertebrae; nodular density, probably nipple shadow) [N21868/N_000/2004-

12-27/clinstat/diabetes/type1/107.pdf, pg 75; N21868/N_000/2004-12-27/crt/datasets/107/xray_1v.xpt].

High Resolution Computed Tomography
An HRCT substudy was conducted at selected study sites. Thirteen Exubera subjects and 15 SC insulin subject had HRCT scans performed at baseline and end of study. One subject in the Exubera group had a significant change on the end of study HRCT. The subject had a new lingular linear density, which was interpreted as probable linear atelectasis. One subject in the SC insulin group had an abnormal scan at the end of study. The subject was noted to have increased reticular changes in the right posterior subpleural lung [N21868/N_000/2004-12-27/clinstat/diabetes/type1/107.pdf, pg 75]. *Reviewer's Comment: Two subjects in the HRCT dataset for Study 107 were noted to not have lung windows. For these two subjects, there was no change code for the change from baseline [N21868/N_000/2004-12-27/crt/datasets/108/ctscn_1v.xpt].*

10.4.3.3 Conclusions

Study 217-107 was a phase 3, open-label, 6-month, parallel group study in 328 males and females with type 1 diabetes mellitus to compare BID SC NPH plus pre-meal Exubera to BID SC NPH plus pre-meal SC regular insulin. The results indicate that respiratory adverse events were more common in the Exubera group. Increased cough, dyspnea, epistaxis, respiratory disorder, respiratory tract infection, sputum increased, and pharyngitis were more common in the Exubera group than in the SC insulin group. A review of the mean change in pulmonary function at 24 weeks showed that the FEV_1, FVC, and TLC were essentially unchanged in the Exubera group. A decrease in DLCO was noted in both groups, but a greater decrease in DLCO was noted in the Exubera group compared to the SC insulin group. The CXR and HRCT data did not suggest any significant changes associated with Exubera use.

10.4.4 Study 217-1026

Longitudinal Insulin PK and PD Associated with an Inhaled Insulin (Exubera) Treatment Regimen versus a Subcutaneous Insulin Treatment Regimen: A 24-Week Prospective, Randomized, Open-Label, Parallel Group Comparative Trial in Subjects with Type 1 Diabetes

10.4.4.1 Protocol

Study 217-1026 was a phase 2 and 3, single center, randomized, open-label, 24-week, parallel group study comparing Exubera to SC insulin in 47 males and females with type 1 diabetes mellitus on a stable subcutaneous insulin regimen. Subjects must have had an evaluation within the last three months by a pulmonologist to rule out significant pulmonary disease. Subjects with the following were excluded:

- Subjects unable to properly perform pulmonary function test procedures during the run in period
- History of any active lung disease
- Pulmonology assessment performed within 3 months of screening in which the subjects is found unsuitable for study participation

- Subjects with frankly abnormal PFTs at Week -3, defined as FVC or FEV_1 < 70% predicted, FEV_1/FVC <70%, TLCO > 130% predicted or <70% predicted, DLCO <70%, or DLCO >120% predicted
- Any smoking within the last 6 months

[N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 215-216].

A screening visit was followed by a baseline lead-in period (1 month) during which subjects received NPH BID and SC regular insulin pre-meal. At the Week -3 Visit, subjects underwent pulmonary function testing to determine eligibility. At the Week -2 Visit, subjects underwent PFTs again to determine baseline pulmonary function. At the end of the lead-in-period, subjects were instructed on the proper use of Exubera. Eligible subjects were then randomized to either an NPH BID and subcutaneous insulin regimen or Exubera therapy (pre-meals) and NPH BID for a 24 week dosing period [N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 217-220].

Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: FVC, FEV_1, TLC, and DLCO. PFT testing was performed at baseline (week -3), week -2, week -1, week 11 (spirometry only), and week 23. PFTs were performed using ATS certified methods. If a subject had a decrease of ≥ 15% in any FEV_1, FVC, TLC, or DLCO in the absence of intercurrent illness, the PFTs were repeated. If the ≥ 15% decrease persisted, then further pulmonary evaluation, including pulmonologist consultation, CXR, or HRCT were obtained. For subjects who discontinued study medication prior to study completion, PFTs were performed within 48 hours of discontinuation as well as 6 and 12 weeks after discontinuation of study medication [N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 246].

10.4.4.2 Results

The study commenced on April 9, 2002, and was completed on April 15, 2003. One center in Germany participated in the study. A total of 47 subjects were randomized, 23 to the Exubera and 22 to the subcutaneous arm. One subject randomized to each group never received treatment. More subjects in the SC insulin group were discontinued from the study than in the Exubera group. No subjects discontinued the study due to AEs. Subject disposition is summarized in Table 84 [N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 246].

Table 84 Subject Disposition Study 217-1026

	Exubera	SC Insulin
Randomized (47)	24	23
Randomized but never treated	1	1
Completed	22	18
Discontinued Study	1	4
Subject defaulted (withdrew consent, lost to follow up)	1	4

[N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 94].

The mean age of the subjects was between 35-38 years. The majority of the subjects were Caucasian and male as shown in Table 85.

Table 85 Baseline Characteristics Study 217-1026			
		Exubera n = 23	SC Insulin n = 22
Gender	Male	17 (74%)	12 (55%)
	Female	6 (26%)	10 (45%)
Age	Mean	37.6	35.9
	Range	20-50	22-47
Race	Caucasian	23 (100%)	21 (95%)
	Other	0	1 (5%)

[N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 77]

Respiratory Adverse Events

Respiratory adverse events occurred at a similar frequency in both treatment groups. Cough was more common in the Exubera group and respiratory tract infection was more common in the SC insulin group. A detailed summary of the respiratory AEs is listed in Table 86. All of the respiratory AEs were mild in severity [N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 69].

Table 86 Number of Subjects with Respiratory Adverse Events in Study 217-1026		
	Exubera n = 23	SC Insulin n = 22
Serious adverse events	2	0
Any adverse event	23 (100%)	22 (100%)
Respiratory	**11 (48%)**	**12 (55%)**
Bronchitis	1 (4.3%)	0
Cough increased	**4 (17%)**	**0**
Pharyngitis	**1 (4.3%)**	**3 (13.6%)**
Respiratory tract infection	**7 (30%)**	**11 (50%)**
Sinusitis	2 (8.6%)	0

[N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 121]

Reviewer's Comment: None of the SAEs were respiratory. The SAEs were all hypoglycemia. Hypoglycemia was the most common AE in both treatment groups [N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 267].
Reviewer's Comment: A further analysis of the cough AEs was not performed.

Pulmonary Function Tests

Results for only the FEV_1 and DLCO were reported in the study report. Baseline FEV_1 was slightly lower in the SC insulin group than in the Exubera group. A review of the mean change in pulmonary function at 23 weeks shows that the Exubera group demonstrated a decline in FEV_1 and DLCO whereas the SC insulin group demonstrated an increase in FEV_1 and DLCO. A summary of the mean changes in pulmonary function parameters is shown in Table 87.

Table 87 Pulmonary Function Tests for Study 217-1026 – Summary of Mean Changes

	Exubera			Subcutaneous Insulin		
PFT	BL	Week 23	Change from BL	BL	Week 23	Change from BL
FEV_1	N=23	N=23	N=23	N=22	N=19	N=19
Mean (L)	4.103	4.030	-0.074	3.830	3.814	0.017
SD	0.731	0.763	0.152	0.745	0.737	0.105
DLCO	N=23	N=23	N=23	N=22	N=19	N=19
Mean (ml/min/mmHg)	30.724	30.613	-0.111	29.702	31.233	1.955
SD	5.399	5.089	1.869	6.909	7.868	1.816

[N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 143, 145]

A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group who had a decline of >10% in DLCO and FEV_1 than in the SC insulin group as shown in Table 88.

Table 88 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation in Study 217-1026

	Exubera			Subcutaneous Insulin		
	-10 to -15%	**-15 to -20%**	**> -20%**	**-10 to -15%**	**-15 to -20%**	**> -20%**
FEV_1	6 (26%)	0	0	1 (5.2%)	0	0
DLCO	2 (8.6%)	0	0	0	0	0

The n for the categorical analyses of each PFT parameter is the same n as listed in the change from baseline in Table 87

[N21868/N_000/2004-12-27/hpbio/hupharm/1026.pdf, pg 144, 146]

10.4.4.3 Conclusions

Study 217-1026 was a phase 2 and 3, single center, randomized, open-label, 24 week, parallel group study comparing Exubera to SC insulin in 47 males and females with type 1 diabetes mellitus on a stable subcutaneous insulin regimen. The results indicate that respiratory adverse events were similar between both treatment groups; however, cough was more common in the Exubera group and respiratory tract infection was more common in the SC insulin group.

Results for only the FEV_1 and DLCO were reported in the study report. A review of the mean change in pulmonary function at 23 weeks shows that the Exubera group demonstrated a decline in FEV_1 and DLCO whereas the SC insulin group demonstrated an increase in FEV_1 and DLCO. A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group who had a decline of >10% in DLCO and FEV_1 than in the SC insulin group.

10.4.5 Study 217-1027

A Short-Term, Multicenter, Randomized, Open-Label, Parallel Group Study Assessing the Pulmonary Effects of Chronically Dosed Exubera or Subcutaneous Insulin Therapy

10.4.5.1 Protocol

Study 217-1027 was a phase 3, open-label, 24 week, parallel group study in 226 males and females with type 1 diabetes mellitus to compare an Exubera regimen to a SC insulin regimen. Following a run-in period, subjects underwent a 12 week treatment period. The 12 week comparative treatment phase was followed by a 12 week follow up phase. Subjects must have been on a stable insulin regimen. Subjects with the following were excluded:

- Clinically significant abnormalities on screening CXR
- Unable to perform pulmonary function test procedures
- History of any active lung disease
- Subjects with abnormal PFTs at Week -3, defined as FEV_1/FVC <70%, DLCO <70% or >120%, TLC >130% or <70%, FVC <70% predicted, or FEV_1<70% predicted
- Any smoking within the last 6 months
- Concomitant therapy with systemic or inhaled glucocorticoids, oral or inhaled bronchodilators, and/or leukotriene blockers.

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 582].

A screening visit was followed by a baseline run-in period (3 weeks) during which subjects were treated with SC short acting insulin plus one or two doses of an intermediate/long-acting insulin or a single daily dose at bedtime of insulin glargine. At the end of the run-in period, all subjects must have demonstrated proper use of the inhaler. Eligible subjects were then randomized to either continuation of the subcutaneous insulin regimen (run-in regimen) or Exubera therapy. At the end of the 12 week treatment comparator phase, all subjects who received Exubera resumed the SC insulin regimen used during run-in for the 12 week follow up phase [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 585].

Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: spirometry, lung volumes by gas dilution, and DLCO. PFT testing was performed at screening (Week -3), Week -2, -1, 0, 1, 2, 3, 4, 6, 8, 12, 14, 16, 20, and 24. PFTs were performed pre-dose and 10 and 60 minutes post dose Exubera at Week 0, 4, 8, and 12. Subjects performed the pre-dose PFTs in the fasting condition. The Exubera dose was administered and subjects were given a glass of orange juice. Subjects completed the 10 min post Exubera PFTs. Subjects were then provided a breakfast and performed the 60 minutes post Exubera PFTs. PFTs were performed using ATS standards. If a subject had a decrease of $\geq$ 15% in any FEV_1, FVC, TLC, or DLCO in the absence of intercurrent illness, the PFTs were repeated. If the $\geq$ 15% decrease persisted, then further pulmonary evaluation was obtained. CXRs were taken at the screening and Week 12 [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 596, 613-614].
Reviewer's Comment: PFTs were performed more frequently in this study than other studies. In addition, this study included the collection of PFTs pre and post insulin dosing. Finally, this study design also looks at the effect on pulmonary function of discontinuing treatment with Exubera; however, the treatment period was only 12 weeks.

A cough questionnaire was completed at baseline by all subjects. The cough questionnaire was administered again if cough was reported as an AE and not explained by a concomitant condition such as an URI. The cough questionnaire consisted of 6 questions addressing the following:

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

The answers ranged from 0 to 4 for each question. Zero meaning none/never and 4 meaning almost constant/severe [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 615].
Reviewer's Comment: This is the first of several studies to utilize the cough questionnaire to further assess the cough AEs.

The primary endpoints of Study 1027 were the treatment group differences in the percent of subjects experiencing declines outside the variability established during the run-in period for FEV_1 and DLCO. The baseline values of FEV_1 and DLCO were determined for the mean of eligible values collected during the run-in period. A decline was defined as any value of FEV_1 or DLCO observed during the comparative portion of the study that decreases from the run-in mean value by $\geq$ half of the run-in intra-subject standard deviation. The Applicant also administered the Baseline Dyspnea Index at baseline. The Transitional Dyspnea Index was administered at Week 2, 6, 12, and 24 [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 608, 613, 616].
Reviewer's Comment: Although the Applicant declared the primary endpoints as above, the change in pulmonary function over time were reviewed.

10.4.5.2 Results

The study commenced on April 24, 2002, and was completed on October 13, 2003. Thirty-four centers participated in the study (United States 21). A total of 353 subjects were screened for the study and 226 were randomized, 110 to the Exubera and 116 to the subcutaneous arm. Subject disposition is summarized in Table 89. Three subjects discontinued the comparative phase of the study due to a respiratory AE. None of the subjects discontinued the follow up phase of the study due to respiratory AEs [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 53, 170-175].

Table 89 Subject Disposition Study 217-1027		
	Exubera	SC Insulin
Randomized (226)	110	116
Completed 12 Weeks	94	102
Discontinued Study prior to completion of 12 weeks	16	14
Subject died	1	0
Adverse Event	**6**	**1**
Cough/laryngitis/pharyngitis	**1**	**0**
Reactive airways disease/URI	**1**	**0**
Cough (non-productive)	**1**	**0**
Lack of efficacy	1	1
Other (includes protocol violation)	2	5
Subject defaulted (includes lost to F/U)	6	7
Completed 12 week follow up phase	92	97
Discontinued during follow up phase	2	5
Adverse Event	0	1
Other (includes protocol violation)	2	0
Subject defaulted (includes lost to F/U)	0	4
Source: N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 53, 170-175		

Reviewer's Comment: The one death was due to myocardial infarction.

The mean age of the subjects was 40 years and the majority of the subjects were Caucasian and male as shown in Table 90.

Table 90 Baseline Characteristics for Treatment Phase Study 217-1027			
		Exubera n = 110	SC Insulin n = 116
Gender	Male	61 (55%)	63 (54%)
	Female	49 (45%)	53 (46%)
Age	Mean	39.7	40.6
	Range	20-65	23-63
Race	Caucasian	99 (90%)	104 (90%)
	Black	4 (4%)	3 (2.6%)
	Asian	0	3 (2.6%)
	Hispanic	5 (5%)	4 (3.4%)
	Other	2 (2%)	2 (1.7%)
Source: N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 117			

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera group than in the SC insulin group. Increased cough, dyspnea, epistaxis, pharyngitis, respiratory disorder, and rhinitis were more common in the Exubera group than in the SC insulin group. A detailed summary of the respiratory AEs is listed in Table 91. All of the respiratory AEs were mild to moderate in severity except one cough AE in the Exubera group, which was graded as severe. None of the SAEs were respiratory .

Table 91 Number of Subjects with Respiratory Adverse Events in the Comparative Phase of Study 217-1027 (1st 12 weeks)

	Exubera n = 110	SC Insulin n = 116
Serious adverse events	2 (1.8%)	5 (4.3%)
Any adverse event	107 (97%)	110 (95%)
Respiratory	**71 (65%)**	**51 (44%)**
Asthma	1 (0.9%)	1 (0.9%)
Bronchitis	3 (2.7%)	2 (1.7%)
Cough increased	**34 (30.9%)**	**9 (7.8%)**
Dyspnea	**2 (1.8%)**	**0**
Epistaxis	0	1 (0.9%)
Hyperventilation	1 (0.9%)	0
Hypoventilation	1 (0.9%)	0
Laryngitis	1 (0.9%)	1 (0.9%)
Pharyngitis	**18 (16.4%)**	**12 (10.3%)**
Respiratory disorder	**4 (3.6%)**	**2 (1.7%)**
Respiratory tract infection	29 (26.4%)	28 (24%)
Rhinitis	**15 (13.6%)**	**9 (7.8%)**
Sinusitis	4 (3.6%)	3 (2.6%)
Sputum increased	4 (3.6%)	3 (2.6%)

Source : N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 231, 233, 239

Reviewer's Comment: Fifteen investigators terms were coded to the COSTART preferred term "cough increased."
Reviewer's Comment: Hypoglycemia was the most common AE in both treatment groups.

For the follow up phase, the respiratory AEs occurred at a similar frequency between treatment groups, as shown in Table 92. Cough increased was reported at a similar frequency in both treatment groups. Respiratory tract infection was the most common respiratory AE. Sinusitis was more common in the Exubera group than in the SC insulin group.

Table 92 Number of Subjects with Respiratory Adverse Events in the Follow Up Phase of Study 217-1027 (Week 12-24)

	Exubera n = 94	SC Insulin n = 102
Respiratory	36 (38.3%)	36 (35.3%)
Asthma	0	1 (1%)
Bronchitis	2 (2.1%)	2 (2%)
Cough increased	**8 (8.5%)**	**7 (6.9%)**
Dyspnea	1 (1.1%)	1 (1%)
Epistaxis	1 (1.1%)	0
Laryngitis	1 (1.1%)	1 (1%)
Pharyngitis	3 (3.2%)	6 (5.9%)
Respiratory disorder	1 (1.1%)	3 (2.9%)
Respiratory tract infection	17 (18%)	22 (22%)
Rhinitis	4 (4.3%)	6 (5.9%)
Sinusitis	**8 (8.5%)**	**1 (1%)**
Sputum increased	1 (1.1%)	1 (1%)

Source: N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 247

Reviewer's Comment: The follow up phase data suggests that the respiratory AEs in both groups decreased following discontinuation of Exubera, which suggests that many of the respiratory AEs were treatment related.

Cough was more common in the Exubera group than in the SC insulin group. Two subjects in the Exubera group discontinued from the study due to cough AEs. One subject (1004 154) discontinued treatment on Day 84 due to severe cough, which eventually resolved. Another subject (1012 503) discontinued Exubera on Day 46 due to moderate nonproductive cough, which eventually resolved after discontinuation. Thirty-four subjects in the Exubera group reported 39 cough events, while 10 subjects in the SC insulin group reported 10 cough events. In the Exubera group, half of the cough AEs were reported in the first 3 weeks, while in the SC insulin group, the cough events occurred from week 3-12 [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 329, 331, 333].

The majority of the cough AEs were mild to moderate in severity. One event in the Exubera group was graded as severe. The Applicant determined the mean duration of cough based upon the reported onset to the reported end of each event. The Applicant determined the duration of cough was 3.68 weeks and 1.74 weeks for the Exubera group and SC insulin group, respectively. Five of the cough AEs in the inhaled group were of duration >8weeks, whereas none of the cough AEs in the SC insulin group were >8 weeks in duration [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 329, 331, 333].

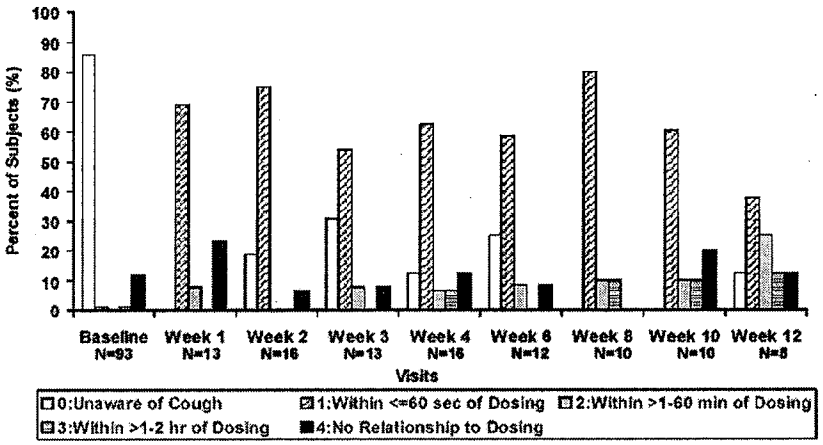
This study included a cough questionnaire assessing 6 domains of cough on a quantitative scale. A cough questionnaire was completed for about ¾ of the cough AEs (29 out of 39 events) in the Exubera group and half the cough AEs (5 out of 10 events) in the SC insulin group. The following is a synopsis of the results of the cough questionnaire for the treatment phase:

- Cough frequency at night

- In Exubera group, most reports none/rare
- Cough frequency throughout the day
  - In Exubera group, most reports rare (cough only after Exubera or only now and then)/occasional (less than hourly), few reports of frequent (one or more times an hour), 1 report of almost constant
- Cough severity throughout the day
  - In Exubera group, mostly mild (does not interfere with usual activity), few moderate (must stop activity during coughing episode), no marked or severe
- Cough timing related to short-acting insulin dosing
  - In Exubera group, most within 60 seconds of dosing as shown in Figure 53.

Figure 53

Q4. Cough Timing Related to Short-acting Insulin Dosing, Inhaled Insulin Subjects



Source: Table 6.9.4.1

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 86]

- Cough severity related to insulin dosing
  - In Exubera group, most mild or unaware of coughing, few moderate severity (must stop activity during coughing), no marked or severe
- Sputum production
  - In Exubera group, most never or rarely, few reports of occasionally, 1 report of frequently, five reports of almost constantly

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 85-87].

Reviewer's Comment: The cough questionnaire data suggests that cough in the Exubera group was rare at night and rare or occasionally during the day. The daytime cough was predominantly mild in severity, non-productive, and usually occurred within 60 seconds of dosing of Exubera.

Reviewer's Comment: Several issues are worth noting about the Cough Questionnaire. First of all, the Cough Questionnaire was not administered to all subjects with cough AEs, but was administered to subjects with cough AEs not attributable to another condition. Allowing the investigator to determine if the cough was attributable to another condition is not ideal in this open label study. Ideally, the Applicant would have administered the cough questionnaire to every subject with report of a cough AE. Second, the cough questionnaire is confusing for some of the questions in which a grade 0 means no cough or unaware of cough. So a subject can report a cough AE, but respond no cough or unaware of cough for certain questions. Finally, the question of cough severity related to insulin dosing depends upon if the subject noted a relationship of cough to insulin dosing. For details of the Cough Questionnaire, refer to the Appendices, Section 10.11.

The Applicant reported the results for the BDI/TDI. Baseline dyspnea indices were similar between treatment groups. The mean TDI total score decreased slightly in the Exubera group, while the mean TDI total score was essentially unchanged in the SC insulin group [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 89].

Pulmonary Function Tests

For the PFT analyses, the Applicant designated 2 populations: the primary analysis population and the full analysis population. The primary analysis population was defined as randomized subjects who had at least 2 FEV_1 measurements between screening and randomization, had at least 2 post-baseline FEV_1 measurements, and received study drug for at least 50% of the required comparative treatment duration. The full analysis population was defined as randomized subjects who had a baseline value between screening and randomization and had at least 1 post-baseline measurement [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 59].
Reviewer's Comment: The results for the primary analysis population are presented in the following tables; however, when the data was pooled for the ISS, all subjects with a baseline PFT measurement were utilized.

Baseline FEV_1 and DLCO were well-matched between the treatment groups. A review of the mean change in pulmonary function at 12 weeks shows that the Exubera group had a slightly larger decline in FEV_1 than the SC insulin group. During the 12 week follow up phase, the SC insulin group demonstrated a small decline in mean FEV_1 from Week 12 to Week 24, whereas the Exubera group demonstrated an improvement in FEV_1 from Week 12 to Week 24. Thus, at Week 24, the decline in FEV_1 was similar between treatment groups. For DLCO, at Week 12, the Exubera group demonstrated a greater decline than the SC insulin group. Both groups demonstrated an improvement in DLCO between Week12 and Week 24. At Week 24, the SC insulin group had a greater decline in DLCO than the Exubera group. A summary of the mean change in pulmonary function tests is shown in Table 93.

Table 93 Pulmonary Function Tests Pre-Insulin Dose for Study 217-1027
Summary of Mean Change
Primary analysis population

	Exubera				Subcutaneous Insulin			
PFT	BL	Week 6	Week 12	Week 24 W/O	BL	Week 6	Week 12	Week 24 W/O
FEV_1	N=99	N=89	N=96	N=85	N=103	N=100	N=97	N=93
Mean (L)	3.370	3.271	3.309	3.329	3.299	3.246	3.252	3.251
Δ from BL, L (%)		-0.061, (-1.871)	-0.065, (-1.903)	-0.057, (-1.827)		-0.066, (-1.864)	-0.056, (-1.472)	-0.062 (-1.836)
FVC	N=99	N=89	N=96	N=85	N=103	N=100	N=97	N=93
Mean (L)	4.242	4.140	4.165	4.178	4.172	4.119	4.116	4.101
Δ from BL, L (%)		-0.055 (-1.309)	-0.078 (-1.824)	-0.076 (-1.882)		-0.071 (-1.628)	-0.073 (-1.689)	-0.092 (-2.208)
TLC	N=99	N=89	N=95	N=84	N=103	N=99	N=96	N=92
Mean (L)	5.834	5.728	5.821	5.896	5.754	5.750	5.724	5.752
Δ from BL, L (%)		-0.036 (-0.554)	0 (0.044)	0.041 (0.863)		-0.035 (-0.581)	-0.041 (-0.562)	-0.040 (-0.589)
DLCO	N=99	N=90	N=95	N=85	N=103	N=100	N=97	N=93
Mean(ml/min/mmHg)	27.218	26.104	25.775	26.660	26.917	26.547	26.203	26.513
Δ from BL		-1.147 (-3.926)	-1.359 (-4.944)	-0.426 (-1.781)		-0.450 (-1.524)	-0.740 (-2.564)	-0.585 (-1.948)

Source : N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 370, 404

The above table displays the pre-dose PFTs. The Applicant also measured the 10 minute and 60 minute post-insulin dose PFTs. For the 10 minute post dose FEV_1 in the Exubera group there was a decrease at Week 12 of 2.0% compared to a decrease of 1.4% in the SC insulin group. For the 60 minute post-insulin dose FEV_1 in the Exubera group there was a decrease in Week 12 percent change FEV_1 60 minutes post dose of 1.53% compared to a decrease of 0.69% in the SC insulin group [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 389, 396].

Reviewer's Comments: The Applicant also performed a 'responder' analysis and 'responsiveness' analysis. Responders were defined as subjects with a >50% decline from baseline intrasubject variation. For FEV_1, in general, the Exubera group had a higher number of responders during the comparative phase. During the follow-up phase, for FEV_1, the SC insulin group had a higher number of responders. Responsiveness was defined as the difference between the 10 or 60 minutes post-dose FEV_1 and the pre-dose FEV_1. In general, the responsiveness declined in the Exubera group and remained stable in the SC insulin group during the treatment phase.

A categorical analysis of the PFT data suggests that there were a similar number of subjects who demonstrated a decrease in FEV_1 of >10% at Week 12. By Week 24, more subjects in the SC insulin group demonstrated a decline in FEV_1 >10%. For DLCO at Week 12, more subjects in the Exubera group demonstrated a decrease in DLCO of >10%. By Week 24, the number of subjects with a decline in DLCO >10% was similar between treatment groups. Table 94 displays the results for the categorical analyses of the PFT data.

Table 94 Categorical Analyses of Percent Change in PFTs from Pre-Dose Baseline to Pre-Dose Week 12 in Study 217-1027 Primary Analysis Set

	Exubera			Subcutaneous Insulin		
	-10 to -15%	-15 to -20%	> -20%	-10 to -15%	-15 to -20%	> -20%
FEV_1 – Wk 12	4 (4.2%)	1 (1.0%)	0	3 (3.1%)	1 (1%)	0
FEV_1 – Wk 24	2 (2.4%)	0	0	5 (5.4%)	1 (1.1%)	0
DLCO – Wk 12	26 (27.4%)	6 (6.3%)	0	13 (13.4%)	1 (1.0%)	0
DLCO – Wk 24	11 (12.9%)	2 (2.4%)	0	9 (9.7%)	3 (3.2%)	2 (2.2%)

Source: N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 376-377, 410-411

Narratives were provided for 7 subjects (6 Exubera and 1 SC insulin) who had >15% decline from baseline into the abnormal range at last observation. The majority of subjects in the narratives experienced the >15% decline in DLCO. The following is a brief synopsis of the narratives [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 300-322].

- Exubera
  - 25 yo F demonstrated decrease in DLCO from 24.23 ml/min/mmHg at baseline to 20.51 ml/min/mmHg at day 85 (-15%); DLCO increased to 21.01ml/min/mmHg after discontinuation of Exubera
  - 27 yo F demonstrated decrease in DLCO from 19.96 ml/min/mmHg at baseline to 14.87 ml/min/mmHg at day 29 (-25%); DLCO recovered slightly to 16.62ml/min/mmHg after discontinuation of Exubera; subject had reported URI, dry throat for which study drug was stopped temporarily; Exubera was resumed and severe bronchospasm was noted; subject was permanently discontinued from the study; pulmonary consult revealed a history of exercise-induced asthma
  - 51 yo M demonstrated decrease in DLCO from 25.95 ml/min/mmHg at baseline to 22.03 ml/min/mmHg at day 83 (-15%); DLCO recovered to approximately baseline 25.31ml/min/mmHg after discontinuation of Exubera; subject reported a URI on Day 79
  - 20 yo M demonstrated decrease in DLCO from 31.67 ml/min/mmHg at baseline to 26.48 ml/min/mmHg at day 86 (-16%); DLCO recovered to -8% to -17% after discontinuation of Exubera
  - 41yo F demonstrated decrease in TLC from 4.09L at baseline to 3.39 L at Day 85 (-17%); other pulmonary function parameters declined – DLCO decreased 13%, FEV_1 4.6%, FVC 5.6%; TLC improved to -4.8% on Day 120, but was -13% on Day 147; subject reported URI on Day 66
  - 48 yo F demonstrated decrease in DLCO from 19.19 ml/min/mmHg at baseline to 15.66 ml/min/mmHg at day 84 (-18%); DLCO recovered to baseline after discontinuing Exubera (15 days after discontinuation), but was decreased 8.7% 29 days after discontinuation; subject reported cough after insulin administration from Day 8 to Day 36 and cough due to influenza reported on Day 82
- SC insulin

- 27 yo F with h/o asthma demonstrated decrease in FEV_1 from 3.10L at baseline to 2.62L (-15%) on Day 88; no consistent significant improvement in FEV_1 during follow up phase; subject reported sore throat and viral infection Day 53, Day 95, Day 98

Chest Radiography
A chest x-ray was taken at the beginning and end of the comparative phase of the study. According to the Applicant, one subject in each treatment group had a significant change from baseline [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 105-106].

10.4.5.3 Conclusions

Study 217-1027 was a phase 3, open-label, 24 week, parallel group study in 226 males and females with type 1 diabetes mellitus to compare an Exubera regimen to a SC insulin regimen. Following a run-in period, subjects underwent a 12 week treatment period. The 12 week comparative treatment phase was followed by a 12 week follow up phase.

During the comparative phase, respiratory adverse events were more common in the Exubera group than in the SC insulin group. Increased cough, dyspnea, epistaxis, pharyngitis, respiratory disorder, and rhinitis were more common in the Exubera group than in the SC insulin group. For the follow up phase, the respiratory AEs occurred at a similar frequency between treatment groups. Two subjects in the Exubera group discontinued from the study due to cough AEs. The majority of the cough AEs were mild to moderate in severity. One cough event in the Exubera group was graded as severe. Further data was obtained regarding the cough AEs through the use of a cough questionnaire. The cough questionnaire data suggested that cough in the Exubera group was rare at night and rare or occasionally during the day. The cough was predominantly mild in severity, non-productive, and usually occurred within 60 seconds of dosing of Exubera.

A review of the mean change in pulmonary function at 12 weeks shows that the Exubera group had a larger decline in FEV_1 than the SC insulin group. After the 12 weeks recovery (Week 24), the SC insulin group continued to decline, whereas the Exubera group demonstrated an increase; thus, the decline in FEV_1 at Week 24 was similar between treatment groups. For DLCO, at Week 12, the Exubera group demonstrated a greater decrease than the SC insulin group. Both groups demonstrated an improvement in DLCO at Week 24. The SC insulin group had a greater decline at Week 24 than the Exubera group. The Exubera group also demonstrated a larger decline in post 10min and post 60min FEV_1 compared to baseline than in the SC insulin group.

10.5 Review of Individual Study Reports – Ongoing Studies in Type 1 Diabetes

10.5.1 Study 217-1022 (Ongoing)

Efficacy and Safety of Exubera Compared with Subcutaneous Human Insulin Therapy in Adult Subjects with Type I Diabetes Mellitus: A Two-Year, Outpatient, Open-Label, Parallel Group Comparative Trial

10.5.1.1 Protocol

Study 217-1022 is an ongoing phase 3, open-label, 2 year, parallel group study in 600 males and females with type 1 diabetes mellitus to compare an Exubera regimen to a SC insulin regimen. Following a 4 –week run-in period, subjects undergo a 2 year treatment period. Subjects must have been on a stable insulin regimen for 2 months prior to screening. Subjects with the following were excluded:

- Clinically significant abnormalities on screening pulmonary consultation

Reviewer's Comment: A pulmonary consultation is specified instead of a screening CXR as some countries (e.g. Germany) are sensitive about repeated radiation exposure. The PI in conjunction with the pulmonary consultant can determine if a CXR is necessary.

- History of poorly controlled asthma, significant COPD, or other significant respiratory diseases
- Subjects with abnormal PFTs at Week -3, defined as DLCO <70% or >120%, TLC >130% or <70%, FVC <70% predicted, or FEV_1<70% predicted
- Any smoking within the last 6 months
- Concomitant therapy with systemic glucocorticoids

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/1022.pdf, pg 493].

A screening visit (ECG, pulmonary consultation, history and physical, laboratories) is followed by a baseline run-in period (4 weeks) during which subjects are treated with SC short acting insulin plus one or two doses of an intermediate/long-acting insulin or a single daily dose at bedtime of insulin glargine. At the end of the run-in period, all subjects must demonstrate proper use of the inhaler. Eligible subjects are then randomized to either continuation of the subcutaneous insulin regimen (run-in regimen) or Exubera therapy. At the end of the 2 year treatment phase, all subjects who received Exubera resume the SC insulin regimen used during run-in [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1022.pdf, pg 494].

Safety monitoring includes AEs, laboratories, pulmonary consultation, and pulmonary function testing. PFTs include: spirometry, lung volumes by gas dilution, and DLCO. PFT testing is performed at screening (Week -3), Week -2, -1, 12 weeks and Months 6, 9, 12, 15, 18, 21, and 24 or end of study. In addition, PFTs are conducted Months 1, 3, and 6 post-study completion or discontinuation. Subjects perform the PFTs in a fasting condition in the morning prior to AM insulin. If a subject had a decrease of ≥15% in any FEV_1, FVC, TLC, or DLCO in the absence of intercurrent illness, the PFTs are repeated. If the ≥15% decrease persists, then further pulmonary evaluation is obtained. A

pulmonary consultation is performed at Week -4, Month 12 and Month 24 or end of study [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1022.pdf, pg 498, 521-522].

A cough questionnaire is completed at baseline (Week 0) and at other visits if cough is reported as an AE and not explained by a concomitant condition such as an URI. The cough questionnaire consists of 6 questions addressing the following:

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

The answers range from 0 to 4 for each question. Zero meaning none/never and 4 meaning almost constant/severe [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1022.pdf, pg 523].

The primary endpoints are the annual rate of change for the PFT parameters FEV_1 and DLCO. Both parameters are measured at Weeks -3, -2, -1, 12, and Months 6, 9, 12, 15, 18, 21, 24, or End of Study, and at Months 1, 3, and 6 post-study completion or discontinuation. The baseline value is the mean of the Week -2 and Week -1 values [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1022.pdf, pg 506].

The primary analysis will be performed on the primary analysis set and the completers group. The primary analysis set is defined as those subjects receiving at least one dose of treatment, while having a baseline and at least two post-baseline PFT measurements. The primary analysis set will be analyzed according to the actual treatment received. The completers group will be a subset of the primary analysis set, where subjects who have 12-month and 24-month data will respectively fall into 12-month and 24-month cohorts. An interim analysis will be performed to assess safety when approximately 50-75% of the subjects have their one year data [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1022.pdf, pg 514-515].

The protocol specifies administration of the Baseline Dyspnea Index at baseline (Week -1). The Transitional Dyspnea Index is administered at Weeks 4 and 12 as well as Months 6, 12, 18, 24 or end of study. In addition, the TDI is administered at Months 1, 3, and 6 post-study completion or discontinuation [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1022.pdf, pg 498].

10.5.1.2 Results

The following discussion of the results of Study 217-1022 is based upon an interim study report submitted by the Applicant with the original NDA on December 27, 2004, and a full two-year interim study report submitted on July 19, 2005. The full two-year interim study report includes safety data results up to and including April 6, 2005 [N21868/N_000/2005-07-19/clinstat/a2171022_2y_int.pdf, pg 29].

Study 217-1022 commenced on May 9, 2002, and is currently ongoing. A total of 64 centers are participating in the study (US, Argentina, Brazil, Canada, Mexico, and Venezuela). A total of 874 subjects were screened and 582 were randomized, 291 to Exubera and 291 to subcutaneous insulin. One subject from each group was randomized but never received treatment.

More subjects have discontinued due to AEs in the Exubera group. Of the subjects who discontinued due to AEs in the Exubera group, the majority of the subjects discontinued due to respiratory AEs. The most common reasons for discontinuation due to respiratory AEs were cough and dyspnea/SOB. More subjects in the Exubera group had temporary discontinuations due to AEs. About half of the temporary discontinuations in the Exubera group were due to respiratory AEs. Respiratory AEs leading to discontinuation varied and included: cough, sore throat/pharyngitis, URI, and bronchitis. Subject disposition is summarized in Table 95 [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 166-185].

Table 95 Subject Disposition for Ongoing Study 217-1022
Two Year Interim Study Report

	Exubera	SC Insulin
Randomized (582)	291	291
Randomized but never treated	1	1
Discontinued	67	58
Subject died	2	0
Adverse Event	**13**	**4**
Sinusitis, cough	**1**	**0**
Cough	**3**	**0**
Shortness of breath	**1**	**0**
Cough, dyspnea, decreased DLCO	**1**	**0**
Cough, SOB	**1**	**0**
Bronchial spasm, cough,	**1**	**0**
Cough, sore throat	**1**	**0**
Laboratory abnormality	2	0
Lack of efficacy	9	0
Other (includes protocol violation)	17	14
Subject defaulted (includes lost to F/U)	24	40

N21868/N_000/2005-07-19/clinstat/a2171022_2y_int.pdf, pg 166-172

Reviewer's Comment: There were 2 deaths in the Exubera group. One death was due to a myocardial infarction. One death the cause is unknown (58 yo male found dead at home). In addition, there were two additional deaths discussed in the interim study report, which are not included in the above table. One death (myocardial infarction) occurred in a subject three weeks after discontinuation of Exubera. The fourth case was the death of an infant (pre-term) after birth to a mother who had received Exubera during the first few weeks of the pregnancy. Exubera was stopped ~June 29, 2003, and delivered the baby on [redacted] The neonate was diagnosed with cardiomegaly and macrosomia. The baby developed CHF and cardiogenic shock and died on [redacted] [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 77, 322, 325].

Reviewer's Comment: Of the 580 subjects who were treated, 217 Exubera subjects and 224 SC insulin subjects completed the first 24 months of the study.

The Applicant's pulmonary narratives provided additional information on subjects who discontinued due to respiratory AEs. The following are brief summaries of the narratives provided for subjects discontinued for respiratory AEs in the Exubera group. There were no subjects who discontinued due to respiratory AEs in the comparator group [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 389-451]:

- 1005241 – 42 yo F developed mild sputum increased on Day 2, which persisted throughout dosing. She developed mild sinusitis on Day 26 and discontinued from the study. Both AEs were resolved 2 weeks after discontinuation. PFTs were normal, according to the Applicant.
- 1009487 – 34 yo M experienced mild dry cough attributed to allergy on treatment day 332 and was discontinued from the study.
- 1017949 – 28 yo M developed cough on day 92 of treatment and discontinued after 251 days of treatment due to cough and decreased DLCO; DLCO declined 15% from baseline; CXR unchanged
- 10251425 – 54 yo F discontinued due to dyspnea after 14 days of dosing. Dyspnea attributed to anxiety. PFTs remained normal.
- 10321841 – 59 yo M experienced several episodes of cough during 538 days of treatment with Exubera. Episodes resolved without treatment. Last episode noted on treatment day 468 and continued until subject permanently discontinued on treatment day 538.
- 10472728 – 31 yo M who discontinued after 88 days of dosing due to cough, dyspnea, and decreased DLCO. Cough reported on Day 2 and continued through the end of study. Dyspnea occurred on Day 28 and continued through the end of study. He also developed nasal congestion. DLCO decreased from 32.64 at baseline to 29.69ml/min/mmHg at the end of Exubera dosing (9% decrease). After discontinuation, cough, and dyspnea resolved within 2-4 weeks. DLCO trended back towards baseline in follow up PFTs. Nasal congestion continued.
- 50743085 – 58 yo F discontinued on Day 246 due to shortness of breath and cough. Subject reported SOB on day 141, which continued through day 225. This subject reportedly had a h/o COPD but no smoking history. Baseline PFTs with FEV_1/FVC of 61%. PFTs and CXR reportedly without change from baseline. Cough and dyspnea resolved after discontinuation.
- 50983260 – 26 yo F with history of asthma discontinued after 493 days of treatment due to cough AE. On day 481, subjects experienced moderate cough and bronchial spasm, which continued until discontinuation on day 494. FEV_1 and FVC declined around the time of cough/bronchial spasm (treatment day 496), but returned to baseline by treatment day 506.
- 51563797 - 34 yo F discontinued on Day 269 due to cough and sore throat. A mild cough developed on Day 57 and led to discontinuation. The sore throat developed on Day 249 and led to discontinuation. PFTs were reportedly normal.

The mean age of the subjects was 36-37 years and the majority of the subjects were Caucasian and male as shown in Table 96.

Table 96 Baseline Characteristics for Ongoing Study 217-1022 Interim Study Report			
		Exubera n = 290	SC Insulin n = 290
Gender	Male	169 (58%)	161 (56%)
	Female	121 (42%)	129 (44%)
Age	Mean	37.6	36.5
	Range	18-63	18-64
Race	Caucasian	254 (88%)	261 (90%)
	Black	11 (4%)	5 (2%)
	Asian	1 (<1%)	3 (1%)
	Hispanic	19 (6.5%)	18 (6%)
	Other	5 (1.7%)	3 (1%)
N21868/N_000/2005-07-19/clinstat/a2171022_2y_int.pdf, pg 94			

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera group than in the SC insulin group. Increased cough, dyspnea, epistaxis, laryngitis, respiratory disorder, rhinitis, sinusitis and sputum increased were more common in the Exubera group than in the SC insulin group. A detailed summary of the respiratory AEs is listed in Table 97. Most of the respiratory AEs were mild to moderate in severity except the following: bronchitis AEs (2 SC), pharyngitis (1 INH, 1 SC), pleural disorder (1 INH – pleurisy attributed to viral illness), respiratory tract infection (1 INH), and sinusitis (1 SC) [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 232-233].

Table 97 Number of Subjects with Respiratory Adverse Events (All Causality) in the Ongoing Study 217-1022
Interim Report

	Exubera n = 290	SC Insulin n = 290
Serious adverse events	31 (10.7%)	34 (11.7%)
Any adverse event	290 (100%)	289 (99.7%)
Respiratory	**248 (86%)**	**217 (75%)**
Asthma	5 (1.7%)	5 (1.7%)
Bronchiolitis	1 (0.3%)	0
Bronchitis	11 (3.8%)	19 (6.6%)
Cough increased	**109 (38%)**	**39 (13%)**
Dyspnea	**22 (7.6%)**	**4 (1.4%)**
Edema pharynx	0	2 (0.7%)
Epistaxis	**4 (1.4%)**	**1 (0.3%)**
Laryngitis	**4 (1.4%)**	**1 (0.3%)**
Lung disorder	1 (0.3%)	0
Lung edema	0	1 (0.3%)
Nasal polyp	1 (0.3%)	1 (0.3%)
Pharyngitis	56 (19%)	59 (20%)
Pleural disorder	1 (0.3%)	0
Pneumonia	4 (1.4%)	5 (1.7%)
Respiratory disorder	**29 (10%)**	**15 (5.2%)**
Respiratory distress syndrome	0	1 (0.3%)
Respiratory tract infection	158 (55%)	159 (55%)
Rhinitis	**56 (19%)**	**43 (15%)**
Sinusitis	**45 (16%)**	**31 (11%)**
Sputum increased	**14 (4.8%)**	**2 (0.7%)**
Voice alteration	1 (0.3%)	1 (0.3%)
Yawn	1 (0.3%)	1 (0.3%)

N21868/N_000/2005-07-19/clinstat/a2171022_2y_int.pdf, pg 232-233

Reviewer's Comment: There was one SAE which was respiratory in the SC insulin group - a 49 year old male with nephrolithiasis and pneumonitis. One case of mycobacterium avium complex was noted in a 50 year old male in the Exubera group [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 275-316].

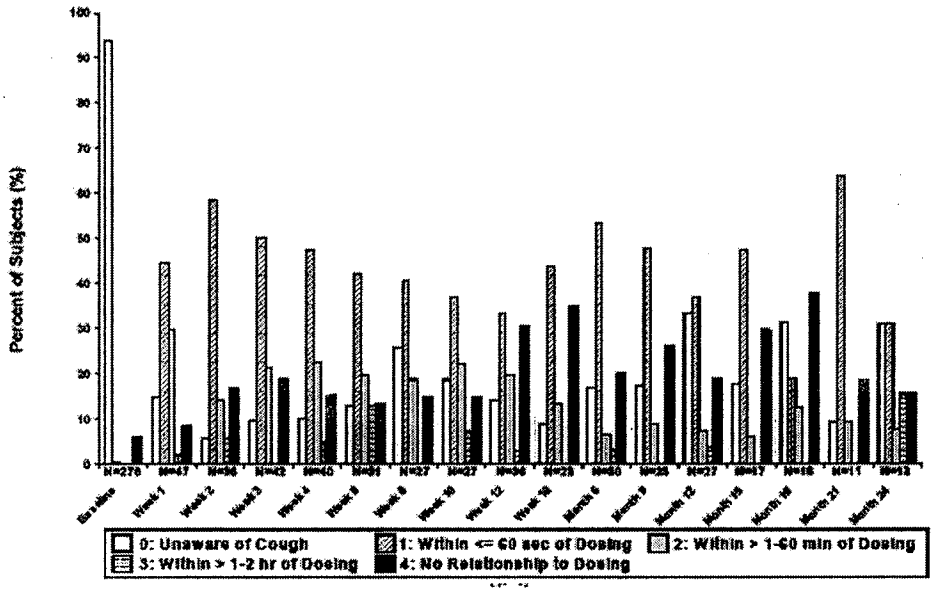
Cough was more common in the Exubera group than in the SC insulin group. Twenty-three investigator terms were coded to the preferred term cough increased. Eight subjects in the Exubera group discontinued from the study with cough as one of the reasons for discontinuation. No SC insulin subjects discontinued due to cough. The incidence, prevalence, and crude event rate for cough were greater in the Exubera group than in the SC insulin group. One hundred nine subjects in the Exubera group reported 168 cough events, while 38 subjects in the SC insulin group reported 46 cough events. In the Exubera group and SC insulin group, over half of the cough events were reported in the first 3 months [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 69, 478-479].
Reviewer's Comment: The Applicant's study report states that 7 subjects were discontinued for cough in the Exubera group. However the Applicant does not include subject 1005241 who discontinued due to sinusitis and productive cough. The number of discontinuations due to cough AEs includes subject 1005241; thus, the number of subjects who discontinued secondary to cough AE listed above is eight.

All of the cough events were mild to moderate in severity. None of the cough events were graded as severe. The Applicant determined the mean duration of cough based on the reported onset to the reported end of each event. The Applicant determined the mean duration of cough was 7.84 weeks and 6.31 weeks for the Exubera group and SC insulin group, respectively. Approximately 19% of subjects reported cough duration of >3 months [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 478-480].

This study included a cough questionnaire assessing 6 domains of cough on a quantitative scale. A cough questionnaire was completed at baseline and at each clinic visit if the subject reported a cough AE, which was not attributed to another cause. The following is a synopsis of the results of the cough questionnaire [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 481-487]:

- Cough frequency at night
  - In Exubera group, most reports none/rare; some occasional; few frequent
- Cough frequency throughout the day
  - In Exubera group, most reports rare (cough only after Exubera or only now and then)/occasional (less than hourly), some reports of frequent (one or more times an hour), 3 reports of almost constant
- Cough severity throughout the day
  - In Exubera group, mostly mild (does not interfere with usual activity), some moderate (must stop activity during coughing episode), a few reports of marked (must stop activity during and for a brief period after coughing episode) and 2 reports of severe (stops all activity for some time and is exhausting)
- Cough timing related to short-acting insulin dosing
  - Majority of subjects reported cough within 60 seconds of dosing or within 1-60 minutes of dosing, some within hours of dosing, and many without relationship to dosing as shown in Figure 54.

Figure 54 Cough Timing Related to Exubera



[N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 72].

- Cough severity related to insulin dosing
  - In Exubera group, most mild (does not interfere with usual morning or daily activity), few moderate severity (must stop activity during coughing), few marked (must stop activity during and for brief period after coughing), no severe reports
- Sputum production
  - In Exubera group, most never or rarely productive, some reports of occasionally or frequently, few reports of almost constantly.

Reviewer's Comment: The cough questionnaire data suggests that cough in the Exubera group was rare at night and rare or occasional during the day. The cough was predominantly mild in severity, non-productive, and usually occurred within 60 seconds of dosing of Exubera.

Dyspnea

There were three subjects who discontinued due to dyspnea as one of reported reasons for discontinuation. All three of the subjects were in the Exubera group. To assess dyspnea, the Applicant administered the BDI at baseline and the TDI at Weeks 4 and 12 as well as Months 6, 12, 18, 24 or end of study. The Applicant reported the interim results for the BDI/TDI. Baseline dyspnea indices were similar between treatment groups. The mean TDI total score was essentially unchanged in either treatment group [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 76].

Pulmonary Function Tests

For the primary PFT analysis, the protocol specified using the primary analysis dataset and the completers dataset. The primary analysis set is defined as those subjects receiving at least one dose of treatment, while having a baseline and at least two post-baseline PFT measurements. The completers group is a subset of the primary analysis set, in which

subjects who have 12-month and 24-month data will respectively fall into 12-month and 24-month completers group cohorts [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 76].

Baseline FEV_1 was well-matched between the treatment groups. A review of the mean change in pulmonary function shows that the Exubera group had a larger decline in FEV_1 than the SC insulin group at all time points. The treatment group difference was noted at Week 12 and then increased at Week 48. Although the treatment group difference fluctuated throughout the 2 year treatment period, the treatment group difference did not increase from Week 48 to Week 96. At Week 96, there was a 41mL treatment group difference favoring the comparator. Table 98 and Figure 55 display the results for the FEV_1 in Study 1022.

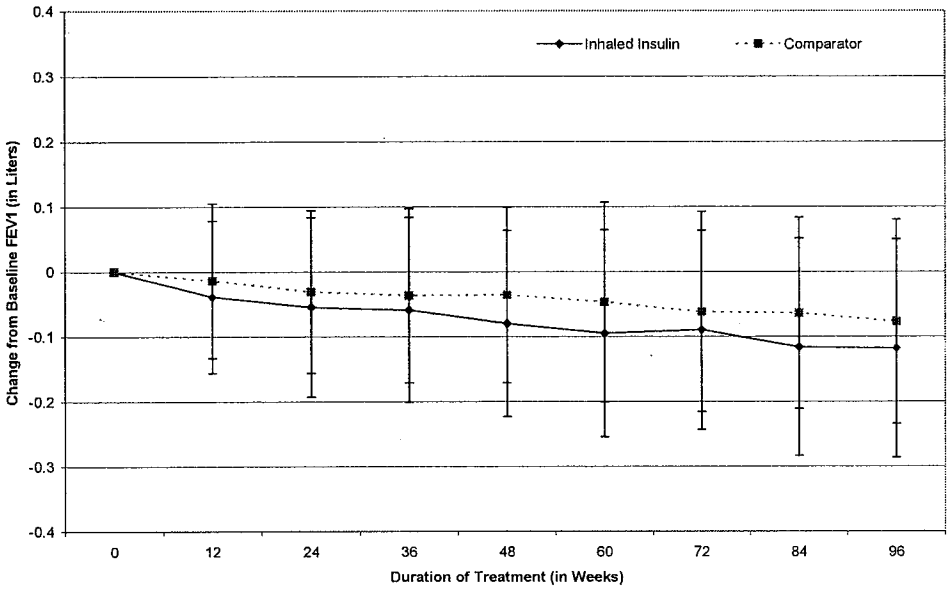
Table 98 Mean Baseline FEV_1 (L), Observed Change from Baseline FEV_1 (L), and Treatment Group Difference (L) - Interim Results Study 1022
Observed

	Exubera			SC Insulin			
	N	Mean FEV_1 (SD)	Mean Change from BL	N	Mean FEV_1 (SD)	Mean Change from BL	Treatment Group Difference
Baseline	290	3.49 (0.8)		290	3.48 (0.8)		
Week 12	277	3.46 (0.8)	-0.04	263	3.48 (0.8)	-0.01	-0.026
Week 24	260	3.47 (0.8)	-0.06	273	3.44 (0.8)	-0.03	-0.024
Week 36	247	3.47 (0.7)	-0.06	264	3.43 (0.8)	-0.04	-0.022
Week 48	240	3.47 (0.7)	-0.08	259	3.43 (0.8)	-0.04	-0.044
Week 60	235	3.45 (0.8)	-0.10	250	3.42 (0.8)	-0.05	-0.047
Week 72	226	3.46 (0.7)	-0.09	230	3.43 (0.8)	-0.06	-0.029
Week 84	217	3.45 (0.8)	-0.12	224	3.42 (0.8)	-0.06	-0.052
Week 96	208	3.47 (0.7)	-0.12	216	3.40 (0.8)	-0.08	-0.041

Source: Dr. Joan Buenconsejo's Review, includes 2 year interim data submitted July 5, 2005

Reviewer's Comment: The Applicant also adjusted the FEV_1 for treatment, month, baseline PFT, center, age, sex, and baseline height. The trends are similar to the observed unadjusted data shown above [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 504].

Figure 55 Mean Observed Change from Baseline FEV_1 (L) by Time in Study 1022 Mean +/- SD



Source: Dr. Joan Buenconsejo's Biometrics Review

Baseline DLCO was well-matched between the treatment groups. A review of the mean change in pulmonary function shows that the Exubera group had a larger decline in DLCO than the SC insulin group at all time points. The decrease in DLCO was noted at Week 12 and the difference between treatment groups was fairly constant throughout the treatment period. At Week 96, the treatment group difference was 0.582 mL/min/mmHg, favoring the comparator. Table 99 and Figure 56 display the results for the DLCO in Study 1022.

Table 99 Mean Baseline DLCO, Observed Change from Baseline DLCO, and Treatment Group Difference DLCO - Interim Results Study 1022
Observed (mL/min/mmHg)

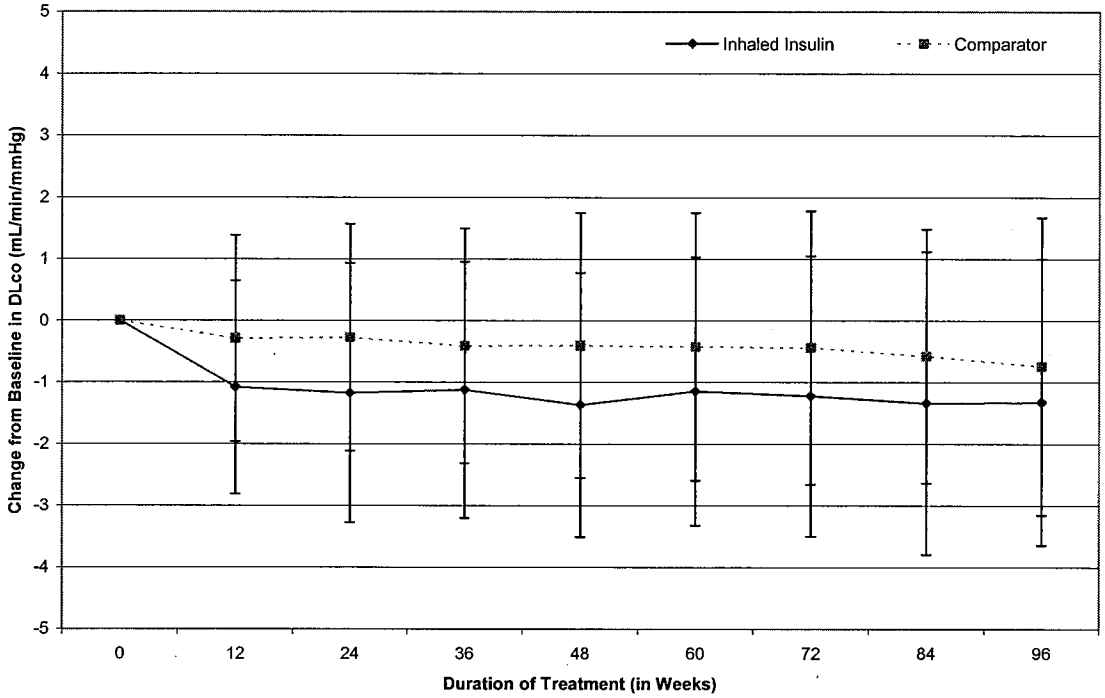
	Exubera			SC Insulin			
	N	Mean DLCO (SD)	Mean Change from BL	N	Mean DLCO (SD)	Mean Change from BL	Treatment Group Difference
Baseline	290	27.95 (6.2)		290	27.28 (6.5)		
Week 12	276	26.98 (6.1)	-1.08	264	27.06 (6.4)	-0.29	-0.723
Week 24	260	26.97 (6.1)	-1.17	273	26.83 (6.5)	-0.28	-0.899
Week 36	246	27.00 (6.1)	-1.13	266	26.76 (6.4)	-0.41	-0.714
Week 48	239	26.93 (6.0)	-1.37	257	26.75 (6.1)	-0.40	-0.964
Week 60	234	27.17 (6.2)	-1.15	249	26.76 (6.1)	-0.42	-0.723
Week 72	226	27.07 (6.0)	-1.22	230	26.70 (6.4)	-0.44	-0.783
Week 84	216	27.08 (6.1)	-1.34	224	26.73 (6.2)	-0.58	-0.765
Week 96	206	27.09 (6.0)	-1.32	216	26.48 (6.0)	-0.74	-0.582

Source: Dr. Joan Buenconsejo's Review, includes 2 year interim data submitted July 5, 2005

Reviewer's Comment: The Applicant also adjusted the DLCO for treatment, month, baseline PFT, center, age, sex, and baseline height. The trends are similar to the

observed unadjusted data shown above [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 504].

Figure 56 Mean Change from Baseline DLCO (mL/min/mmHg) in Study 1022



Source: Dr. Joan Buenconsejo's Biometrics Review

The primary endpoints were the annualized rate of change in FEV_1 and DLCO. The Applicant determined the adjusted annual rate of change in FEV_1 in the Primary Analysis Set from baseline to Month 24 to be -0.051L/yr in the Exubera group and -0.035L/yr in the SC insulin group. For the DLCO, the annual rate of change in DLCO in the Primary Analysis Set from baseline to Month 24 in the Exubera group was -0.403 mL/min/mmHg/yr and -0.275mL/min/mmHg/yr in the SC insulin group [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 81-82].

Reviewer's Comment: The Applicant analyzed the change from baseline in other PFTs, such as TLC, RV, and $FEF_{25-75\%}$. A significant treatment group difference was not noted for FVC, TLC, or RV. However, a treatment group difference favoring the comparator was noted for $FEF_{25-75\%}$, which is consistent with the FEV_1 findings [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 84].

A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group than in the SC insulin group who demonstrated a decrease in FEV_1 or DLCO of >10% at Week 12, Month 6, 12, and 24.

Table 100 Categorical Analyses of Percent Change in PFTs in Study 217-1022 Full Analysis Set						
	Exubera			Subcutaneous Insulin		
	-10 to -15%	-15 to -20%	> -20%	-10 to -15%	-15 to -20%	> -20%
FEV_1 – Month 3	2 (0.7%)	0	0	0	0	0
FEV_1 – Month 6	10 (3.8%)	0	0	3 (1.1%)	0	0
FEV_1 – Month 12	6 (2.5%)	1 (0.4%)	0	2 (0.8%)	0	0
FEV_1 – Month 24	12 (5.8%)	3 (1.4%)	0	6 (2.8%)	2 (0.9%)	0
DLCO – Month 3	33 (12.0%)	4 (1.4%)	0	13 (4.9%)	2 (0.8%)	0
DLCO – Month 6	39 (15.0%)	6 (2.3%)	1 (0.4%)	17 (6.2%)	4 (1.5%)	0
DLCO – Month 12	36 (15.1%)	9 (3.8%)	2 (0.8%)	23 (8.9%)	3 (1.2%)	1 (04%)
DLCO – Month 24	22 (10.7%)	17 (8.3%)	4 (1.9%)	28 (13.0%)	5 (2.3%)	3 (1.4%)
[N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 506, 518]						

The Applicant provided narratives for subjects who experienced a decline of ≥ 15% from baseline into the abnormal range in PFTs at the last observation during the treatment period. The Applicant noted 21 subjects who fulfilled such criteria, 11 in the Exubera group and 10 in the SC insulin group. The most common decline >15% was noted for DLCO, which is consistent with the above table [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 85].

Chest Radiography

Some subjects underwent CXRs at baseline and last observation. Of the 246 INH subjects who underwent CXRs, seven (2.8%) had more abnormal findings compared with baseline. The abnormalities included: rib fracture (2), bronchovascular markings, an increase in compression fracture, parenchymal density, nodular density, and density. Of the 254 SC subjects who underwent CXRs, five (2.0%) had CXR results that were more abnormal than baseline [N21868/N_000/2005-07-19/a2171022_2y_int.pdf, pg 498; N21868/N_000/2005-07-19/a2171022_2y_int-a.pdf, pg 21744-21733].

10.5.1.3 Conclusions

Study 217-1022 is an ongoing phase 3, open-label, 2 year, parallel group study in 580 males and females with type 1 diabetes mellitus to compare an Exubera regimen to a SC insulin regimen. The conclusions are based upon a 2 year interim study report submitted by the Applicant on July 19, 2005.

More subjects discontinued due to AEs in the Exubera group. Of the subjects who discontinued due to AEs in the Exubera group, the majority of the subjects discontinued due to respiratory AEs. The most common reasons for discontinuation due to respiratory AEs were cough and dyspnea/SOB. More subjects in the Exubera group had temporary discontinuations due to AEs. About half of the temporary discontinuations in the Exubera group were due to respiratory AEs.

Respiratory adverse events were more common in the Exubera group than in the SC insulin group. Increased cough, dyspnea, epistaxis, laryngitis, respiratory disorder, rhinitis, sinusitis and sputum increased were more common in the Exubera group than in the SC insulin group. Most of the respiratory AEs were mild to moderate in severity. Further information regarding the cough AEs was obtained through the use of a cough

questionnaire. The cough questionnaire data suggests that cough in the Exubera group was rare at night and rare or occasional during the day. The cough was predominantly mild in severity, non-productive, and typically occurred within 60 seconds of dosing of Exubera.

A review of the mean change in pulmonary function shows that the Exubera group had a larger decline in FEV_1 than the SC insulin group at all time points. The treatment group difference was noted at Week 12 and then increased at Week 48. Although the treatment group difference fluctuated throughout the 2 year treatment period, the treatment group difference did not increase from Week 48 to Week 96. At Week 96, there was a 41mL mean treatment group difference for change from baseline FEV_1 favoring the comparator. The Exubera group had a larger decline in DLCO than the SC insulin group at all time points. The decrease in DLCO was noted at Week 12 and the difference between treatment groups was fairly constant throughout the treatment period. At Week 96, the mean treatment group difference for change from baseline DLCO was 0.582 mL/min/mmHg, favoring the comparator.

A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group than in the SC insulin group who demonstrated a decrease in FEV_1 or DLCO of >10% at Week 12, Month 6, 12, and 24.

There was a similar percentage of subjects in each treatment group who had an abnormal CXR finding on last observation.

10.6 Review of Individual Study Reports – Completed Studies in Type 2 Diabetes

10.6.1 Study 217-103

Inhaled Human Insulin vs. Usual Subcutaneous Human Insulin Therapy in Subjects with Type 2 Diabetes Mellitus: A Three-Month, Open-Label, Parallel Comparative Trial with Optional One-Year Extension

10.6.1.1 Protocol

Study 217-103 was a phase 2 open-label, 3-month, parallel group study in 60 males and females with type 2 diabetes mellitus who were on a stable insulin regimen of 2-3 injections daily. Inclusion criteria specified a normal CXR and normal pulmonary function test results. Subjects with asthma, other respiratory disease, or suspected abnormality of oropharyngeal or pulmonary function or anatomy were to be excluded. Smokers (any smoking in past 6 months) were also excluded. Subjects who successfully completed the 3-month trial were eligible to received Exubera treatment in a one-year open-label protocol extension [N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, 181-183].

A screening visit was followed by a baseline lead-in period (4 weeks) during which subjects underwent pulmonary function testing. At the end of the lead-in-period, subjects

were admitted to the study site for a 2-day period of instruction and dosing experience with Exubera. Eligible subjects were randomized prior to discharge to either continuation of their pre-study regimen or Exubera therapy (pre-meals) with a single bedtime SC long-acting (ultralente) insulin injection [N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, 183-185].

Safety monitoring included AEs, laboratories, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, DLCO, and resting oxygen saturation. PFT testing was performed at baseline (week -3), week 6 (spirometry only) and week 12. PFTs were performed using ATS certified methods [N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, 194-195].

Open-Label Extension
Subjects who completed the 12-week study were eligible for the non-randomized, one-year open-label extension. According to the protocol, each patient had the choice in the extension of using Exubera or conventional subcutaneous insulin. Each investigator was to recruit at least one patient for the conventional SC insulin regimen for every two subjects choosing Exubera. Newly recruited subjects were matched with one of the two subjects selecting Exubera therapy by age, sex, smoking history, diabetic complications, and degree of glucose control at week 12 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, pg 200-207].
Reviewer's Comment: From a pulmonary standpoint, the new recruits had the same inclusion/exclusion criteria listed above.

Safety monitoring during the one-year open-label extension included PFTs at baseline (screening for new recruits or week 12 for subjects completing the previous protocol), 3, 6, 9 (spirometry only), and 12 months [N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, pg 207].

10.6.1.2 Results

The 12-week study commenced on November 15, 1996, and was completed on September 11, 1997. Ten centers participated in the study. A total of 112 subjects were screened for the study and 56 were randomized (28 Exubera, 28 SC insulin). Two subjects discontinued due to AEs as shown in Table 101. One subject discontinued the study due to a respiratory AE, cough.

Table 101 Subject Disposition Study 217-103

	Exubera	SC Insulin
Randomized (56)	28	28
Completed Study	25	26
Discontinued Study	3	2
Adverse Event	**2**	**0**
Cough	1	0
Cerebrovascular accident	1	0
Defaulted	0	2
Other	1	0

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, pg 27-28]

Reviewer's Comment: A 60 yo male subject (103 50020002) discontinued secondary to cough on Day 55. He developed bronchitis between the 3rd and 5th week of treatment. Exubera was temporarily discontinued. When restarted, the subject noted irritation and cough, which led to permanent discontinuation [N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, pg 138].

The mean age of the subjects was about 52 years and the mean FEV_1 percent predicted at baseline was between 93-97% as shown in Table 102.

Table 102 Baseline Characteristics Study 217-103

		Exubera n = 28	SC Insulin n = 28
Gender	Male	18 (64%)	15 (54%)
	Female	10 (36%)	26 (46%)
Age	Mean	51.8	52.5
	Range	39-64	35-66
FEV_1 (% predicted)	Mean	93%	97%

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, pg 48, 149]

Reviewer's Comment: A review of the summary of medical history of the subjects indicates that one subject in each treatment group reported COPD and bronchitis in the past [N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, pg 51-59].

Reviewer's Comment: Subject 103 50110081 entered the study with an abnormal CXR which was a protocol violation [N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, pg 550].

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera group than in the SC insulin group. Increased cough, pharyngitis, and sinusitis were more common in the Exubera group than in the SC insulin group. One subject (103 50020002) discontinued secondary to cough on Day 55. A detailed summary of the respiratory AEs is listed in Table 103. All the respiratory AEs were mild to moderate in severity. There were no respiratory SAEs.

Table 103 Summary of Respiratory Adverse Events for Study 217-103		
	Exubera n = 28	SC Insulin n = 28
Serious adverse events	2 (7.2%)	0
Surgical removal of spinal rods	1 (3.6%)	0
Cerebrovascular accident, bradycardia, PVCs	1 (3.6%)	0
Any adverse event	26 (93%)	28 (100%)
Respiratory	**20 (71%)**	**15 (54%)**
Asthma	1 (3.6%)	0
Bronchitis	0	2 (7.1%)
Cough increased	**12 (43%)**	**1 (3.6%)**
Dyspnea	1 (3.6%)	0
Pharyngitis	**7 (25%)**	**2 (7.1%)**
Respiratory disorder (burning in lungs)	4 (14%)	4 (14%)
Respiratory tract infection	4 (14%)	7 (25 %)
Rhinitis	4 (14%)	5 (18%)
Sinusitis	**2 (7.1%)**	**0**
Sputum increased	0	0 (3.6%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, pg 37, 98, 102]

Reviewer's Comment: Hypoglycemia was the most common AE in both treatment groups.

Pulmonary Function Tests

A review of the mean change in FEV_1, FVC, and DLCO shows that the SC insulin group demonstrated a slight decrease in pulmonary function at week 12, whereas the Exubera group demonstrated a slight increase in pulmonary function at week 12. A summary of the PFTs is displayed in Table 104.

Table 104 Summary of Pulmonary Function Tests for Study 217-103		
Mean values	Exubera n = 28	SC Insulin n = 28
Baseline FEV_1 L (% predicted)	3.02 (93%)	3.05 (97%)
FEV_1 change from baseline at week 12 L (% change)	0.05 (2.5%)	-0.08 (-1.8%)
Baseline FVC L (% predicted)	3.72 (90%)	3.72 (94%)
FVC change from baseline at week 12 L (% change)	0.11 (3.7%)	-0.09 (-1.7%)
DLCO mL/min/mmHg (% predicted)	24.9 (94%)	24.9 (99%)
DLCO change from baseline at week 12 mL/min/mmHg (% change)	0.21 (1.8%)	-0.77 (-0.5%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/103.pdf, pg 149-151]

Reviewer's Comment: Two subjects (1 Exubera, 1 SC insulin) were noted to have a 15% drop from baseline in pulmonary function tests. Both of these subjects continued into the extension period and will be discussed in the extension study, Study 217-111.
Reviewer's Comment: Although oxygen saturation was specified to be collected with the PFTs, the Applicant did not report the results for the oxygen saturation in the study report. An information request regarding the oxygen saturation data was sent to the Applicant on July 7, 2005. In a response to the information request dated August 12, 2005, the Applicant stated that no signal was observed for the oxygen saturation data

and oxygen saturation data was not collected in the new Phase 3 studies. The Applicant did not formally analyze the oxygen saturation data as part of the clinical trial reports and the oxygen saturation data was not subject to the normal data clarification processes [N21868/2005-08-12/07july05_clin-responses.pdf].

10.6.1.3 Conclusions

Study 217-103 was an open-label, 3-month, parallel group study of Exubera versus SC insulin in 66 males and females with type 2 diabetes mellitus who were on a stable insulin regimen of 2-3 injections daily. The results indicate that respiratory adverse events were more common in the Exubera group. Respiratory adverse events which were more common in the Exubera group than in the SC insulin group were increased cough, pharyngitis, and sinusitis. A review of the mean change in FEV_1, FVC, and DLCO shows that the SC insulin group demonstrated a slight decrease in pulmonary function at week 12, whereas the Exubera group demonstrated a slight increase in pulmonary function at week 12.

10.6.2 Study 217-104

Inhaled Human Insulin as Adjunctive Therapy in Subjects with Type 2 Diabetes Mellitus Not Well Controlled on Sulfonylurea and/or Metformin Therapy: A Three-Month, Open-Label, Parallel Comparative Trial with Optional One-Year Extension

10.6.2.1 Protocol

Study 217-104 was a phase 2 open-label, 3-month, parallel group study in 60 males and females with type 2 diabetes mellitus who were not well controlled on sulfonylurea and/or metformin therapy. Inclusion criteria specified a normal CXR and normal pulmonary function test results. Subjects with asthma, other respiratory disease, or suspected abnormality of oropharyngeal or pulmonary function or anatomy were to be excluded. Smokers (any smoking in past 6 months) were also excluded [N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, 176-178].

A screening visit was followed by a baseline lead-in period (4 weeks) during which subjects underwent pulmonary function testing. At the end of the lead-in-period, subjects were admitted to the study site for a 2-day period of instruction and dosing experience with Exubera. Eligible subjects were randomized prior to discharge to either continuation of their pre-study oral agent regimen or Exubera therapy (pre-meals) with their pre-study oral agent regimen [N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, 179].

Safety monitoring included AEs, laboratories, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, DLCO, and resting oxygen saturation. PFT testing was performed at baseline (week -3), week 6 (spirometry only) and week 12. PFTs were performed using ATS certified methods [N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, 193-194].

Open-Label Extension
Subjects who completed the 12-week study were eligible for the non-randomized, one-year open-label extension. According to the protocol, each patient had the choice in the

extension of using Exubera or conventional subcutaneous insulin. Each investigator recruited at least one patient for the conventional SC insulin regimen for every two subjects choosing Exubera. Newly recruited subjects were matched with one of the two subjects selecting Exubera therapy by age, sex, smoking history, diabetic complications, and degree of glucose control at week 12 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, pg 198].
Reviewer's Comment: From a pulmonary standpoint, the new recruits had the same inclusion/exclusion criteria listed above.

Safety monitoring during the one-year open-label extension included PFTs at baseline (screening for new recruits or week 12 for subjects completing the previous protocol), 3 (spirometry only), 6, 9 (spirometry only), and 12 months [N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, pg 205, 207].

10.6.2.2 Results

The study commenced on October 10, 1997, and was completed on July 23, 1998. Nine centers participated in the study. A total of 100 subjects were screened for the study and 69 were randomized, 33 to the Exubera and 36 to the oral agent arm. No subjects discontinued the study [N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, pg 24].

The mean age of the subjects was between 50 and 53 years and the mean FEV_1 percent predicted at baseline was 92-93% as shown in Table 105.

Table 105 Baseline Characteristics Study 217-104

		OA & Exubera n = 33	Oral Agents n = 36
Gender	Male	19 (56%)	26 (72%)
	Female	14 (44%)	10 (28%)
Age	Mean	52.7	49.9
	Range	34-65	33-64
FEV_1 (% predicted)	Mean	93%	92%

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, pg 45, 146]

Reviewer's Comment : A review of the summary of medical history of the subjects indicates that 5 subjects (2 Exubera, 3 oral agents) reported a history of COPD in the past and 1 subject in the oral agent group reported a past history of asthma [N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, pg 49-59].

Respiratory Adverse Events
Respiratory adverse events were more common in the Exubera group than in the oral agent group. Increased cough, respiratory disorder, rhinitis, and sinusitis were more common in the Exubera group than in the oral agent group. A detailed summary of the respiratory AEs is listed in Table 106. All the respiratory AEs were mild to moderate in severity.

Table 106 Summary of Respiratory Adverse Events for Study 217-104		
	Oral Agents & Exubera n = 33	Oral Agents n = 36
Serious adverse events	0	1 (2.8%)
Skin boil	0	1 (2.8%)
Any adverse event	33 (100%)	30 (83%)
Respiratory	**17 (52%)**	**14 (39%)**
Cough increased	**5 (15%)**	**3 (8.3%)**
Laryngitis	0	1 (2.8%)
Pharyngitis	3 (9.1%)	3 (8.3%)
Respiratory disorder	**2 (6.1%)**	**1 (2.8%)**
Respiratory tract infection	5 (15.2%)	8 (22.2%)
Rhinitis	**4 (12.1%)**	**1 (2.8%)**
Sinusitis	**3 (9.1%)**	**2 (5.6%)**

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, pg 37, 98, 101]

Reviewer's Comment: Hypoglycemia was the most common AE in both treatment groups.

Pulmonary Function Tests

A review of the mean change in FEV_1, FVC, and DLCO shows that both treatment groups demonstrated a slight decrease in pulmonary function at week 12. The results are displayed in Table 107. The Exubera group had a greater mean decrease in FEV_1 and FVC than the oral agent group; however, the oral agent group had a greater mean decline in DLCO than the Exubera group.

Table 107 Summary of Pulmonary Function Tests for Study 217-104		
Mean values	Exubera n = 33	Oral Agents n = 36
Baseline FEV_1 L (% predicted)	3.05 (93%)	3.20 (92%)
FEV_1 change from baseline at week 12 L (% change)	-0.09 (-2.7)	-0.03 (-0.6%)
Baseline FVC L (% predicted)	3.78 (92%)	3.93 (90%)
FVC change from baseline at week 12 L (% change)	-0.07 (-1.7%)	-0.02 (-0.2%)
DLCO mL/min/mmHg (% predicted)	26.0 (98%)	27.0 (102%)
DLCO change from baseline at week 12 mL/min/mmHg (% change)	-1.10 (-3.8%)	-1.26 (-4.7%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/104.pdf, pg 146-148]

Reviewer's Comment: Five subjects (2 Exubera, 3 oral agent) were noted to have a 15% drop from baseline in pulmonary function tests. The two subjects in the Exubera group continued into the extension period and will be discussed in the extension study, Study 217-111.

10.6.2.3 Conclusions

Study 217-104 was an open-label, 3-month, parallel group study of Exubera as adjunctive therapy to oral agents versus oral agents alone in 72 males and females with type 2 diabetes mellitus who were not well controlled on sulfonylurea and/or metformin therapy.

The results indicate that respiratory adverse events were more common in the Exubera group. Respiratory adverse events which were more common in the Exubera group than in the oral agent group were increased cough, respiratory disorder, rhinitis, and sinusitis. A review of the mean change in FEV_1, FVC, and DLCO shows that both treatment groups demonstrated a slight decrease in pulmonary function at Week 12. The Exubera group had a greater mean decrease in FEV_1 and FVC than the oral agent group; however, the oral agent group had a greater mean decline in DLCO than the Exubera group.

10.6.3 Study 217-108

Efficacy and Safety of Exubera Compared to Subcutaneous Insulin Therapy in Subjects with Type 2 Diabetes Mellitus: A Six-Month, Outpatient, Parallel Comparative Trial

10.6.3.1 Protocol

Study 217-108 was a phase 3, open-label, 6-month, parallel group study comparing Exubera to SC insulin in 320 males and females with type 2 diabetes mellitus on a stable subcutaneous insulin regimen. Subjects with the following were excluded:

- Clinically significant abnormalities on screening CXR
- Poorly-controlled asthma, clinically significant COPD, or other significant respiratory disease
- Subjects with frankly abnormal PFTs at Week -3, defined as DLCO <75%, TLC >120% or <80%, or FEV_1<70% predicted
- Any smoking within the last 6 months

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 297-300].

A screening visit was followed by a baseline lead-in period (4 weeks) during which subjects underwent pulmonary function testing. At the end of the lead-in-period, subjects were instructed on the proper use of Exubera. Eligible subjects were then randomized to either continuation of their pre-study subcutaneous insulin regimen or Exubera therapy (pre-meals) and Ultralente SC HS [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 300-302].

Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, DLCO, and resting oxygen saturation. PFT testing was performed at baseline (week -3), week 12 (spirometry only), and week 24. PFTs were performed using ATS certified methods. If a subject had a decrease of >15% in any FEV_1, FVC, TLC, FRC, or DLCO in the absence of intercurrent illness, the PFTs were repeated. If the >15% decrease persisted, then further pulmonary evaluation, including pulmonologist consultation, CXR, or HRCT were obtained. CXRs were taken at the beginning and end of the study [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 315, 322-323].

An HRCT substudy was included in Studies 217-106, 217-107, and 217-108. Approximately 100 subjects were recruited prior to randomization for the HRCT substudy at participating sites. Baseline HRCTs were obtained prior to randomization. HRCTs were performed without contrast by taking 1 mm cuts starting 2 cm above the

carina and continuing inferiorly every 2cms for a total of 10 cuts. Enrollment continued until at least 50 of the subjects were randomized to Exubera. Both the baseline HRCT and 24 week HRCT were forwarded together to a central radiology site for a blinded review. A second original set of films was kept at the investigative site. Abnormalities noted on the baseline HRCT were discussed with a Pfizer clinician prior to randomization. The number and percentage of new abnormalities at the end of treatment was summarized across the 100 subjects in the substudy [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, 328].

Open-Label Extension

Subjects who completed the 24-week study were eligible for the one-year open-label extension. The details of the open-label extension will be described in the review of Study 217-111.

10.6.3.2 Results

The study commenced on September 27, 1999, and was completed on December 22, 2000. Fifty-one centers participated in the study (United States 40, Canada 11). A total of 520 subjects were screened for the study and 299 were randomized, 149 to the Exubera and 150 to the subcutaneous arm. One subject randomized to the subcutaneous insulin arm never received treatment. More subjects in the Exubera group were discontinued from the study than in the SC insulin group. No subject discontinued the study due to respiratory AEs. Subject disposition is summarized in Table 108 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 35]

Table 108 Subject Disposition Study 217-108

	Exubera	SC Insulin
Randomized (299)	149	150
Randomized but never treated	0	1
Completed	132	140
Discontinued Study	17	9
Subject died	2	0
Adverse Event	2	2
Cardiac ischemia	0	1
Gingivitis, glossitis	1	0
Hyperglycemia	1	0
Motor vehicle accident	0	1
Subject defaulted (withdrew consent, lost to follow up)	10	6
Lack of efficacy	1	1
Other (includes protocol violation, does not meet entry criteria)	2	0

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 124-126]

Reviewer's Comment: Because one subject withdrew consent after randomization and before treatment the number of the subjects in the SC insulin group will be 149, not 150.
Reviewer's Comment: Two subjects in the Exubera group died. One subject was diagnosed with esophageal cancer and died. The second subject developed hematemesis secondary to esophageal bleeding. The subject died secondary to esophageal bleeding [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 57]

The mean age of the subjects was between 56-58 years. The majority of the subjects were Caucasian and male as shown in Table 109.

Table 109 Baseline Characteristics Study 217-108

		Exubera n = 149	SC Insulin n = 149
Gender	Male	99 (66%)	99 (66%)
	Female	50 (34%)	50 (34%)
Age	Mean	58.7	56.2
	Range	35-80	23-78
Race	Caucasian	116 (78%)	110 (74%)
	Black	17 (11%)	15 (10%)
	Asian	4 (2.7%)	5 (3.3%)
	Hispanic	11 (7.4%)	12 (8%)
	Other	1 (<1%)	7 (4.7%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 70]

Reviewer's Comment: A review of the summary of medical history of the subjects indicates that some subjects reported a history of asthma and obstructive airway disease. For example, asthma (unspecified) was reported in the past in 5 subjects and in the present in 9 subjects. Chronic airway obstruction (NOS) was reported in the past in 1 subject and in the present in 2 subjects [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 74].

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera group than in the SC insulin group. Asthma, increased cough, dyspnea, epistaxis, pharyngitis, respiratory tract infection, sputum increased, and voice alteration were more common in the Exubera group than in the SC insulin group. A detailed summary of the respiratory AEs is listed in Table 110. Most of the respiratory AEs were mild to moderate in severity. Two cases of bronchitis and one case of pneumonia in the Exubera group were graded as severe. One case of respiratory distress syndrome was graded as severe in the SC insulin group [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 165-166].

Table 110 Number of Subjects with Respiratory Adverse Events in Study 217-108

	Exubera n = 149	SC Insulin n = 149
Serious adverse events	13 (8.7%)	12 (8.1%)
Any adverse event	141 (95%)	143 (96%)
Respiratory	**94 (63%)**	**68 (46%)**
Asthma	**5 (3.4%)**	**1 (0.7%)**
Atelectasis	0	1 (0.7%)
Bronchiectasis	0	1 (0.7%)
Bronchitis	4 (2.7)	4 (2.7%)
Cough increased	**32 (21.5%)**	**4 (2.7%)**
Dyspnea	**9 (6.0%)**	**1 (0.7%)**
Emphysema	0	1 (0.7%)
Epistaxis	**2 (1.3%)**	**0**
Hemoptysis	1 (0.7%)	0
Laryngitis	0	1 (0.7%)
Lung edema	1 (0.7%)	0
Pharyngitis	**14 (9.4%)**	**11 (7.4%)**
Pneumonia	1 (0.7%)	4 (2.7%)
Respiratory disorder	8 (5.4%)	8 (5.4%)
Respiratory distress syndrome	0	1 (0.7%)
Respiratory tract infection	**48 (32.2%)**	**40 (26.8%)**
Rhinitis	13 (8.7%)	13 (8.7%)
Sinusitis	6 (4.0%)	7 (4.7%)
Sputum increased	**6 (4.0%)**	**0**
Voice alteration	**3 (2.0%)**	**0**

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 165-166]

Reviewer's Comment: One of the SAEs in the Exubera group was respiratory. A 73 yo male was reported to be hospitalized for bronchitis and congestive heart failure. Two subjects in the SC insulin group had respiratory SAEs. One subject was a 41 yo male who was hospitalized for pneumonia, ulcerative esophagitis, respiratory distress, and atrial fibrillation. The other subject was a 67 yo female who was hospitalized with unstable angina and pneumonia [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 198-203]

Reviewer's Comment: Hypoglycemia was the most common AE in both treatment groups.

Cough was the most common AE which was reported more frequently in the Exubera group than in the SC insulin group. A total of 42 cough events were reported in the Exubera group compared to 3 in the SC insulin group. In the Exubera group, about half of the cough AEs were reported in the first 4 weeks and the majority of cough AEs were reported in the first 12 weeks. All of the cough AEs were mild to moderate in severity. The Applicant determined the mean duration of cough based upon the reported onset to the reported end of each event. The mean duration of cough was 5.02 weeks and 5.38 weeks for the Exubera group and SC insulin group, respectively. About 40% of subjects reporting cough in the Exubera group had a duration of cough of 2 weeks or less [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 55-56, 222-225].

Pulmonary Function Tests

Baseline pulmonary function as measured by PFTs was well-matched between the treatment groups. A review of the mean change in pulmonary function at 24 weeks shows that both treatment groups demonstrated a slight decrease in FEV_1, FVC, and DLCO. The decreases appeared to be greater in the SC insulin group except for the DLCO, which had a slightly larger decrease in the Exubera group. The TLC increased slightly in the Exubera group and decreased slightly in the SC insulin group. A summary of the mean changes in pulmonary function parameters is shown in Table 111.

Table 111 Pulmonary Function Tests for Study 217-108 – Summary of Mean Changes

	Exubera			Subcutaneous Insulin		
PFT	BL	Week 24 (LOCF)	Change from BL	BL	Week 24 (LOCF)	Change from BL
FEV_1	N=149	N=144	N=144	N=149	N=145	N=145
Mean (L)	2.840	2.785	-0.062	2.980	2.898	-0.071
SD	0.669	0.659	0.213	0.683	0.642	0.221
FVC	N=149	N=144	N=144	N=149	N=145	N=145
Mean (L)	3.587	3.551	-0.046	3.734	3.641	-0.081
SD	0.832	0.851	0.298	0.907	0.813	0.318
DLCO	N=146	N=135	N=133	N=147	N=140	N=138
Mean (ml/min/mmHg)	23.55	22.76	-1.05	24.10	23.39	-0.59
SD	5.25	5.65	3.10	5.45	5.50	3.37
TLC	N=149	N=134	N=134	N=149	N=139	N=139
Mean (L)	5.72	5.73	0.024	5.84	5.79	-0.06
SD	1.17	1.20	0.53	1.19	1.24	0.59

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 237-248]

Reviewer's Comment: The Applicant used the last observation carried forward (LOCF) for missing data, which is displayed in Table 111. The results for the mean change from baseline were quite similar for the Week 24 data and the Week 24 (LOCF) data.

A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group who had a decline of >10% in DLCO and FVC than in the SC insulin group. However, more subjects in the SC insulin group had a decline of >10% in TLC and FEV_1 than in the Exubera group. Table 112 displays the categorical analyses of the change from baseline in the PFTs. More subjects appeared to have a decline in DLCO than other PFT parameters. The majority of subjects with a >15% decline in a PFT parameter continued into the extension study and will be discussed further in Study 217-111.

Table 112 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation in Study 217-108

	Exubera			Subcutaneous Insulin		
	-10 to -15%	-15 to -20%	> -20%	-10 to -15%	-15 to -20%	> -20%
FEV_1	10 (6.9%)	3 (2.1%)	1 (0.7%)	15 (10.3%)	3 (2.1%)	1 (0.7%)
FVC	12 (8.3%)	5 (3.5%)	1 (0.7%)	8 (5.5%)	2 (1.4%)	1 (0.7%)
DLCO	18 (13.5%)	11 (8.3%)	15 (11.3%)	20 (14.5%)	9 (6.5%)	5 (3.6%)
TLC	5 (3.7%)	2 (1.5%)	4 (3.0%)	7 (5.0%)	7 (5.0%)	3 (2.2%)

The n for the categorical analyses of each PFT parameter is the same n as listed in the change from baseline in Table 111 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 237-248]

Four subjects that did not continue into the extension study who had a >15% drop in PFT parameter and a below normal value at last observation. One subject was a 70 yo female in the Exubera group who had a decline in DLCO from 25.7 to 19.4 ml/min/mmHg. The subject reportedly experienced some mild cold symptoms during the study. The subject's end of study FEV_1, FVC, and TLC all measured higher than at screening. The end of study CXR was within normal limits. One subject was a 56 yo male in the Exubera group who was diagnosed with mild heart failure at the end of study had a decrease in all his PFTs (FVC from 4.27L to 2.82 L, FEV_1 from 3.21L to 1.87L, DLCO from 23.5 to 18.2 ml/min/mmHg). His end of study CXR was also abnormal and notable for mild heart failure. One subject in the SC insulin group was a 57 yo male who had a decline in TLC from 4.86L to 4.13L. His baseline and end of study CXR were normal. His FVC, FEV_1, and DLCO were all similar to screening. One subject was a 70 yo female in the SC insulin group who had a decline in DLCO from 18.3 to 10.7ml/min/mmHg. Her FEV_1, FVC, and TLC were similar to baseline [N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 207-216].
Reviewer's Comment: The significance of the change in pulmonary function in these subjects is unclear without further follow-up.

Chest Radiography
A chest x-ray was taken at the beginning and end of the study in each of the subjects. Ten subjects in the Exubera group and 3 subjects in the SC insulin group had a significant change. The following is a listing of the changes noted on the end of study CXRs [N21868/N_000/2004-12-27/crt/datasets/108/xray_1v.xpt]:

- Exubera
    - 8mm nodule in right base, confirmed on follow-up
    - hiatal hernia noted
    - questionable nodular density right base; heart size ULN; right hilar lymph nodes
    - heart size appears slightly larger than screening
    - s/p CABG; mild pulmonary edema; sternotomy wires
    - healing rib fracture
    - new 1 cm nodular opacity overlying the lower thoracic spine
    - elevation of right hemidiaphragm
    - retrosternal opacity; ct scan to follow
    - mild heart failure

- SC Insulin
    - LLL pneumonia; persistent left lingular atelectasis
    - 1.6cm pulmonary nodule; CT performed 8/23/00
    - LLL infiltrate
    - right basilar poorly defined opacity, unchanged versus comparison study; two small LUL peripheral nodules

Reviewer's Comment: In reviewing the individual studies, it was unclear to this reviewer why the number of CXR changes in the dataset differed from the Applicant's summary in the study report. An information request was sent to the Applicant for clarification of the CXR data and the discrepancy between the individual study data and the dataset on June 21, 2005. In a response to the information request, the Applicant provided several reasons for the difference between the study report and the study dataset [N21868/N_000/2005-07-26/response_ir_request_21jun05.pdf, pg 6; N21868/N_000/2005-08-12/07july05_clin_responses.pdf, pg 3].

- *The individual study data for Study 106 and 107 include CXR data for some subjects <18 years of age. The summary is based upon data from subjects ≥ 18 years of age.*
- *The individual study data for Study 1027 include CXR data for the follow up phase, but the summary includes only the treatment phase CXR data.*
- *The individual study CXR data for Study 1001-1002 are based upon Week 104 completers, while the summary includes all subjects with a baseline and post-baseline CXR.*
- *The individual study data includes data for subjects with multiple CXRs. The summary data are based upon a change from baseline at the last observation CXR examination. Thus, the individual study data may have a subject with an abnormal CXR on interim evaluation, but if the CXR findings resolved by the last observation CXR, the subject would not be included in the above table.*

Reviewer's Comment: Several of the noted changes were for nodules, but the Applicant did not provide much information regarding further evaluation for these subjects. An information request was sent to the Applicant on June 21, 2005, requesting follow-up information for subjects with significant new changes in CXR, such as a new nodule or density. In a response dated July 29, 2005, the Applicant provided follow-up information for subjects with nodules in all of the controlled studies. In general, the follow-up imaging was negative/normal.

High Resolution Computed Tomography

An HRCT substudy was conducted at selected study sites. Thirty-four Exubera subjects and 31 SC insulin subjects had HRCT scans performed at baseline and end of study. There were 4 subjects in the Exubera group that had new abnormal changes noted and 2 subjects in the SC insulin group who had new abnormal changes noted. The following is a summary of changes noted:

- Exubera
    - One subject had a new left basilar linear density, probably atelectasis
    - One subject had a dependent density in the bases, not consistent with fibrosis
    - One subject had a new dependent density, unlikely to be fibrosis

- Subcutaneous insulin
  - One subject had a linear density in RLL, which was thicker
  - One subject had an increased RML subpleural lines and bands

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/108.pdf, pg 669-672; N21868/N_000/2004-12-27/crt/datasets/108/ctscan_1v.xpt].

10.6.3.3 Conclusions

Study 217-108 was an open-label, 6-month, parallel group study of Exubera versus SC insulin in 298 males and females with type 2 diabetes mellitus. The results indicate that respiratory adverse events were more common in the Exubera group than in the SC insulin group. Asthma, increased cough, dyspnea, epistaxis, pharyngitis, respiratory tract infection, sputum increased, and voice alteration were more common in the Exubera group than in the SC insulin group.

A review of the mean change in pulmonary function at 24 weeks shows that both treatment groups demonstrated a slight decrease in FEV_1, FVC, and DLCO. The decreases appeared to be greater in the SC insulin group except for the DLCO, which had a slightly larger decrease in the Exubera group than in the SC insulin group. A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group who had a decline of >10% in DLCO and FVC than in the SC insulin group. However, more subjects in the SC insulin group had a decline of >10% in TLC and FEV_1 than in the Exubera group. The CXR data indicated several subjects in both treatment groups had a nodule/nodular density noted on the end of study CXR. The HRCT data showed a new density in some subjects in both treatment groups. The significance of the new density finding is unclear.

10.6.4 Study 217-109

Efficacy and Safety of Exubera Therapy in Subjects with Type 2 Diabetes Mellitus Not Well Controlled with Combination Oral Agents: A Three-Month, Outpatient, Parallel Comparative Trial

10.6.4.1 Protocol

Study 217-109 was a phase 3, open-label, 3-month, parallel group study in 300-345 males and females with type 2 diabetes mellitus on a stable oral hypoglycemic regimen involving two anti-diabetic medications. Subjects were not on an insulin regimen. Subjects with the following were excluded:

- Clinically significant abnormalities on screening CXR
- Poorly-controlled asthma, clinically significant COPD, or other significant respiratory disease
- Subjects with frankly abnormal PFTs at Week -3, defined as DLCO <75%, TLC >120% or <80%, or FEV_1<70% predicted
- Any smoking within the last 6 months

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 286-289].

A screening visit was followed by a baseline lead-in period (4 weeks) during which subjects were maintained on their combination oral agent regimen. Subjects underwent pulmonary function testing at Week -3. At the end of the lead-in-period, subjects were instructed on the proper use of Exubera. Eligible subjects were then randomized to one of the following regimens [N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 291-292]:

- Combination oral agent therapy (continuation of lead in period regimen)
- Pre-meal Exubera in addition to combination oral agent therapy
- Pre-meal Exubera therapy instead of combination oral agent therapy.

Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, DLCO, and resting oxygen saturation. PFT testing was performed at baseline (week -3) and week 12. PFTs were performed using ATS certified methods. If a subject had a decrease of >15% in any FEV_1, FVC, TLC, FRC, or DLCO in the absence of intercurrent illness, the PFTs were repeated. If the >15% decrease persisted, then further pulmonary evaluation, including pulmonologist consultation, CXR, or HRCT were obtained. CXRs were taken at the beginning and end of the study [N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 303,311-312].

Open-Label Extension
Subjects who completed the 24-week study were eligible for the open-label extension. The details of the open-label extension will be described in the review of Study 217-111.

10.6.4.2 Results

The study commenced on June 10, 1999, and was completed on September 5, 2000. Fifty-two centers participated in the study (United States 40, Canada 12). A total of 580 subjects were screened for the study and 309 were randomized, 105 to the Exubera monotherapy, 102 subjects to Exubera plus oral agents and 102 to oral agents. Three subjects randomized never received treatment, thus 306 subjects received study medication. One subject was randomized to Exubera monotherapy, but received Exubera plus oral agents.

Two subjects discontinued the study due to respiratory AEs. One was a 70 yo male in the Exubera monotherapy group who developed recurrent (4) lower respiratory tract infections. The second subject was a 65 yo female in the Exubera plus oral agent group reported to be hospitalized for SOB and ankle edema Subject disposition for Study 217-109 is summarized in Table 113 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 35]

Table 113 Subject Disposition Study 217-109			
	Exubera	Exubera + OA	Oral Agents
Randomized (309)	105	102	102
Randomized but never treated	0	0	3
Randomized and received wrong tx	1	0	0
Treated	104	103	99
Discontinued Study	7	4	6
Adverse Event	1	1	0
Lower respiratory tract infection	1	0	0
Dyspnea/ SOB	0	1	0
Subject defaulted (withdrew consent, lost to F/U)	2	2	2
Lack of efficacy	3	0	2
Other (includes protocol violation, does not meet entry criteria)	1	1	2

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 129-131]

The mean age of the subjects was between 56-58 years. The majority of the subjects were Caucasian and male as shown in Table 114.

Table 114 Baseline Characteristics Study 217-109				
		Exubera n=105	Exubera + OA n = 102	Oral Agents n = 99
Gender	Male	75 (71%)	65 (64%)	62 (63%)
	Female	30 (29%)	37 (36%)	37 (37%)
Age	Mean	57.4	58.3	56.4
	Range	35-77	38-77	33-80
Race	Caucasian	83 (79%)	80 (78%)	82 (83%)
	Black	8 (8%)	9 (9%)	5 (5%)
	Asian	2 (2%)	0	2 (2%)
	Hispanic	8 (8%)	8 (8%)	7 (7%)
	Other	4 (4%)	5 (5%)	3 (3%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 72]

Reviewer's Comment: A review of the summary of medical history of the subjects indicates that some subjects reported a history of asthma, obstructive airway disease, emphysema, or bronchitis NOS. For example, asthma (unspecified) was reported in the past in 7 subjects and in the present in 9 subjects. Chronic airway obstruction (NOS) was reported in the present in 5 subjects [N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 77].

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera groups than in the oral agent group. Increased cough, respiratory tract infection, rhinitis, sinusitis, and sputum increased were more common in the Exubera groups than in the oral agent group. A detailed summary of the respiratory AEs is listed in Table 115. Most of the respiratory AEs were mild to moderate in severity. One case of dyspnea in the Exubera plus oral

agent was graded as severe [N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 171].

Table 115 Number of Subjects with Respiratory Adverse Events in Study 217-109

	Exubera n=104	Exubera + OA n = 103	Oral Agents n = 99
Serious adverse events	3 (2.9%)	3 (2.9%)	1 (1.0%)
Any adverse event	99 (95.2%)	100 (97.1%)	76 (76.8%)
Respiratory	59 (56.7%)	48 (46.6%)	30 (30.3%)
Asthma	1 (1.0%)	0	0
Bronchitis	3 (2.9%)	1 (1.0%)	2 (2.0%)
Cough increased	**15 (14.4%)**	**12 (11.7%)**	**2 (2.0%)**
Dyspnea	1 (1.0%)	1 (1.0%)	0
Epistaxis	0	2 (1.9%)	1 (1.0%)
Laryngitis	1 (1.0%)	0	0
Lung disorder	0	1 (1.0)	0
Pharyngitis	10 (9.6%)	8 (7.8%)	7 (7.1%)
Respiratory disorder	5 (4.8%)	6 (5.8%)	3 (3.0%)
Respiratory tract infection	**32 (30.8%)**	**17 (16.5%)**	**19 (19.2%)**
Rhinitis	**8 (7.7%)**	**9 (8.7%)**	**2 (2.0%)**
Sinusitis	**4 (3.8%)**	**5 (4.9%)**	**2 (2.0%)**
Sputum increased	**4 (3.8%)**	**1 (1.0%)**	**0**
Voice alteration	1 (1.0%)	0	0

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 171]

Reviewer's Comment: One of the SAEs in the Exubera plus oral agent group was respiratory. A 65 yo female was reported to be hospitalized for SOB and ankle edema [N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 201-203]

Reviewer's Comment: Hypoglycemia was the most common AE in the Exubera groups. Respiratory tract infection was the most common AE in the oral agent monotherapy group.

Cough was reported more frequently in the Exubera groups than in the oral agents group. A total of 16 cough events were reported in the Exubera monotherapy group compared to 12 in the Exubera and oral agent group and 2 in the oral agent group. In the Exubera groups, about half of the cough AEs were reported in the first 4 weeks. All of the cough AEs were mild to moderate in severity. The Applicant determined the mean duration of cough based upon the reported onset to the reported end of each event to be 3.42 weeks, 3.81 weeks, and 1.62 weeks for the Exubera monotherapy group, the Exubera plus oral agent group, and the oral agent group, respectively. About half of the subjects reporting cough in the Exubera groups had a duration of cough of 2 weeks or less [N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 211-213].

Pulmonary Function Tests

Baseline pulmonary function as measured by PFTs were well-matched between the treatment groups. A review of the mean change in pulmonary function at 12 weeks shows that all three treatment groups demonstrated a small decrease in FEV_1, FVC, and DLCO. The decrease was larger in the Exubera groups than in the oral agent

monotherapy group. The Exubera plus oral agent group had the largest decline in FEV_1, FVC, and DLCO. A summary of the mean changes in pulmonary function parameters is shown in Table 116.

Table 116 Pulmonary Function Tests for Study 217-109 – Summary of Mean Changes

	Exubera n=104			Exubera + OA n=103			Oral Agents n=99		
PFT	BL	Week 12 (LOCF)	Change from BL	BL	Week 12 (LOCF)	Change from BL	BL	Week 12 (LOCF)	Change from BL
FEV_1	n=104	n= 99	n=99	n=103	n=100	n=100	n=99	n=91	n=91
Mean (L)	3.015	2.914	-0.084	2.963	2.865	-0.106	2.968	2.936	-0.053
SD	0.641	0.621	0.215	0.685	0.682	0.224	0.750	0.751	0.200
FVC	n=104	n=99	n=99	n=103	n=100	n=100	n=99	n=91	n=91
Mean (L)	3.806	3.729	-0.050	3.750	3.674	-0.084	3.723	3.712	-0.031
SD	0.826	0.813	0.239	0.911	0.906	0.267	0.964	0.941	0.271
DLCO	n=102	n=99	n=97	n=103	n=99	n=99	n=98	n=89	n=88
Mean (ml/min/mmHg)	24.861	24.006	-0.687	25.096	24.270	-0.984	25.124	25.041	-0.353
SD	6.078	5.563	3.322	6.427	6.055	3.580	6.599	6.322	3.006
TLC	n=104	n=97	n=97	n=103	n=100	n=100	n=99	n=89	n=89
Mean (L)	5.900	5.857	0.004	5.966	5.875	-0.084	5.799	5.821	-0.002
SD	1.126	1.196	0.501	1.333	1.346	0.425	1.311	1.305	0.521

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 226-235]

Reviewer's Comment: The Applicant used the last observation carried forward (LOCF) for missing data, which is displayed in Table 116. The results for the mean change from baseline were the same for the Week 12 observed data and the Week 12 (LOCF) data.

A categorical analysis of the PFT data suggests the number of subjects who had a decline of FEV_1 or FVC >10% was similar between the Exubera plus OA group and oral agent monotherapy group. The Exubera monotherapy group had fewer subjects with a decline in FEV_1or FVC >10%. The Exubera plus OA group had the most subjects with a decline in DLCO >10%. Table 117 displays the categorical analyses of the PFTs. More subjects had a decline of more than 10% in DLCO than any other PFT parameter. The majority of subjects with a significant decline in a PFT parameter continued into the extension study. The results will be discussed further in Study 217-111.

Table 117 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation in Study 217-109

	Exubera n=99			Exubera + OA n=100			Oral Agents n=91		
PFT	-10 to -15%	-15 to -20%	> -20%	-10 to -15%	-15 to -20%	> -20%	-10 to -15%	-15 to -20%	> -20%
FEV_1	6 (6.1%)	1 (1%)	2 (2%)	11 (11%)	2 (2%)	2 (2%)	8 (8.8%)	2 (2.2%)	1 (1.1%)
FVC	7 (7%)	0	0	8 (8%)	1 (1%)	1 (1%)	7 (7.7%)	2 (2.2%)	1 (1.1%)
DLCO	8 (8.2%)	6 (6.2%)	6 (6.2%)	10 (10%)	9 (9%)	10 (10%)	10 (11%)	2 (2%)	5 (5.7%)
TLC	9 (9.2%)	1 (1%)	0	7 (7%)	3 (3%)	1 (1%)	6 (6.7%)	4 (4.5%)	1 (1.1%)

Source : N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 227-236

Two subjects that did not continue into the extension study had a >15% drop in PFT parameter and a below normal value at last observation. One subject was a 63 yo male in the Exubera group who had a decline in DLCO from 26.6 to 16.4 ml/min/mmHg. The subject reportedly experienced two mild URIs during the study. The subject's end of study FEV_1 and FVC were slightly decreased from baseline (50mL and 100mL, respectively). The end of study CXR was within normal limits. One subject was a 64 yo male in the oral agent group who was a former smoker. He had a decrease in all his PFTs (FVC from 4.64L to 3.71 L, FEV_1 from 2.94L to 2.42L, DLCO from 31.2 to 19.3

ml/min/mmHg) [N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 207-209].

Chest Radiography
A chest x-ray was taken at the beginning and end of the study in each of the subjects. Four subjects had a significant change. One subject in the Exubera group had prominence of the right hilum, but the CT did not show a mass. One subject in the Exubera plus OA group showed a widened mediastinum. The other two subjects with reported abnormalities were in the OA group [N21868/N_000/2004-12-27/clinstat/diabetes/type2/109.pdf, pg 62].

10.6.4.3 Conclusions

Study 217-109 was an open-label, 3-month, parallel group study in 309 males and females with type 2 diabetes mellitus. Subjects were randomized to Exubera monotherapy, Exubera plus oral agents or oral agent therapy. The results indicate that respiratory adverse events were more common in the Exubera groups, especially the Exubera monotherapy group. Increased cough, respiratory tract infection, rhinitis, sinusitis, and sputum increased were more common in the Exubera groups than in the oral agent monotherapy group.

A review of the mean change in pulmonary function at 12 weeks shows that all three treatment groups demonstrated a decrease in FEV_1, FVC, and DLCO. The decreases appeared to be slightly greater in the Exubera groups than in the oral agent monotherapy group. The Exubera plus oral agent group had the largest decline in pulmonary function. A categorical analysis of the PFT data suggests the number of subjects who had a decline of FEV_1 or FVC >10% was similar between the Exubera plus OA group and oral agent monotherapy group. The Exubera monotherapy group had the fewest subjects with a decline in FEV_1or FVC >10%. The Exubera plus OA group had the most subjects with a decline in DLCO >10%. The majority of subjects with a decline in a PFT parameter >15% continued into the extension study. The results will be discussed further in Study 217-111. The CXR data did not suggest any significant changes associated with Exubera use.

10.6.5 Study 217-110

Efficacy and Safety of Exubera Therapy in Subjects with Type 2 Diabetes Mellitus Not Optimally Controlled with Diet and Exercise: A Three-Month, Outpatient, Parallel Comparative Trial

10.6.5.1 Protocol

Study 217-110 was a phase 3, open-label, 3-month, parallel group study in 224 males and females with type 2 diabetes mellitus not optimally controlled on a stable diet and exercise regimen. Subjects could not be any pharmacologic therapy for diabetes. Subjects with the following were excluded:

- Clinically significant abnormalities on screening CXR
- Poorly-controlled asthma, clinically significant COPD, or other significant respiratory disease

- Subjects with frankly abnormal PFTs at Week -3, defined as DLCO <75%, TLC >120% or <80%, or FEV_1<70% predicted
- Any smoking within the last 6 months

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 255-258].

A screening visit was followed by a baseline lead-in period (4 weeks) during which subjects underwent pulmonary function testing. At the end of the lead-in-period, subjects were instructed on the proper use of Exubera. Eligible subjects were then randomized to either rosiglitazone therapy or Exubera therapy (pre-meals) [N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 259].

Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, DLCO, and resting oxygen saturation. PFT testing was performed at baseline (week -3) and week 12. PFTs were performed using ATS certified methods. If a subject had a decrease of >15% in any FEV_1, FVC, TLC, FRC, or DLCO in the absence of intercurrent illness, the PFTs were repeated. If the >15% decrease persisted, then further pulmonary evaluation, including pulmonologist consultation, CXR, or HRCT was obtained. CXRs were taken at the beginning and end of the study [N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 270, 273].

Open-Label Extension
Subjects who completed the 12-week study were eligible for an open-label extension. The details of the open-label extension will be described in the review of Study 217-111.

10.6.5.2 Results

The study commenced on October 7, 1999, and was completed on March 30, 2001. Forty centers in the Unites States participated in the study. A total of 402 subjects were screened for the study and 145 were randomized, 76 to the Exubera and 69 to the rosiglitazone arm. One subject randomized to each arm never received treatment. Therefore 75 subjects received Exubera and 68 subjects received rosiglitazone treatment.

The discontinuation was similar between the treatment groups. One subject in the Exubera group discontinued due to a respiratory AE. A 56 yo female developed moderately severe bronchitis requiring antibiotic treatment. A CXR was performed and showed a minimal left lingular infiltrate. An end of study follow up CXR showed resolution of the infiltrate. She did have a decline in her PFTs, FEV_1 from 2.11 L to 1.77L, FVC from 2.75L to 2.23L, DLCO from 15.23 to 12.69 ml/min/mmHg. Subject disposition is summarized in Table 118 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 34, 173-174]
Reviewer's Comment: The study did not enroll as many subjects as specified in the protocol, which was 224.

Table 118 Subject Disposition Study 217-110		
	Exubera	Rosiglitazone
Randomized (145)	76	69
Randomized but never treated	1	1
Completed	71	63
Discontinued Study	4	5
Adverse Event	1	3
Bronchitis, pneumonia	1	0
Duodenal ulcer/gastric ulcer	0	1
Chest pain, headache, ankle edema, muscle aches	0	1
Elevated ALT	0	1
Subject defaulted (withdrew consent, lost to follow up)	2	0
Lack of efficacy	0	1
Other (includes protocol violation, does not meet entry criteria)	1	1

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 108, 110]

Reviewer's Comment: Because two subjects withdrew consent after randomization and before treatment the number of the subjects in the Exubera and rosiglitazone group is 75 and 68, respectively.

The mean age of the subjects was between 53-54 years. The majority of the subjects were Caucasian as shown in Table 119.

Table 119 Baseline Characteristics Study 217-110			
		Exubera n = 75	Rosiglitazone n = 68
Gender	Male	48 (64%)	31 (46%)
	Female	27 (36%)	37 (54%)
Age	Mean	53.0	54.4
	Range	28-76	29-80
Race	Caucasian	58 (77%)	48 (71%)
	Black	7 (9%)	10 (15%)
	Asian	1 (1%)	0
	Hispanic	9 (12%)	9 (13%)
	Other	0	1 (1%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 67]

Reviewer's Comment: A review of the summary of medical history of the subjects indicates that some subjects reported a history of asthma, bronchitis, chronic bronchitis. For example, asthma (unspecified) was reported in the past in 3 subjects and in the present in 2 subjects [N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 71].

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera group than in the rosiglitazone group. Overall, respiratory tract infection was the most common respiratory AE reported and was reported at similar frequency in both treatment groups. Increased cough, pharyngitis, respiratory disorder, and sinusitis were reported more frequently in

the Exubera group than in the rosiglitazone group. A detailed summary of the respiratory AEs is listed in Table 120. Most of the respiratory AEs were mild to moderate in severity. One case of pharyngitis in the Exubera group and one case of respiratory tract infection in the rosiglitazone group were graded as severe. None of the SAEs was respiratory [N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 151].

Table 120 Number of Subjects with Respiratory Adverse Events in Study 217-110

	Exubera n = 75	SC Insulin n = 68
Serious adverse events	0	2 (2.9)
Any adverse event	71 (94.7%)	59 (86.8%)
Respiratory	35 (46.7%)	26 (38.2%)
Bronchitis	2 (2.7%)	1 (1.5%)
Cough increased	**6 (8.0%)**	**1 (1.5%)**
Dyspnea	**3 (4.0%)**	**1 (1.5%)**
Epistaxis	**2 (2.7%)**	**0**
Pharyngitis	**4 (5.3%)**	**2 (2.9%)**
Respiratory disorder	**5 (6.7%)**	**1 (1.5%)**
Respiratory tract infection	19 (25.3%)	19 (27.9%)
Rhinitis	**5 (6.7%)**	**3 (4.4%)**
Sinusitis	**5 (6.7%)**	**2 (2.9%)**
Sputum increased	1 (1.3%)	0
Voice alteration	1 (1.3%)	0

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 151]

Reviewer's Comment: Neither SAE was respiratory related [N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 171]

Reviewer's Comment: Hypoglycemia was the most common AE in both treatment groups.

Increased cough was reported more frequently in the Exubera group than in the rosiglitazone group. A total of 7 cough events were reported in the Exubera group compared to 1 cough event in the rosiglitazone group. In the Exubera group, most of the cough AEs were reported in the first 4 weeks. All of the cough AEs were mild in severity. The Applicant determined the mean duration of cough based upon the reported onset to the reported end of each event, which was 5.37 weeks and 8 weeks for the Exubera group and rosiglitazone group, respectively. Over 50% of subjects reporting cough in the Exubera group had a duration of cough of >4-8 weeks [N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 181-183].

Pulmonary Function Tests

Baseline pulmonary function as measured by PFTs was numerically higher in the Exubera group than in the rosiglitazone group. A review of the mean change in pulmonary function at 12 weeks shows that both treatment groups demonstrated very little change in FEV_1 or FVC. Both groups demonstrated a decrease in DLCO at 12 weeks. The Exubera group had a slightly larger decrease in DLCO than the rosiglitazone group. A summary of the mean changes in pulmonary function parameters is shown in Table 121.

Table 121 Pulmonary Function Tests for Study 217-110 – Summary of Mean Changes

	Exubera			Rosiglitazone		
PFT	BL	Week 12 (LOCF)	Change from BL	BL	Week 12 (LOCF)	Change from BL
FEV_1	N=75	N=74	N=74	N=68	N=64	N=64
Mean (L)	2.984	2.966	-0.016	2.787	2.772	-0.003
SD	0.711	0.747	0.196	0.730	0.774	0.181
FVC	N=75	N=74	N=74	N=68	N=64	N=64
Mean (L)	3.721	3.710	-0.009	3.456	3.450	-0.001
SD	0.899	0.947	0.251	0.910	0.951	0.251
DLCO	N=74	N=74	N=73	N=67	N=64	N=63
Mean (ml/min/mmHg)	26.487	25.773	-0.691	24.277	23.689	-0.459
SD	6.303	6.786	2.957	6.160	6.919	2.692
TLC	N=75	N=74	N=74	N=68	N=64	N=64
Mean (L)	5.843	5.858	0.014	5.570	5.574	0.037
SD	1.150	1.287	0.626	1.234	1.315	0.459

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 195-204]

Reviewer's Comment: The Applicant used the last observation carried forward (LOCF) for missing data. The results for the mean change from baseline were the same for the Week 12 data and the Week 12 (LOCF) data.

A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group who had a decline of >10% in FEV_1, DLCO, and TLC than in the rosiglitazone group. However, more subjects in the rosiglitazone group had a decline of >10% in FVC than in the Exubera group. Table 122 displays the categorical analyses of the PFT data. DLCO appeared to have the most subjects with a decline of more than 10%.

Table 122 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation in Study 217-110

	Exubera n=74			Rosiglitazone n=64		
	-10 to -15%	**-15 to -20%**	**> -20%**	**-10 to -15%**	**-15 to -20%**	**> -20%**
FEV_1	6 (8.1%)	1 (1.4%)	0	3 (4.7%)	1 (1.6%)	0
FVC	3 (4.1%)	1 (1.4%)	0	6 (9.4%)	0	0
DLCO	7 (9.6%)	7 (9.6%)	5 (6.8%)	8 (12.7%)	1 (1.6%)	4 (6.3%)
TLC	9 (12.2%)	3 (4.1%)	1 (1.4%)	5 (7.8%)	1 (1.6%)	0

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 196-205]

Four subjects that did not continue into the extension study had a >15% drop in PFT parameter and a below normal value at last observation (2 in the Exubera group and 2 in the rosiglitazone group). One subject was a 59 yo female in the Exubera group who had a decline in DLCO from 20.5 to 10.85 ml/min/mmHg. The subject reportedly experienced a mild sinus infection, cough, and URI during the study. The subject's end of study FEV_1, FVC, and TLC all measured higher than at screening. The end of study CXR was unchanged. It should be noted that the end of study PFTs were performed at a different

laboratory than the screening laboratory. The other subject in the Exubera group discontinued from the study due to an AE. She was a 56 yo female who developed moderately severe bronchitis requiring antibiotic treatment and discontinued from the study. A CXR was performed and showed a minimal left lingular infiltrate. An end of study follow up CXR showed resolution of the infiltrate. She did have a decline in her PFTs, FEV_1 from 2.11 L to 1.77L, FVC from 2.75L to 2.23L, DLCO from 15.23 to 12.69 ml/min/mmHg.

Chest Radiography
A chest x-ray was taken at the beginning and end of the study in each of the subjects. Three subjects in the Exubera group had a significant change from baseline (subsegmental atelectasis in the RML and linear atelectasis in the LLL, F/U CXR showed resolution (Study 217-111); resolution of baseline atelectasis on the end of study CXR; possible soft tissue nodule on CXR) [N21868/N_000/2004-12-27/clinstat/diabetes/type2/110.pdf, pg 58] and [N21868/N_000/2004-12-27/crt/datasets/110/xray_1v.xpt].
Reviewer's Comment: An end of study CXR showed a possible soft tissue nodule for a subject in the Exubera group. A follow up CXR was normal.

10.6.5.3 Conclusions

Study 217-110 was an open-label, 3-month, parallel group study of Exubera in 145 males and females with type 2 diabetes mellitus who were not optimally controlled on diet and exercise. Subjects were randomized to Exubera or rosiglitazone. The results indicate that respiratory adverse events were more common in the Exubera group than in the rosiglitazone group. Increased cough, pharyngitis, respiratory disorder, and sinusitis were reported much more frequently in the Exubera group than in the rosiglitazone group.

A review of the mean change in pulmonary function at 12 weeks shows that both treatment groups demonstrated very little change in FEV_1 or FVC. Both groups demonstrated a decrease in DLCO at 12 weeks. The Exubera group had a slightly larger decrease in DLCO than the rosiglitazone group. A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group who had a decline of >10% in FEV_1, DLCO and TLC than in the rosiglitazone group. However, more subjects in the rosiglitazone group had a decline of >10% in FVC than in the Exubera group. The CXR data did not suggest any significant changes associated with Exubera use.

10.6.6 Study 217-1001

An open, randomized, parallel group study to compare the safety (104 weeks) and efficacy (24 weeks) of Exubera with metformin as adjunctive therapy in people with type 2 diabetes poorly controlled on a sulphonylurea

10.6.6.1 Protocol

Study 217-1001 was a phase 3, multinational, open-label, 104 week, randomized, parallel group design study of adjunctive treatment with metformin or Exubera in 450 subjects with type 2 diabetes mellitus who are poorly controlled on a sulphonylurea.

Subjects with type 2 diabetes poorly controlled on sulphonylurea (HbA1c 8-12%) were screened. Subjects with the following were excluded [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 561]:

- Moderate or severe asthma (PEFR $\leq$ 80%) predicted and/or oral steroids <6 months of screening
- Moderate or severe stable chronic obstructive pulmonary disease (COPD) (PEFR $\leq$ 80% predicted and/or antibiotics for chest infection < 3months of screening (Week -6).
- Clinically significant abnormalities on screening CXR
- Any smoking within the last 6 months prior to randomization.

A screening visit (Week -6) was followed by a 4 week run-in period (Week -4 to 0). At Week -4, pulmonary function tests were performed. Subjects were required to have PFTs within the following range to be eligible for randomization.

- Carbon monoxide transfer factor (Tco) $\geq$ 75%
- TLC between 80-120% predicted
- $FEV_1 \geq$ 75% predicted

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 561-562].
Reviewer's Comment: The inclusion/exclusion criteria are a little more liberal in this protocol. According to the protocol, subjects with self reported mild asthma or COPD could be enrolled in the study.

At Week 0, eligible subjects were randomized to one of the two treatment groups, metformin or Exubera and were stratified by HbA1c. All subjects continued their usual regimen/brand of sulfonylurea. Thus, the two treatment groups were the following:

- Sulphonylurea and Exubera
- Sulphonylurea and metformin

After the treatment was completed there was an additional 12 weeks of washout period.
Reviewer's Comment: Originally the protocol specified a 24 week treatment period, but this period was extended to 52 weeks (protocol amendment X, November 10, 2000), then extended to 104 weeks (protocol amendment XVII, October 26, 2001). Thus, there will be a population of subjects who completed treatment at 24 week, 52 weeks, 104 weeks.

Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, Tco, alveolar volume, Tco/VA, and resting oxygen saturation. PFT testing was performed at baseline (Week -4), Week 24, 36 (spirometry and lung volumes only), 52, 65, 78, 91, and 104. PFTs were repeated again after the 12 week washout period (Week 58/64 or Week 110/116). If a subject had a decrease of >15% in any FEV_1, FVC, TLC, FRC, or DLCO in the absence of intercurrent illness, the PFTs were repeated. If the >15% decrease persisted, then a CXR was performed and the subject was referred to a specialist. A CXR was performed at baseline and end of treatment (Week 52 or 104).
[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 593-594].

The objective of the first 24 weeks was to compare the efficacy of the two treatments. The objective for the additional 80 weeks treatment and 12 week washout period was to evaluate safety. Information regarding device durability was also collected during the study.

10.6.6.2 Results

The report for Study 217-1001 is an interim study report. The final study report for Study 217-1001 is the combined report with Study 217-1002 for the 2 year extension.

Study 217-1001 commenced on February 29, 2000, and was completed on December 20, 2001. The study was multinational. No centers in the United States participated in the study. A total of 774 subjects were screened for the study and 427 were randomized, 225 to the Exubera adjunctive therapy and 202 to the metformin adjunctive treatment arm. Four subjects who were randomized never received study medication; therefore, 423 subjects received study medication. The discontinuation rate was slightly higher in the metformin group. One subject discontinued for respiratory adverse event (bronchitis). The subject disposition for Study 217-1001 is shown in Table 123 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1101.pdf, pg 34]

Table 123 Subject Disposition Study 217-1001

	Exubera	Metformin
Randomized (427)	225	202
Randomized but never treated	3	1
Randomized and treated	222	201
Completed	207	178
Discontinued Study	15	23
Adverse Event	4	8
Respiratory AE discontinuations	1	0
Bronchitis	1	0
Lab data (increased GGT)	1	0
Subject defaulted (withdrew consent, lost to follow up)	7	5
Lack of efficacy	0	2
Other (includes protocol violation, does not meet entry criteria)	3	9

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 153-159]

Reviewer's Comment: It is unclear to this reviewer from the study report how many subjects completed the 24 week treatment period in each treatment arm. The flowsheet on page 56 of the study report is unclear. However, for the purposes of the pulmonary safety, the safety data on all randomized subjects will be reviewed.

The mean age of the subjects was between 60 years with an age range of 35-79 years. The majority of the subjects were Caucasian as shown in Table 124.

Table 124 Baseline Characteristics Study 217-1001			
		Exubera n =222	Metformin n = 201
Gender	Male	122 (55%)	102 (51%)
	Female	100 (45%)	99 (49%)
Age	Mean	60.8	60.0
	Range	37-79	35-79
Race	Caucasian	211 (95%)	192 (96%)
	Black	4 (2%)	3 (1%)
	Asian	3 (1%)	3 (1%)
	Other	4 (2%)	3 (1%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 98]

Reviewer's Comment: A review of the summary of medical history of the subjects indicates that some subjects reported a current respiratory condition, including asthma, bronchitis, chronic bronchitis, emphysema, and chronic airway obstruction [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 108].

Ten subjects in the Exubera group and 21 in the metformin group temporarily discontinued dosing due to adverse events. The respiratory AEs which led to temporary discontinuation in the Exubera group were respiratory tract infection, pneumonia, and pharyngitis.

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera group than in the metformin group. Overall, respiratory tract infection was the most common respiratory AE reported and was reported at similar frequency in both treatment groups. Increased cough, pharyngitis, pneumonia, and rhinitis were reported much more frequently in the Exubera group than in the metformin group. A detailed summary of the respiratory AEs are listed in Table 125. Most of the respiratory AEs were mild to moderate in severity. One case of pneumonia in the Exubera group was graded as severe and one case of respiratory tract infection in the metformin group was graded as severe [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 259 & 301].