Table 125 Number of Subjects with Respiratory Adverse Events for Study 217-1001

	Exubera n = 222	Metformin n = 201
Serious adverse events	6 (2.7%)	12 (6.0%)
Deaths	2 (0.9%)	1 (0.5%)
Any adverse event	183 (82.4%)	155 (77.1%)
Respiratory	62 (27.9%)	39 (19.4%)
Asthma	1 (0.5%)	0
Bronchitis	**8 (3.6%)**	**1 (0.5%)**
Cough increased	20 (9.0%)	3 (1.5%)
Dyspnea	6 (2.7%)	0
Epistaxis	0	3 (1.5%)
Pharyngitis	**10 (4.5%)**	**6 (3.0%)**
Pneumonia	**3 (1.4%)**	**1 (0.5%)**
Respiratory disorder	0	1 (0.5%)
Respiratory tract infection	23 (10.4%)	23 (11.4%)
Rhinitis	**5 (2.3%)**	**1 (0.5%)**
Sinusitis	1 (0.5%)	2 (1.0%)
Sputum increased	1 (0.5%)	1 (0.5%)
Voice alteration	1 (0.5%)	0
Other		
Allergic Reaction	2 (0.9%)	1 (0.5%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 259]

Reviewer's Comment: The SAEs reported in the study tables include SAEs reported during the extension period. The SAEs were reviewed for any respiratory SAEs. One subject in the metformin group was diagnosed with pneumocystis carinii pneumonia and deterioration of lung function. Several reports of chest pain were noted and one report of chest pain and shortness of breath was noted in the metformin group [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 329-338]

Reviewer's Comment: None of the 3 deaths were respiratory (acute cardiac failure, ventricular tachycardia and ascites with ovarian cancer) [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 338]

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 metformin group. A total of 20 cough events were reported in the Exubera group compared to 4 in the metformin group. In the Exubera group, half of the cough AEs were reported in the first 6 weeks, while the other half of the cough AEs were reported in Week 6-24. No subject discontinued due to cough. Most of the cough AEs were mild in severity. One subject in the Exubera group reported cough of moderate severity. The Applicant determined the mean duration of cough based upon the reported onset to the reported end of each event. The Applicant determined the mean duration of cough was 6.00 weeks and 2.46 weeks for the Exubera group and metformin group, respectively.

About 45% 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/type2/1001.pdf, pg 364-373]. *Reviewer's Comment: The term "increased cough" includes the following: cough, tickling cough after inhalation, dry cough, coughing, worsening of cough, clearing cough, dry cough after use of 3mg blisters and congestive cough.*

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 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 77].

Pulmonary Function Tests

Baseline pulmonary function as measured by PFTs was similar between the two treatment groups. A review of the mean change in pulmonary function at 24 weeks shows that both treatment groups demonstrated a decline in FEV_1 and FVC. The decline in the Exubera group was higher than the decline in the metformin group. The Exubera group demonstrated a decline in DLCO whereas the metformin group demonstrated an increase. A summary of the mean changes in pulmonary function parameters is shown in Table 126.

Table 126 Mean Change from Baseline Pulmonary Function Tests for Study 217-1001 at Week 24

	Exubera			Metformin		
PFT	BL	Week 24 (LOCF)	Change from BL	BL	Week 24 (LOCF)	Change from BL
FEV_1	N=222	N=202	N=202	N=200	N=175	N=174
Mean (L)	2.796	2.706	-0.098	2.844	2.796	-0.025
SD	0.739	0.703	0.247	0.742	0.751	0.212
FVC	N=221	N=202	N=202	N=199	N=175	N=173
Mean (L)	3.445	3.360	-0.086	3.508	3.455	-0.027
SD	0.923	0.894	0.260	0.895	0.894	0.240
DLCO	N=211	N=195	N=185	N=193	N=169	N=161
Mean (ml/min/mmHg)	24.827	24.558	-0.241	24.753	24.796	0.112
SD	5.767	6.076	3.762	6.176	6.186	3.609
TLC	N=222	N=201	N=201	N=199	N=174	N=172
Mean (L)	5.653	5.654	0.017	5.528	5.573	0.055
SD	1.299	1.434	0.835	1.201	1.274	0.575

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 397-424]

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 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 FEV_1, FVC, DLCO and TLC than in the metformin group. Table 127 displays the categorical analyses of the PFT data.

Table 127 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation (24 Weeks) in Study 217-1001

	Exubera			Metformin		
	-10 to -15%	-15 to -20%	> -20%	-10 to -15%	-15 to -20%	> -20%
FEV_1	19 (9.4%)	6 (3.0%)	4 (2.0%)	10 (5.7%)	2 (1.1%)	4 (2.3%)
FVC	21 (10.4%	7 (3.5%)	1 (0.5%)	12 (6.9%)	5 (2.9%)	2 (1.2%)
DLCO	17 (9.2%)	7 (3.8%)	10 (5.4%)	8 (5.0%)	6 (3.7%)	6 (3.7%)
TLC	18 (9.0%)	12 (6.0%)	6 (3.0%)	12 (7.0%)	2 (1.2%)	4 (2.3%)

The n for the categorical analyses of each PFT parameter is the same n as listed in the change from baseline in Table 126
Source : N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 400-427

Seven subjects that did not continue into the extension study had a >15% drop in PFT parameter and a below normal value at last observation (3 in the Exubera group and 4 in the metformin group). The following is a list of the Exubera subjects with the baseline and end of study PFTs [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001.pdf, pg 340-345]:

- Exubera
  - 61 yo female
    - FEV_1 1.93L → 1.62L; FVC 2.23 L → 1.90 L; DLCO (hgb adj) 22.78 → 22.85ml/min/mmHg
    - No respiratory AEs
  - 58 yo male
    - FEV_1 3.17L → 2.71L; FVC 3.50L →2.97L; DLCO (hgb adj) 34.65 → 33.90 ml/min/mmHg
    - Mild URI AE reported
  - 64 yo male
    - FEV_1 3.76L → 3.09L; FVC 4.65L → 4.05L; DLCO (hgb adj) 30.90 → 22.70 ml/min/mmHg
    - No respiratory AEs reported

Chest Radiography

A chest x-ray was taken at the beginning and end of the study in each of the subjects. The study report did not contain a summary of changes in CXR. The CXR dataset contained data for some of the subjects. Six subjects were noted to have a new change on CXR as shown below:

- Exubera
  - Bilateral atelectasis
  - Hypertrophy of left ventricle
  - Pulmonary congestion
  - Bilateral medio-basal peribronchitis
- Metformin
  - Atelectasis in lower part of left lung
  - Calcific micronodulus in the right upper field

[N21868/N_000/2004-12-27/crt/datasets/1001/xray_1v.xpt].

Conclusions

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 were randomized to Exubera or metformin as adjunctive therapy. 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.

The results of the first 24 weeks indicated that respiratory adverse events were more common in the Exubera group than in the metformin group. Increased cough, pharyngitis, pneumonia, and rhinitis were reported more frequently in the Exubera group than in the metformin group.

The mean change in pulmonary function at 24 weeks shows that both treatment groups demonstrated a decline in FEV_1 and FVC. The decline in the Exubera group was higher than the decline in the metformin group. The Exubera group demonstrated a decline in DLCO whereas the metformin group demonstrated an increase. 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, FVC, DLCO and TLC than in the metformin group. Limited CXR data was submitted in this study report and did not suggest any significant changes associated with Exubera use.

The results for the entire 104 week treatment period were combined with Study 217-1002 and will be discussed in the review of the combined 1001/1002 review.

10.6.7 Study 217-1002

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

10.6.7.1 Protocol

Study 217-1002 was a phase 3, multinational, open-label, 104 week, randomized, parallel group design study of adjunctive treatment with glibenclamide or Exubera in 450 subjects with type 2 diabetes mellitus who were poorly controlled on metformin.

Subjects with type 2 diabetes poorly controlled on metformin (HbA1c 8-12%) were screened. Subjects with the following were excluded [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 572-573]:

- Moderate or severe asthma (PEFR ≤ 80%) predicted and/or oral steroids <6 months of screening
- Moderate or severe stable chronic obstructive pulmonary disease (COPD) (PEFR ≤ 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 (T_{co}) $\geq$ 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 mild asthma or COPD could be enrolled in the study.

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

- Metformin and Exubera
- Metformin and glibenclamide

After the treatment was completed there was an additional 12 week 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 6 and 12 weeks of washout (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/type2/1002.pdf, pg 606].

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 the safety of Exubera. Information regarding device durability was also collected during the study.

A protocol amendment dated March 30, 2001, specified collection of additional pulmonary function data, specifically DLCO/VA. The DLVO/VA data was to be collected both retrospectively and prospectively [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 627].

10.6.7.2 Results

The report for Study 217-1002 is an interim study report. The final study report for Study 217-1002 is the combined report with Study 217-1002 for the 2 year extension. This results section is based upon the 24 week interim study report.

Study 217-1002 commenced on March 9, 2000, and was completed on May 9, 2002. The study was multinational. No centers in the United States participated in the study. A total of 768 subjects were screened for the study and 476 were randomized, 239 subjects to Exubera adjunctive therapy and 231 to the glibenclamide adjunctive treatment arm. Six subjects who were randomized never received study medication; therefore, 470 subjects received study medication. The discontinuation rate was higher in the glibenclamide group than in the Exubera group. Four subjects in the Exubera group discontinued due to respiratory AEs: increased cough (2), lung pain/headache/chest pain, and respiratory tract infection/sputum increased/headache. The subject disposition for Study 217-1002 is shown in Table 128 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 56, 154-159].

Table 128 Subject Disposition Study 217-1002

	Exubera	Glibenclamide
Randomized (476)	243	233
Randomized but never treated	4	2
Randomized and treated	239	231
Completed	219	205
Discontinued Study	20	26
Death	0	3
Adverse Event	8	3
Respiratory AE discontinuations	4	2
Cough	2	0
Lung pain	1	0
Respiratory tract infection/productive cough	1	0
Bronchial carcinoma	0	1
Dyspnea	0	1
Subject defaulted (withdrew consent, lost to follow up)	4	6
Lack of efficacy	0	4
Other (includes protocol violation, does not meet entry criteria)	8	10

Source : N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 56, 154-159

Nine subjects in the Exubera group and 7 in the glibenclamide group temporarily discontinued dosing due to adverse events. The respiratory AEs which led to temporary discontinuation in the Exubera group was cough in one subject [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 161-164].

The mean age of the subjects was 55 years with an age range of 36-77 years. The majority of the subjects were Caucasian as shown in Table 129.

Table 129 Baseline Characteristics Study 217-1002			
		Exubera n =239	Glibenclamide n = 231
Gender	Male	136 (57%)	132 (57%)
	Female	103 (43%)	99 (43%)
Age	Mean	55.5	55.5
	Range	37-77	36-77
Race	Caucasian	222 (93%)	220 (95%)
	Black	6 (2.5%)	4 (1.7%)
	Asian	5 (2%)	4 (1.7%)
	Other	6 (2.5%)	3 (1.3%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 97]

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera group than in the glibenclamide group. Increased cough, pharyngitis, sputum increased, respiratory tract infection, and rhinitis were reported more frequently in the Exubera group than in the glibenclamide group. A detailed summary of the respiratory AEs is listed in Table 130. Most of the respiratory AEs were mild to moderate in severity. In the Exubera group, one case of increased cough and once case of respiratory tract infection were graded as severe. One case of respiratory tract infection and one case of lung carcinoma in the glibenclamide group were graded as severe [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 257-258].

Table 130 Number of Subjects with Respiratory Adverse Events for Study 217-1002		
	Exubera n =239	**Glibenclamide n = 231**
Serious adverse events	5 (2.1%)	18 (7.8%)
Deaths	0	3
Any adverse event	192 (80%)	168 (73%)
Respiratory	72 (30%)	52 (22%)
Asthma	1 (0.4%)	0
Bronchitis	4 (1.7%)	6 (2.6%)
Carcinoma of lung	0	1 (0.4%)
Cough increased	**20 (8.4%)**	**6 (2.6%)**
Dyspnea	0	4 (1.7%)
Epistaxis	0	1 (0.4%)
Laryngitis	1 (0.4%)	0
Pharyngitis	**14 (5.9%)**	**9 (3.9%)**
Respiratory disorder	1 (0.4%)	3 (1.3%)
Respiratory tract infection	**38 (15.9%)**	**25 (10.8%)**
Rhinitis	**5 (2.1%)**	**3 (1.3%)**
Sinusitis	3 (1.3%)	3 (1.3%)
Sputum increased	**4 (1.7%)**	**1 (0.4%)**

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 257-258]

Reviewer's Comment: The SAEs table in the study report included SAEs for the entire 104 week treatment period, not just the first 24 weeks. The 44 SAEs were reviewed for any respiratory SAEs. The following SAEs were noted in the Exubera group: bronchopneumonia, thoracalgia, pneumonia, and pneumothorax/adenocarcinoma of lung. One respiratory SAE was noted in the glibenclamide/metformin group, a case of small cell bonchus carcinoma [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 329-344]

Reviewer's Comment: Five deaths were noted in the 104 week treatment period. None of the 5 deaths were respiratory (myocardial infarction (3), car accident, unknown) [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 345]

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 glibenclamide group. A total of 28 cough events were reported in the Exubera group compared to 4 in the glibenclamide group. In the Exubera group, half of the cough AEs were reported in the first 4 weeks, while the other half of the cough AEs were reported in Week 6-24. Two subjects discontinued due to cough. Most of the cough AEs were mild or moderate in severity. Three subjects in the Exubera group reported severe cough. The Applicant determined the mean duration of cough based upon the reported onset to the reported end of each event. The Applicant determined the mean duration of cough was 4.14 weeks and 3.32 weeks for the Exubera group and glibenclamide group, respectively. About 30% 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/type2/1002.pdf, pg 375-384].
Reviewer's Comment: The term "increased cough" includes the following: cough, persistent cough, excitive cough, severe cough, cough after inhalation, dry cough, coughing, coughing due to ACE inhibition and intermittent nocturnal cough.

Two cases of cancer were noted in this interim study report for Study 217-1002. One case in the Exubera group and one in the oral agent group. Subject #01336266 in the Exubera group was a 62 yo male diagnosed with squamous cell carcinoma of the lung. He had a nodule noted at screening and was treated with Exubera for 98 days before discontinuing the study. The nodule enlarged and was subsequently diagnosed with squamous cell carcinoma. Subject #00835165 in the oral agent group was a 58 year old male diagnosed with small cell bronchial carcinoma after 63 days of treatment with metformin and glibenclamide.

Pulmonary Function Tests

Baseline pulmonary function as measured by PFTs was similar between the two treatment groups. A review of the mean change in pulmonary function at 24 weeks shows that both treatment groups demonstrated a decline in FEV_1, FVC, and DLCO. The decline in FEV_1 in the Exubera group was larger than the decline in the glibenclamide group. The decline in FVC was similar between the two groups. The glibenclamide group demonstrated a larger decline in DLCO than the Exubera group. The Exubera

group actually demonstrated an increase in TLC, while the glibenclamide group demonstrated a decrease in TLC. A summary of the mean changes in pulmonary function parameters is shown in Table 131.

Table 131 Pulmonary Function Tests for Study 217-1002 – Summary of Mean Changes

	Exubera			Glibenclamide		
PFT	BL	Week 24 (LOCF)	Change from BL	BL	Week 24 (LOCF)	Change from BL
FEV_1	N=238	N=220	N=220	N=230	N=201	N=200
Mean (L)	2.991	2.895	-0.089	2.926	2.885	-0.049
SD	0.718	0.738	0.229	0.718	0.718	0.225
FVC	N=239	N=220	N=220	N=230	N=200	N=199
Mean (L)	3.643	3.584	-0.059	3.596	3.548	-0.052
SD	0.871	0.879	0.267	0.900	0.913	0.282
DLCO	N=224	N=217	N=204	N=216	N=199	N=189
Mean (ml/min/mmHg)	26.747	26.315	-0.581	26.414	25.626	-0.785
SD	6.752	6.666	3.548	6.305	6.272	3.309
TLC	N=235	N=218	N=214	N=227	N=201	N=197
Mean (L)	5.727	5.776	0.042	5.735	5.657	-0.072
SD	1.191	1.288	0.613	1.215	1.235	0.557

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 408-435]

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 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 FEV_1 than the glibenclamide group. However, for the other PFT parameters (FVC, DLCO, and TLC) the categories of decline were similar between the groups. Table 127 displays the categorical analyses of the PFT data.

Table 132 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation in Study 217-1002

	Exubera			Glibenclamide		
	-10 to -15%	**-15 to -20%**	**> -20%**	**-10 to -15%**	**-15 to -20%**	**> -20%**
FEV_1	25 (11.4%)	8 (3.6%)	3 (1.4%)	16 (8.0%)	5 (2.5%)	0
FVC	16 (7.3%)	4 (1.8%)	2 (0.9%)	20 (10.1%)	2 (1.0%)	1 (0.5%)
DLCO	25 (12.3%)	10 (4.9%)	8 (3.9%)	22 (11.6%)	16 (8.5%)	8 (4.2%)
TLC	13 (6.1%)	6 (2.8%)	5 (2.3%)	12 (6.1%)	7 (3.6%)	6 (3.0%)

The n for the categorical analyses of each PFT parameter is the same n as listed in the change from baseline in Table 126

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 411-438]

Nine subjects that did not continue into the extension study had a >15% drop in PFT parameter and a below normal value at last observation (4 in the Exubera group and 5 in the glibenclamide group). The following is a brief list of the Exubera subjects [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1002.pdf, pg 351-358]:

- Exubera
  - 70 yo female
    - DLCO (hgb adj) 20.53 → 15.49 mL/min/mmHg; FEV_1 1.92L → 1.81 L; FVC 2.30L → 2.16L
    - No respiratory AEs reported
  - 44 yo male
    - FEV_1 2.80L → 2.26L; FVC 3.87L →3.24L; DLCO (hgb adj) 39.59 → 43.22 ml/min/mmHg
    - No respiratory AEs reported
  - 64 yo female
    - FVC 2.14L → 1.85L; FEV_1 1.52L → 1.67L; DLCO (hgb adj) 15.22 → 14.79 ml/min/mmHg
    - No respiratory AEs reported
  - 50 yo male
    - FEV_1 3.20L →2.69L; FVC 3.61L →3.37L; TLC and DLCO increased
    - Flu and pharyngitis reported

Chest Radiography
A chest x-ray was taken at the beginning and end of the study in each of the subjects. The study report did not contain a summary of changes in CXR. The CXR dataset contained data for some of the subjects. None of the subjects were noted to have a new change on CXR [N21868/N_000/2004-12-27/crt/datasets/1002/xray_1v.xpt].

Conclusions

Study 217-1002 was a phase 3, multinational, open-label, 104 week, randomized, parallel group study of adjunctive treatment with glibenclamide or Exubera in 476 subjects with type 2 diabetes mellitus who were poorly controlled on a metformin. Subjects were randomized to Exubera or glibenclamide as adjunctive therapy. 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.

The results of the first 24 weeks indicated that respiratory adverse events were more common in the Exubera group than in the glibenclamide group. Increased cough, pharyngitis, sputum increased, respiratory tract infection, and rhinitis were reported much more frequently in the Exubera group than in the glibenclamide group.

Two cases of cancer were noted in this interim study report for Study 217-1002. One case in the Exubera group and one in the oral agent group. Subject #01336266 in the Exubera group was a 62 yo male diagnosed with squamous cell carcinoma of the lung. He had a nodule noted at screening and was treated with Exubera for 98 days. The nodule enlarged and was subsequently diagnosed with squamous cell carcinoma. Subject #00835165 in the oral agent group was a 58 year old male diagnosed with small cell bronchial carcinoma after 63 days of treatment with metformin and glibenclamide.

The mean change in pulmonary function at 24 weeks showed that both treatment groups demonstrated a decline in FEV_1, FVC, and DLCO. The decline in FEV_1 in the Exubera

group was larger than the decline in the glibenclamide group. The decline in FVC was similar between the two groups. The glibenclamide group demonstrated a larger decline in DLCO than the Exubera group. The Exubera group actually demonstrated an increase in TLC, while the glibenclamide group demonstrated a decrease in TLC.

The results for the entire 104 week treatment period were combined with Study 217-1001 and will be discussed in the review of the combined 1001/1002 review.

10.6.8 Study 217-1001/217-1002

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

AND

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

10.6.8.1 Protocol

The protocols for Study 217-1001 and Study 217-1002 were reviewed in Section 10.1.11.1and 10.1.12.1, respectively. Briefly, both studies are 104 week open-label, randomized, parallel group studies comparing Exubera as adjunctive therapy versus oral agent adjunctive therapy in subjects with type 2 diabetes. 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.

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. At Week 0, eligible subjects were randomized to one of the two treatment groups (Exubera or additional oral agent as adjunct therapy) for 104 week treatment period. After the treatment was completed there was a 12 week 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. When the protocols were amended, additional therapies, including SQ insulin, were allowed in all subjects.

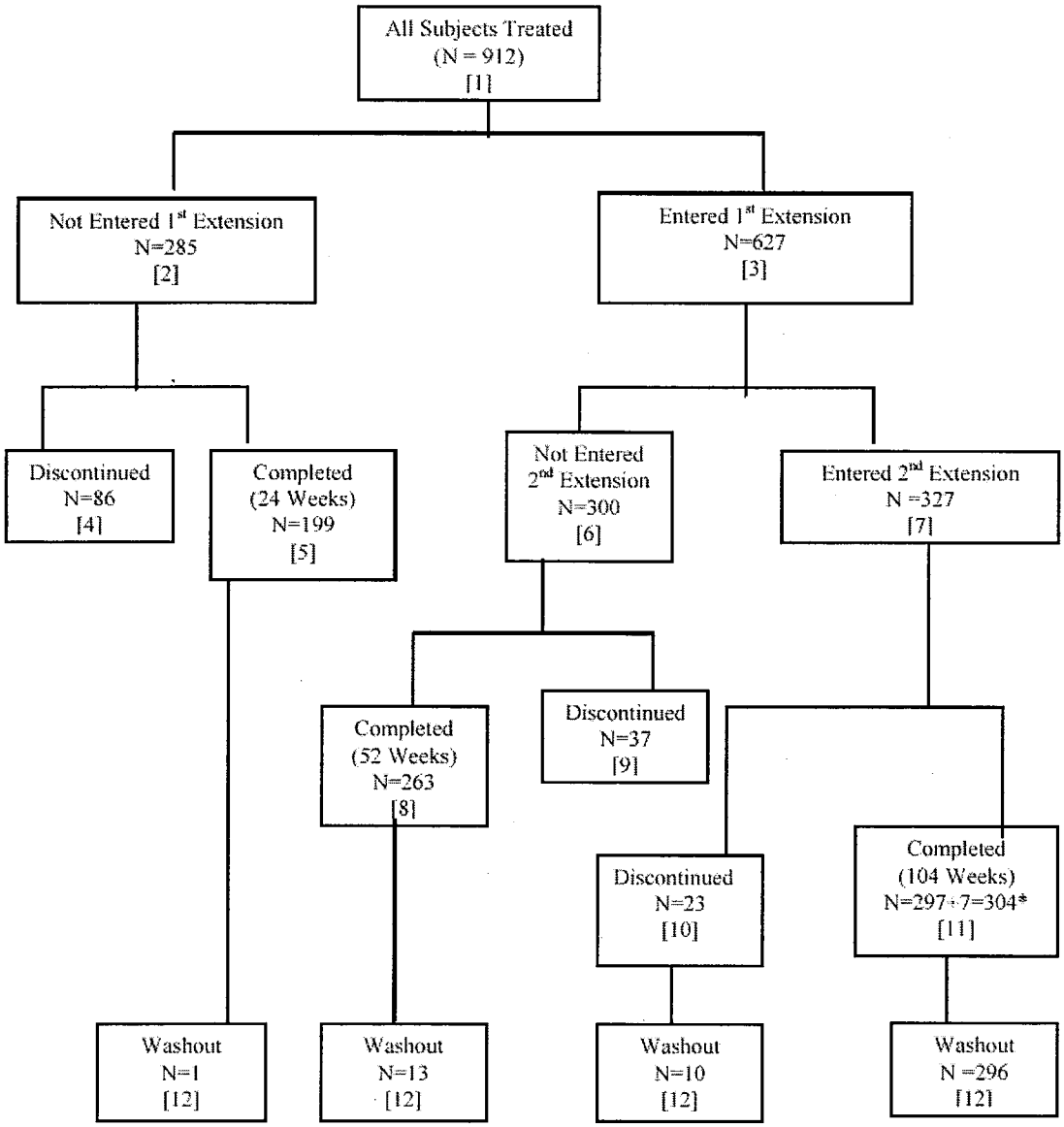
Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, Tco, alveolar volume, Tco/VA, and resting oxygen saturation. PFT testing was performed at baseline (Week -4), Week 24, 36 (spirometry and lung volumes only), 52, 65, 78, 91, and 104. PFTs were repeated again at 6 weeks and 12 weeks during the washout period (Week 58/64 or Week 110/116). A CXR was performed at baseline and end of treatment (Week 52 or 104) [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 35-36].

10.6.8.2 Results

The results are from a final study report for the combined Study 217-1001 and Study 217-1002.

Both studies were multinational. No centers in the United States participated in either study. A total of 1550 subjects were screened for the studies and 922 were randomized, 478 subjects to Exubera adjunctive therapy and 444 to oral agent adjunctive therapy. Ten subjects who were randomized never received study medication; therefore, 912 subjects received study medication (471 Exubera, 441 oral agents). The disposition for the combined studies is complex and is displayed in Figure 57. One hundred ninety-nine subjects completed the 24 week period, 263 completed the 52 week period and 297 completed the 104 week treatment period [N21868/04-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 58-60].

Figure 57 Subject Disposition Flow Chart for Studies 217-1001 and 217-1002



Source: [N21868/04-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 60]
* Includes all subjects who had ≥ 694 days of treatment, including seven who discontinued after that cutoff

Reviewer's Comment: The subject disposition flowsheet is quite complex. A total of 310 subjects completed treatment and underwent a washout period: one subject after 24 weeks, 13 subjects after 52 weeks, and 296 subjects after 104 weeks.

According to the Applicant, the following reasons were listed on the CRF for subjects not continuing into the extension period [N21868/05-07-26/response_ir_request_21jun05]:

- *Site not participating in extension*
- *Ethics Committee and/or regulatory approval not available*
- *Subject does not wish to participate*

- *Subject is not suitable for the extension study*
  - *Subjects who withdrew from the study for whatever reason during the trial period*
  - *Subjects who finished the study before the decision to extend was made*
- *Reason missing.*

The majority of subjects who discontinued from the Exubera group due to AEs were due to respiratory AEs. Cough was the most common respiratory AE leading to discontinuation. Table 133 displays the disposition for Studies 217-1001 & 217-1002.

Table 133 Subject Disposition Studies 217-1001 & 217-1002

	Exubera	Oral Agents
Randomized (922)	478	444
Randomized but never treated	7	3
Randomized and treated	471	441
Analyzed at 24 weeks (199 completed 24 weeks and stopped)	425	380
Analyzed at 52 weeks (263 completed 52 weeks and stopped)	315	265
Analyzed at 104 weeks (297 completed 104 weeks and stopped)	155	141
Week 104 LOCF	457	423
Discontinued Study	71	82
Death	1	3
Adverse Event	26	17
Discontinuations due to respiratory AEs	15	2
Cough	7	0
Lung pain/respiratory disorder	1	0
Respiratory tract infection/productive cough	1	0
Lung carcinoma	1	1
Dyspnea	1	1
Cough and dyspnea	1	0
Bronchitis	1	0
Bronchospasm	1	0
Asthma	1	0
Lab abnormality	1	0
Subject defaulted (withdrew consent, lost to follow up)	24	30
Lack of efficacy	1	7
Other (includes protocol violation, does not meet entry criteria)	19	24

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 189-204]

Reviewer's Comment: It is unclear to this reviewer why Table 1.4.1 (Discontinuations from Study, All Subjects) lists 4 total deaths, but the individual listings of deaths lists 8 deaths. The individual listings were reviewed and there were no respiratory deaths noted [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 340-341].

The baseline characteristics of the subjects were discussed in the individual studies and will not be addressed again in this combined study review.

Respiratory Adverse Events

Safety analyses were based on three cohorts: Week 104 completers (n=304), all subjects (n=912), and the washout cohort (n=320). Although the Applicant considers the Week 104 completers the primary cohort of interest, the safety results are presented for all subjects in the following sections.

Respiratory adverse events were more common in the Exubera group than in the oral agent group. Increased cough, dyspnea, asthma, sputum increased, and respiratory tract infection were reported more frequently in the Exubera group than in the oral agent group. A detailed summary of the respiratory AEs for all subjects is shown in Table 134. Most of the respiratory AEs were mild to moderate in severity [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 251].

Table 134 Number of Subjects with Respiratory Adverse Events for Study 217-1001 & Study 217-1002 All Subjects

	Exubera n =471	Oral Agent n =441
Serious adverse events	48 (10%)	51 (11.6%)
Any adverse event	416 (88%)	360 (82%)
Respiratory	**219 (46%)**	**149 (34%)**
Apnea	1 (0.2%)	0
Asthma	**6 (1.3%)**	**3 (0.7%)**
Bronchitis	25 (5.3%)	23 (5.2%)
Carcinoma of lung	1 (0.2%)	1 (0.2%)
Cough increased	**71 (15%)**	**18 (4%)**
Dyspnea	**14 (3.0%)**	**8 (1.8%)**
Emphysema	1 (0.2%)	0
Epistaxis	3 (0.6%)	0
Laryngitis	2 (0.4%)	1 (0.2%)
Lung disorder	1 (0.2%)	0
Lung edema	0	1 (0.2%)
Pharyngitis	36 (7.6%)	26 (5.9%)
Pneumonia	8 (1.7%)	4 (0.9%)
Respiratory disorder	10 (2.1%)	6 (1.4%)
Respiratory tract infection	**102 (22%)**	**81 (18.4%)**
Rhinitis	20 (4.2%)	13 (2.9%)
Sinusitis	9 (1.9%)	9 (2.0%)
Sputum increased	**13 (2.8%)**	**3 (0.7%)**
Voice alteration	5 (1.1%)	2 (0.5%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 251]

Reviewer's Comment: The SAEs were reviewed for respiratory SAEs. The following SAEs were noted in the Exubera group: pneumonia/AMI/VFIB/CHF, vocal cord polyp, asthma, bronchopneumonia, thoracalgia, pneumonia, metastatic bronchial carcinoma, epistaxis, pneumothorax/adenocarcinoma of the lung [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 288-339].

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

Three cases of lung cancer were noted in this combined study report. Two cases in the Exubera group and one in the oral agent group. Subject #01336266 in the Exubera group was a 62 yo male diagnosed with squamous cell carcinoma of the lung. He had a nodule noted at screening and was treated with Exubera for 98 days. The nodule enlarged and was subsequently diagnosed with squamous cell carcinoma. Subject 01195236 was a 67 yo male diagnosed with metastatic bronchial carcinoma after 663 days of treatment. The subject had a history of asbestos exposure and smoking. Subject #00835165 in the oral agent group was a 58 year old female diagnosed with small cell bronchial carcinoma after 63 days of treatment with metformin and glibenclamide [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 702, 943, 957].
Reviewer's Comment: It is difficult to draw any firm conclusions from these three cases of lung cancer.

Increased cough was reported more frequently in the Exubera group than in the oral agents group. A total of 92 cough events were reported in the Exubera group compared to 18 in the oral agent group. In the Exubera group, over half of the cough AEs were reported in the first 10-14 weeks. Seven subjects in the Exubera group discontinued due to cough. Most of the cough AEs were mild or moderate in severity [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 342-343].

Pulmonary Function Tests

Baseline pulmonary function as measured by PFTs was similar between the two treatment groups. The mean change in pulmonary function for all subjects was reviewed at Week 104, Week 104 (LOCF), and after 12 weeks of washout. A review of the mean change in pulmonary function at 104 weeks and Week 104 (LOCF) shows that both treatment groups demonstrated a decline in FEV_1, FVC, and DLCO. The decrease in FEV_1 and FVC was larger in the Exubera group, while the decrease in DLCO was larger in the oral agents group. The Exubera group demonstrated a decline in TLC, while the oral agents group demonstrated an increase in TLC.

After the 12 week washout period, the FEV_1 and FVC were essentially unchanged from Week 104 observed in the Exubera group. In the oral agent group, the FEV_1 and FVC showed some additional decline after the 12 week washout period. The DLCO improved slightly in both groups after the 12 week washout period. A summary of the mean changes in pulmonary function parameters is shown in Table 135.

Table 135 Summary of Mean Changes in Pulmonary Function Tests for Studies 217-1001 & 217-1002 (All Subjects)

	Exubera				Oral Agents			
PFT	BL	Week 104	Week 104 (LOCF)	12 Week W/O	BL	Week 104	Week 104 (LOCF)	12 Week W/O
FEV_1	N=471	N=143	N=436	N=132	N=439	N=126	N=380	N=128
Mean (L)	2.901	2.663	2.767	2.689	2.892	2.709	2.785	2.689
Δ from BL		-0.170	-0.134	-0.164		-0.128	-0.103	-0.150
FVC	N=470	N=143	N=436	N=132	N=438	N=125	N=379	N=127
Mean (L)	3.557	3.342	3.456	3.345	3.565	3.412	3.477	3.394
Δ from BL		-0.121	-0.102	-0.124		-0.112	-0.084	-0.147
DLCO	N=445	N=136	N=410	N=112	N=418	N=119	N=360	N=119
Mean(ml/min/mmHg)	25.972	23.977	25.130	24.218	25.742	23.975	24.782	24.569
Δ from BL		-1.529	-0.839	-1.253		-1.583	-1.037	-1.149
TLC	N=467	N=143	N=432	N=132	N=435	N=125	N=375	N=127
Mean (L)	5.708	5.559	5.690	5.515	5.649	5.597	5.632	5.582
Δ from BL		-0.022	-0.006	-0.035		0.008	0.006	-0.030

LOCF – last observation carried forward; W/O – washout; BL – baseline
Source: N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 344, 347, 353, 356, 365, 371, 374

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 and FVC than the oral agent group. However, for the other PFT parameters (DLCO, and TLC) the categories of decline were similar between the groups. Table 136 displays the categorical analyses of the PFT data.

Table 136 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation in Studies 217-1001 & 217-1002 (All Subjects)

	Exubera			**Oral Agents**		
	-10 to -15%	**-15 to -20%**	**> -20%**	**-10 to -15%**	**-15 to -20%**	**> -20%**
FEV_1	47 (10.8%)	23 (5.3%)	20 (4.6%)	43 (11.3%)	14 (3.7%)	11 (2.9%)
FVC	40 (9.2%)	19 (4.4%)	12 (2.8%)	39 (10.3%)	13 (3.4%)	8 (2.1%)
DLCO	52 (12.7%)	30 (7.3%)	29 (7.1%)	56 (15.6%)	29 (8.1%)	22 (6.1%)
TLC	39 (9.0%)	16 (3.7%)	9 (2.1%)	25 (6.7%)	9 (2.4%)	13 (3.5%)

The n for the categorical analyses of each PFT parameter is the same n as listed as the Week 104 (LOCF) in Table 135

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, pg 345, 354, 363]

Chest Radiography

A chest x-ray was taken at the beginning and end of the extension period. The study report only contained a summary of changes in CXR for the Week 104 completers population. However, the dataset (Section 13, Table 20), appeared to have the CXR data for all subjects. The following table displays the changes from baseline noted on CXR. In general, more CXR changes were noted in the Exubera group than in the comparator group.

Table 137 Summary of Chest X-Ray Changes From Baseline in Study 1001-1002			
Study Number	**Patient Number**	**Exubera**	**Comparator**
1001	00043011	Atelectasis	
1001	00381084	Minor arterial redistribution of pulmonary circulation	
1001	00452393	Enhanced vascular picture	
1001	00471103	Left ventricular hypertrophy	
1001	00472009	Pulmonary congestion	
1001	01301253	Peribronchitis	
1001	01333308	?Left ventricular hypertrophy	
1001	01333331	Nodule (F/U CT negative)	
1001	01412067	Atelectasis and pulmonary node (F/U CXR nl)	
1001	01423058	Cardiomegaly	
1001	01423430	Cardiomegaly	
1001	00452344		Transparent lungs,
1001	00453361		Atelectasis
1001	00472387		? Granuloma
1001	00590133		S/P Peribronchitis
1001	01301254		Calcific micronodulus
1001	01400302		Rib fracture
1001	01413399		Focal consolidation
1002	00035021	Diffuse inflammatory change	
1002	00297349	Peribrachial thickening	
1002	00357011	Infiltrate	
1002	00375063	Chronic heart failure	
1002	00455079	Transparent lungs, enhanced vascular picture	
1002	00468315	Pulmonary venous enrichment	
1002	00477393	?Tumor (CT and biopsy → thymoma)	
1002	01195236	Infiltrative changes →lung adenocarcinoma	
1002	01275252	Pleural adhesions	
1002	01308330	Peribronchitis	
1002	01335267	Chronic bronchitis, ?early bronchiectasis	
1002	00357327		Pulmonary edema
1002	00516094		?COPD
1002	00745151		?accentuation of bronchitis system
1002	01086285		?Slight decompensatio cordos
1002	01308329		Increase left ventricle
1002	01427041		Metallic clips present
Source : N21868/N_000/2004-12-27/clinstat/diabetes/type2/1001-1002.pdf, Section 13, Table 20			

10.6.8.3 Conclusions

Studies 217-1001 and 217-1002 were phase 3, multinational, open-label, 104 week, randomized, parallel group study of adjunctive treatment with an oral agent or Exubera in 912 subjects with type 2 diabetes mellitus. Subjects were randomized to Exubera or an oral agent as adjunctive therapy. 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.

More subjects discontinued due to respiratory AEs in the Exubera group than in the oral agent group. The primary respiratory AE leading to discontinuation was cough. Respiratory adverse events were more common in the Exubera group than in the oral agent group. Increased cough, dyspnea, asthma, respiratory tract infection, and sputum

increased were reported more frequently in the Exubera group than in the oral agent group.

Three cases of lung cancer were noted in the final study report. Two cases in the Exubera group and one in the oral agent group. Subject #01336266 in the Exubera group was a 62 yo male diagnosed with squamous cell carcinoma of the lung. He had a nodule noted at screening and was treated with Exubera for 98 days. The nodule enlarged and was subsequently diagnosed with squamous cell carcinoma. Subject 01195236 was a 67 yo male diagnosed with metastatic bronchial carcinoma after 663 days of treatment. The subject had a history of asbestos exposure and smoking. Subject #00835165 in the oral agent group was a 58 year old female diagnosed with small cell bronchial carcinoma after 63 days of treatment with metformin and glibenclamide.

A review of the mean change in pulmonary function at Week 104 and Week 104 (LOCF) showed that both treatment groups demonstrated a decline in FEV_1, FVC, and DLCO. The decrease in FEV_1 and FVC were larger in the Exubera group, while the decrease in DLCO was larger in the oral agents group. The Exubera group demonstrated a decline in TLC, while the oral agents group demonstrated an increase in TLC. After the 12 week washout period, the FEV_1 and FVC were essentially unchanged from Week 104 observed in the Exubera group. In the oral agent group, the FEV_1 and FVC showed some additional decline after the 12 week washout period. The DLCO improved slightly in both groups after the 12 week washout period.

A number of changes on CXR were noted during the study, but it is difficult to draw any definitive conclusions from the CXR data.

10.7 Review of Individual Study Reports from Ongoing Studies in Type 2 Diabetes

10.7.1 Study 217-1029 (Ongoing)

Efficacy and Safety of Inhaled Human Insulin Compared with Subcutaneous Human Insulin Therapy in Adult Subjects with Type 2 Diabetes Mellitus: A Two-year, Outpatient, Open-label, Parallel-Group Comparative Trial

10.7.1.1 Protocol

Study 217-1029 is a phase 3, open-label, 2 year, parallel group outpatient study in 600 males and females with type 2 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. The 2 year comparative treatment phase is followed by a 6 month follow up phase. 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 CXR
- Subjects with poorly controlled asthma, significant COPD, or history of any other significant respiratory 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 glucocorticoids

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 491-494].

A screening visit 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. Both short acting and long acting insulin will be continued throughout the study. At Week -3, subjects undergo PFTs to confirm eligibility. 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. As stated above, both short acting and long acting insulin are continued in both treatment groups throughout the study. At the end of the 2 year treatment comparator phase, all subjects who received Exubera resume the SC insulin regimen used during run-in for a 6 month follow up phase [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 494-498].

Safety monitoring includes AEs, laboratories, CXR, and pulmonary function testing. PFTs included: spirometry, lung volumes by gas dilution, and DLCO. PFTs are performed according to ATS criteria. PFTs are performed in a fasting state, pre-insulin dose. Full PFT testing is performed during the run-in period (Week -3, -2, -1). In addition, full PFT testing is performed at Week 12 and Months 6, 9, 12, 15, 18, 21, and 24 as well as Months 1, 3, and 6 following study completion. If a subject has 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 persisted, then further pulmonary evaluation was obtained [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 511, 519, 522-523].

CXRs are taken at the screening, Month 12 and 24. At participating sites, approximately 100 subjects will undergo high resolution CT scans (HRCTs). Subjects are recruited prior to randomization and enrollment will continue until at least 50 subjects randomized to Exubera have been enrolled in the substudy or enrollment in the parent protocol is complete. The selected cut HRCTs are performed without contrast by taking 1mm cuts starting 2 cm above the carina and continuing inferiorly every 2 cms for a total of 10 cuts. An HRCT is obtained at Week -1 prior to randomization. Follow up HRCTs are obtained Month 12 and 24. All baseline and Month 12 original HRCTs are forwarded together to Pfizer. HRCTs are forwarded to a central radiology site that is blinded to treatment group [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 532].
Reviewer's Comment: The HRCT substudy was not part of the original protocol, but was part of a December 11, 2002, protocol amendment.

A cough questionnaire was completed at baseline (Week 0) and if cough was 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/type2/1029.pdf, pg 524-525].

The primary endpoints of the study are the annual rate of change for the PFT parameters FEV_1 and DLCO. An interim analysis to assess safety is specified when approximately >70% of subjects have 1 year data [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 506, 515].

The Applicant also administered the Baseline Dyspnea Index at baseline (Week -1). The Transitional Dyspnea Index is administered at Weeks 4, 12, Months 6, 12, 18, and 24 plus Months 1, 3, and 6 post-study completion [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 499].

10.7.1.2 Results

Study 217-1029 commenced on June 17, 2002, and is currently ongoing. A total of 630 subjects were randomized, but 625 were treated, 314 with Exubera and 311 with subcutaneous insulin. More subjects have discontinued due to AEs in the Exubera group. Of the subjects who have discontinued due to AEs in the Exubera group, the majority of the subjects discontinued due to respiratory AEs. 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. Common respiratory AEs leading to temporary discontinuation were cough, bronchitis, asthma, and URI. Subject disposition is summarized in Table 138 [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 168-184].

Table 138 Subject Disposition for Ongoing Study 217-1029 Interim Study Report		
	Exubera	SC Insulin
Randomized (630)	316	314
Randomized but never treated	2	3
Discontinued	55	51
Subject died	1	0
Adverse Event	**12**	**2**
Asthma exacerbation/acute bronchitis	**1**	**0**
Cough increased	**2**	**0**
Asthma/bronchospasm/cough increased/URI	**1**	**0**
Asthma	**2**	**0**
Asthma/cough increased/dyspnea	**1**	**0**
Dyspnea	**1**	**0**
Pharyngitis	**1**	**0**
Lack of efficacy	3	2
Other (includes protocol violation)	13	16
Subject defaulted (includes lost to F/U)	26	31
Source : N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 168-173, 277		

Reviewer's Comment: The one subject death was due to metastatic colon cancer.
Reviewer's Comment: The Applicant's pulmonary narratives provided additional information on subjects discontinued for respiratory AEs. The following are brief summaries of the subjects discontinued for respiratory AEs in the Exubera group [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 168-184]:

- *10251913 – 64 yo F discontinued on Day 299 due to bronchitis/asthma exacerbation; developed acute bacterial bronchitis on Day 292 requiring tx and experienced asthma exacerbation (also SAE);subject had reported sinusitis, rhinitis, URI, bronchitis, wheezing, dyspnea, and moderate cough; CXR unchanged; PFTs unchanged from baseline; HRCT without significant findings; repeat HRCT with subtle central lobular emphysematous changes; 3rd HRCT without acute changes*
- *1029788 – 65 yo M discontinued on ~ 5 mo due to cough; CXR and PFTs unchanged*
- *10452319 – 68 yo M discontinued due to possible bronchospasm reaction to Exubera on Day 21*
- *10652783 – 58 yo M who developed cough on Day 2 and discontinued on Day 8; PFTs unchanged*
- *10681197 – 56 yo M developed moderate asthma on Day 296; seen by pulmonary consultant who noted a questionable h/o asthma and noted decline in PFTs ? secondary to Exubera; discontinued from study Day 366; CXR and HRCT unchanged; PFTs with decline in FEV_1 12% and decline in FVC 11% from baseline*
- *10833445 – 58 yo M discontinued on Day 73 due to cough, bronchospasm, dyspnea; subject also c/o allergies, rhinitis, cough (moderate); CXR unchanged; no post-randomization PFTs obtained*

- *10853552 – 50 yo M discontinued due to acute respiratory failure and dyspnea; subject hospitalized for bacterial sepsis and acute respiratory failure (dyspnea) following cholecystectomy*
- *11135158 – 67 yo F discontinued due to wheezing when lying down which developed on Day 149; discontinued on Day 310 due to wheezing; seen by pulmonary consultant who related wheezing to Exubera; wheezing resolved 22 days after discontinuation of Exubera*

The mean age of the subjects was 55-57 years and the majority of the subjects were Caucasian and male as shown in Table 139.

Table 139 Baseline Characteristics for Ongoing Study 217-1029
Interim Study Report

		Exubera n = 314	SC Insulin n = 311
Gender	Male	204 (65%)	193 (62%)
	Female	110 (35%)	118 (38%)
Age	Mean	56.7	55.5
	Range	34-75	33-75
Race	Caucasian	233 (74%)	222 (71%)
	Black	27 (9%)	28 (9%)
	Asian	6 (2%)	6 (2%)
	Hispanic	38 (12%)	42 (14%)
	Other	10 (3%)	13 (4%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 90]

Respiratory Adverse Events

Respiratory adverse events were more common in the Exubera group than in the SC insulin group. Increased cough, bronchitis, epistaxis, pharyngitis, sputum increased, and rhinitis were more common in the Exubera group than in the SC insulin group. Most of the respiratory AEs were mild to moderate in severity except four in the Exubera group (asthma (2), bronchitis, cough) and 1 in the SC insulin group (respiratory tract infection), which were severe. Some of the SAEs were respiratory . A detailed summary of the respiratory SAEs and AEs is listed in Table 140.

Table 140 Number of Subjects with Respiratory Adverse Events in the Ongoing Study 217-1029 (Interim Report)

	Exubera n = 314	SC Insulin n = 311
Serious adverse events	22 (7%)	23 (7.4%)
Shortness of breath	0	2
Asthma exacerbation	1	0
Pneumonia	0	1
Acute bronchospasm/?allergic reaction	1	0
Acute bronchitis	1	0
Respiratory failure	1	0
Cough	1	0
Any adverse event	308 (98%)	299 (96%)
Respiratory	**237 (76%)**	**183 (59%)**
Asthma	12 (3.8%)	7 (2.3%)
Bronchitis	**23 (7.3%)**	**11 (3.5%)**
Cough increased	**109 (35%)**	**30 (9.6%)**
Dyspnea	11 (3.5%)	7 (2.3%)
Edema of pharynx	1 (0.3%)	0
Epistaxis	**6 (1.9%)**	**2 (0.6%)**
Laryngitis	3 (1%)	1 (0.3%)
Lung disorder	2 (0.6%)	1 (0.3%)
Pharyngitis	**37 (11.8%)**	**29 (9.3%)**
Pleural disorder (pneumothorax)	0	1 (0.3%)
Pneumonia	2 (0.6%)	2 (0.6%)
Respiratory disorder	22 (7.0%)	29 (9.3%)
Respiratory tract infection	112 (36%)	105 (34%)
Rhinitis	**35 (11%)**	**25 (8%)**
Sinusitis	29 (9.2%)	27 (8.7%)
Sputum increased	**8 (2.5%)**	**3 (1.0%)**
Voice alteration	3 (1.0%)	0

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 200, 209-210, 249-275]

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. Three subjects in the Exubera group discontinued from the study due to cough AEs. There were no subjects discontinuing due to cough in the SC insulin group. The following is a summary of the discontinuations due to cough AEs.

- 65 yo subject (1029788) developed cough on Day 90 lasting 10 days. The subject was discontinued 2 months later
- 58 yo subject (10652783) developed cough on Day 2, which led to discontinuation on Day 8; Subject's cough resolved 6 months after discontinuation
- 58 yo subject (10833445) developed moderate cough on Study Day 49, which resolved after 3 weeks; he subsequently developed bronchospasm and dyspnea and was discontinued from the study; cough developed on last day of treatment (Day 73) and has not resolved

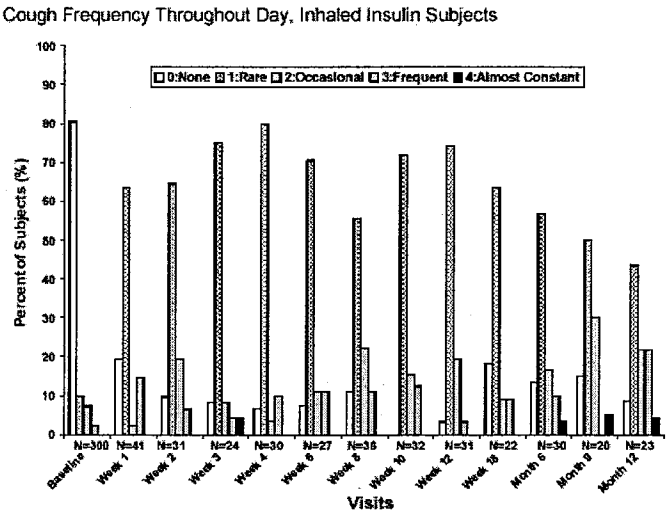
One hundred nine subjects in the Exubera group reported 138 cough events, while 30 subjects in the SC insulin group reported 32 cough events. In the Exubera group, over half of the cough AEs were reported in the first 3 months [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 342-343].

The majority 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 Applicant determined the duration of cough was 9.30 weeks and 6.68 weeks for the Exubera group and SC insulin group, respectively. Of the 138 cough events in the Exubera group, 34 were of duration between 1 to 3 months and 42 were of duration 3-6 months [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 341-345].

This study included a cough questionnaire assessing 6 domains of cough on a quantitative scale. The following is a synopsis of the results of the cough questionnaire to date [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 345-350]:

- Cough frequency at night
  - In Exubera group, most report none/rare/occasional; 3 report frequent; 1 report almost constant
- Cough frequency throughout the day
  - In Exubera group, most report rare (cough only after Exubera or only now and then)/occasional (less than hourly), some report frequent (one or more times an hour), 4 report almost constant (2SC subjects rated constant daytime cough). At month 12, there appears to be more subjects with frequent cough than earlier in the study as shown in Figure 58

Figure 58



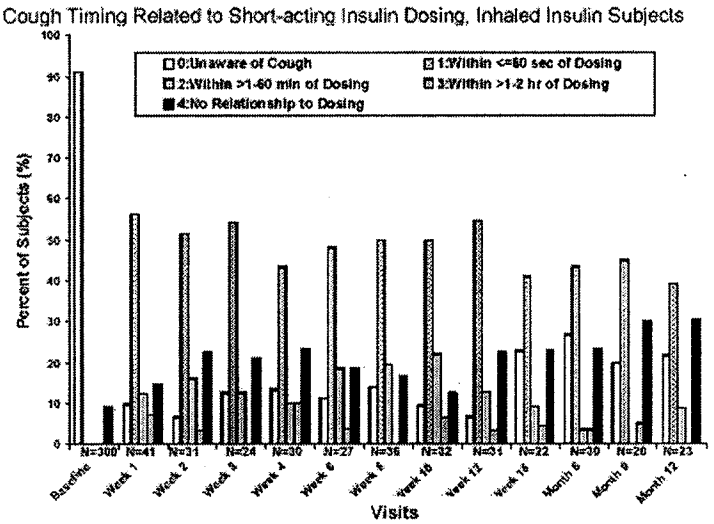
[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 69]

- Cough severity throughout the day
  - In Exubera group, most report mild (does not interfere with usual activity), some moderate (must stop activity during coughing episode), 8 report marked (must stop activity during and for a brief period after coughing

episode); 1 report severe (stops all activity for some time and is exhausting); 2 SC insulin subjects rate cough as severe

- Cough timing related to short-acting insulin dosing
  - In Exubera group, most within 60 seconds of dosing as shown in Figure 59; however, many report within 1to 60 minutes, within hours, or no relationship to dosing

Figure 59



[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 70].

- Cough severity related to insulin dosing
  - In Exubera group, most mild or unaware of coughing, few moderate severity (must stop activity during coughing), 5 marked (must stop activity during and for a brief period after coughing), 1 severe (stops all activity for some time and is exhausting)
- Sputum production
  - In Exubera group, most never or rarely, although some report occasionally, frequently, or 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; although there were some subjects who reported occasional and frequent daytime cough frequency. The cough was predominantly mild to moderate in severity and non-productive. Initially most subjects reported the cough occurred within 60 seconds of insulin dosing; however, by Month 12, the number of subjects reporting cough within 60 seconds of insulin dosing and the cough with no relationship to dosing was similar.

The Applicant reported the results for the BDI/TDI. Baseline dyspnea indices were similar between treatment groups. At Month 12, the mean TDI total score was essentially unchanged in the Exubera group (-0.01), while the mean TDI total score decreased slightly in the SC insulin group (-0.05) [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 74].

Reviewer's comment: A decline in the TDI score indicates a deterioration.

Pulmonary Function Tests

The Applicant performed the interim analysis on the PFTs for the "full analysis set, FEV_1" which includes every subject who received at least one dose of study treatment, had a baseline FEV_1 measurement, and at least one post-baseline FEV_1 measurement. The "full analysis set, FEV_1" includes 306 subjects in the Exubera group and 302 subjects in the SC insulin group. An additional dataset, the "Month 12 Completers Analysis Set," includes subjects with baseline and Month 12 FEV_1 data who received study drug for at least 50% of the required treatment duration. The Month 12 Completers Analysis Set includes 228 subjects in the Exubera group and 235 subjects in the SC insulin group.

Baseline FEV_1 was well-matched between the treatment groups. A review of the mean change in FEV_1 shows that the Exubera group had a larger decline in FEV_1 than the SC insulin group. The increase in decline was noted at Week 12; however, the mean change from baseline was similar at Months 6 and 9. However, by Month 12, the Exubera group had a larger decline in FEV_1 than the SC insulin group. A summary of the mean change in FEV_1 is shown in Table 141.

Table 141 FEV_1 Mean Baseline and Observed Change from Baseline Interim Results Study 1029, Full Analysis Set

	Exubera			SC Insulin		
	N	Mean L (SD)	Mean Change from BL, L	N	Mean L (SD)	Mean Change from BL, L
Baseline	306	2.91 (0.68)		302	2.93 (0.71)	
Week 12	293	2.85 (0.67)	-0.06	290	2.93 (0.70)	-0.01
Month 6	282	2.89 (0.68)	-0.05	281	2.90 (0.71)	-0.05
Month 9	265	2.86 (0.68)	-0.08	275	2.88 (0.72)	-0.07
Month 12	227	2.85 (0.65)	-0.09	235	2.88 (0.72)	-0.07

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 367]

The annualized rate of change in FEV_1 was one of the pre-specified primary endpoints. The Applicant reports the annual rate of change as -0.083 L/yr in both the Exubera and Sc insulin group (Month 12 Completers Analysis Set) [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 364].

Baseline DLCO was well-matched between the treatment groups. A review of the mean change in DLCO shows that the Exubera group had a larger decline in DLCO than the SC insulin group. The increase in decline was noted at Week 12; however, the mean change from baseline was higher in the SC insulin group at Month 9. However, by Month 12, the Exubera group had a larger decline in mean DLCO than SC insulin. A summary of the mean change in DLCO is shown in Table 142.

**Table 142 DLCO (ml/min/mmHg) Mean Baseline and Observed Change from Baseline
Interim Results Study 1029, Full Analysis Set**

	Exubera			SC Insulin		
	N	Mean (SD)	Mean Change from BL	N	Mean (SD)	Mean Change from BL
Baseline	305	24.16 (5.55)		301	23.95 (5.72)	
Week 12	292	23.58 (5.56)	-0.55	291	23.78 (5.46)	-0.26
Month 6	279	23.73 (5.45)	-0.55	282	23.60 (5.72)	-0.38
Month 9	266	23.71 (5.39)	-0.66	271	23.24 (5.56)	-0.73
Month 12	226	23.81 (5.14)	-0.75	233	23.46 (5.85)	-0.49

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 372]

The annualized rate of change in DLCO was one of the pre-specified primary endpoints. The Applicant reports the annual rate of change as -0.690 ml/min/mmHg/yr in the Exubera group and -0.545 ml/min/mmHg/yr in the SC insulin group (Month 12 Completers Analysis Set) [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 364].

A categorical analysis of the PFT data suggests that there were a similar number of subjects in both treatment groups who demonstrated a decrease in FEV_1 of >10% at Week 12. By Month 12, more subjects in the Exubera group demonstrated a decline in FEV_1 >10%. For DLCO, more subjects in the Exubera group demonstrated a decrease in DLCO of >10%. Table 143 displays the results for the categorical analyses of the PFT data.

**Table 143 Categorical Analyses of Percent Change in PFTs from Baseline to Month 12 in Study 217-1029 Interim Analysis
Full Analysis Set**

	Exubera			**Subcutaneous Insulin**		
	-10 to -15%	**-15 to -20%**	**> -20%**	**-10 to -15%**	**-15 to -20%**	**> -20%**
FEV_1 – Wk 12	11 (3.8%)	1 (0.3%)	1 (0.3%)	9 (3.1%)	1 (0.3%)	1 (0.3%)
FEV_1 – Month 12	15 (6.6%)	4 (1.8%)	3 (1.3%)	11 (4.7%)	2 (0.9%)	1 (0.4%)
DLCO – Wk 12	26 (8.9%)	5 (1.7%)	0	14 (4.8%)	3 (1.0%)	1 (0.3%)
DLCO – Month 12	26 (11.5%)	6 (2.7%)	3 (1.3%)	20 (8.6%)	4 (1.7%)	3 (1.3%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 366, 371]

Narratives were written for pulmonary SAEs, significant new CXR findings, and abnormal PFT (>15% decline from baseline into the abnormal range). The following is a brief synopsis of the narratives for subjects with change in PFTs [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1027.pdf, pg 302-334].

- Exubera
  - 10592620 – 50 yo F discontinued on Month 9 due to decline in PFTs and difficulty in performing PFTs (near syncope); FEV_1 declined from 3.69L to 3.35L; FVC declined from 4.63L to 3.83L (-17%); reported cough – pulmonologist thought secondary to Exubera

- 10691288 – 49 yo F discontinued from study on Day 36 for use of prednisone and decline in DLCO (-20%); no other changes in PFTs; reported cough

Reviewer's Comment: The narrative did not give the reason for the steroid use.

- 11114859 – 68 yo M discontinued on Day 155 due to decline in FEV_1 (-24%); subjects noted to have decline at Week 12 and Week 24; FVC and DLCO unchanged; reported cough during study

- SC insulin
  - 10141667 - 58 yo M demonstrated decline in PFTs and pulmonary SAE (dyspnea); subjects demonstrated decline of 21%, 16%, and 9% at Month 6 for FEV_1, FVC, and DLCO, respectively; subject was discontinued; PFTs post discontinuation continued to decline; 39 days after study drug discontinuation FEV_1, FVC, TLC, and DLCO had declined 39%, 37%, 24%, and 20% from baseline; CXR prior to discharge showed basilar consolidation ; subject c/o dyspnea early in tx period, URI, cough, rhinitis, influenza (2)
  - 1044961 – 50 yo M withdrew consent on Day 239; noted to have decline in TLC by 15% at Month 6; FEV_1 and FVC declined 5% and 7%, respectively
  - 10883614 – 61 yo M demonstrated decline in FEV_1 (-18%) and DLCO (-18%); noted to have decline on Day 295 and 362; subject withdrew consent on Day 363

Chest Radiography

Routine chest x-rays were taken at the baseline and Month 12. A similar number in each treatment group (7 Exubera, 6 SC insulin) had more abnormal findings at Month 12 compared to baseline [N21868/N_000/2004-12-27/clinstat/diabetes/type2/1029.pdf, pg 75; N21868/N_000/2004-12-27/crt/datasets/1029/xray_1v.xpt].

High Resolution Computed Tomography

The protocol specifies an HRCT at baseline, Month 12, and Month 24 in a subset of subjects. The Applicant submitted one year HRCT data from ongoing Study 1029 in the original December 27, 2004, submission. On June 22, 2005, the Applicant submitted a "Summary of Partial Two Year HRCT Results from Subjects in Study 1029." On July 21, 2005, the Applicant submitted additional HRCT data from Study 1029. This section includes the updated two year HRCT results from Study 1029 submitted on July 21, 2005.

Reviewer's Comment: Although this review includes HRCT data from the July 21, 2005, submission, Study 1029 is ongoing and the two-year HRCT data is not complete.

The HRCT data from Study 1029 does not suggest an increase in abnormal HRCT findings at Month 24 in the Exubera group. At Month 24 there were 71 subjects in the Exubera group and 73 subjects in the SC insulin group who underwent a Month 24 HRCT. In both treatment groups approximately 65-67% of subjects had normal HRCTs at baseline and Month 12. At Month 24, the percentage of subjects with a normal HRCT was less in the Exubera group compared to the SC group; however, there was a similar

percentage of subjects with normal HRCT at baseline and abnormal findings at Month 24 in both treatment groups. In subjects with abnormal HRCTs at baseline, there were 2 subjects in the SC insulin group who had more abnormal findings at Month 12 and one subject in the SC insulin group who had more abnormal findings at Month 24. None of the Exubera subjects had more abnormal HRCT scans at Month 12 or Month 24. Table 52 displays a summary of the HRCT data in Study 1029.

Table 144 Number of Subjects with Change in HRCT Between Baseline and Last Observation in Study 1029 n (%)

		Month 12		Month 24		Month 24 (LOCF)	
WNL at Baseline	**WNL at Specified Time Point**	**Exubera N=95**	**SC Insulin N=97**	**Exubera N=71**	**SC Insulin N=73**	**Exubera N=98**	**SC Insulin N=98**
Yes	Yes	64 (67.4)	63 (64.9)	41 (57.7)	49 (67.1)	62 (63.3)	62 (63.3)
	No	4 (4.2)	13 (13.4)	9 (12.7)	9 (12.3)	9 (9.2)	15 (15.3)
No	Yes	6 (6.3)	5 (5.2)	4 (5.6)	6 (8.2)	8 (8.2)	7 (7.1)
	No	21 (22.1)	16 (16.5)	17 (23.9)	9 (12.3)	19 (19.4)	14 (14.3)
	No significant change	20 (21.1)	11 (11.3)	17 (23.9)	7 (9.6)	19 (19.4)	10 (10.2)
	More abnormal	0	2 (2.1)	0	1 (1.4)	0	2 (2.0)
	Less abnormal	1 (1.1)	3 (3.1)	0	1 (1.4)	0	2 (2.0)

Source: [N21868/N_000/2005-07-21/a2171029_prelim_int_2y.pdf, pg. 99-100]

Reviewer's Comment: As discussed in the September 8, 2005, Endocrine and Metabolic Advisory Committee Meeting, the radiologist reading the HRCTs was blinded to treatment, but not time.

Of interest are the subjects who had normal HRCT at baseline and had abnormal HRCT at Month 12 and 24. The following summarizes the HRCT findings for subjects who had a normal HRCT at baseline and abnormal HRCT at Month 24. Atelectasis was the most common abnormal finding [N21868/N_000/2005-07-21/a2171029_prelim_int_2y.pdf, pg. 103-126].

HRCTs WNL at baseline and not WNL at Month 24

- Exubera (9)
  - 10472434 - Minimal right base linear atelectasis
  - 10641079 – RML and lingular subpleural nodules
  - 10641086 – Minimal left base atelectasis
  - 10652790 – Increased bibasilar density, probable atelectasis
  - 11135160 – Mild increased bibasilar density, probably atelectasis
  - 11185579 – Bibasilar density, probably atelectasis
  - 11185588 – Minimal basilar atelectasis/fibrosis
  - 11185596 – Mild anterior RML scar
  - 11195656 – RLL subpleural linear scar
- SC insulin (9)
  - 1010376 – New basilar subpleural atelectasis vs. fibrosis
  - 10221849 – Bibasilar fibrosis vs. atelectasis – stable
  - 10332145 – New L effusion, 2 mm LLL superior nodule unchanged
  - 10462377 – Increased atelectasis vs. early fibrosis

- 10652795 – Increased RLL atelectasis or scar
- 11115037 – New 2mm RLL nodule – subpleural
- 11185577 – Minimal lingular atelectasis/scar
- 11185599 – New 4mm RML nodule
- 11195631 – Minimal RML atelectasis/scar

Reviewer's Comment: The HRCT data from Study 1029 does not suggest an increase in abnormal HRCT findings at Month 12 or 24 in the Exubera group. However, it should be noted that Study 1029 is ongoing and the two year HRCT data is not complete.

10.7.1.3 Conclusions

Study 217-1029 is an ongoing phase 3, open-label, 2 year, parallel group outpatient study in 630 males and females with type 2 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. The 2 year comparative treatment phase is followed by a 6 month follow up phase.

The following conclusions are based upon the interim study report from this ongoing study. Thus, it is difficult to draw firm conclusions from this study.

More subjects have discontinued due to AEs in the Exubera group. Of the subjects who have discontinued due to AEs in the Exubera group, the majority of the subjects discontinued due to respiratory AEs. 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. Common respiratory AEs leading to temporary discontinuation were cough, bronchitis, asthma, and URI.

Respiratory adverse events were more common in the Exubera group than in the SC insulin group. Increased cough, bronchitis, epistaxis, pharyngitis, sputum increased, and rhinitis were more common in the Exubera group than in the SC insulin group. Most of the respiratory AEs were mild to moderate in severity except four in the Exubera group (asthma (2), bronchitis, cough) and 1 in the SC insulin group (respiratory tract infection), which were severe.

Cough was more common in the Exubera group than in the SC insulin group. Three 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. The cough questionnaire data suggests that cough in the Exubera group was non-productive, rare at night and rare or occasional during the day; although there were some subjects who reported occasional and frequent daytime cough frequency. Initially most subjects reported the cough occurred within 60 seconds of insulin dosing; however, by Month 12, the number of subjects reporting cough within 60 seconds of insulin dosing and the cough with no relationship to dosing was similar.

Baseline FEV_1 and DLCO were well-matched between the treatment groups. The Exubera group had a larger decline in FEV_1 and DLCO than the SC insulin group.

The Applicant submitted two year HRCT data on 144 subjects in the Exubera group and 59 subjects in the SC insulin group. The interim HRCT data does not suggest an increase in abnormal HRCT findings at Month 12 or 24 in the Exubera group.

10.7.2 Study 217-1017 (Ongoing)

A One-Year, Open, Randomized, Parallel, Three-Arm Study Comparing Exubera (Insulin dry powder pulmonary inhaler) vs. Avandia (Rosiglitazone maleate) as Add-On Therapy vs. Exubera Substitution of Sulfonylurea in Patients with Type 2 Diabetes, Poorly Controlled on Combination Sulfonylurea and Metformin Treatment

10.7.2.1 Protocol

Study 217-1017 is a phase 3b, multinational, open-label, 52 week, randomized, parallel group design study of adjunctive treatment with Avandia or pre-prandial Exubera in 223 subjects with type 2 diabetes mellitus who are poorly controlled on a sulphonylurea and metformin.

Subjects with type 2 diabetes poorly controlled (HbA1c 8-12%) on sulphonylurea AND metformin or glucovance were screened. Subjects with the following were excluded [N21868/N_000/2005-04-26/update/1017_interim_2005.pdf, pg 55-56]:

- Subjects with poorly controlled asthma, significant COPD, or history of any other significant respiratory disease
- Frankly abnormal PFTs at Week -3, defined as DLCO >120% or <70%; or FVC or FEV_1 <70% predicted
- Clinically significant abnormalities on screening CXR (within 6 months prior acceptable)
- Any smoking within the last 6 months prior to randomization.

A screening visit (Week -4) was followed by a 4 week run-in period (Week -4 to 0). At Week -3, pulmonary function tests were performed to determine eligibility. Subjects underwent additional PFTs at Week -2 and Week -1 to establish baseline PFTs.
Reviewer's Comment: The protocol did not specify how the "baseline" PFT value will be determined.

A cough questionnaire was administered at Week 0. All subjects were instructed on the use of Exubera at Week 0 and eligible subjects (failing metformin and a sulphonylurea) were randomized to one of the following three treatment groups [N21868/N_000/2005-04-26/update/1017_interim_2005.pdf, pg 59-60]:

- Metformin, sulphonylurea, and Exubera
- Metformin, sulphonylurea, and Avandia
- Metformin and Exubera

Reviewer's Comment: The above treatment groups were obtained from the protocol. However, the Applicant's study summary describes the following treatment groups: oral

agents (sulfonylurea and metformin), Exubera monotherapy, and oral agents plus Exubera and also describes the above treatment groups.

Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: spirometry, lung volumes, and diffusion capacity. All PFTs were performed in accordance with the 1995 ATS guidelines. PFT testing was performed at during the run in period (Week -3, -2, -1), and Week 12, 24, 36, 52, or end of study. Subjects who had an intercurrent illness were to refrain from PFTs until recovered. PFTs were performed fasting and prior to the AM study medication dose. If a subject had a decrease of $\geq$ 15% in any FEV_1, FVC, or DLCO in the absence of intercurrent illness, the PFTs were repeated. If the $\geq$ 15% decrease persisted, then consultation with a pulmonologist was to be obtained. A CXR was performed at screening and end of treatment (Week 52). A cough questionnaire was administered at Week 0 and if subjects experienced a cough AE not explained by a concomitant condition, such as an URI [N21868/N_000/2005-04-26/update/1017_interim_2005.pdf, pg 61-62, 77, 87, 93].

10.7.2.2 Results

Study 217-1017 is currently ongoing. An interim clinical safety summary was submitted with a database cutoff date of December 13, 2004, in the April 26, 2005, safety update. Limited information was provided in the summary. Only AEs and SAEs were included. No PFT data was reported. Data from the ongoing study was reported as blinded therapy until the study has completed.

Study 217-1017 commenced on April 28, 2003, and is ongoing. The study is being conducted at 56 centers in the United States. A total of 223 subjects have been randomized. Seventeen subjects discontinued due to AEs, four of these discontinuations were due to cough AEs and one was due to asthma. However, the treatment group assignment was not listed. One hundred ninety adverse events have been reported. Hypoglycemia, respiratory tract infection, and increased cough were the most frequently reported AEs. As of the December 13, 2004, cut off date, no deaths have been reported. Sixteen SAEs have been reported [N21868/N_000/2005-04-26/update/1017_interim_2005.pdf, pg 6-7].

Of the SAEs listed, two involved respiratory AEs: shortness of breath (Exubera, metformin) and pneumonia (Exubera, metformin). Respiratory AEs were listed, but the treatment groups were not provided. Increased cough, respiratory tract infection, pharyngitis, respiratory disorder, rhinitis, and sinusitis were the most common reported AEs [N21868/N_000/2005-04-26/update/1017_interim_2005.pdf, pg 10-18].

10.7.2.3 Conclusions

Study 217-1017 is a phase 3b, multinational, open-label, 52 week, randomized, parallel group design study of adjunctive treatment with Avandia or pre-prandial Exubera in 223 subjects with type 2 diabetes mellitus who are poorly controlled on a sulphonylurea and metformin.

Because the study is ongoing, limited data is available. Adverse events were reported, but the treatment group assignment is not available. Four subjects have discontinued due to respiratory AEs: cough (3) and asthma (1). Of the SAEs to date, two involved respiratory AEs: shortness of breath (Exubera, metformin) and pneumonia (Exubera, metformin). Increased cough, respiratory tract infection, pharyngitis, respiratory disorder, rhinitis, and sinusitis were the most common reported AEs.

10.8 Review of Individual Study Report from Ongoing Study in Subjects with Asthma

10.8.1 Study 217-1028 (Ongoing)

Efficacy and Safety of Inhaled Human Insulin Compared with Subcutaneous Human Insulin in the Therapy of Adult Subjects with Type 1 or Type 2 Diabetes Mellitus and Chronic Asthma: A One-year, Multicenter, Randomized, Outpatient, Open-label, Parallel-Group Comparative Trial

10.8.1.1 10.1.19.1 Protocol

Study 217-1028 is an ongoing phase 3, open-label, 15 month, parallel group study of Exubera versus SC insulin in 250 males and females with diabetes mellitus (type 1 or type 2) who have asthma. A diagnosis of mild intermittent or mild to moderate persistent asthma for at least 6 months prior to screening is required. Asthma is defined according to ATS guidelines (episodic coughing, wheezing, dyspnea, and chest tightness associated with airflow limitation that is at least partially reversible). The following are pertinent inclusion criteria [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 245-247]:

- Subjects must be on a stable insulin and asthma regimens for at least 2 months prior to screening.
- Subjects using only quick-relief medications (short acting bronchodilators) and not long-term control medications must require the regular use of a short-acting inhaled beta agonist bronchodilator at least twice a week or be approved by the Pfizer clinician.
- Subjects with mild intermittent asthma or EIB who are asymptomatic at screening are not required to meet specific FEV_1 or beta agonist reversibility requirements, but must have a documented clinical history consistent with asthma. All such subjects must be approved by the Pfizer clinician.
- Subjects with persistent asthma who are using only short-acting bronchodilators and no controller medications must have an unmedicated (no bronchodilator for at least 8 hours) FEV_1 of 50 - 85% of the predicted value. These subjects must also have a significant component of reversible airway obstruction, as evidenced by an improvement in FEV_1 of at least 12% at 30 minutes (±5 min) after inhaling two (2) puffs of albuterol administered from a metered-dose inhaler (MDI).
- Subjects with persistent asthma using controller medications must have an unmedicated (no short-acting bronchodilator for at least 8 hours) FEV_1 of $\geq$ 50% of predicted, plus either a documented $FEV_1 \leq 85\%$ of predicted at some time in

the past or a documented methacholine response of less than 8 mg/mL required to decrease the FEV_1 by 20% (PC20). These subjects must also have either a demonstrated reversibility of at least 12%, as described above, or a documented history of at least 12% response to a bronchodilator or a baseline improvement in FEV_1 of $\geq$ 12% through the use of controller medications. Subjects being treated with controller medications, but lacking documentation of a previous $FEV_1 \leq 85\%$ or reversibility $\geq$ 12% may be discussed with the Pfizer Clinician or designated representative and are considered on an individual basis.

The following are pertinent exclusion criteria [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 249-250]:

- Clinically significant abnormalities on screening CXR
- Unable to perform pulmonary function test procedures
- Initiation of immunotherapy or change in dose within 3 months of screening
- Post bronchodilator FEV_1, FVC, or DLCO outside the range 50-120% of predicted
- Poorly controlled, unstable, or steroid-dependent asthma
    - More than one hospitalization (past year)
    - More than two ER visits (past year)
    - Any hospitalization or ER visits for asthma (past month)
    - Treatment with systemic corticosteroids or high-dose inhaled corticosteroids (NAEPP, 1997)
    - Regular use of more than 8 puffs per day of a short acting inhaled bronchodilator
- Use of any other short-acting bronchodilator except inhaled albuterol
- History of respiratory tract infection requiring antibiotic treatment within one month of screening
- History of life threatening asthma (intubation or ICU care) during past 5 years
- Any smoking within the last 6 months

Concomitant therapy with systemic glucocorticoids is not permitted unless a short course of asthma exacerbation. Subjects are allowed to continue long acting bronchodilators, inhaled corticosteroids, and other controller therapies for their asthma. Albuterol is specified as the short acting bronchodilator permitted for rescue use. [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 238].

A screening visit (Week -4) was followed by a baseline run-in period (3 weeks) during which subjects were treated with SC short acting insulin +/- oral agents. At the end of the run-in period, eligible subjects are then randomized to:

- continuation of the subcutaneous insulin regimen (run-in regimen) +/- oral agents or Ultralente/NPH/insulin glargine OR
- Exubera therapy +/- oral agents or Ultralente/NPH/insulin glargine

for the 52 week comparative treatment period. The 52 week comparative treatment phase is followed by a 6 week follow up phase during which all subjects resume the SC insulin regimen used during run-in [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 238].

Safety monitoring includes AEs, laboratories, CXR, peak flows, and pulmonary function testing. Subjects perform peak flows at home twice daily (AM, evening) using the PiKo electronic flow meter. Subjects also record bronchodilator use and record PEFR, bronchodilator use, and asthma symptoms in an electronic symptom diary.

PFTs include: spirometry and single breath DLCO. Methacholine challenge testing is performed at selected sites. PFTs were performed using ATS standards. PFTs are postponed if a subject experiences an acute exacerbation of asthma or respiratory tract infection. At screening PFTs are performed pre and post-bronchodilator. Subjects perform AM PFTs in the fasting condition prior to their insulin dose and should refrain from all asthma medications, if possible. At most visits, PFTs are performed pre and post-bronchodilator. PFT (pre- and 30minutes post-bronchodilator) testing was performed at Week -4, -3, -2, -1, 1, 2, 3, 4, 6, 18, 26, 39, 52, 52+2, and 52+6. On the day of randomization (Week 0) and at Weeks 9 and 51, subjects have full PFTs pre- and post-insulin administration (10 and 60 minutes following insulin administration). If a subject has a decrease of ≥15% in post bronchodilator FEV_1, FVC, or DLCO in the absence of intercurrent illness, the PFTs are repeated. If the ≥15% decrease persisted, then further pulmonary evaluation was obtained. CXRs are taken at screening and Week 52 [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 254, 265-267].

Methacholine challenge testing (MCT) is performed at selected sites. Testing is performed according to ATS guidelines. Methacholine challenge testing is conducted at separate clinic visits occurring 1-2 days following the Week -3, -1, 11, 50, and 52+2 visits. MCT is performed while fasting prior to the AM insulin dose. Subjects with FEV_1 <70% of predicted on the day of testing will not undergo MCT [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 267].

The Applicant also administered the Baseline Dyspnea Index at baseline and the asthma control questionnaire at screening and Week 0. At Weeks 4, 12, 26, 39, 52 and 52+6 subjects will complete both the asthma control questionnaire and the Transitional Dyspnea Index [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 268].

Baseline short acting bronchodilator use is determined based upon the mean of the daily usage during the last two weeks of the run-in period. A step classification of asthma severity based upon medication use (NAEPP) is specified in the protocol [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 258].

Sites must establish an asthma management plan for subjects to follow during asthma exacerbations. The plan should be in accordance with established guidelines, e.g. NAEPP. Sites are responsible for reporting the subject-reported asthma exacerbations as AEs. A severe asthma exacerbation is defined by the use of oral corticosteroids or an unscheduled visit to a physician, ER, or hospital for asthma treatment if the subject requires additional asthma therapy (systemic corticosteroids). A protocol-defined non-severe asthma exacerbation is determined *retrospectively* based upon one of the following:

- Home-monitored morning FEV_1 <80% of baseline for two(2) or more consecutive days
- Home-monitored FEV_1 <60% of baseline at any time.

Subjects who require more than 2 corticosteroid rescues or more than 2 weeks of corticosteroid therapy are discontinued from the study, but will complete the 6 week follow up phase [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 285-286].

The primary endpoints of the study are the annualized rate of change for the FEV_1 and hemoglobin-adjusted DLCO measured 30 minutes following the administration of albuterol. Baseline PFTS are the averages of 30 minutes post bronchodilator values at Week -3, -2, and -1. The primary analysis is to be performed on the primary analysis set, which includes all subjects who were randomized, did not violate the protocol, had a baseline post-albuterol PFT measure, and had at least 2 post-baseline, post-albuterol PFT measurements with one measurement at least 6 months post-baseline. An interim safety analysis is specified to support this regulatory submission. In addition, a second interim safety analysis is specified to support a post-submission safety update [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 288-290].

At the end of the 52 week treatment period, Exubera is discontinued and subjects resume the anti-diabetic regimen used during the run-in period for a 6 week follow up period [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 263].

Reviewer's Comment: In general, the protocol design is reasonable. Asthma is rigorously defined and subjects are followed with frequent pulmonary function tests. However, the Applicant specified the post-bronchodilator FEV_1 as one of the primary efficacy variables. Typically, the pre-bronchodilator FEV_1 is the primary efficacy variable.

10.8.1.2 Results (Interim)

The Applicant submitted an interim study report. The study commenced on January 10, 2003, and is ongoing. Randomization and enrollment in the study is not complete. Sixty-two centers participated in the study (United States 51). A total of 259 subjects have been screened and 139 subjects have been randomized, 72 to the Exubera and 67 to the subcutaneous arm. Of the 72 subjects randomized to the Exubera group, 11 have completed the comparative phase of the study. Of the 67 subjects randomized to the SC insulin arm, 22 have completed the comparative phase of the study. Five subjects in the Exubera group discontinued the study. Three subjects discontinued the study due to a respiratory AE, asthma exacerbation (2) and respiratory disorder. Temporary discontinuations due to respiratory AEs were noted in 3 (asthma exacerbation (2), asthma exacerbation and lung infection (1)). Subject disposition is summarized in Table 145 [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 263].

Table 145 Subject Disposition Study 217-1028 – Interim Results		
	Exubera	SC Insulin
Randomized (139)	72	67
Completed	11	22
Discontinued Study	15	4
Adverse Event	**5**	**0**
Asthma exacerbation	**2**	**0**
Respiratory d/o, decreased lung function	**1**	**0**
Lack of efficacy	1	0
Other (includes protocol violation)	3	1
Subject defaulted (includes lost to F/U)	6	3

[N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 51, 69-71]

Reviewer's Comment: Three of the 5 discontinuations due to AEs were due to respiratory AEs.

- *A 34 yo F on beclamethasone for asthma experienced multiple asthma exacerbations and respiratory tract infections during the study. She was discontinued on Day 333.*
- *A 66 yo M on salmeterol, monteleukast, and fluticasone for asthma experienced decline in lung function followed by SAE of severe asthma exacerbation requiring hospitalization on Day34. Study drug restarted, but subject later discontinued. Pre- bronchodilator FEV_1 decreased from 1.42L at baseline to 0.99L (-42%) on Day 78. At 6 weeks follow up, FEV_1 still decreased 36% from baseline.*
- *71 yo M on salmeterol and fluticasone for asthma; subject reported coughing and severe asthma exacerbation and subject withdrawn; pre-bronchodilator FEV_1 declined from 1.77L at baseline to 1.49L (-15%) prior to discontinuation from study; on day 64 following discontinuation from study, FEV_1 increased to 2.05L (+16%) from baseline.*

The other two discontinuations were for hypoglycemia (1) and asthenia/tremor/sweating.

The mean age of the subjects was between 47-50 years and the majority of the subjects were Caucasian and female as shown in Table 146.

Table 146 Baseline Characteristics for Study 217-1028 – Interim Results			
		Exubera n = 72	SC Insulin n = 67
Gender	Male	24 (33%)	24 (36%)
	Female	48 (67%)	43 (67%)
Age	Mean	49.3	47.3
	Range	18-73	19-74
Race	Caucasian	52 (72%)	49 (73%)
	Black	7 (10%)	3 (4%)
	Asian	1 (1%)	0
	Hispanic	10 (14%)	13 (19%)
	Other	2 (2%)	2 (3%)
Diabetes	Type 1	34 (47%)	30 (45%)
	Type 2	38 (53%)	37 (55%)

[N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 52, 53, 55]

Reviewer's Comment: Less than half of the subjects in each treatment group used inhaled corticosteroids at baseline.

Respiratory Adverse Events

The number of subjects with respiratory adverse events was similar between treatment groups. Increased cough, dyspnea, pharyngitis, respiratory disorder, respiratory tract infection, and voice alteration were more common in the Exubera group than in the SC insulin group. A detailed summary of the interim results for the respiratory AEs is listed in Table 147. Most of the respiratory AEs were mild to moderate in severity with the following exceptions:

- asthma (4) in the Exubera group and asthma (2) in the SC insulin group
- bronchitis (1) in the SC insulin group
- respiratory disorder (2) in the Exubera group
- respiratory tract infection (1) in the SC insulin group

[N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 92-96].

Table 147 Number of Subjects with Respiratory Adverse Events in Study 217-1028 – Interim Results

	Exubera n = 72	SC Insulin n = 67
Serious adverse events	4 (5.6%)	2 (3.0%)
Any adverse event	70 (97.2%)	62 (92.5%)
Respiratory	**48 (66.7%)**	**47 (70.1%)**
Asthma, including asthma exacerbation	25 (35%)	31 (46%)
Bronchitis	7 (10%)	7 (10%)
Cough increased	**10 (14%)**	**2 (3%)**
Dyspnea	**2 (3%)**	**1 (1.5%)**
Laryngitis	1 (1.4%)	1 (1.5%)
Nasal polyp	0	1 (1.5%)
Pharyngitis	**12 (17%)**	**8 (12%)**
Pneumonia	0	3 (4.5%)
Respiratory disorder, including ↓lung fctn	**4 (5.6%)**	**2 (3.0%)**
Respiratory tract infection	**31 (43%)**	**22 (33%)**
Rhinitis	4 (5.6%)	4 (6%)
Sinusitis	2 (3%)	8 (12%)
Sputum increased	1 (1.4%)	2 (3%)
Stridor	0	1 (1.5%)
Voice alteration	**3 (4.2%)**	**1 (1.5%)**

[N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 78, 83-84]

Reviewer's Comment: The study adverse events table lists 6 SAEs; however, 13 SAEs are listed in Table 6.4. According to the Applicant, the difference in numbers is due to the expedited reporting of the corporate adverse event monitoring database. Of the 13 subjects with SAEs, 2 were respiratory – asthma exacerbations, one in each treatment group.

- *A 38 year old female randomized to SC insulin experienced mild asthma exacerbations and URIs. On Day 108, she required nebulizer treatment at work, then awoke at night with asthma exacerbation. She went to ER and received nebulizer treatment and oral corticosteroids.*
- *A 66 year old male randomized to Exubera experienced asthma exacerbation requiring a hospital visit on Day 34. The subject was also noted to have approximately a 30% decrease in FEV_1. He was discontinued from the study on Day 77.*

One squamous cell carcinoma of the tongue was also reported in the Exubera group.

Reviewer's Comment: The Applicant did not provide further analyses of the increased cough AEs.

Pulmonary Function Tests

For the PFT analysis, the Applicant designated 2 populations: the primary analysis population and the full analysis population. The primary analysis population includes all subjects who were randomized, did not violate the protocol, had a baseline post-albuterol PFT measure, and had at least 2 post-baseline, post-albuterol PFT measurements with one measurement at least 6 months post-baseline. The full analysis population was defined as all randomized subjects who had a baseline post albuterol PFT measurement, and had at

least 2 post-baseline post-albuterol measurements [N21868/N_000/2005-04-26/clinstat/diabetes/type1/1027.pdf, pg 288].
Reviewer's Comment: Although the primary analysis was to be performed on the primary analysis population, the Applicant presented the data for the full analysis population. According to Table 3.1 of the study report, only 30 subjects in the Exubera group and 43 subjects in the SC insulin group had duration of treatment longer than 180 days (6 months). Thus, the primary analysis population for this ongoing study is much smaller than the full analysis population.

The primary analysis variables as specified in the protocol were the post bronchodilator FEV_1 and DLCO. In terms of pulmonary function, the Exubera group had a slightly lower baseline pre- and post-bronchodilator FEV_1 than the SC insulin group. Both treatment groups demonstrated a decline from baseline FEV_1. The decline from baseline FEV_1 (post-bronchodilator) was greater in the Exubera group than in the SC insulin group at almost all time points as shown below in Table 148. At Week 52, the Exubera group had a mean decline from baseline of 278mL, while the comparator group had a mean decline from baseline of 122mL. However, it should be noted that the number of subjects is quite small at Week 52.

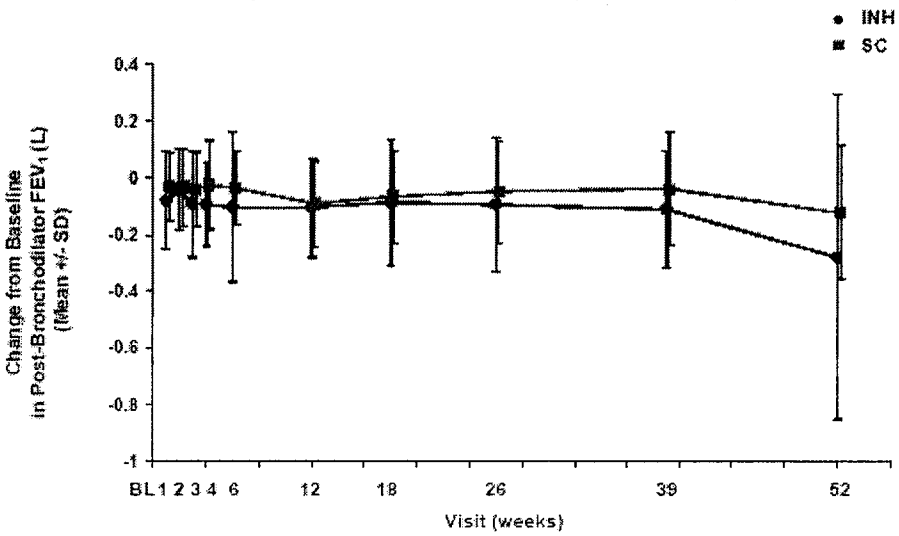
Table 148 Mean Change from Baseline FEV_1 (Post-Bronchodilator FEV_1) in Study 1028 – Interim Results

FEV_1 in Liters	Mean Change from Baseline FEV_1 (N)		Mean Treatment Group Difference (95% CI) Unadjusted
	Exubera	Comparator	
Baseline	2.502 (70)	2.704 (65)	
Week 1	-0.077 (64)	-0.031 (59)	-0.046 (-0.099, 0.008)
Week 2	-0.042 (63)	-0.033 (54)	-0.009 (-0.060, 0.042)
Week 3	-0.091 (62)	-0.038 (57)	-0.053 (-0.112, 0.006)
Week 4	-0.093 (55)	-0.024 (61)	-0.069 (-0.125, -0.013)
Week 6	-0.103 (61)	-0.035 (62)	-0.067 (-0.141, 0.007)
Week 12	-0.104 (46)	-0.092 (49)	-0.013 (-0.079, 0.054)
Week 18	-0.088 (42)	-0.066 (48)	-0.022 (-0.120, 0.058)
Week 26	-0.094 (33)	-0.049 (42)	-0.045 (-0.140, 0.050)
Week 39	-0.110 (17)	-0.038 (29)	-0.071 (-0.195, 0.052)
Week 52	-0.278 (10)	-0.122 (17)	-0.157 (-0.478, 0.165)

Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 37;
Dr. Joan Buenconsejo's Biometrics Review

In general, from Week 1 through Week 18 there was a small treatment group difference favoring the comparator. From Week 26 through Week 52, the treatment groups further separated as shown below in Figure 60.

Figure 60 Mean Change from Baseline in Post-Bronchodilator FEV_1 (L) in Study 1028 - Interim Results (Mean +/-SD)

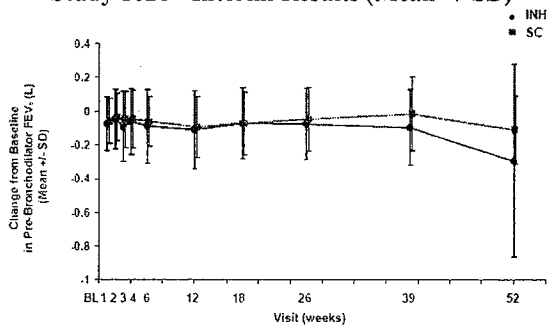


Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 37

Reviewer's Comment: The Applicant asserted that the treatment group difference after Week 26 is based upon a small number of subjects and may be influenced by outliers. At Week 52, there were 2 subjects in the Exubera group with >20% decrease from baseline FEV_1 and in the SC insulin group there were 2 subjects with 15-20% decrease from baseline FEV_1 [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 131].

Reviewer's Comment: The Applicant also measured pre-bronchodilator FEV_1 and in general the change from baseline in pre-bronchodilator FEV_1 produces a similar pattern as shown in the figure below.

Figure 61 Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) in Study 1028 - Interim Results (Mean +/-SD)



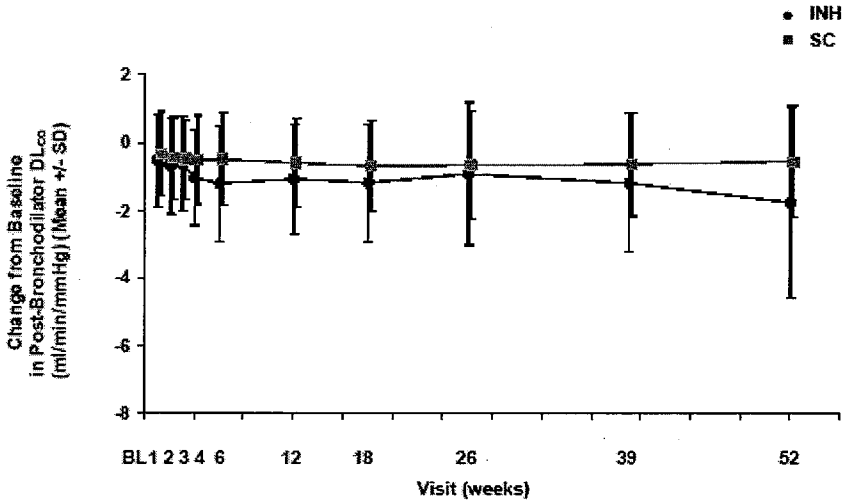
Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 39

The decline from baseline DLCO (post-bronchodilator) was greater in the Exubera group than in the SC insulin group at all time points as shown below in Table 149. At Week 52, the Exubera group had a mean decline from baseline post-bronchodilator DLCO of 1.76mL/min/mmHg, while the comparator group had a mean decline from baseline post-bronchodilator DLCO of 0.54mL/min/mmHg. However, it should be noted that the number of subjects is quite small at Week 52.

Table 149 Mean Change from Baseline DLCO (Post-Bronchodilator DLCO) in Study 1028 – Interim Results			
DLCO in mL/min/mmHg	Mean Change from Baseline DLCO (N)		Mean Treatment Group Difference (95% CI) Unadjusted
	Exubera	Comparator	
Baseline	23.121 (70)	23.649 (65)	
Week 1	-0.536 (63)	-0.330 (59)	-0.206 (-0.672, 0.261)
Week 2	-0.705 (63)	-0.477 (53)	-0.228 (-0.718, 0.261)
Week 3	-0.646 (61)	-0.512 (57)	-0.134 (-0.606, 0.339)
Week 4	-1.053 (55)	-0.522 (60)	-0.531 (-1.033, -0.029)
Week 6	-1.218 (61)	-0.503 (62)	-0.714 (-1.265, -0.164)
Week 12	-1.066 (46)	-0.621 (47)	-0.446 (-1.048, 0.157)
Week 18	-1.195 (42)	-0.696 (47)	-0.499 (-1.154, 0.155)
Week 26	-0.920 (33)	-0.658 (42)	-0.262 (-1.111, 0.588)
Week 39	-1.176 (17)	-0.641 (29)	-0.535 (-1.599, 0.530)
Week 52	-1.755 (10)	-0.545 (17)	-1.211 (-2.975, 0.554)
Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 41; Dr. Joan Buenconsejo's Biometrics Review			

In general, the treatment group difference fluctuated throughout the treatment period. However, from Week 39 to Week 52, there was a large increase in treatment group difference favoring the comparator as shown below in Figure 62.

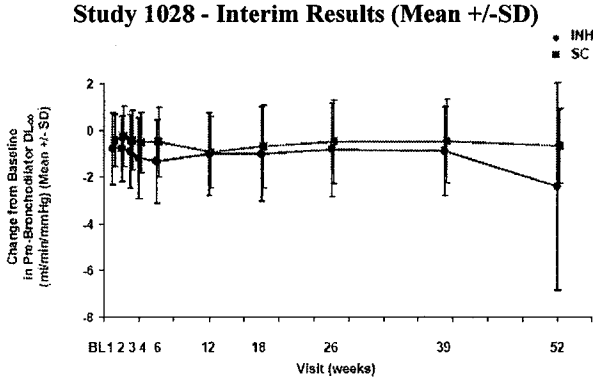
Figure 62 Mean Change from Baseline in Post-Bronchodilator DLCO (mL/min/mmHg) in Study 1028 – Interim Results (Mean +/-SD)



Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 42

Reviewer's Comment: The Applicant also measured pre-bronchodilator DLCO and in general the change from baseline in pre-bronchodilator DLCO produces a similar pattern as shown in the figure below.

Figure 63 Mean Change from Baseline in Pre-Bronchodilator DLCO (mL/min/mmHg) in Study 1028 - Interim Results (Mean +/-SD)



Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 43

The Applicant provided narratives on subjects who discontinued from treatment due to a ≥ 15% decrease from baseline pulmonary function. There were 5 narratives in each treatment group, 4 narratives for a >15% decline from baseline FEV_1 and one narrative for a >15% decline from baseline DLCO in each group [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 97-122].
Reviewer's Comment: It should be noted that in the Exubera group there were two subjects who had a >40% decline from baseline FEV_1.

FEV_1 pre-insulin dosing and post-insulin dosing (10min and 60 min) were measured at Weeks 0, 9, and 51. In general, the mean observed 10 minute post Exubera FEV_1 was lower than the pre-Exubera observed FEV_1. The mean observed 60 minute post Exubera FEV_1 was similar to the pre-dose FEV_1.

Table 150 Mean Observed FEV_1 Pre- and Post-Exubera Dose in Study 1028

	Inhaled Insulin		
FEV_1 in liters	Pre-Dose	10 Minutes Post-Dose	60 Minutes Post-Dose
	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	2.361 (0.8)	2.352 (0.8)	2.354 (0.8)
Week 9	2.328 (0.9)	2.265 (0.9)	2.322 (0.9)
Week 51	2.340 (0.8)	2.297 (0.7)	2.328 (0.8)

Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 149-151

Reviewer's Comment: This data suggests that there may a slight decrease in FEV_1 within 10 minutes following the Exubera dose; however, the FEV_1 returns to pre-dose after approximately 60 minutes post-Exubera dose.

A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group who demonstrated a decrease in FEV_1 of >10%. For DLCO, more subjects in the Exubera group demonstrated a decrease in DLCO of >15%. In general, there were less subjects at Week 52 in both treatment groups with a decrease in FEV_1 or DLCO >10%. Table 151 displays the results for the categorical analyses of the Interim PFT data.

Table 151 Categorical Analyses of Percent Change in Pre- and Post Bronchodilator FEV_1 and DLCO from Baseline to Week 26 and 52 in Study 217-1028 Full Analysis Set

	Exubera			Subcutaneous Insulin		
	-10 to -15%	-15 to -20%	> -20%	-10 to -15%	-15 to -20%	> -20%
Pre-BD FEV_1 – Wk 26	3 (9.1%)	1 (3%)	2 (6.1%)	0	1 (2.4%)	1 (2.4%)
Pre-BD FEV_1 – Wk 52	0	0	2 (20%)	0	2 (11.8%)	0
Post BD-FEV_1 – Wk 26	4 (12.1%)	0	2 (6.1%)	3 (7.1%)	1 (2.4%)	1 (2.4%)
Post BD-FEV_1 – Wk 52	1 (10%)	0	2 (20%)	0	2 (11.8%)	0
Pre-BD DLCO – Wk 26	3 (9.4%)	3 (9.4%)	0	4 (9.5%)	2 (4.8%)	1 (2.4%)
Pre-BD DLCO – Wk 52	1 (10%)	2 (20%)	1 (10%)	4 (23.5%)	0	0
Post BD-DLCO– Wk 26	5 (15.2%)	2 (6.1%)	0	4 (9.5%)	0	0
Post BD-DLCO – Wk 52	2 (20%)	2 (20%)	0	3 (17.6%)	1 (5.9%)	0

[N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 130, 133, 140-143]

Narratives were provided for subjects who had abnormal PFT results (>15% decline from baseline into the abnormal range) at last observation. The following is a brief synopsis of the narratives [N21868/N_000/2005-04-26/clinstat/diabetes/type1/1027.pdf, pg 97-122]:

- Exubera
  - 44 yo M on formoterol and budesonide for asthma treatment experienced a decline in pre-bronchodilator DLCO from 32.13ml/min/mmHg at baseline to 26.89 ml/min/mmHg (-16%) at Week 52; pre-bronchodilator FEV_1 declined 7%; subject reported cough, viral infection, head cold (sinusitis), mild influenza (3), pharyngitis
  - 32 yo F on salbutamol and inhaled beclomethasone for asthma treatment experienced a decline in pre-bronchodilator FEV_1 from 2.39L at baseline to 1.87L (-22%) on Day 161; subject reported dyspnea, mild respiratory tract infection (2), and mild asthma exacerbation during the comparative treatment phase
  - 42 yo F on fluticasone/salmeterol for asthma treatment experienced decline in pre-bronchodilator FEV_1 from 2.95L at baseline to 2.27L (-23%) on Day 364; subject reported moderate asthma exacerbation during study
  - 42 yo M on albuterol for asthma experienced decline in pre-bronchodilator FEV_1 from 3.62 L at baseline to 1.85L (-49%) on Day 373; similar decline in post bronchodilator FEV_1; pre-bronchodilator DLCO declined 37%; subject reported moderate asthma exacerbation (2), mild sinus infection, mild asthma exacerbation, bulk of decline noted from Day 267 to Day 373, but no AEs provided in narrative for that time period
  - A 66 yo M on salmeterol, monteleukast, and fluticasone for asthma experienced decline in lung function followed by SAE of severe asthma exacerbation requiring hospitalization on Day34. Study drug restarted, but subject later discontinued. Pre- bronchodilator FEV_1 decreased from 1.42L at baseline to 0.99L (-42%) on Day 78. At 6 weeks follow up, FEV_1 still decreased 36% from baseline
- SC insulin

- 59 yo M on formoterol and budesonide for asthma experienced decline in pre-bronchodilator FEV_1 from 2.66L at baseline to 2.21L (-17%) at 52 Weeks; post-bronchodilator demonstrated similar decline; subject reported multiple mild episodes of asthma exacerbation and two one episode of moderate asthma exacerbations and two reports of cough
- 48 yo F on fluticasone/salmeterol for asthma experienced decline in pre-bronchodilator DLCO from 16.52 ml/min/mmHg at baseline to 13.10 (-21%) at Day 274; DLCO improved to 14.49 ml/min/mmHg (-12%) on Day 387; subject reported mild sinusitis, mild asthma exacerbation during the comparative treatment phase
- 54 yo F on beclomethasone and theophylline for asthma treatment experienced decline in pre-bronchodilator FEV_1 from 1.66L at baseline to 1.32L (-20%) on Day 273; pre-bronchodilator DLCO also declined from 16.98 ml/min/mmHg at baseline to 13.84 ml/min/mmHg (-18%) on day 273; subject reported URI (3)
- 50 yo M on budesonide for asthma treatment experienced decline in pre-bronchodilator FEV_1 from 3.21L at baseline to 2.63L on day 365 (-18%); subject reported mild flu several times, acute sinusitis, and moderate asthma exacerbation
- 22 yo M on salmeterol and fluticasone for asthma experienced decline in pre-bronchodilator FEV_1 from 2.99L at baseline to 2.40L (-20%) on Day 190; subject experienced mild asthma exacerbation

Reviewer's Comment: There were 5 narratives in each treatment group, 4 narratives for a >15% decline from baseline FEV_1 and one narrative for a >15% decline from baseline DLCO in each group. It should be noted that in the Exubera group there were two subjects who had a >40% decline from baseline FEV_1.

Asthma Exacerbations

Although asthma exacerbations were reported as adverse events, the Applicant defined severe and non-severe asthma exacerbations in the protocol. According to the protocol, a severe asthma exacerbation is defined by the use of oral corticosteroids or an unscheduled visit to a physician, ER, or hospital for asthma treatment. A non-severe asthma exacerbation is determined *retrospectively* based upon one of the following:

- Home-monitored morning FEV_1 <80% of baseline for two(2) or more consecutive days
- Home-monitored FEV_1 <60% of baseline at any time.

The event rates of both non-severe and severe asthma exacerbations were higher in the Exubera group than in the SC insulin group. The Exubera group had 30 subjects who had 203 non-severe asthma exacerbations and the SC insulin group had 26 subjects who had 155 non-severe asthma exacerbations. For severe asthma exacerbations, the Exubera group had 11 subjects with 15 events, while the SC insulin group had 9 subjects with 10 events. In the Exubera group 3 subjects accounted for 7 of the 15 severe exacerbations [N21868/N_000/2005-04-26/clinstat/diabetes/type1/1027.pdf, pg 167-168].

The number of subjects requiring systemic corticosteroid treatment was similar between treatment groups. The Exubera group had 6 subjects requiring 7 systemic corticosteroid rescues, while the SC insulin group had 5 subjects requiring 5 systemic corticosteroid rescues [N21868/N_000/2005-04-26/clinstat/diabetes/type1/1027.pdf, pg 169].

Asthma Control Questionnaire

The Applicant administered an Asthma Control Questionnaire periodically throughout the study. The questions are on a scale of 0 to 6, with higher scores reflecting poor control. Six of the questions are determined by the subject, while the 7th question is determined by the Applicant using the FEV_1 data collected during the study visit. At Week 52, the Exubera group showed a small increase in both the subject and clinical evaluation score, while the SC insulin group showed a small decrease in both the subject and clinical evaluation score [N21868/N_000/2005-04-26/clinstat/diabetes/type1/1027.pdf, pg 171].

Chest Radiography

The results for the CXR were not reported in the interim study report.

10.8.1.3 Conclusions

Study 217-1028 is an ongoing phase 3, open-label, 15 month, parallel group study of Exubera versus SC insulin in 250 males and females with diabetes mellitus (type 1 or type 2) who have asthma. The interim results of Study 217-1028 were reviewed. While 139 subjects were randomized at the time of this interim report, PFT data is only available only 27 subjects for 52 weeks of treatment. The results for the 6 week follow up phase were not provided. Thus, in this reviewer's opinion, this interim study report provides very limited data about the long term effect of Exubera on pulmonary safety in subjects with asthma.

The number of subjects with respiratory adverse events was similar between the two treatment groups. Increased cough, dyspnea, pharyngitis, respiratory disorder, respiratory tract infection, and voice alteration were more common in the Exubera group than in the SC insulin group. Most of the respiratory AEs were mild to moderate in severity. One asthma exacerbation SAE was noted in both treatment group.

The Exubera group had a slightly lower baseline pre- and post-bronchodilator FEV_1 than the SC insulin group. Both groups demonstrated a decline in pre-and post-bronchodilator FEV_1 during the treatment period. An initial decline was noted in both groups and by Week 3 appeared to be somewhat stabilized until Week 26. At Week 52, an increase in the decline was noted in both groups; however, the decline was much greater in the Exubera group

Both treatment groups demonstrated a decline in DLCO; however, the Exubera treatment group had a greater decline than the SC insulin group. At Week 52, the Exubera group had a mean decline from baseline post-bronchodilator DLCO of 1.76mL/min/mmHg, while the comparator group had a mean decline from baseline post-bronchodilator DLCO of 0.54mL/min/mmHg. In general, the treatment group difference fluctuated throughout

the treatment period. However, from Week 39 to Week 52, there was a large increase in treatment group difference favoring the comparator. However, it should be noted that the number of subjects is quite small at Week 52.

The event rates of both non-severe and severe asthma exacerbations were higher in the Exubera group than in the SC insulin group. However, the number of subjects requiring systemic corticosteroid treatment was similar between treatment groups.

Asthma control was assessed by the Asthma Control Questionnaire. At Week 52, the Exubera group showed a small increase in both the subject and clinical evaluation score suggesting a decline in asthma control, while the SC insulin group showed a small decrease in both the subject and clinical evaluation score, suggesting an improvement in asthma control.

10.9 Review of Individual Study Report from Ongoing Study in Subjects with COPD

10.9.1 Study 217-1030 (Ongoing)

Efficacy and Safety of Inhaled Human Insulin Compared with Subcutaneous Human Insulin in the Therapy of Adult Subjects with Type 1 or Type 2 Diabetes Mellitus and Chronic Obstructive Pulmonary Disease: A One-year, Multicenter, Randomized, Outpatient, Open-label, Parallel-Group Comparative Trial

10.9.1.1 Protocol

Study 217-1030 is an ongoing phase 3, open-label, 15 month, parallel group study of Exubera versus SC insulin in 250 males and females with diabetes mellitus (type 1 or type 2) who have COPD. A diagnosis of COPD is required based upon the following pertinent inclusion criteria [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 254-255]:

- Prior smokers with a 10 pack year or more smoking history and either:
  - Fixed airflow obstruction as determined at screening to include a post-BD FEV_1/FVC <70% and FEV_1<80% predicted
    and/or
  - History of chronic productive cough present for at least 3 months in each of 2 consecutive years for which no alternative cause has been determined. Subjects who qualify based on this criterion must have a post-BD FEV_1 <80%
    or
  - Less than 10 pack year smokers or never smokers who otherwise meet above criteria are considered on an individual case basis
- Subjects must be on a stable insulin and COPD regimens for at least 2 months prior to screening.

The following are pertinent exclusion criteria [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 254-257]:

- Clinically significant abnormalities on screening CXR other than changes c/w COPD
- Post bronchodilator FEV_1, FVC, or DLCO outside the range 50-120% of predicted
- Poorly controlled, unstable, or steroid-dependent COPD
    - More than one hospitalization or ER visit (past year)
    - Any hospitalization or ER visits for asthma (past month)
    - Treatment for COPD with antibiotics, supplemental oxygen, systemic corticosteroids or high-dose inhaled corticosteroids
    - Regular use of more than 12 puffs per day of a short acting inhaled bronchodilator
- Use of any other short-acting bronchodilator except inhaled albuterol
- SaO_2 <92% or room air on 2 or more occasions during the run-in period
- Carboxyhemoglobin level >5% on any occasion during the run-in period
- Chronic supplemental oxygen therapy
- Any smoking within the last 6 months

Concomitant therapy for COPD is in accordance with ATS and NHLBI/WHO GOLD guidelines. Long acting beta agonists, low to moderate dose inhaled corticosteroids, and methylxanthines are allowed. Subjects may use short acting bronchodilators, such as ipratropium, albuterol, or albuterol/ipratropium for rescue use [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 261, 284,].

A screening visit (Week -4) is followed by a baseline run-in period (3 weeks) during which subjects were treated with SC short acting insulin + oral agents +/- long acting insulin. Eligible subjects must continue to meet inclusion criteria and have no change to their COPD medications. At the end of the run-in period, eligible subjects are then randomized to:

- continuation of the subcutaneous insulin regimen (run-in regimen) +/- oral agents or Ultralente/NPH/insulin glargine OR
- Exubera therapy +/- oral agents +/- Ultralente/NPH/insulin glargine

for the 52 week comparative treatment period. The 52 week comparative treatment phase is followed by a 6 week follow up phase during which all subjects resume the SC insulin regimen used during run-in [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 246].

Safety monitoring includes AEs, laboratories, CXR, and pulmonary function testing. Subjects record bronchodilator use, and COPD symptoms in a diary. Subjects may be withdrawn if significant deterioration of COPD control is noted (>14 days treatment with systemic corticosteroids or >4 treatments with systemic corticosteroids).

PFTs include: spirometry and single breath DLCO. Methacholine challenge testing is performed at selected sites. PFTs are performed using ATS standards. PFTs are postponed if a subject experiences an acute exacerbation of COPD or respiratory tract infection. At screening PFTs are performed pre and post-bronchodilator (ipratropium). Subjects perform AM PFTs in the fasting condition prior to their insulin dose and should refrain from all asthma medications, if possible. At most visits, PFTs are performed pre

and 30 minutes post-bronchodilator (ipratropium). PFT testing is performed at Week -4, -3, -2, -1, 1, 2, 3, 4, 6, 18, 26, 39, 52, 52+2, and 52+6. On the day of randomization (Week 0) and at Weeks 9 and 51, subjects have full PFTs pre- and post-insulin administration (10 and 60 minutes following insulin administration). If a subject has a decrease of ≥15% in post bronchodilator FEV_1, FVC, or DLCO in the absence of intercurrent illness, the PFTs are repeated. If the ≥15% decrease persisted, then further pulmonary evaluation was obtained. CXRs are taken at screening and Week 52 [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 273-275].

Methacholine challenge testing (MCT) is performed at selected sites. Testing is performed according to ATS guidelines. Methacholine challenge testing is conducted at separate clinic visits occurring 1-2 days following the Week -3, -1, 11, 50, and 52+2 visits. MCT is performed while fasting prior to the AM insulin dose. Subjects with FEV_1 <60% of predicted on the day of testing will not undergo MCT [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 275].

The Applicant also administered the Baseline Dyspnea Index at baseline at Week 0. At Weeks 4, 12, 26, 39, 52, and 52+6 subjects will complete the Transitional Dyspnea Index [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 276].

Baseline short acting bronchodilator use is determined based upon the mean of the daily usage during the last two weeks of the run-in period [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 265].

The incidence and severity of COPD exacerbations between the two treatment groups will be compared. The protocol defines a non-severe COPD exacerbation as the need for additional therapy (systemic corticosteroids, antibiotics, or oxygen) but not requiring hospitalization for more than 24 hours. A severe COPD exacerbation is defined as a COPD-related hospitalization of more than 24 hours. Severe COPD exacerbations are also SAEs. Unscheduled visits to a clinic/physician for evaluation of a COPD exacerbation does not qualify as an exacerbation unless systemic steroids, antibiotics, or oxygen are begun. At the discretion of the investigator, subjects with exacerbations of COPD may be treated with systemic corticosteroids up to a maximum of 60 mg/day of prednisone for up to one week with a taper over the ensuing week. Subjects requiring more than four (4) such corticosteroid rescues during the course of the study, or more than two weeks of systemic corticosteroid or supplemental oxygen treatment to resolve a single exacerbation, will be discontinued from the comparator phase of the study, but will be requested to complete the 6-week run-out phase using subcutaneous insulin therapy [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 292].

Exacerbations of COPD will be defined as continuing until the criteria that defined them are not present for two consecutive days. Severe exacerbations will be defined as extending for at least two weeks from the time they were initiated. Days included in a severe exacerbation are excluded from being a non-severe exacerbation. COPD exacerbations captured as adverse events are reconciled with protocol-defined exacerbations [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 292].

The primary endpoints of the study are the annualized rate of change for the FEV_1 and hemoglobin-adjusted DLCO measured 30 minutes following the administration of ipratropium. Baseline PFTS are the averages of 30 minutes post bronchodilator values at Week -3, -2, and -1. The primary analysis is to be performed on the primary analysis set, which includes all subjects who were randomized, did not violate the protocol, had a baseline post-ipratropium PFT measure, and had at least 2 post-baseline, post-ipratropium PFT measurements with one measurement at least 6 months post-baseline. An interim safety analysis is specified. In addition, a second interim safety analysis is specified to support a post-submission safety update [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 294-296].

At the end of the 52 week treatment period, a 6-week post-study run-out is specified, during which Exubera is discontinued and subjects resume the anti-diabetic regimen used during the run-in period [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 257].

Reviewer's Comment: In general, the protocol design is reasonable. One issue with the inclusion criteria as discussed in the September 8, 2005, Endocrine and Metabolic Advisory Committee Meeting is that subjects with no history of smoking could be enrolled on an individual basis. Ideally, all subjects would have a ≥ 10 pack year history of smoking.

10.9.1.2 Results (Interim)

The Applicant submitted an interim study report with the original NDA submission, then submitted an updated interim study report on April 26, 2005. The study commenced on January 10, 2003, and is ongoing. This results section incorporates the interim results of the study (cut-off date February 20, 2005) submitted on April 26, 2005. Randomization and enrollment in the study is not complete. A total of 150 subjects have been screened and 67 subjects have been randomized, 35 to the Exubera and 32 to the subcutaneous arm. Fifteen subjects in each treatment group have completed the study. A similar number of subjects discontinued the study from each treatment arm. One subject from each arm discontinued due to an AE. The subject in the Exubera arm discontinued due to a respiratory AE, COPD exacerbation. Temporary discontinuations were more common in the Exubera group. Respiratory AEs (pneumonia, AECOPD (3)) accounted for about half of the temporary discontinuations in the Exubera arm. Subject disposition is summarized in Table 152 [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 69-72].

Table 152 Subject Disposition Study 217-1030 – Interim Results		
	Exubera	SC Insulin
Randomized (67)	35	32
Completed	15	15
Deaths	0	3
Discontinued Study	5	6
Adverse Event	**1**	**1**
COPD exacerbation	**1**	**0**
Other (includes protocol violation)	2	1
Subject defaulted (includes lost to F/U)	2	1

[N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 28, 66]

Reviewer's Comment: One of the 2 discontinuations due to AEs was respiratory

- *10181691 – 62 yo M discontinued due to COPD exacerbation after 2 months of treatment with Exubera; treated with Exubera discontinuation and oral prednisone; COPD exacerbation resolved; Exubera resumed and 3 days later experienced serious COPD exacerbation, although he was not hospitalized; Exubera permanently discontinued; CXR unchanged; PFTs with decline in FEV_1 of 16% (pre-BD) and 17% (post-BD) [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 107-108]*

The mean age of the subjects was 63 years and the majority of the subjects were Caucasian and male as shown in Table 153. The majority of subjects have type 2 diabetes mellitus.

Table 153 Baseline Characteristics for Study 217-1030 – Interim Results			
		Exubera n = 35	SC Insulin n = 32
Gender	Male	24 (69%)	26 (81%)
	Female	11 (31%)	6 (19%)
Age	Mean	63.5	63.9
	Range	42-76	40-77
Race	Caucasian	30 (86%)	30 (94%)
	Black	4 (11%)	0
	Hispanic	1 (3%)	1 (3%)
	Other	0	1 (3%)
Diabetes	Type 1	5 (14%)	5 (16%)
	Type 2	30 (86%)	27 (84%)

[N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 50-51]

Respiratory Adverse Events

Respiratory adverse events occurred at a similar rate between treatment groups. Increased cough, bronchitis, dyspnea, and voice alteration were more common in the Exubera group than in the SC insulin group. A detailed summary of the interim results for the respiratory AEs is listed in Table 154. Most of the respiratory AEs were mild to moderate in severity with the following exceptions, which were graded as severe:

- dyspnea (1) in the Exubera group

- pneumonia (1) in the Exubera group
- respiratory disorder (1) in the Exubera group
- rhinitis (1) in the SC insulin group

[N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 82-83].

Table 154 Number of Subjects with Respiratory Adverse Events in Study 217-1030 – Interim Results

	Exubera n = 35	SC Insulin n = 37
Serious adverse events	5 (14%)	10 (31%)
Any adverse event	35 (100%)	31 (97%)
Respiratory	21 (60%)	19 (60%)
Asthma	1 (3%)	0
Bronchitis	**3 (8.6%)**	**1 (3.1%)**
Cough increased	**3 (8.6%)**	**1 (3.1%)**
Dyspnea	**4 (11.4%)**	**2 (6.3%)**
Hypoxia	1 (2.9%)	0
Pharyngitis	3 (8.6%)	2 (6.3%)
Pleural effusion	1 (2.9%)	0
Pneumonia	2 (5.7%)	1 (3.1%)
Respiratory disorder (includes COPD exacerbation)	6 (17%)	5 (16%)
Respiratory tract infection	12 (34%)	11 (34%)
Rhinitis	2 (5.7%)	3 (9.4%)
Sinusitis	2 (5.7%)	2 (6.3%)
Sputum increased	1 (2.9%)	0
Voice alteration	**2 (5.7%)**	**0**

[N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 77, 82-83]

Reviewer's Comment: Of the subjects with SAEs (17), 4 were respiratory (pneumonia, COPD exacerbation (2), and URI). All the respiratory SAEs occurred in the Exubera group.

- *10181691 – 62 yo M discontinued due to COPD exacerbation after 2 months of treatment with Exubera; treated with Exubera discontinuation and oral prednisone; COPD exacerbation resolved; Exubera resumed and 3 days later experienced serious COPD exacerbation, although he was not hospitalized; Exubera permanently discontinued; CXR unchanged; PFTs with decline in FEV_1 of 16% (pre-BD) and 17% (post-BD)*
- *10151393-72 yo M with pneumonia requiring hospitalization on Day 35 of Exubera; Exubera temporarily discontinued; pneumonia attributed to immobility due to leg fracture; PFTs without change from baseline*
- *10262489 -67 yo F with COPD exacerbation SAE; PFTs declined >15% (FEV_1, -17%, DLCO -10%) on Day 23 and remained so through last observation; subject reported sinusitis, URI (4), and pneumonia (2) during study*

It is unclear why this last subject was reported as COPD exacerbation because the narrative does not mention the exacerbation, just the decline in PFTs. A narrative was not provided for the URI SAE.

Reviewer's Comment: The Applicant did not provide further analyses of the increased cough AEs.

Pulmonary Function Tests

For the PFT analysis, the Applicant designated 2 populations: the primary analysis population and the full analysis population. The primary analysis population includes all subjects who were randomized, did not violate the protocol, had a baseline post-ipratropium PFT measure, and had at least 2 post-baseline, post-ipratropium PFT measurements with one measurement at least 6 months post-baseline. The full analysis population was defined as all randomized subjects who had a baseline post-ipratropium PFT measurement, and had at least 2 post-baseline post-ipratropium measurements [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 294-296].
Reviewer's Comment: Although the primary analysis was to be performed on the primary analysis population, the Applicant presented the data for the full analysis population. According to Table 3.1 of the study report, only 19 subjects in the Exubera group and 17 subjects in the SC insulin group had duration of treatment longer than 180 days (6 months). Thus, the primary analysis population for this ongoing study is much smaller than the full analysis population.

The primary analysis variables as specified in the protocol were the post bronchodilator FEV_1 and DLCO. However, this reviewer believes the pre-bronchodilator FEV_1 and DLCO are important safety variables, thus, the results for both the pre- and post-bronchodilator FEV_1 will be presented. DLCO is not typically measured post bronchodilator and will not be addressed in this review.

The Exubera group has a slightly higher baseline pre- and post-bronchodilator FEV_1 than the SC insulin group. Both treatment groups demonstrated a decline from baseline pre and post-bronchodilator FEV_1. The treatment group difference for mean change from baseline post-bronchodilator FEV_1 fluctuated during the treatment period, but consistently favored the comparator group. At Week 52, there was a decline from baseline post-bronchodilator FEV_1 of 109mL in the Exubera group and 82mL in the comparator group as shown in Table 155. It should be noted that the Week 52 data is based upon PFT data from 28 subjects.

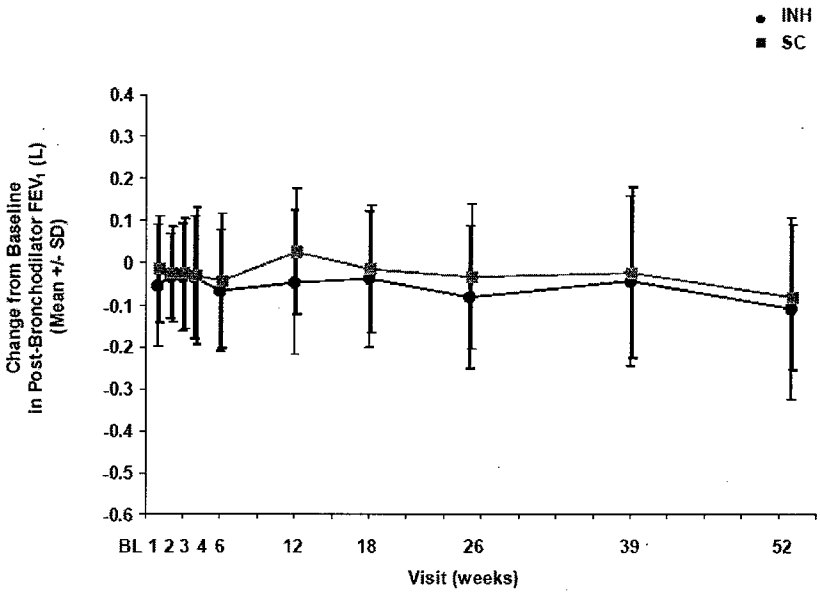
Table 155 Mean Change from Baseline FEV_1 (Post-Bronchodilator FEV_1) in Study 1030 – Interim Results

FEV_1 in Liters	Mean Change from Baseline FEV_1 (N)		Mean Treatment Group Difference (95% CI) Unadjusted
	Exubera	Comparator	
Baseline	2.204 (35)	2.147 (32)	
Week 1	-0.054 (32)	-0.016 (29)	-0.037 (-0.107, 0.032)
Week 2	-0.032 (29)	-0.027 (30)	-0.005 (-0.062, 0.051)
Week 3	-0.034 (28)	-0.026 (30)	-0.007 (-0.075, 0.061)
Week 4	-0.035 (29)	-0.031 (30)	-0.005 (-0.085, 0.076)
Week 6	-0.066 (30)	-0.043 (27)	-0.023 (-0.104, 0.058)
Week 12	-0.047 (28)	0.026 (29)	-0.073 (-0.158, 0.013)
Week 18	-0.039 (29)	-0.015 (24)	-0.024 (-0.111, 0.063)
Week 26	-0.081 (26)	-0.033 (21)	-0.048 (-0.149, 0.053)
Week 39	-0.042 (21)	-0.023 (20)	-0.020 (-0.148, 0.108)
Week 52	-0.109 (13)	-0.082 (15)	-0.027 (-0.178, 0124)

Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 35; Dr. Joan Buenconsejo's Review

At Week 52, the treatment group difference was 27mL, favoring the comparator. Figure 64 displays the change from baseline post- bronchodilator FEV_1 in Study 1030.

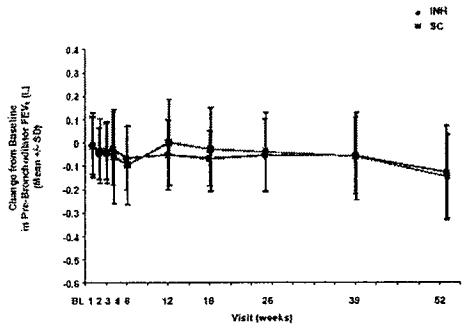
Figure 64 Mean Change from Baseline in Post-Bronchodilator FEV_1 (L) in Study 1030 – Interim Results (Mean +/-SD)



Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 36

Reviewer's Comment: The Applicant also measured the pre-bronchodilator FEV_1. As shown below in Figure 48 the treatment group difference for the mean change from baseline pre-bronchodilator FEV_1 did not follow a consistent pattern. At Week 52 there was a mean treatment group difference for change from baseline pre-bronchodilator FEV_1 of 17mL, favoring the Exubera group.

Figure 65 Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) in Study 1030 – Interim Results (Mean +/- SD)



Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 38

FEV_1 pre-insulin dosing and post-insulin dosing (10min and 60 min) were measured at Weeks 0, 9, and 51. At Weeks 9 and 51, the 10 minute post-Exubera mean FEV_1 was less than the pre-Exubera mean FEV_1 by approximately 30mL; however, by the 60 minute FEV_1 measurement, the mean $FEV1_1$ had increased and was similar to the mean pre-Exubera FEV_1 measurement.

The Applicant also performed a responsiveness analysis for response to bronchodilator. Responsiveness was defined as the difference between the post-BD FEV_1 and the pre-BD FEV_1. The baseline bronchodilator responsiveness was similar between treatment groups. In general, throughout the treatment period, the mean bronchodilator responsiveness was greater than baseline bronchodilator responsiveness in both treatment groups.

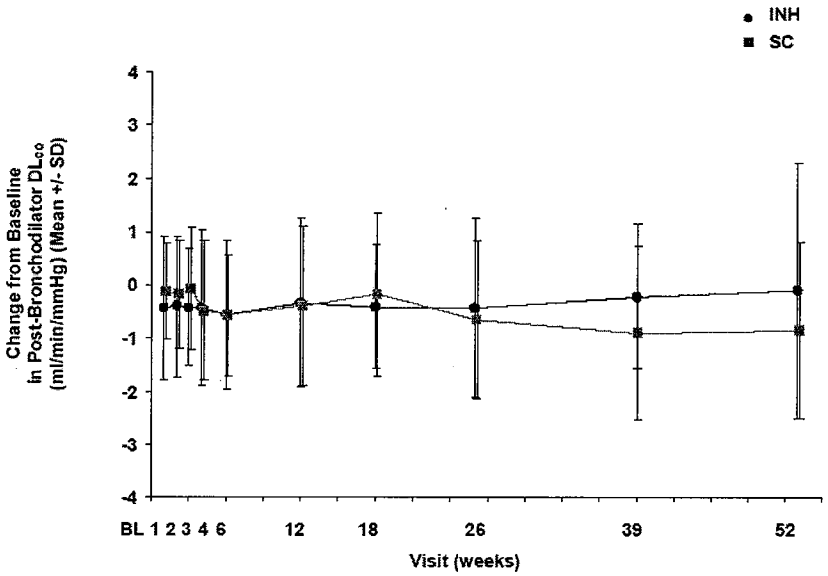
Baseline DLCO was similar between treatment groups. In general, both treatment groups demonstrated a decline in post-bronchodilator DLCO at most time points. The treatment group difference for mean change from baseline post-bronchodilator DLCO fluctuated throughout the treatment period, and did not consistently favor any particular treatment group. As shown below in Table 156, the data suggests that the post-bronchodilator DLCO increases from baseline at Week 52, which is difficult to interpret. The Week 52 data is based upon PFT data from 28 subjects.

Table 156 Mean Change from Baseline DLCO (Post-Bronchodilator DLCO) in Study 1030- Interim Analysis

DLCO in mL/min/mmHg	Mean Change from Baseline DLCO (N)		Mean Treatment Group Difference (95% CI) Unadjusted
	Exubera	Comparator	
Baseline	19.276 (35)	19.105 (32)	
Week 1	-0.437 (31)	-0.126 (29)	-0.311 (-0.912, 0.289)
Week 2	-0.402 (29)	-0.176 (29)	-0.227 (-0.850, 0.397)
Week 3	-0.427 (28)	-0.074 (30)	-0.353 (-0.946, 0.240)
Week 4	-0.435 (29)	-0.481 (30)	0.046 (-0.676, 0.767)
Week 6	-0.572 (30)	-0.568 (27)	-0.003 (-0.683, 0.676)
Week 12	-0.332 (28)	-0.394 (28)	0.062 (-0.766, 0.890)
Week 18	-0.415 (28)	-0.170 (24)	-0.245 (-0.997, 0.507)
Week 26	-0.427 (26)	-0.664 (21)	0.237 (-0.706, 1.180)
Week 39	-0.219 (21)	-0.907 (20)	0.688 (-0.259, 1.634)
Week 52	0.092 (13)	-0.839 (15)	0.934 (-0.653, 2.521)

Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 40; Dr. Joan Buenconsejo's Review

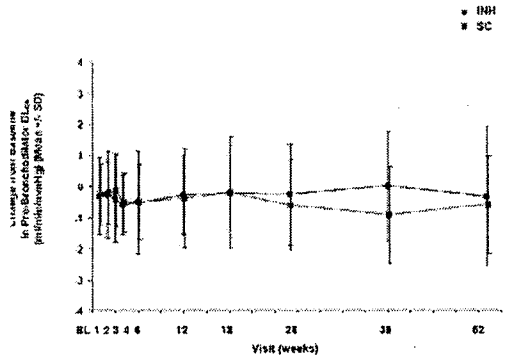
Figure 66 Mean Change from Baseline Post-Bronchodilator DLCO (mL/min/mmHg) in Study 1030 (Mean +/- SD)



Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 41

Reviewer's Comment: The post-bronchodilator DLCO data from Study 1030 is difficult to interpret because the treatment group difference was quite variable throughout the 52 week treatment period. The Applicant also measured the pre-bronchodilator DLCO. The treatment group difference for the mean change from baseline pre-bronchodilator DLCO was also quite variable. Initially, the treatment group difference favored the comparator group, but after Week 26, the treatment group difference favored the Exubera group as shown below.

Figure 67 Mean Change from Baseline Pre-Bronchodilator DLCO in Study 1030- Interim Results (Mean +/- SD)



Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 42

A categorical analysis of the FEV_1 and DLCO data suggests that in general, there were a similar number of subjects in both treatment groups who demonstrated a decrease in FEV_1 or DLCO of >10%. Narratives were provided for subjects who had abnormal PFT results (>15% decline from baseline into the abnormal range) at last observation. There were 2 narratives in the Exubera group for decline from baseline FEV_1 and there 6 narratives in the SC insulin group mostly for decline from baseline FEV_1.

FEV_1pre-insulin dosing and post-insulin dosing (10min and 60 min) were measured at Weeks 0, 9, and 51. The Applicant performed a responsiveness analysis for insulin dosing. Insulin dose responsiveness was defined as the difference between pulmonary function following a dose of insulin and pulmonary function before a dose of insulin. In general, the Exubera group showed a decline in responsiveness for FEV_1 at 10 minutes post-dose, but showed an increase in responsiveness for FEV_1 at 60 minutes post dose. The SC insulin group did not demonstrate a consistent pattern [N21868/N_000/2005-04-26 /update/1030_interim_2005.pdf, pg 40].

The Applicant also performed a responsiveness analysis for response to bronchodilator. Responsiveness was defined as the difference between the post-BD FEV_1 and the pre-BD FEV_1. The baseline bronchodilator responsiveness was similar between treatment groups. In general, throughout the treatment period, the mean bronchodilator responsiveness was greater than baseline bronchodilator responsiveness in both treatment groups [N21868/N_000/2005-04-26 /update/1030_interim_2005.pdf, pg 147].

A categorical analysis of the PFT data suggests that there were a similar number of subjects in both treatment groups who demonstrated a decrease in FEV_1 or DLCO of >10%. Table 157 displays the results for the categorical analyses of the interim PFT data.

Table 157 Categorical Analyses of Percent Change in Pre- and Post Bronchodilator FEV_1 and DLCO PFTs from Baseline to Week 52 in Study 217-1030 Full Analysis Set

	Exubera			Subcutaneous Insulin		
	-10 to -15%	-15 to -20%	> -20%	-10 to -15%	-15 to -20%	> -20%
Pre-BD FEV_1 – Wk 26	5 (18.5%)	1 (3.7%)	0	2 (9.5%)	0	1 (4.8%)
Pre-BD FEV_1 – Wk 52	3 (20%)	1 (6.7%)	1 (6.7%)	2 (13.3%)	2 (13.3%)	2 (13.3%)
Post BD-FEV_1 – Wk 26	4 (15.4%)	2 (7.7%)	0	4 (19%)	1 (4.8%)	0
Post BD-FEV_1 – Wk 52	2 (15.4%)	0	1 (7.7%)	1 (6.7%)	2 (13.3%)	1 (6.7%)
Pre-BD DLCO – Wk 26	2 (7.4%)	1 (3.7%)	0	1 (4.8%)	0	1 (4.8%)
Pre-BD DLCO – Wk 52	1 (10%)	2 (20%)	1 (10%)	4 (23.5%)	0	0
Post BD-DLCO– Wk 26	3 (11.5%)	1 (3.8%)	0	1 (4.8%)	1 (4.8%)	1 (4.8%)
Post BD-DLCO – Wk 52	1 (6.7%)	1 (6.7%)	0	3 (20%)	0	0

[N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 140-143, 150-153]

Narratives were provided for subjects who had abnormal PFT results (>15% decline from baseline into the abnormal range) at last observation. The following is a brief synopsis of the narratives [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 112-132]:

- Exubera
  - 1011993 – 76 yo F with decline in FEV_1; subject had small decline in FEV_1 and DLCO on Day 21, but had progressive decline in FEV_1 to -21% on Day 372; subject reported multiple respiratory AEs: AECOPD, URI, rhinitis, pharyngitis
  - 10262489 – 67 yo F with decline in FEV_1; subject with decline in FEV_1 between -11% to -21% throughout study; last observation Day 380 (-18%); DLCO not consistent, but decline -10% on Day 380; subject reported sinusitis, URI, and pneumonia (2)
- SC insulin
  - 100499 – 63 yo F with decline in DLCO and discontinuation due to AE (bowel obstruction); subject developed bowel obstruction on Day 315 and was hospitalized; PFTs on Day 146 (last observation) demonstrated decline in DLCO of 24%
  - 1004100 – 65 yo M with decline in DLCO; subject had decline in DLCO -18% on Day 85 and -14% on Day 358; FEV_1 unchanged to slight increase on Day 358; subject reported several chest colds
  - 10171593 – 63 yo M with decline in DLCO; subject had small decline in DLCO until Day 279 when had -15% decline DLCO; on Day 370 DLCO improved to only -5% decline; FEV_1 at Day 370, however, was -21% from baseline; subject reported URI, bruised ribs (Day 179), bladder obstruction requiring TURP on Day 249
  - 10211989 – 71 yo M with decline in post-BD FEV_1 (-18%) on Day 372; no pre-BD FEV_1 available on Day 372; subject reported allergies, SOB due to allergic rhinitis
  - 10565767 – 71 yo M with decline in FEV_1; FEV_1 and DLCO declined at first post-baseline measurement ; improved some during study; Day 365 FEV_1 -22% and DLCO +1%

- 10606164 – 65 yo F with decline in FEV_1; FEV_1 declined on first baseline measurement and fluctuated thereafter; Day 364 FEV_1 -12%; DLCO unchanged; subject reported sinusitis, AECOPD, sinus infection, pneumonia

Reviewer's Comment: There were 2 narratives in the Exubera group for decline from baseline FEV_1 and there 6 narratives in the SC insulin group mostly for decline from baseline FEV_1.

COPD Exacerbations

Although COPD exacerbations were reported as adverse events, the Applicant defined severe and non-severe COPD exacerbations in the protocol. The protocol defined a non-severe COPD exacerbation as the need for additional therapy (systemic corticosteroids, antibiotics, or oxygen) but not requiring hospitalization for more than 24 hours. A severe COPD exacerbation was defined as a COPD-related hospitalization of more than 24 hours. Severe COPD exacerbations are also SAEs. Unscheduled visits to a clinic/physician for evaluation of a COPD exacerbation did not qualify as an exacerbation unless systemic steroids, antibiotics, or oxygen were begun.

The total number of both non-severe and severe COPD exacerbations was higher in the Exubera group than in the SC insulin group. The Exubera group had 10 subjects who had 14 non-severe COPD exacerbations and the SC insulin group had 4 subjects who had 9 non-severe COPD exacerbations. For severe COPD exacerbations, the Exubera group had one subject with one event, while the SC insulin group had none [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 177-178].

The number of subjects requiring systemic corticosteroid treatment was slightly higher in the Exubera group. The Exubera group had 5 subjects requiring 6 systemic corticosteroid rescues, while the SC insulin group had 3 subjects requiring 5 systemic corticosteroid rescues [N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 179].

Chest Radiography

The results for the CXRs were not reported in the interim study report.

10.9.1.3 Conclusions

Study 217-1030 is an ongoing phase 3, open-label, 15 month, parallel group study of Exubera versus SC insulin in 250 males and females with diabetes mellitus (type 1 or type 2) who have COPD. A screening visit (Week -4) was followed by a baseline run-in period (3 weeks) during which subjects were treated with SC short acting insulin +/- oral agents. At the end of the run-in period eligible subjects are then randomized to continuation of the run-in regimen OR Exubera therapy +/- oral agents or Ultralente/NPH/insulin glargine for the 52 week comparative treatment period. The 52 week comparative treatment phase is followed by a 6 week follow up phase, during which all subjects resume the SC insulin regimen.

This results of this study are based upon an interim study report with a cut-off date of February 20, 2005. While 67 subjects have been randomized, 35 to the Exubera and 32

to the subcutaneous arm, only 30 subjects have completed the treatment phase. The results for the 6 week follow up phase were not provided. Thus, in this reviewer's opinion, this interim study report provides limited data about the long term effect of Exubera on pulmonary safety in subjects with COPD.

Respiratory adverse events occurred at a similar rate between treatment groups. Increased cough, bronchitis, dyspnea, and voice alteration were more common in the Exubera group than in the SC insulin group. All the respiratory SAEs (4) occurred in the Exubera group.

In terms of pulmonary function, the Exubera group has a slightly higher baseline pre- and post-bronchodilator FEV_1 than the SC insulin group. Both treatment groups demonstrated a decline from baseline pre and post-bronchodilator FEV_1. The treatment group difference for mean change from baseline post-bronchodilator FEV_1 fluctuated during the treatment period, but consistently favored the comparator group. At Week 52, there was a decline from baseline post-bronchodilator FEV_1 of 109mL in the Exubera group and 82mL in the comparator group, with a treatment group difference of 27mL, favoring the comparator at Week 52. It should be noted that the Week 52 data is based upon PFT data from 28 subjects.

FEV_1 pre-insulin dosing and post-insulin dosing (10min and 60 min) were measured at Weeks 0, 9, and 51. At Weeks 9 and 51, the 10 minute post-Exubera mean FEV_1 was less than the pre-Exubera mean FEV_1 by approximately 30mL; however, by the 60 minute FEV_1 measurement, the mean $FEV1_1$ had increased and was similar to the mean pre-Exubera FEV_1 measurement.

Baseline pre-bronchodilator DLCO and post-bronchodilator DLCO were similar between treatment groups. Both treatment groups demonstrated a decline in post-bronchodilator DLCO. The treatment group difference for mean change from baseline post-bronchodilator DLCO fluctuated throughout the treatment period, and did not consistently favor any particular treatment group, which is difficult to interpret. The treatment group difference for the mean change from baseline pre-bronchodilator DLCO was also quite variable. Initially, the treatment group difference favored the comparator group, but after Week 26, the treatment group difference favored the Exubera group.

The total number of both non-severe and severe COPD exacerbations was higher in the Exubera group than in the SC insulin group. The Exubera group had 10 subjects who had 14 non-severe asthma exacerbations and the SC insulin group had 4 subjects who had 9 non-severe asthma exacerbations. For severe asthma exacerbations, the Exubera group had 1 subjects with 1 event, while the SC insulin group had none.

10.10 Review of Individual Study Report From Completed Study in Pediatric Subjects

10.10.1 Study 217-1009

Efficacy and Safety of Inhaled compared with SC Human Insulin Therapy in Children Ages 6-11 years with Type 1 Diabetes Mellitus: A Three-month, Outpatient, Parallel Comparative Trial

10.10.1.1 Protocol

Study 217-1009 was an open-label, multicenter, 3-month, parallel group study in 120 6-11 year old males and females with type 1 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 poorly controlled asthma, clinically significant COPD, or other significant respiratory disease were excluded. Smokers (any smoking in past 6 months) were also excluded. Subjects who successfully completed the 3-month trial were eligible to receive Exubera treatment in a one-year open-label protocol extension [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009.pdf, 215-218].

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 or BID SC long-acting (ultralente or NPH) insulin injection [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009.pdf, 219-220].

Safety monitoring included AEs, laboratories, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, 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. A CXR was obtained at baseline and Week 12 [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009.pdf, 244].

Open-Label Extension
Subjects who completed the 12-week study were eligible to receive Exubera in the long-term extension study, Study 111.

10.10.1.2 Results

The 12-week study commenced on March 15, 2000, and was completed on November 30, 2000. Fourteen centers in the United States participated in the study. A total of 127 subjects were screened for the study and 121 were randomized (61 Exubera, 60 SC

insulin). One subject was randomized to SC insulin but never received treatment. Subject disposition in displayed in Table 158.

Table 158 Subject Disposition Study 217-1009

	Exubera	SC Insulin
Randomized (121)	61	60
Randomized but never treated	0	1
Completed Study	59	59
Discontinued Study	2	0
Withdrew consent	2	0

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009.pdf, pg 33, 86]

Reviewer's Comment : Although the study report indicates that 2 subjects withdrew consent from the Exubera group, the pulmonary narratives suggest one subject discontinued from the Exubera group due to cough adverse event.

The mean age of the subjects was approximately 9 years of age. Baseline characteristics were matched between treatment groups. The majority of subjects were Caucasian.

Table 159 Baseline Characteristics Study 217-1009

		Exubera n = 61	SC Insulin n = 59
Gender	Male	27 (44%)	28 (47%)
	Female	34 (56%)	31 (53%)
Age (years)	Mean	8.6	9.1
	Range	6-11	5-11
Race	White	54 (89%)	56 (95%)
	Black	3 (5%)	0
	Hispanic	4 (6.5%)	2 (3%)
	Other	0	1 (2%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009.pdf, pg 63]

Respiratory Adverse Events

More subjects reported respiratory adverse events in the SC insulin group than in the Exubera group. Cough increased, asthma, and dyspnea were more common in the Exubera group than in the SC insulin group. All of the respiratory adverse events were mild in severity. Although Table 4.1 of the study report indicates that there were no discontinuations due to adverse events, the pulmonary narratives describe one 10 year old subject (1009 50883383) who discontinued due to cough. The subject also had a decline in FEV_1 from 2.63L to 2.30L and DLCO from 21.5 to 14.1 ml/min/mmHg. None of the SAEs were respiratory . A detailed summary of the respiratory AEs is listed in Table 160.

Table 160 Summary of Subjects with Respiratory Adverse Events for Study 217-1009

	Exubera n = 61	SC Insulin n = 59
Subjects with serious adverse events	3 (4.9)	2 (3.4)
Subjects with any adverse event	61 (100%)	58 (98.3%)
Subjects with respiratory adverse events	**32 (52.5%)**	**37 (62.7%)**
Asthma	**3 (4.9%)**	**1 (1.7%)**
Bronchitis	1 (1.6%)	0
Cough increased	**15 (24.6%)**	**4 (6.8%)**
Dyspnea	**2 (3.3%)**	**0**
Epistaxis	0	3 (5.1%)
Pharyngitis	5 (8.2%)	10 (16.9%)
Pneumonia	0	1 (1.7%)
Respiratory disorder	2 (3.3%)	2 (3.4%)
Respiratory tract infection	12 (19.7%)	14 (23.7%)
Rhinitis	8 (13.1%)	8 (13.6%)
Sinusitis	1 (1.6%)	3 (5.1%)
Sputum increased	0	1 (1.7%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009.pdf, pg 111-112]

Increased cough was reported more frequently in the Exubera group than in the SC insulin group. A total of 31 cough events were reported in the Exubera group compared to 4 in the SC insulin group. In the Exubera group, most of the cough AEs were reported in the first 4 weeks. The majority 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. The Applicant determined the mean duration of cough was 2 weeks and 1 week for the Exubera group and SC insulin group, respectively [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009.pdf, pg 50-51].

Pulmonary Function Tests

Baseline pulmonary function was well-matched between treatment groups. A review of the mean change from baseline FEV_1, FVC, TLC, FEF25-75%, and PEFR suggests that neither group had a decline in mean values at 12 weeks. The Exubera group demonstrated a larger decrease from baseline DLCO than the SC insulin group. A summary of the PFTs is displayed in Table 161.

Table 161 Pulmonary Function Tests for Study 217-1009 – Summary of Mean Changes

	Exubera			Subcutaneous Insulin		
PFT	BL	Week 12	Change from BL	BL	Week 12	Change from BL
FEV_1	N=59	N=60	N=60	N=59	N=59	N=59
Mean (L)	1.835	1.906	0.061	1.867	1.953	0.085
SD	0.349	0.346	0.146	0.398	0.414	0.128
FVC	N=61	N=60	N=60	N=59	N=59	N=59
Mean (L)	2.119	2.255	0.124	2.150	2.261	0.111
SD	0.423	0.421	0.145	0.462	0.486	0.166
DLCO	N=60	N=60	N=59	N=58	N=57	N=57
Mean (ml/min/mmHg)	16.017	15.342	-0.583	15.808	15.883	-0.028
SD	3.151	2.922	2.637	3.253	3.253	2.812
TLC	N=61	N=59	N=59	N=59	N=59	N=59
Mean (L)	2.852	2.968	0.129	2.938	3.025	0.087
SD	0.586	0.514	0.285	0.593	0.563	0.286
FEF25-75%	N=61	N=60	N=60	N=59	N=59	N=59
Mean (L/sec)	2.154	2.165	0	2.223	2.281	0.059
SD	0.527	0.590	0.386	0.577	0.628	0.288
PEFR	N=61	N=60	N=60	N=59	N=59	N=59
Mean (L/sec)	3.892	4.010	0.116	4.013	4.313	0.300
SD	0.866	0.922	0.740	0.996	1.041	0.582

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009..pdf, pg 152, 155, 158, 161, 164, 167]

Reviewer's Comment: The Applicant also presented the data for the LOCF which was the same as the Week 12 observed.

A categorical analysis of the change in pulmonary function testing suggests that the Exubera group had more subjects with >10% decrease in DLCO and FEF25-75% than the SC insulin group as shown in Table 162.

Table 162 Categorical Analyses of Percent Change in PFTs from Baseline to Last Observation in Study 217-1009

	Exubera			Subcutaneous Insulin		
	-10 to -15%	**-15 to -20%**	**> -20%**	**-10 to -15%**	**-15 to -20%**	**> -20%**
FEV_1	3 (5%)	0	1 (1.7%)	1 (1.7%)	0	1 (1.7%)
FVC	0	0	1 (1.7%)	1 (1.7%)	0	1 (1.7%)
DLCO	8 (13.6%)	3 (5.1%)	8 (13.6%)	3 (5.3%)	2 (3.5%)	6 (10.5%)
TLC	2 (3.4%)	1 (1.7%)	0	4 (6.8%)	2 (3.4%)	0
FEF25-75%	6 (10%)	3 (5%)	4 (6.7%)	1 (1.7%)	4 (6.8%)	3 (5.1%)
PEFR	0	1 (1.7%)	4 (6.7%)	1 (1.7%)	0	3 (5.1%)

The n for categorical analyses of each PFT parameter is the same n as listed in the change from baseline in Table 161
[N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009..pdf, pg 153, 156, 159, 162, 165, 168]

Chest X-Rays

Chest x-rays were taken at final observation in 59 subjects in the Exubera group and 58 subjects in the SC insulin group. One subject in each group showed a significant change since screening. In the Exubera group, one 8 year old male subject (100950913389) had mild peribronchial thickening on CXR. This subject had a decrease in PFTs also. His

FEV_1 declined from 1.39 L to 1.09L and DLCO declined from 15.18 ml/min/mmHg to 14.09 ml/min/mmHg. One subject in the SC insulin group had a possible vascular anomaly [N21868/N_000/2004-12-27/clinstat/diabetes/type1/1009.pdf, pg 55, 132-133].

10.10.1.3 Conclusions

Study 217-1009 was an open-label, multicenter, 3-month, parallel group study in 120 6-11 year old males and females with type 1 diabetes mellitus who were on a stable insulin regimen of 2-3 injections daily. The results indicate that respiratory adverse events were slightly more common in the SC insulin group than in the Exubera group. However, cough increased, asthma, and dyspnea were more common in the Exubera group than in the SC insulin group. One subject in the Exubera group discontinued due to cough adverse event.

A review of the mean change from baseline FEV_1, FVC, TLC, FEF25-75%, and PEFR suggests that neither group had a decline in mean values at 12 weeks. The Exubera group demonstrated a larger decrease from baseline DLCO than the SC insulin group. A categorical analysis of the change in pulmonary function testing suggests that the Exubera group had more subjects with >10% decrease in DLCO and FEF25-75% than the SC insulin group.

The Applicant is not seeking an indication in the pediatric population in this Application. Study 1009 provides some information regarding the safety of Exubera, but the amount of information this study provides is not enough to draw definitive conclusions regarding the safety of Exubera in the pediatric population.

10.11 Cough Questionnaire

The following is the cough questionnaire utilized in Study 1022, 1027, and 1029.

APPENDIX D: COUGH QUESTIONNAIRE

The cough questionnaire will be administered by the study coordinator to all subjects at Week 0. At Week 0, all subjects should complete the questionnaire with reference to the past 4 weeks. At all other visits, the cough questionnaire should be completed IF AND ONLY IF subjects have experienced an adverse event of cough not explained by a concomitant condition, such as an upper respiratory tract infection.

Q1: Cough frequency at night:

0 = None: Unaware of coughing.
1 = Rare: Cough in the morning, but I don't waken from sleep.
2 = Occasional: Wake a few times, but I fall back asleep right away.
3 = Frequent: Waken many times through the night with fits of coughing.
4 = Almost constant: Up all night long with coughing.

Q2: Cough frequency throughout the day:

0 = None: Unaware of coughing.
1 = Rare: Cough only after taking inhaled insulin or only now and then.
2 = Occasional: Less than hourly.
3 = Frequent: One or more times an hour.
4 = Almost constant: Never free of cough or feeling free of the need to cough.

Q3: Cough severity throughout the day:

0 = None: Unaware of coughing.
1 = Mild: Does not interfere with usual morning or daily activity.
2 = Moderate: Must stop activity during coughing episode.
3 = Marked: Must stop activity during and for a brief period after coughing episode.
4 = Severe: Stops all activity for some time and is exhausting; can be accompanied by dizziness, headache, or pain.

Q4: Cough timing related to short-acting insulin dosing:

0 = Unaware of cough
1 = Within seconds of dosing: ≤ 60 seconds
2 = Within minutes of dosing: 1 to 60 minutes
3 = Within hours of dosing: 1 to 2 hours
4 = No relationship to insulin dosing

Q5: Cough severity related to insulin dosing (subcutaneous or inhaled):

0 = None: Unaware of coughing.
1 = Mild: Does not interfere with usual morning or daily activity.
2 = Moderate: Must stop activity during coughing episode.
3 = Marked: Must stop activity during and for a brief period after coughing episode.
4 = Severe: Stops all activity for some time and is exhausting; can be accompanied by dizziness, headache, or pain.

Q6: Was your cough productive?

0 = Never
1 = Rarely
2 = Occasionally
3 = Frequently
4 = Almost constantly

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/s/

Sally Seymour
1/6/2006 05:29:43 PM
MEDICAL OFFICER

Eugene Sullivan
1/9/2006 08:12:04 AM
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CLINICAL REVIEW

Application Type	NDA
Submission Number	000
Submission Code	N
Letter Date	27 Dec 04
Stamp Date	27 Dec 04
PDUFA Goal Date	27 Oct 05
Reviewer Name	Karen Murry Mahoney, MD
Review Completion Date	5 Oct 05
Established Name	Exubera®
(Proposed) Trade Name	Exubera®
Therapeutic Class	Inhaled insulin
Applicant	Pfizer
Priority Designation	S
Formulation	Pulmonary inhalation powder for use with specified pulmonary inhaler
Dosing Regimen	Dose-titrated premeal inhalation
Indication	Treatment of hyperglycemia in Type 1 and Type 2 diabetes mellitus
Intended Population	Adult Type 1 and Type 2 diabetics

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