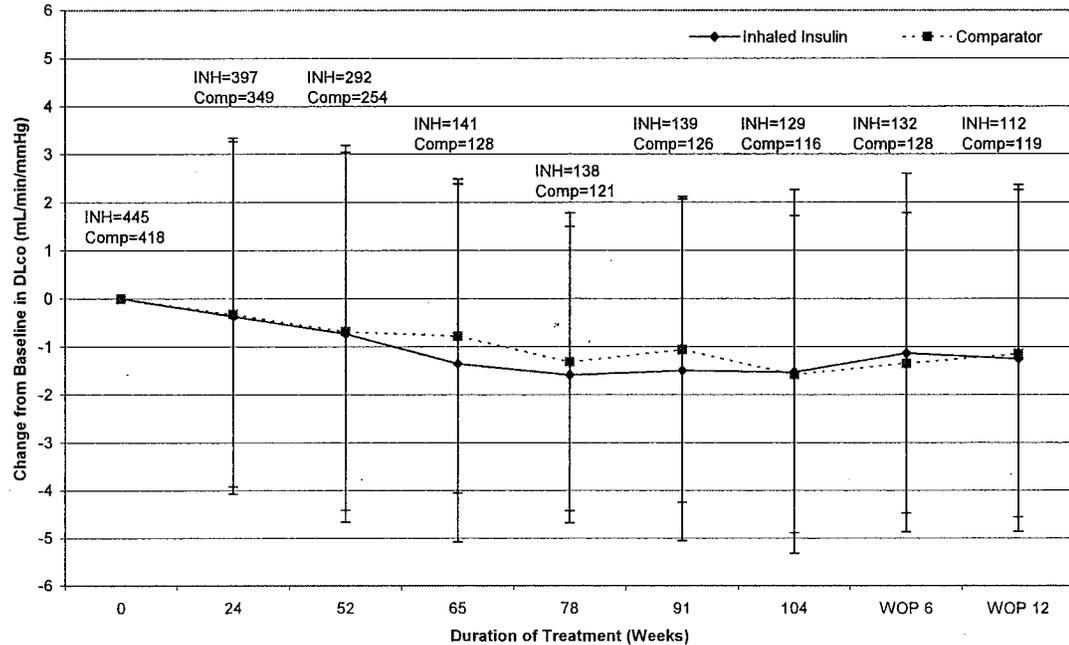**Figure 36 Mean Change from Baseline DLCO by Time in Combined Study 1001-1002 in Type 2 Diabetes (Mean +/-SD)**
All Subjects

Source: Dr. Joan Buenconsejo's Biometrics Review

Reviewer's Comment: The Applicant asserts that this supports reversal of the effect of Exubera on DLCO. It is interesting that the comparator group demonstrated an increase in DLCO in the follow up phase.

7.1.6.3.2.4 Study 1036

Study 1036 is an ongoing uncontrolled extension study of the phase 2 protocols 102 (Type 1), 103, and 104 (Type 2). Study 1036 provides some long term PFT data on subjects with both type 1 and type 2 diabetes exposed to Exubera up to 84 months. Study 1036 was discussed in Section 7.1.6.2.1.4 and is not discussed in detail here. The results for Study 1036 suggests that the decline in DLCO over a 78 month treatment period is - 2mL/min/mmHg, which is approximately an annual rate of decline from baseline DLCO of 0.3mL/min/mmHg. However, due to the uncontrolled nature of the study, the results should be interpreted with caution.

Reviewer's Comment: The uncontrolled data from Study 1036 suggests that between 1 and 7 years of exposure to Exubera, the change from baseline DLCO stabilizes.

7.1.6.3.2.5 Study 111

Study 111 was an open-label extension study of the phase 3 protocols 106 and 107 (Type 1) and 108, 109, 110 (Type 2). The design of Study 111 was discussed in the Methods Section 7.1.6.1. Like Study 1036, Study 111 provides some long term non-controlled PFT data on subjects exposed to Exubera.

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Study 111 included 664 subjects with type 1 diabetes and 626 subjects with type 2 diabetes. As shown in Table 43, subjects with type 2 diabetes demonstrated a decline in DLCO at 6 months which progressed through 30 months. At 36 months, there was data on only 4 subjects.

Table 43 Mean Observed DLCO (mL/min/mmHg) and Change From Baseline DLCO (mL/min/mmHg) in Study 111 – Adult Subjects with Type 2 Diabetes (Studies 108, 109, 110, 111)			
Exubera			
	Type 2		
DLCO in mL/min/mmHg	**Observed**	**Change from Baseline**	
	Mean (SD)	N	Mean (SD)
Baseline	24.687 (6.0)	608	
6 months	23.625 (6.0)	604	**-1.090 (3.4)**
12 months	23.233 (6.0)	520	**-1.459 (3.6)**
18 months	23.035 (5.8)	474	**-1.556 (3.9)**
24 months	23.284 (5.8)	370	**-1.724 (4.0)**
30 months	23.787 (5.7)	139	**-1.893 (4.2)**
36 months	29.483 (5.3)	4	**-1.185 (6.4)**
*Baseline is based on pre-Exubera measurements Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 978, 980			

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

The mean observed DLCO and mean change from "baseline" DLCO in the discontinuation phase are shown in Table 44 and Figure 36 below. The results show subjects who continued on Exubera had an increase in DLCO at Month 6 and subjects who discontinued Exubera initially had an increase in DLCO, but by Month 6 the DLCO decreased slightly.

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

Table 44 Mean Observed DLCO (mL/min/mmHg) and Change from "Baseline"* in DLCO (mL/min/mmHg) in Discontinuation Phase of Study 111 – Adult Subjects with Type 2 Diabetes (Primary Analysis Set)**					
	Exubera				
	Continued Exubera			Discontinued Exubera		
DLCO (mL/min/mmHg)	Observed	Change from "Baseline"		Observed	Change from "Baseline"	
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)
"Baseline"*	22.855 (6.2)	192		23.497 (5.6)	200	
Month 1	22.564 (5.7)	185	-0.267 (2.8)	23.769 (5.8)	197	0.279 (3.1)
Month 3	22.649 (5.8)	189	-0.214 (2.5)	24.062 (6.2)	195	0.613 (3.0)
Month 6	23.049 (6.3)	184	0.208 (2.8)	23.386 (5.9)	190	-0.048 (2.9)

*Baseline for the discontinuation phase was the last value prior to or within 7 days after being randomized to continuation or discontinuation of Exubera
**Primary analysis set includes all randomized subjects who had a baseline FEV_1 measurement and a post-baseline measurements and received study drug for at least 50% of the duration of the controlled segment
Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 1754

Figure 37 Mean Change in DLCO from "Baseline" in the Discontinuation Phase of Study 111 in Adults Type 2 Subjects
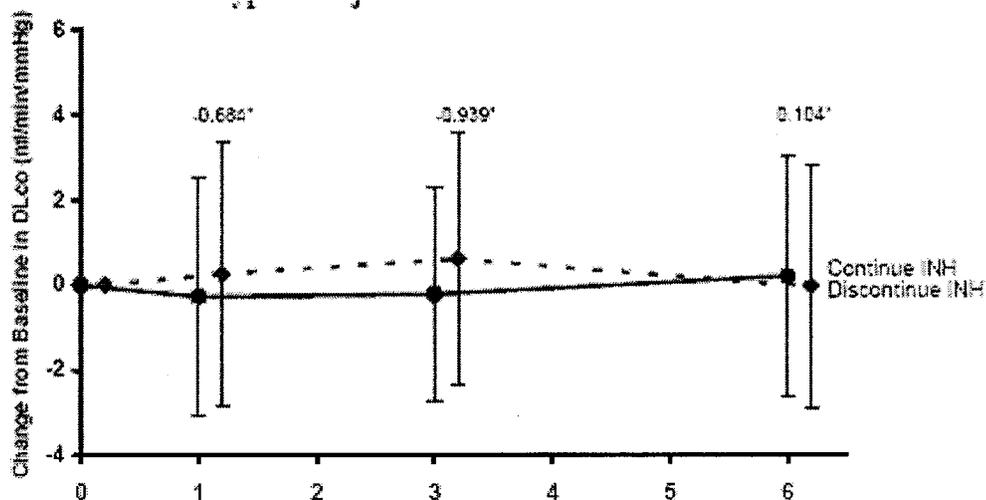
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 60.

Reviewer's Comment: The Applicant also followed the group who was randomized to continued Exubera for an additional 6 months after the discontinuation phase. In this follow up phase Exubera was discontinued. In subjects with type 2 diabetes ≥ 18 years of age, at 6 months the DLCO decreased 0.39mL/min/mmHg from the last DLCO value on Exubera [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 181].

Reviewer's Comment: The Applicant asserts that this data supports reversal of the effect of Exubera after discontinuation; however, the following should be noted. First, as mentioned above, there are design issues with this discontinuation phase, such as a potentially enriched population and varying lengths of Exubera exposure. Second, in

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order to assess reversal of effect, a treatment effect should be established first. It is unclear what the mean change from baseline DLCO was for the group entering the discontinuation phase.

7.1.6.3.2.6 Conclusions of the Effect of Exubera on DLCO in Type 2 Diabetes

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

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

Exposure to Exubera longer than 24 months in type 1 diabetes has not been studied in controlled studies. One non-controlled extension study (Study 1036) has exposed subjects to Exubera up to 84 months and the data suggest that the decline from baseline DLCO stabilizes between 2 to 3 years.

Reversal of the effect of long term Exubera use on DLCO was also assessed in a controlled fashion in Study 1001-1002. At Week 104 there was no significant treatment group difference prior to discontinuation of Exubera. Following discontinuation of study medication, both treatment groups demonstrated an improvement in DLCO. After 12 weeks of discontinuation, there was a slight mean treatment group difference favoring the comparator.

7.1.6.3.3 Additional Pulmonary Function Tests

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

The Division reviewed the forced vital capacity (FVC), total lung capacity (TLC), and functional residual capacity (FRC) data for the controlled adult phase 2 and 3 study dataset. The Biometrics reviewer determined the treatment group difference for each pulmonary function test using the observed change from baseline to determine the unadjusted treatment group difference. In addition, the Biometrics reviewer adjusted the

treatment group difference for protocol and adjusted for treatment, protocol, visit, baseline measurement, age, gender, and baseline height.

In general, in type 2 diabetes, there was no significant change from baseline in FVC and TLC during the 96 week treatment period. There was a treatment group difference in FRC at Week 96 of approximately -70mL as shown below in Table 45.

	Mean Observed Change from Baseline (N)		Mean Treatment Group Difference	
	Exubera	Comparator	Treatment Group Difference Unadjusted (95% CI)	Treatment Group Difference Adjusted* (95% CI)
FVC				
Week 12	-0.051 (763)	-0.031 (648)	-0.020 (-0.044, 0.004)	-0.029 (-0.054, -0.005)
Week 24	-0.059 (848)	-0.058 (793)	-0.001 (-0.025, 0.023)	-0.001 (-0.024, 0.022)
Week 36	-0.087 (576)	-0.083 (531)	-0.004 (-0.031, 0.023)	0.003 (-0.023, 0.030)
Week 48/52	-0.086 (535)	-0.079 (496)	-0.006 (-0.036, 0.023)	-0.002 (-0.031, 0.026)
Week 65	-0.046 (158)	-0.068 (134)	0.022 (-0.039, 0.083)	-0.008 (-0.039, 0.055)
Week 78	-0.080 (160)	-0.098 (139)	0.018 (-0.044, 0.080)	0.012 (-0.040, 0.063)
Week 91	-0.081 (154)	-0.093 (133)	0.012 (-0.053, 0.077)	0.007 (-0.047, 0.061)
Week 104	-0.121 (143)	-0.112 (124)	-0.010 (-0.082, 0.063)	-0.008 (-0.064, 0.049)
TLC				
Week 12	-0.026 (620)	-0.003 (503)	-0.024 (-0.075, 0.028)	-0.016 (-0.072, 0.040)
Week 24	0.011 (829)	-0.029 (783)	0.040 (-0.014, 0.094)	0.028 (-0.019, 0.076)
Week 36	-0.021 (559)	-0.005 (509)	-0.016 (-0.077, 0.045)	-0.011 (-0.068, 0.045)
Week 48/52	-0.047 (531)	0.013 (487)	-0.060 (-0.120, -0.001)	-0.055 (-0.116, 0.004)
Week 65	-0.036 (156)	0.052 (133)	-0.088 (-0.221, 0.046)	-0.094 (-0.194, 0.007)
Week 78	-0.008 (158)	0.020 (138)	-0.027 (-0.177, 0.122)	-0.021 (-0.131, 0.088)
Week 91	-0.010 (153)	0.017 (133)	-0.027 (-0.161, 0.108)	-0.032 (-0.145, 0.082)
Week 104	-0.022 (143)	0.008 (124)	-0.030 (-0.160, 0.101)	-0.028 (-0.146, 0.091)
FRC				
Week 12	-0.051 (615)	-0.029 (495)	-0.022 (-0.083, 0.038)	-0.009 (-0.066, 0.047)
Week 24	-0.011 (820)	-0.043 (772)	0.032 (-0.022, 0.085)	0.011 (-0.036, 0.059)
Week 36	-0.062 (552)	-0.062 (503)	0.00002 (-0.059, 0.059)	-0.021 (-0.078, 0.035)
Week 48/52	-0.076 (523)	-0.031 (483)	-0.045 (-0.109, 0.018)	-0.068 (-0.128, -0.009)
Week 65	-0.089 (154)	-0.001 (132)	-0.088 (-0.218, 0.043)	-0.096 (-0.198, 0.006)
Week 78	-0.071 (156)	-0.056 (137)	-0.015 (-0.140, 0.110)	-0.018 (-0.127, 0.091)
Week 91	-0.016 (151)	0.017 (133)	-0.033 (-0.202, 0.136)	-0.064 (-0.177, 0.049)
Week 104	-0.080 (141)	-0.012 (123)	-0.068 (-0.197, 0.061)	-0.072 (-0.190, 0.046)

Table 45 Mean Change from Baseline and Treatment Group Difference for Additional Pulmonary Function Tests in Controlled Phase 2 and 3 Studies in Type 2 Diabetes (Adults)

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

The following figures display the mean change from baseline FVC, FRC, and TLC for the pooled adult controlled phase 2 and 3 studies in type 2 diabetes.
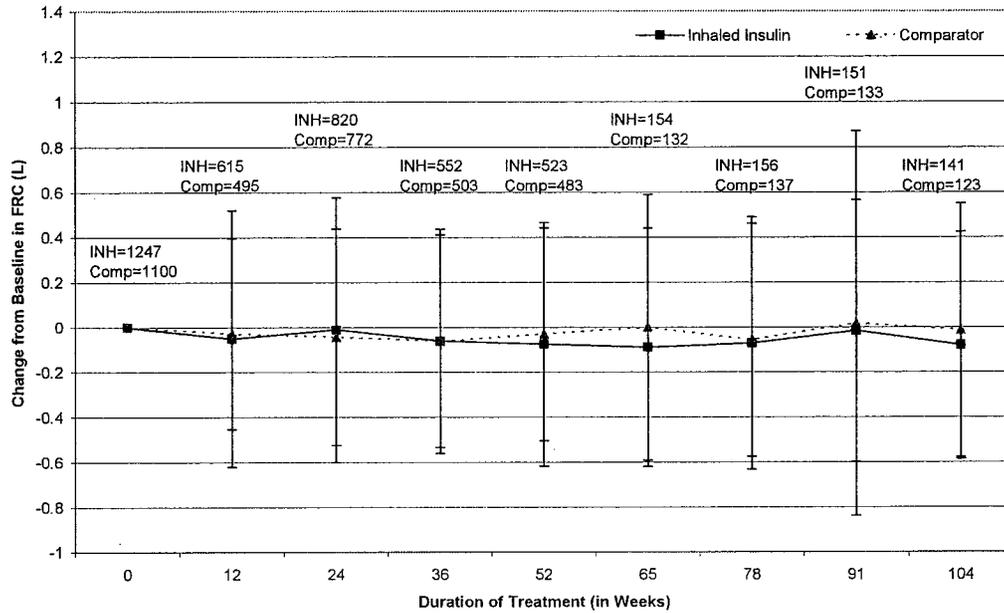
Figure 38 Mean Change from Baseline FVC (L) by Time in Adult Phase 2 and 3 Controlled Studies in Type 2 Diabetes (Mean +/-SD)
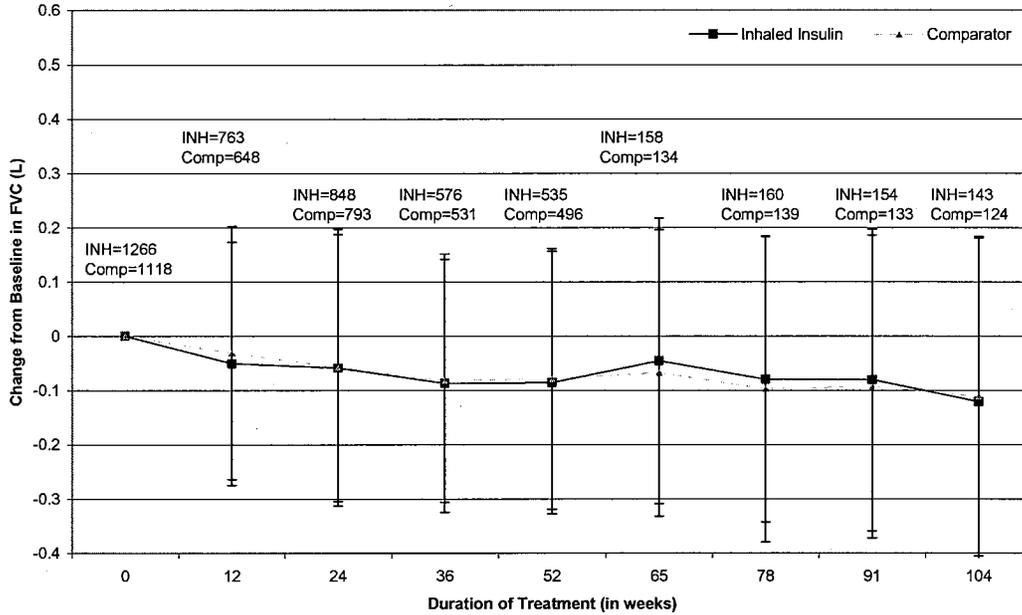
Source: Dr. Joan Buenconsejo's Biometrics Review

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Figure 39 Mean Change from Baseline FRC (L) by Time in Adult Phase 2 and 3 Controlled Studies in Type 2 Diabetes (Mean +/- SD)

Source: Dr. Joan Buenconsejo's Biometrics Review

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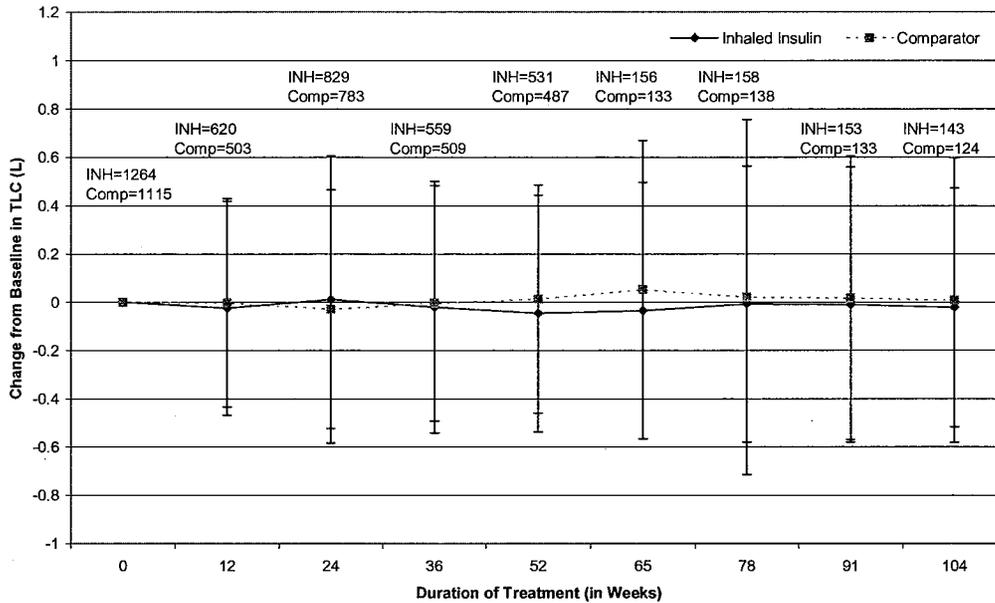
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**Figure 40 Mean Change from Baseline TLC (L) by Time in Adult Phase 2 and 3
Controlled Studies in Type 2 Diabetes (Mean +/- SD)**

Source: Dr. Joan Buenconsejo's Biometrics Review

The Applicant determined the treatment group difference for $FEV_1/FVC\%$, residual volume (RV), and forced expiratory flow 25-75% ($FEF_{25-75\%}$) at 12 months. A small treatment group difference (-24mL) was noted for change from baseline RV at Month 24. A treatment group difference for change from baseline $FEV_1/FVC\%$ favoring the comparator was noted at Month 24. This is consistent with a decline from baseline FEV_1 coupled with no significant change from baseline FVC in the pooled controlled phase 2 and 3 dataset. A treatment group difference for change from baseline $FEF_{25-75\%}$ favoring the comparator of -0.098L/s was noted at Month 24. However, the clinical significance of this is unclear, since $FEF_{25-75\%}$ is less reproducible than FEV_1. The results for these additional PFTs are shown below in Table 46.

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Table 46 Mean Change from Baseline and Treatment Group Difference for Additional Pulmonary Function Tests in Controlled Adult Phase 2 and 3 Studies in Type 2 Diabetes

	Mean Observed Change from Baseline (N)		Mean Treatment Group Difference
	Exubera	Comparator	Treatment Group Difference (95% CI) Adjusted by Applicant[+]
FEV₁/FVC (%)			
Month 3	-0.640 (763)	-0.122 (648)	-0.517 (-0.900, -0.134)
Month 6	-0.762 (847)	-0.158 (793)	-0.531 (-0.891, -0.172)
Month 9	-0.670 (576)	-0.344 (531)	-0.197 (-0.613, 0.220)
Month 12	-1.083 (535)	-0.268 (496)	-0.631 (-1.081, -0.181)
Month 24	-2.027 (143)	-1.306 (124)	-0.412 (-1.338, 0.515)
RV (L)			
Month 3	0.019 (62)	0.015 (503)	0.008 (-0.041, 0.057)
Month 6	0.050 (829)	0.002 (784)	0.037 (-0.004, 0.078)
Month 9	0.036 (559)	0.028 (510)	0.002 (-0.047, 0.051)
Month 12	0.034 (531)	0.045 (488)	-0.019 (-0.071, 0.033)
Month 24	0.055 (143)	0.102 (124)	-0.024 (-0.128, 0.080)
FEF 25-75% (L/s)			
Month 3	0.103 (763)	-0.040 (648)	-0.069 (-0.122, -0.016)
Month 6	-0.155 (757)	-0.060 (716)	-0.094 (-0.146, -0.042)
Month 9	-0.159 (513)	-0.075 (474)	-0.078 (-0.140, -0.017)
Month 12	-0.199 (473)	-0.069 (441)	-0.118 (-0.184, -0.052)
Month 24	-0.422 (111)	-0.305 (102)	-0.098 (-0.239, 0.043)

+Applicant adjustment includes: Treatment, protocol, visit, baseline measurement, age, gender, and baseline height
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg. 130, 131, 134, 135, 138, 139

7.1.6.4 Discontinuation due to Decline in Pulmonary Function

Subjects who discontinued because of a decline in pulmonary function are of interest. In an Information Request dated September 13, 2005, the Applicant was asked to provide information regarding subjects who discontinued due to a decline in pulmonary function tests. In a response to information request dated September 21, 2005, the Applicant provided a list of subjects who discontinued due to a change in pulmonary function. The Applicant identified 7 subjects (6 Exubera and 1 comparator) who discontinued from the controlled phase 2 and 3 studies or Studies 1028 and 1030 secondary to decline in pulmonary function. The following is a brief summary [N21868/N_000/2005-09-21/13sep05_clin_responses.pdf, pg 12-53]:

- Study 1002, Subject 00695134, Exubera
  - o 59 year old WM treated with Exubera and metformin with a 62% decline in FEF on Day 182. However, his FEV₁ only had a 3.3% decline on Day 182. No further follow-up was available/provided. The narrative title indicates discontinuation due to decline in pulmonary function.
- Study 1022, Subject 10472728, Exubera
  - o 31 year old WM treated with Exubera discontinued due to cough, dyspnea, and decrease in DLCO. The subject had a decline in DLCO from 32.6 mL/min/mmHg to 29.7mL/min/mmHg after approximately 88 days of dosing with Exubera. Follow up DLCO increased to 31mL/min/mmHg.
- Study 1028, Subject 10484586, Exubera
  - o 66 year old BM treated with Exubera discontinued on Day 77 due to a decrease in pulmonary function. On treatment Day 9, the subject

experienced decline in FEV_1 and DLCO (post-bronchodilator) of 15% and 9%, respectively. By treatment Day 21 the decline was 21% and 17%, respectively. The subject experienced an SAE (asthma exacerbation). Exubera was temporarily discontinued, but restarted. The subject was discontinued on Day 77 with a decline in post-bronchodilator FEV_1 of 19% and DLCO of 18%. By 6 weeks after discharge, there was no improvement in PFTs.

- Study 1029, Subject 10141667, Subcutaneous insulin
  - o 58 year old WM treated with SC insulin discontinued for decline in pulmonary function after 168 days of dosing. FEV_1 declined 21% and DLCO declined 9%. There was no improvement in PFTs following 39 days of discontinuation of SC insulin. The subject experienced severe dyspnea during the study attributed to URI.
- Study 1029, Subject 10221848, Exubera
  - o 68 year old WM discontinued due to decline in pulmonary function after 507 days of treatment with Exubera. The subject experienced a decline in FEV_1 of 23% on treatment day 498. He appeared to have a decline in FEV_1 that increased at each measurement. He experienced cough and dyspnea. DLCO also decreased 12% while on study medication. A pulmonary consult and HRCT were obtained. The HRCT was reportedly normal. The pulmonary consultant reported an "indication of restrictive lung disease" and recommended discontinuation of Exubera. The decline in FEV_1, cough, and dyspnea persisted after discontinuation of study medication.
- Study 1029, Subject 10482491, Exubera
  - o 57 year old Asian male discontinued due to decline in pulmonary function (decrease in TLC of 18%) after 106 days of treatment with Exubera. He also experienced a decline in FEV_1 of 7% and an increase in DLCO. The PFT changes did not resolve after 59 days off study medication. An HRCT was obtained which was reportedly normal except a small region of interstitial infiltrate in the LLL medial basal segment.
- Study 1029, Subject 11114859, Exubera
  - o 68 year old WM treated with Exubera discontinued on Day 155 for decline in FEV_1 of 24%. The subject declined follow up evaluations.

Reviewer's Comment: More subjects were discontinued due to a decline in PFTs in the Exubera group than in the comparator groups. It should be noted that the protocol specified further evaluation (e.g. pulmonary consultation) with a "notable" decline in pulmonary function; however, there were no specific criteria for discontinuation from the study for a decline in pulmonary function.

Reviewer's Comment: A few subjects were noted to have reasons for discontinuation such as "other", "withdrawn consent", and "not willing to participate". The Applicant was asked to provide a listing of investigator terms/text and reasons for discontinuation which were coded as "withdrawn consent", "other", or "not willing to participate". In a response to information request dated June 10, 2005, the Applicant provided the

listings. Several subjects with discontinuation coded as "other", "withdrawn consent" or "not willing to participate" had investigator text indicating PFT abnormalities [N21868/N_000/2005-06-10/response.pdf, pg. 54-71].

7.1.6.5 Outlier Analyses

Subjects who demonstrated a significant decline in pulmonary function are of particular interest. Although subjects treated with Exubera showed a greater decline from baseline FEV_1 and DLCO over time than the comparator group, there were subjects in both the Exubera treated and comparator treated treatment groups who experienced a significant decline in pulmonary function. The categorical response analyses performed by the Biometrics Reviewer showed that the Exubera group had a higher percentage of subjects with a decline of FEV_1 and DLCO than the comparator group, but the pattern of the response was similar between treatment groups (Figure 13, Figure 19, Figure 29, and Figure 35). The conclusion was that the overall difference in change from baseline FEV_1 and DLCO between the treatment groups was not driven by outliers.

In this Application, the Applicant defined a "notable" decline in PFTs as a decline from baseline to last observation of $\geq$ 15% in FEV_1, TLC, or FVC, and/or a $\geq$ 20% decline in DLCO in the adult phase 2 and 3 controlled studies. In an Information Request dated September 9, 2005, the Agency requested data on subjects with declines of $\geq$ 15% in FEV_1 or $\geq$ 20% in DLCO at any time during. In a response to information request dated September 21, 2005, the Applicant provided an updated listing of subjects with notable declines in FEV_1 and DLCO, which included some two year data from ongoing Study 1029. The Biometrics Reviewer analyzed the data. Table 47 displays the percentage of subjects with a decline in pulmonary function from baseline of $\geq$ 15% in FEV_1 and/or a $\geq$ 20% decline in DLCO at last observation for the phase 2 and 3 controlled adult studies and for the two year data from ongoing Study 1022 and the completed Study 1001-1002.

Table 47 Number of Subjects with Notable Declines from Baseline FEV_1 or DLCO at Last Observation		
Treatment Group	**$\geq$ 15% Decline from Baseline FEV_1 n (%)**	**$\geq$ 20% Decline from Baseline DLCO n (%)**
Type 1 Phase 2 and 3 Controlled Studies		
Exubera (n=698)	11 (1.6%)	28 (4.0%)
Comparator (n=705)	9 (1.4%)	21 (3.0%)
Study 1022		
Exubera (n=290)	3 (1.0%)	4 (1.4%)
Comparator (n=290)	2 (0.7%)	3 (1.0%)
Type 2 Phase 2 and 3 Controlled Studies with 1-year Study 1029 Data		
Exubera (n=1277)	64 (5.0%)	71 (5.6%)
Comparator (n=1132)	38 (3.4%)	42 (3.7%)
Study 1001-1002		
Exubera (n=471)	43 (9.1%)	29 (6.2%)
Comparator (n=441)	25 (5.7%)	22 (5.0%)
Source: Dr. Joan Buenconsejo; N21868/N_000/2005-09-21/13sep05_clin_responses.pdf, pg 59-70		

There were subjects in both the Exubera treated and comparator treated treatment groups who experienced a notable decline in pulmonary function; however, there was a greater percentage of subjects in the Exubera treatment group than in the comparator group. Notable declines were more common in subjects with type 2 diabetes than in subjects with type 1 diabetes. Finally, notable declines in DLCO were seen in a higher percentage of type 1 subjects than notable declines in FEV_1.

It should be noted that subjects who experienced a notable decline in FEV_1 were not necessarily the same subjects who experienced a notable decline in DLCO as shown in the table below. Thus a notable decline in FEV_1 will not necessarily predict a notable decline in DLCO or vice versa.

Table 48 Number of Subjects with Notable Declines from Baseline FEV_1, DLCO, or FEV_1 and DLCO at Any Time During the Treatment Period			
Treatment Group	≥ 15% Decline from Baseline FEV_1 n (%)	≥ 20% Decline from Baseline DLCO n (%)	≥ 15% Decline from Baseline FEV_1 AND ≥ 20% Decline from Baseline DLCO n (%)
Type 1 Phase 2 and 3 Controlled Studies			
Exubera (n=698)	17 (2.4%)	36 (5.2%)	2 (0.3%)
Comparator (n=705)	13 (1.8%)	20 (2.8%)	4 (0.6%)
Type 2 Phase 2 and 3 Controlled Studies			
Exubera (n=1277)	80 (6.3%)	79 (6.2%)	20 (1.6%)
Comparator (n=1132)	44 (3.9%)	43 (3.8%)	25 (2.2%)
Source: Dr. Joan Buenconsejo			

In reviewing the narratives for subjects with notable declines, some subjects were noted to have notable declines in pulmonary function during the study; however, the pulmonary function subsequently improved. An important question is in those subjects who experienced a notable decline in FEV_1 or DLCO at any timepoint during the treatment period, how many subjects had persistent declines. To address this issue, the Biometrics Reviewer identified subjects who experienced a notable decline in FEV_1 or DLCO in the two year studies (Study 1001-1002 and ongoing Study 1022) at any timepoint and at last observation. As shown below, approximately half of subjects who had a notable decline in pulmonary function at any time during the study had a notable decline at last observation.

Table 49 Number of Subjects with Notable Declines from Baseline FEV$_1$ or DLCO at Any Timepoint and at Last Observation		
Treatment Group	≥ 15% Decline from Baseline FEV$_1$ n (%)	≥ 20% Decline from Baseline DLCO n (%)
Study 1022 – Any Timepoint		
Exubera (n=290)	7 (2.4%)	14 (4.8%)
Comparator (n=290)	6 (2.1%)	6 (2.1%)
Study 1022 – Last Observation		
Exubera (n=290)	3 (1%)	4 (1.4%)
Comparator (n=290)	2 (0.7%)	3 (1%)
Study 1001-1002 – Any Timepoint		
Exubera (n=471)	67 (14.2%)	56 (11.9%)
Comparator (n=439)	50 (11.3%)	44 (10.0%)
Study 1001-1002 – Last Observation		
Exubera (n=471)	43 (9.1%)	29 (6.2%)
Comparator (n=439)	25 (5.7%)	22 (5.0%)
Source: Dr. Joan Buenconsejo		

In Study 1022 (type 1 diabetes), at last observation there were similar percentages of subjects with notable declines in each treatment group. For type 2 subjects in Study 1001-1002, there were more subjects in the Exubera treatment group with notable decline in pulmonary function at last observation than in the comparator treatment group.

The Applicant performed subgroup analyses comparing subjects with a notable decline in pulmonary function to subjects without a notable decline in pulmonary function using the original NDA data. In general, other than subjects with notable declines being slightly older, baseline demographics and duration of exposure were similar between subjects with notable declines and subjects without notable declines. A baseline FEV$_1$ or DLCO >120% of predicted was more common among subjects with notable declines in pulmonary function [N21868/N_000/2004-12-27/pulm.pdf, pg 64-67].

Reviewer's Comment: It is unclear why subjects with baseline PFTs above normal would demonstrate more notable declines in pulmonary function other than that the baseline PFT could be spuriously high. Some of the earlier studies with less rigorous PFT entry criteria may have contributed to this phenomenon. The final results of Study 1022 and Study 1029, which have more rigorous PFT entry criteria, will provide additional insight.

In addition, the Applicant's analyses determined that the efficacy of Exubera did not differ between subjects with notable declines in pulmonary function and subjects without notable declines. In terms of the adverse event profile, there was no difference in discontinuations or respiratory SAEs between subjects with and without a notable decline in pulmonary function. Severe AEs and severe respiratory AEs were slightly more common in subjects with a notable decline in pulmonary function than in subjects without a notable decline. Dyspnea was reported in a higher percentage of subjects with a notable decline in pulmonary function treated with Exubera than in Exubera treated subjects without a notable decline. There was no consistent pattern between insulin antibodies and notable PFT declines [N21868/N_000/2004-12-27/pulm.pdf, pg 67].

Reviewer's Comment: Discontinuations due to a decline in pulmonary function are discussed in Section 7.1.6.4.

To summarize, there were subjects in both the Exubera and comparator treatment groups who experienced a notable decline in pulmonary function (defined as a ≥ 15% decline from baseline FEV_1 or a ≥ 20% decline from baseline DLCO). Although there were more subjects with a notable decline in the Exubera treatment group, the response analyses do not suggest that the subjects with notable declines are driving the overall difference in change from baseline FEV_1 and DLCO between the treatment groups. Further analyses of subjects with notable declines did not identify subjects at particular risk for notable decline other than a baseline FEV_1 or DLCO >120%. It should be noted that subjects who experienced a notable decline in FEV_1 were not necessarily the same subjects who experienced a notable decline in DLCO.

Approximately half of subjects who experienced a notable decline in pulmonary function at any time point during the two year studies had a notable decline in pulmonary function at last observation, suggesting persistence of the notable decline in approximately half of the subjects in each treatment group. In type 1 subjects in Study 1022, at last observation there were similar percentages of subjects with notable declines in each treatment group. For type 2 subjects in Study 1001-1002, there were more subjects in the Exubera treatment group with notable decline in pulmonary function at last observation than in the comparator treatment group.

7.1.6.6 Subgroup Analyses for Pulmonary Function Tests

Subgroup analyses were performed to assess the effect of age, race, and sex on the treatment difference in the mean change from baseline FEV_1, FVC, DLCO, TLC, and FRC in the adult controlled phase 2 and 3 studies. No consistent association between age (18-44 or ≥ 45 years), sex, or race (white, non-white) was noted for the mean change from baseline FEV_1, FVC, TLC, DLCO, and FRC. However, it should be noted that due to nature of subgroup analyses and a limited number of non-Caucasian subjects, it is difficult to draw any definitive conclusions from the subgroup analyses.
Reviewer's Comments: Refer to Dr. Buenconsejo's Biometric Review for further details.

7.1.6.7 Exploratory Analyses with Pulmonary Function Tests

Insulin Antibodies
Insulin is a polypeptide and may be associated with anti-insulin antibodies. The Applicant measured insulin antibodies in the phase 2 and 3 clinical studies. Two insulin antibody assays were utilized during the clinical development program: the semi-quantitative Mayo assay and the quantitative Esoterix assay. In general, in type 1 diabetes, Exubera was associated with a higher conversion from the absence to the presence of insulin antibodies and a higher titer of insulin antibodies than the comparator treatment. Thus, the association between change in pulmonary function by insulin antibody titer was explored.

The insulin antibody titer (Esoterix) and change from baseline FEV_1, FVC, DLCO, TLC, and FRC were analyzed in Study 1022. Although this is an ongoing study, Study 1022 provides controlled PFT data on type 1 subjects exposed to Exubera for up to two years and data on insulin antibodies for one year. The Biometrics reviewer evaluated the

change from baseline PFT by antibody titer in Study 1022 using a scatter plot at Week 12, 24, 36, and 48. Linear regression was performed to obtain a correlation coefficient, rho (ρ), to determine if there was a correlation between antibody titer and a decline from baseline PFT.

The analyses of change from baseline PFT by insulin antibody titers in Study 1022 do not suggest a significant correlation between mean change from baseline FEV_1, DLCO, FVC, TLC, and FRC and insulin antibody titer.
Reviewer' Comment: The Biometrics reviewer also performed a similar analysis for the PFTs in Study106. As in Study 1022, there did not appear to be a correlation between change from baseline PFT and insulin antibody titer.

For type 2 diabetes, the Biometrics reviewer analyzed Study 1029 and Study 1001-1002, which provide PFT and antibody data for up to one year and two years of exposure to Exubera, respectively. The analyses of change from baseline PFT by insulin antibody titers in Study 1029 and Study 1001-1002 do not suggest a significant correlation between mean change from baseline FEV_1, DLCO, FVC, TLC, and FRC and insulin antibody titer.
Reviewer's Comment: For details of the analyses of the relationship between insulin antibody titer and the change in pulmonary function, refer to the Dr. Joan Buenconsejo's Biometrics review.

The Applicant also explored the association between the change in insulin antibodies in subjects with notable PFT declines ($\geq$ 15% in FEV_1, TLC, or FVC, and/or $\geq$20% in DLCO). The Applicant determined that there was no consistent pattern between insulin antibodies and notable PFT declines [N21868/N_000/2004-12-27/pulm.pdf, pg 76-77].

Insulin Exposure
The association between insulin exposure and change in pulmonary function in type 1 diabetes was explored in Study 1022 and Study 106. In Study 106, subjects were exposed to study medication for 24 weeks. The Biometrics reviewer analyzed the association between the average total daily insulin dose and change from baseline FEV_1, DLCO, FVC, TLC, and FRC and the association between the cumulative insulin dose and the change from baseline FEV_1, DLCO, FVC, TLC, and FRC at Weeks 12 and 24. The Biometrics reviewer evaluated the correlation using a scatter plot. Linear regression was performed to obtain a correlation coefficient, rho (ρ), to determine if there was a correlation between change from baseline PFT and insulin dose. The analyses do not suggest a significant correlation between change from baseline FEV_1, DLCO, FVC, TLC, and FRC and the average total daily Exubera dose or the cumulative Exubera dose.

In Study 1022, subjects were exposed to study medication for up to one year, which was the cut off for insulin dosing data in this ongoing study. The Biometrics reviewer analyzed the association between the average total daily insulin dose and change from baseline FEV_1, DLCO, FVC, TLC, and FRC and the association between the cumulative insulin dose and the change from baseline FEV_1, DLCO, FVC, TLC, and FRC at Weeks 12, 24, 36, and 48. The analyses do not suggest a correlation between change from

baseline FEV_1, DLCO, FVC, TLC, and FRC and the average total daily Exubera dose or the cumulative Exubera dose.

The association between insulin exposure and change in pulmonary function in type 2 diabetes was explored in combined Study 1001-1002. In Study 1001-1002, subjects were exposed to study medication for up to 104 weeks. The Biometrics reviewer analyzed the association between the average total daily insulin dose and change from baseline FEV_1, DLCO, FVC, TLC, and FRC and the association between the cumulative insulin dose and the change from baseline FEV_1, DLCO, FVC, TLC, and FRC at Weeks 24, 36, 52, 65, 78, 91, and 104. The analyses do not suggest a correlation between change from baseline FEV_1, DLCO, FVC, TLC, and FRC and the average total daily Exubera dose or the cumulative Exubera dose.

Reviewer's Comment: Based upon these exploratory analyses, it does not appear that either insulin antibodies or total exposure would be expected to predict who may be at risk for declines in pulmonary function.

7.1.7 Chest X-Ray (CXR)

In type 1 diabetics, baseline and end of study/last observation CXRs were performed in Studies 106, 107, 1022, 1027. Study 1026 was performed in Germany and CXRs were not performed. In type 2 diabetics, baseline and end of study CXRs were performed in Studies 108, 109, 110, 1001, 1002, and 1029. CXR were performed and read locally at radiology departments available to the clinical sites. There were no specific measures to blind the radiologist to the treatment group.

The Applicant pooled the phase 2 and 3 CXR data and reported significant changes in the last observed CXR from baseline. The changes reported included pulmonary and non-pulmonary findings. According to the Applicant's pooled data, both type 1 and type 2 diabetics in the Exubera group had a slightly greater incidence of significant changes in CXR from baseline to last observation as shown in Table 50.

Table 50 Significant Changes in Chest X-Rays Between Baseline & Last Observation* Adult Controlled Phase 2 and 3 Studies			
Number (%) of subjects with significant change from baseline [Number examined]			
	Exubera	SC Insulin	Oral Agents
Type 1	12 (2.2) [543]	6 (1.1) [544]	NA
Type 2	42 (4.4) [962]	9 (2.5) [365]	11 (2.6) [420]
* This table is based upon subjects who had changes from baseline at the last observation CXR examination. This table does not include data for subjects who had interval CXR changes which resolved by the last observation CXR. Source: [N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 2704-2705]			

Reviewer's Comment: The CXR changes from baseline for the individual studies are listed in Table 69 of the Appendices, Section 10.2. As shown in that table, there are more changes from baseline in the individual studies than what the table above displays. On initial review it was unclear how the Applicant pooled the CXR data from the individual studies. The Applicant was asked for clarification of the pooling of the CXR data and the discrepancy between the individual study data and the pooled data. According to the

Applicant there are several reasons for the difference [N21868/N_000/2005-07-26/response_ir_request_21jun05.pdf, pg 6; N21868/N_000/2005-08-12/07july05_clin_responses.pdf, pg 3].

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

Reviewer's Comment: CXR were performed and read locally at radiology departments available to the clinical sites. There were no specific measures to blind the radiologist to the treatment group. Because the radiologists were not blinded, this could explain the increased findings in the Exubera group.

The CXR changes from baseline for the individual studies are listed in Table 69 of the Appendices, Section 10.2. In general, the most common CXR changes from baseline were nodular density, opacity, nodule, atelectasis, cardiomegaly, enhanced vasculature, and pulmonary edema. Consistent with the pooled data, CXR data from the individual studies showed that the Exubera group had more changes from baseline than the comparator group. Of special concern was that nodules, opacities, and densities were more common in the Exubera group than in the comparators. Follow-up data for these subjects were requested during the review period. The Applicant provided follow-up imaging data for the majority of subjects. In most cases, the follow up imaging indicated a resolution of the findings.

Reviewer's Comment: During the Endocrine and Metabolic Drugs Advisory Committee meeting on September 8, 2005, the Applicant provided follow up data for subjects with significant changes in CXR at last observation. According to the Applicant, many subjects had resolution of findings [September 8, 2005, EMDAC meeting, Pfizer presentation, slide #71].

7.1.8 High Resolution Computed Tomography (HRCT)

7.1.8.1 Methods

High resolution computed tomography (HRCT) scans of the thorax were obtained in a subset of subjects in Studies 106, 107, and 108. In these studies, HRCTs were performed at baseline and at Week 24, which was end of study, in a subset of subjects. In addition, HRCTs were obtained in a subset of subjects in Study 1029, which is an ongoing 2-year study. In Study 1029, HRCTs were performed at baseline, 12 months, and 24 months.

The HRCT data from Studies 106, 107, and 108 are discussed together since the length of the studies was similar, 24 weeks. The HRCT data from Study 1029 are discussed separately since HRCTs were obtained at 12 and 24 months.

Reviewer's Comment: During the clinical development program for Exubera, to assess the pulmonary safety of Exubera, the Agency requested that the Applicant obtain HRCT data from approximately 50 subjects on Exubera and 50 subjects on standard therapy at 0 and 24 months.

The Applicant has controlled HRCT data at 24 weeks in 53 subjects treated with Exubera and 63 subjects treated with SC insulin. The Applicant has controlled HRCT data at 24 months on 51 subjects treated with Exubera and 53 subjects treated with SC insulin.

Reviewer's Comment: It should be noted that the 24 month HRCT data is in subjects with type 2 diabetes. The only HRCT data in subjects in type 1 diabetes are the 24 week data from Studies 106 and 107.

In addition to the controlled HRCT data, the Applicant also obtained HRCTs as deemed necessary as part of medical evaluations. These HRCT scans are termed "for cause" HRCTs and are reviewed separately. The HRCT scans were 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. The baseline and follow up HRCTs were forwarded to a central radiology site for a blinded review. The HRCT were read and classified as within normal limits (WNL) or not. If there was a change from baseline, the change was classified as "more abnormal" or "less abnormal."

Reviewer's Comment: Since the HRCTs start 2 cm above the carina, the HRCTs likely do not assess the lung apices.

7.1.8.2 24 Week HRCT Data

The HRCT data from Studies 106, 107, and 108 do not suggest an increase in abnormal HRCT findings at 24 weeks or last observation in the Exubera group. There were 53 subjects in the Exubera group and 63 subjects in the SC insulin group who underwent the HRCT substudy in Studies 106, 107, and 108. In both treatment groups approximately 78-80% of subjects had normal HRCTs at baseline and end of study. The Exubera group had fewer subjects with normal HRCTs at baseline and abnormal at last observation (5.7%) compared to the SC insulin group (6.3%). In subjects with abnormal HRCTs at baseline, the Exubera group had one subject with more abnormal findings at last observation, while the SC insulin group had two subjects with more abnormal findings at last observation. Table 51 displays a summary of the HRCT data in Studies 106, 107, and 108.

Table 51 Number of Subjects with Change in HRCT Between Baseline and Last Observation in Studies 106, 107, and 108			
Within Normal Limits at Baseline	**Within Normal Limits at End of Study**	**Exubera N=53**	**SC Insulin N=63**
Yes	Yes	43 (81.1%)	49 (77.8%)
	No	3 (5.7%)	4 (6.3%)
No	Yes	0	2 (3.2%)
	No	7 (13.2%)	8 (12.7%)
	No significant change	5 (9.4%)	6 (9.5%)
	More abnormal	1 (1.9%)	2 (3.2%)
	Less abnormal	1 (1.9%)	0
Source: N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 2715			

Reviewer's Comment: The Applicant provided a line listing of the HRCTs, which were not within normal limits at baseline or end of study. Included in the line listings were additional comments, such as no lung windows and not HRCT. There were four listings indicating no lung windows and six listings indicating the CT was not a high resolution CT. Therefore, it appears that at least 10 subjects may not have undergone proper HRCT assessment.

Of interest are the subjects who had normal HRCT at baseline and had abnormal HRCT at last observation as well as subjects who had abnormal HRCT at baseline and more abnormal findings at last observation. New findings of densities (linear or dependent) and atelectasis were the most common findings. The following summarizes the HRCT findings for these subjects [N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 2716-2717]:

HRCTs WNL at baseline and not WNL at end of study
- Exubera (3)
    - o Linear density in lingula
    - o Dependent density in basis not consistent with fibrosis
    - o New dependent density, unlikely to be fibrosis
- SC insulin (4)
    - o New right basilar atelectasis
    - o Dependent subpleural density
    - o ? New scar or atelectasis in lingual
    - o Increased reticular subpleural reticular

Abnormal HRCT at baseline and more abnormal HRCT findings at last observation
- Exubera (1)
    - o Persistent linear scar right base; new linear density, probably atelectasis
- SC insulin (2)
    - o Lung nodule unchanged; linear density in right lower lobe is thicker
    - o Increased right middle lobe subpleural lines and bands

Reviewer's Comment: The 24 week HRCT data does not suggest a safety signal in the Exubera group.

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7.1.8.3 One and Two Year HRCT Data

During clinical development, the Agency requested HRCT data on at least 50 subjects on Exubera and 50 subjects on comparator for at least 2 years treatment duration.

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 52 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. This is a potential source of bias because the reading radiologist could be influenced by knowing which HRCT was the baseline HRCT. Therefore, the Applicant should reevaluate the two year HRCT data from ongoing Study 1029 by

blinding the reading radiologist to treatment group and as well as time. This analysis could be a phase four commitment.

Of interest are the subjects who had normal HRCT at baseline and had abnormal HRCT at Month 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.

7.1.8.4 "For Cause" HRCT

Subjects could undergo a "for cause" HRCT in response to a medical condition during the clinical studies. HRCT scans could also be performed for a decline in pulmonary function. Forty-eight subjects underwent "for cause" HRCT examinations. No "for cause" HRCT scans were performed during the controlled treatment periods of the individual studies. All of the "for cause" HRCTs were performed in the extension studies and thus, all the subjects undergoing "for cause" HRCTs were on Exubera.

The Applicant provided a listing of the "for cause" HRCTs. The listings were reviewed and in general, the majority of the "for cause" HRCTs were interpreted as normal. It should be noted that some of the CT scans listed appear to be regular thoracic CT scans

performed with contrast and not HRCTs. In addition, the medical reason for obtaining the HRCT was not included for all subjects. A list of interesting "for cause" HRCTs are described in Section 10.3. One case of sarcoidosis and two cases of fibrosis were noted.

Because of the fact that all of the "for cause" HRCT scans were performed in the extension studies, which were not controlled, all of the "for cause" HRCT scan were performed on subjects on Exubera.

7.1.8.5 Conclusions

HRCT scans were obtained to assess for parenchymal lung changes associated with Exubera use. The Applicant submitted the HRCT data requested by the Agency. The Applicant submitted controlled HRCT data at baseline and 24 weeks in 116 subjects, controlled HRCT data at baseline and 24 months in 144 subjects, and "for cause" HRCT data in 48 subjects. The controlled HRCT data does not suggest an increase in abnormal findings associated with Exubera use compared to SC insulin at 24 weeks or 24 months.

8 Additional Clinical Issues

8.1 Special Populations

8.1.1 Underlying Lung Disease

8.1.1.1 Methods

In the phase 2 studies (102, 103, 104), the protocols specified excluding subjects with any active respiratory disease or significantly abnormal PFT results. However, in the phase 3 studies the Applicant relaxed the exclusion criteria and subjects with mild to moderate asthma or COPD could have enrolled in the studies with the following caveats:

- In Studies 106, 107, 108, 109, and 110 subjects with poorly-controlled asthma, clinically significant COPD, or other significant respiratory disease were excluded. In addition, subjects with DLCO<75% or FEV_1<70% were excluded.
- In Studies 1001 and 1002, subjects with moderate to severe asthma (PEFR ≤ .80%) predicted and/or oral steroids <6 months of screening, or moderate to severe stable chronic obstructive pulmonary disease (COPD) (PEFR ≤ 80% predicted and/or antibiotics for chest infection < 3months of screening (Week -6) were excluded. Subjects were required to have DLCO ≥ 75% and FEV_1 ≥ 75% predicted.
- In Studies 1026, 1027, 1022, and 1029 the FEV_1 and DLCO must be ≥ 70% predicted.
- In all studies, subjects with significant abnormalities on CXR were excluded.

Reviewer's Comment: The phase 3 protocols allowed subjects with mild to moderate underlying lung disease to be enrolled with an FEV_1 or DLCO as low as 70%.

The Agency requested prospective studies in subjects with underlying lung disease to assess the effects of Exubera. To specifically evaluate the safety and efficacy of Exubera

in subjects with underlying lung disease, the Applicant conducted Studies 1028 and 1030, in which subjects with asthma and COPD were enrolled, respectively. In Studies 1028 and 1030, subjects with FEV_1 and DLCO as low as 50% of predicted were allowed to enroll.

The Applicant specified three populations to evaluate subjects with mild to moderate underlying lung disease (ULD), the Controlled ULD Cohort, the 1028/1030 Cohort, and the Integrated Cohort. The Controlled ULD Cohort consists of a sub-population of adult subjects in the controlled phase 2 and 3 studies *retrospectively identified* as meeting criteria compatible with mild to moderate asthma or COPD. According to the Applicant, ULD was categorized as follows in this cohort:

- Asthma
  - Present history of asthma at study entry
- COPD
  - Ratio of FEV_1/FVC <70% at baseline and a history of smoking

Reviewer's Comment: Subjects were not required to have an established history of COPD.

- Neither disorder
  - Subjects without asthma or COPD, including all subjects not meeting the definition of having asthma or COPD at baseline.

Subjects meeting the above criteria for both asthma and COPD were considered to have COPD only. The Applicant *retrospectively identified* 54 subjects with asthma, 101 subjects with COPD, and 3657 subjects with neither disorder in the Controlled ULD Cohort.

The 1028/1030 Cohort includes data from two studies (1028 and 1030) in subjects with type 1 or type 2 diabetes and underlying lung disease in which the inclusion criteria rigorously defined asthma and COPD. In Study 1028, subjects with mild intermittent or mild to moderate persistent asthma for at least 6 months prior to screening was required. Asthma was defined according to ATS guidelines (episodic coughing, wheezing, dyspnea, and chest tightness associated with airflow limitation that is at least partially reversible). In Study 1030, a diagnosis of COPD was based upon a 10 pack year or more smoking history, a fixed airflow obstruction at screening (post-BD FEV_1/FVC <70% and FEV_1 <80%), and/or a 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. *Reviewer's Comment: Study 1030 could have enrolled subjects with chronic bronchitis without obstructive physiology.*

The integrated ULD Cohort combines the 1028/1030 Cohort and the Controlled ULD Cohort. Table 53 displays the number of subjects in each of the proposed ULD Cohorts.

Table 53 Applicant's Proposed Underlying Lung Disease (ULD) Cohorts					
	Asthma		COPD		Neither Disorder	
	Exubera	Comparator	Exubera	Comparator	Exubera	Comparator
Controlled	24	30	50	51	1901	1756
1028/1030	46	49	30	27		
Integrated	70	79	80	78	1901	1756
Source: [N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 1163]						

Reviewer's Comment: Only Studies 1028 and 1030 prospectively specified enrollment of subjects with underlying lung disease. Thus, for the purpose of the pulmonary safety analyses in subjects with underlying lung disease, the focus of this review is on Studies 1028 and 1030, in which subjects with underlying lung disease were prospectively identified.

Although some of the phase 3 studies could have included subjects with a history of mild to moderate asthma, the diagnosis of asthma or COPD was not confirmed in these studies as subjects were retrospectively identified. In the case of asthma, a self reported history categorized a subject as having asthma. However, the diagnosis was not confirmed. For COPD, the diagnosis was retrospectively made based upon a history of smoking and FEV_1/FVC <70%. However, the length of smoking history was not specified and a fixed FEV_1/FVC ratio <70% after bronchodilators was not specified as in Study 1030. Therefore, interpretation of the data from subjects in the Controlled ULD Cohort and the Integrated ULD Cohort is limited. As discussed in the regulatory history, the Agency informed the Applicant that an analysis of data from subjects retrospectively determined to have underlying lung disease was not acceptable to assess the safety of Exubera. The Agency requested controlled data from prospective studies in subjects with underlying lung disease.

8.1.1.2 Asthma

8.1.1.2.1 Prospectively Defined Asthma - Study 1028

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. In this study, asthma is defined according to ATS guidelines (episodic coughing, wheezing, dyspnea, and chest tightness associated with airflow limitation that is at least partially reversible). An FEV_1 between 50 and 85% with 12% reversibility is specified; however, subjects with mild intermittent asthma or EIB do not need to meet the PFT criteria, but these subjects have to be approved by a Pfizer clinician. Eligible subjects undergo a 3 week run-in period (SC insulin). Then subjects are randomized to Exubera or continuation of the run-in regimen for a 52 week treatment period. The treatment period is followed by a 6 week follow up phase during which Exubera is discontinued.

PFT (pre- and 30minutes post-bronchodilator) testing is performed at Week -4, -3, -2, -1, 1, 2, 3, 4, 6, 18, 26, 39, 52, 52+2, and 52+6. In addition, 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). Study 1028 also includes the administration of the BDI/TDI and asthma control questionnaire during the treatment period as well as a CXR at screening and Week 52.

Results
Approximately 139 subjects out of a planned 250 have been enrolled in Study 1028. The mean age of the subjects was 47-49 years of age and approximately half of the subjects have type 1 diabetes, while the other half have type 2 diabetes. Eleven Exubera subjects and 22 comparator group subjects have completed the study.
Reviewer's Comment: At the time of the original submission, 26-week data was submitted on some subjects. The Applicant submitted a safety update on April 26, 2005, and this section contains information from the interim report submitted in the safety update. The safety update contains some information on subjects with asthma who have been exposed to Exubera for one year.

There was one respiratory SAE, asthma exacerbation, in each treatment group. The number of subjects with respiratory adverse events was similar between treatment groups. In general, the types of respiratory AEs noted in subjects with asthma were similar to AEs noted in subjects without asthma. The most common respiratory adverse events were asthma and respiratory tract infection. Of the respiratory AEs reported in Study 1028, increased cough and respiratory tract infection were the AEs with the greatest difference between treatment groups favoring the comparator. In addition, dyspnea, pharyngitis, respiratory disorder, respiratory tract infection, and voice alteration were more common in the Exubera group than in the SC insulin group as shown below in Table 54. More subjects discontinued from the Exubera group due to adverse events (5) than the comparator group (0). The most common adverse event leading to discontinuation was asthma.

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Table 54 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 function	**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%)**
Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 78, 83-84		

Reviewer's Comment: The number of subjects with asthma AEs was greater in the SC insulin group than in the Exubera group. There were 25 (35%) subjects with asthma AEs in the Exubera group and 51 (44%) subjects with asthma AEs in the SC insulin group.

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.

In general, 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. The number of subjects requiring systemic corticosteroid treatment was similar between treatment groups.

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 55. 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 55 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 41.

Figure 41 Mean Change from Baseline in Post-Bronchodilator FEV$_1$ (L) in Study 1028 - Interim Results (Mean +/-SD)
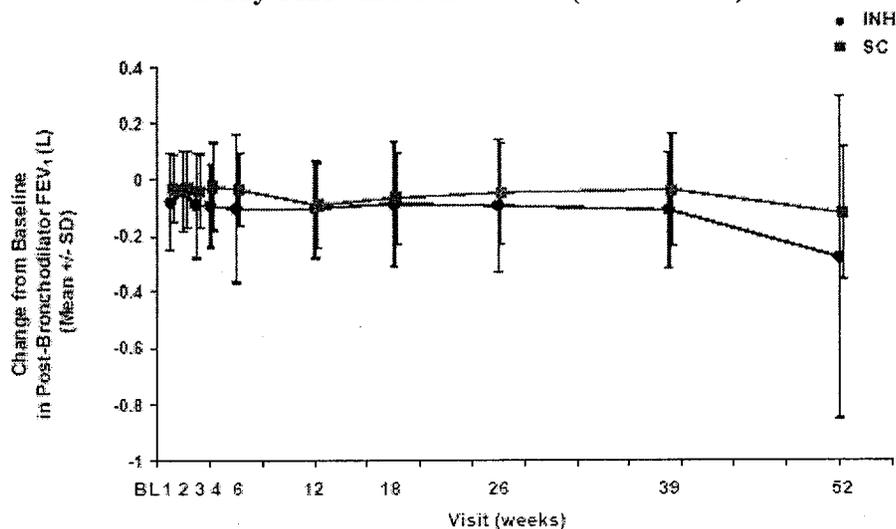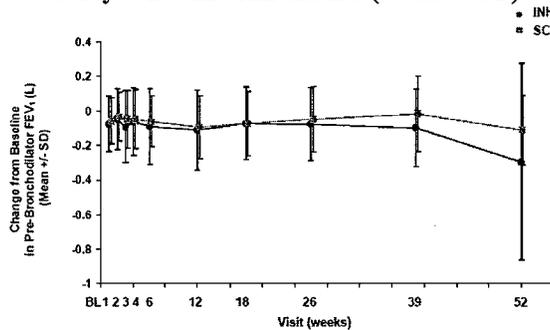

Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 37

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 FEV₁ and in the SC insulin group there were 2 subjects with 15-20% decrease from baseline FEV₁ [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 131].

Reviewer's Comment: The Applicant also measured pre-bronchodilator FEV₁ and in general the change from baseline in pre-bronchodilator FEV₁ produces a similar pattern as shown in the figure below.

Figure 42 Mean Change from Baseline in Pre-Bronchodilator FEV₁ (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 56. 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 56 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			

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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 43.

Figure 43 Mean Change from Baseline in Post-Bronchodilator DLCO (mL/min/mmHg) in Study 1028 – Interim Results (Mean +/-SD)
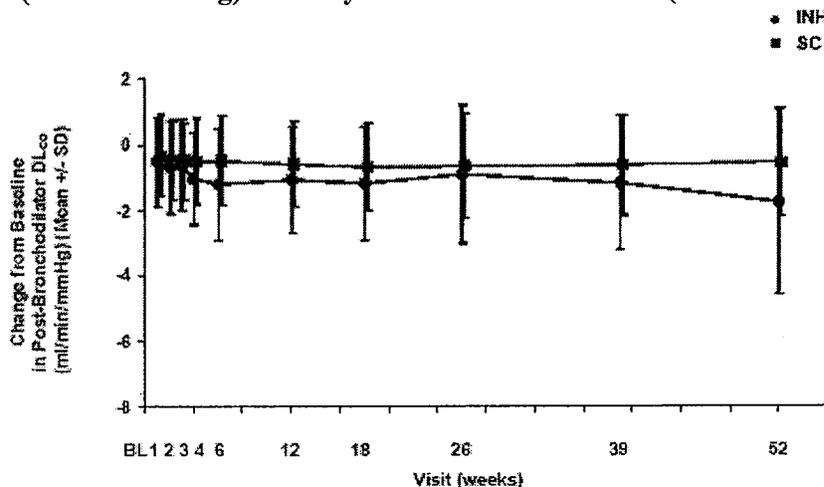
Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 42

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 44 Mean Change from Baseline in Pre-Bronchodilator DLCO (mL/min/mmHg) in Study 1028 - Interim Results (Mean +/-SD)
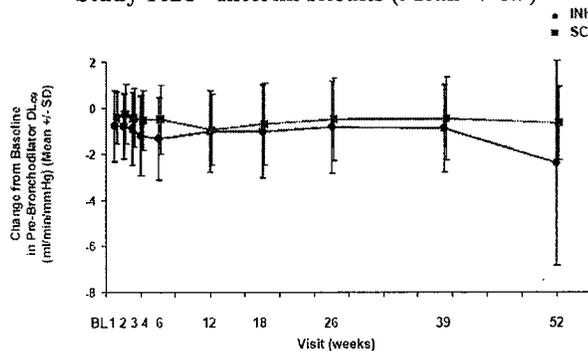
Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 43

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.

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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 from baseline in both the mean subject and mean clinical evaluation score, while the SC insulin group showed a small decrease from baseline in both the mean subject and mean clinical evaluation score [N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 171].

Reviewer's Comment: The Asthma Control Questionnaire data at 52 suggests that the Exubera group reported a slight worsening of asthma control, while the SC insulin group reported an improvement in asthma control. However, it should be noted the limited number of subjects at Week 52.

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 on 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.

There were a similar number of subjects with respiratory AEs in each treatment group. In general, they types of respiratory AEs noted in subjects with asthma were similar to AEs noted in subjects without asthma. Asthma AEs were more common in the comparator group. The protocol specified a definition for a non-severe and severe asthma exacerbation. Although asthma AEs were more common in the comparator group, 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. Most of the respiratory AEs were mild to moderate in severity. One asthma exacerbation SAE was noted in both treatment groups.

The Exubera group had a slightly lower baseline pre- and post-bronchodilator FEV_1 than the SC insulin group. The PFT data from Study 1028 indicates that subjects treated with Exubera demonstrate a greater decline from baseline FEV_1 than the comparator group. The treatment group difference for change from baseline FEV_1 stabilized from the early weeks of the study until Week 26. However, by Week 52, the treatment group difference for change from baseline FEV_1 had increased further favoring the comparator. At Week 52, the Exubera group had a mean decline from baseline post-bronchodilator FEV_1 of 278mL, while the comparator group had a mean decline from baseline post-bronchodilator FEV_1 of 122mL. However, the 52 week data is based upon PFT data from only 27 subjects.

Baseline DLCO was lower in the comparator group than in the Exubera group. The Exubera group demonstrated a greater decline from baseline DLCO than subjects in the comparator group at most time points. The mean treatment group difference is not consistent throughout the treatment period. Towards the end of the treatment period, there is an increase in the separation of the treatment groups, further favoring the comparator. 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, the 52 week data is based upon PFT data from only 27 subjects.

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.

8.1.1.2.2 Retrospectively Defined Asthma

As discussed above in the Methods Section 8.1.1.1, the Applicant *retrospectively identified* 54 subjects with asthma, 101 subjects with COPD, and 3657 subjects with neither disorder in the Controlled ULD Cohort. This section will include a brief review of the pertinent findings in the 54 subjects retrospectively identified with asthma in the controlled phase 2 and 3 studies.

Reviewer's Comment: As discussed earlier, the Agency informed the Applicant that an analysis of data from subjects retrospectively determined to have underlying lung disease was not acceptable to assess the safety of Exubera.

Of the 54 subjects retrospectively identified with asthma, 24 were treated with Exubera and 30 were treated with comparator. Approximately 57% of the subjects had type 2 diabetes and 43% had type 1 diabetes. The mean age of the subjects was 48 years of age and the baseline percent predicted FEV_1 was >80% in the majority of subjects [N21868/N_000/2004-12-26/clinstat/pulm.pdf, pg 1180-1183].

Reviewer's Comment: Although 54 subjects were identified with retrospectively diagnosed asthma, PFT data for 12 months exposure to Exubera is available for only 12 subjects. Thus, these additional retrospectively identified subjects with asthma provide limited data about the long term effect of Exubera on pulmonary safety in subjects with asthma.

There were no respiratory deaths in subjects retrospectively identified with asthma. Three subjects were noted to have serious adverse events (1 in the Exubera group and 2 in the comparator group). None of the SAEs were respiratory. The number of subjects with overall AEs and respiratory AEs was similar between treatment groups. Asthma, bronchitis, increased cough, dyspnea, pharyngitis, respiratory tract infection, and sputum

increased were reported in more than one subject and in a higher percentage of subjects in the Exubera group than subjects in the comparator group as shown below in Table 57 [N21868/N_000/2004-12-26/clinstat/pulm.pdf, pg 1185-1191].

Table 57 Number of Subjects with Respiratory Adverse Events in Subjects Retrospectively Identified with Asthma		
	Exubera n = 24	Comparator n = 30
Any adverse event	24 (100%)	29 (96.7%)
Respiratory	17 (70.8%)	20 (66.7%)
Asthma, including asthma exacerbation	**3 (12.5%)**	**3 (10%)**
Bronchitis	**3 (12.5%)**	**1 (3.3%)**
Cough increased	**2 (8.3%)**	**1 (3.3%)**
Dyspnea	**3 (12.5%)**	**2 (6.7%)**
Nasal polyp	0	1 (3.3%)
Pharyngitis	**6 (25%)**	**6 (20%)**
Respiratory disorder	1 (4.2%)	3 (10%)
Respiratory tract infection	**10 (41.7%)**	**9 (30%)**
Rhinitis	1 (4.2%)	3 (10%)
Sinusitis	3 (12.5%)	4 (13.3%)
Sputum increased	**2 (8.3%)**	**0**
Yawn	1 (4.2%)	0
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 202		

Baseline FEV_1 was lower in the comparator group than in the Exubera group. The Exubera group demonstrated a greater decline from baseline FEV_1 than subjects in the comparator group as shown below in Table 58. After 12 months, the Exubera group demonstrated a mean decline from baseline FEV_1 of 61mL while the comparator group demonstrated a mean decline from baseline FEV_1 of 18mL. However, it should be noted that the 12 month PFT data is based upon 12 subjects.

Table 58 Mean Change from Baseline FEV_1 (L) in Subjects Retrospectively Identified with Asthma		
FEV_1 (L)	Mean Change from Baseline FEV_1 (N)	
	Exubera	Comparator
Baseline	3.043 (23)	2.611 (28)
3 Months	-0.040 (19)	-0.024 (24)
6 Months	-0.079 (18)	-0.026 (21)
9 Months	-0.100 (7)	-0.056 (9)
12 Months	-0.061 (6)	-0.018 (6)
24 Months	-0.070 (1)	-0.030 (1)
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 475		

The treatment group difference can be visualized in Figure 45 below. The mean treatment group difference is fairly consistent throughout the treatment period. The treatment group difference consistently favors the comparator group.

Figure 45 Mean Change from Baseline FEV₁ (L) in Subjects Retrospectively Identified with Asthma

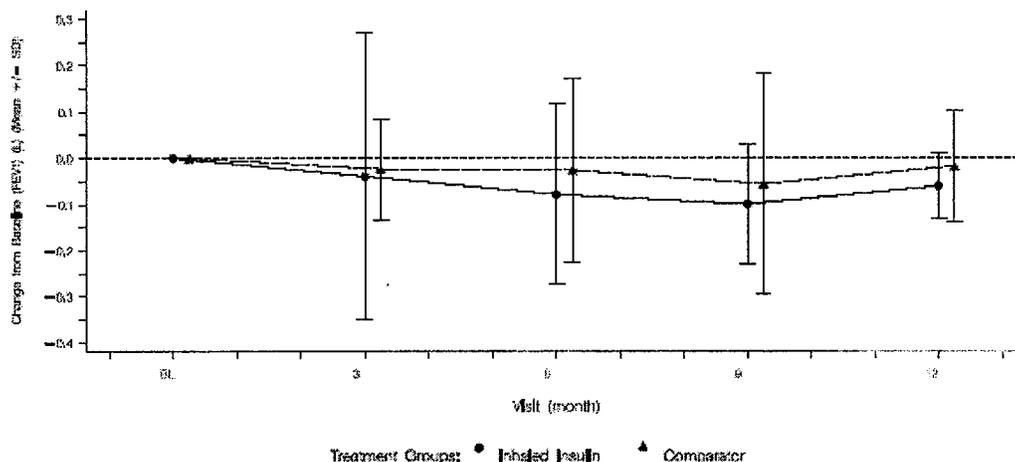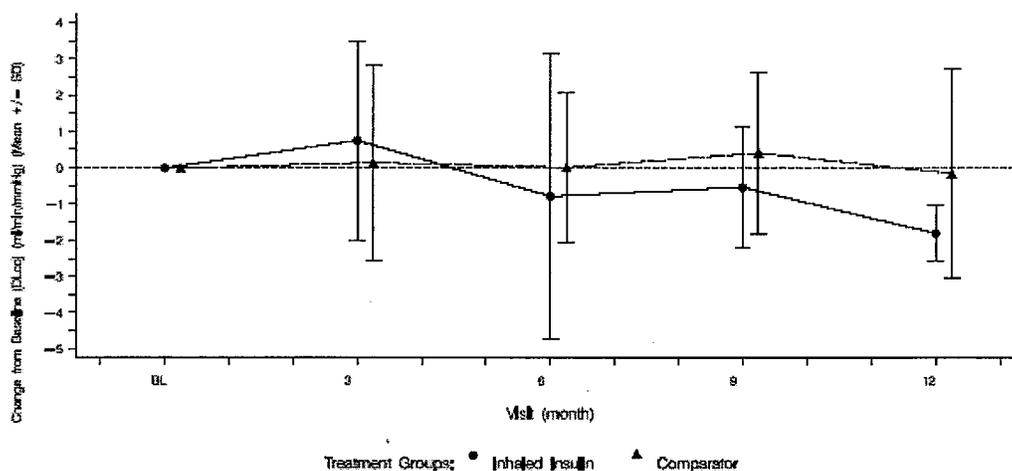Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 1039

The mean baseline DLCO was lower in the comparator group than in the Exubera group. The Exubera group demonstrated a greater decline from baseline DLCO than subjects in the comparator group at most time points as shown below in Table 62. After 12 months, the Exubera group demonstrated a decline from baseline DLCO of 1.802 mL/min/mmHg while the comparator group demonstrated a decline from baseline DLCO of 145mL/min/mmHg. However, it should be noted that the 12 month PFT data is based upon 12 subjects.

Table 59 Mean Change from Baseline DLCO (mL/min/mmHg) in Subjects Retrospectively Identified with Asthma		
DLCO (mL/min/mmHg)	Mean Change from Baseline DLCO (N)	
	Exubera	Comparator
Baseline	25.592 (22)	23.314 (28)
3 Months	0.746 (10) .	0.140 (13)
6 Months	-0.780 (18)	0.015 (21)
9 Months	-0.533 (6)	0.409 (8)
12 Months	-1.802 (6)	-0.145 (6)
24 Months	1.194 (1)	-3.253 (1)
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 481		

The treatment group difference can be visualized in Figure 46 below. The mean treatment group difference is not consistent throughout the treatment period. Initially the treatment group difference favors the Exubera group. However, after 3 months, the treatment group difference favors the comparator. Towards the end of the treatment period, there is a further separation of the curves, favoring the comparator. However, it should be noted that the 12 month PFT data is based upon 12 subjects.

Figure 46 Mean Change from Baseline DLCO (mL/min/mmHg) in Subjects Retrospectively Identified with Asthma

Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 1060

Conclusions – Retrospectively Defined Asthma
The data from the 54 subjects retrospectively identified with asthma provides limited information about the long term safety of Exubera in subjects with asthma.

In subjects retrospectively identified with asthma, the number of subjects with overall AEs and respiratory AEs was similar between treatment groups. Asthma, bronchitis, increased cough, dyspnea, pharyngitis, respiratory tract infection, and sputum increased were reported in more than one subject and in a higher percentage of subjects in the Exubera group than subjects in the comparator group.

Baseline FEV_1 was lower in the comparator group than in the Exubera group. The Exubera group demonstrated a greater decline from baseline FEV_1 than subjects in the comparator group. The mean treatment group difference is fairly consistent throughout the treatment period. After 12 months, the Exubera group demonstrated a mean decline from baseline FEV_1 of 61mL while the comparator group demonstrated a mean decline from baseline FEV_1 of 18mL. However, it should be noted that the 12 month PFT data is based upon 12 subjects.

Baseline DLCO was lower in the comparator group than in the Exubera group. The Exubera group demonstrated a greater decline from baseline DLCO than subjects in the comparator group at most time points. The mean treatment group difference is not consistent throughout the treatment period. Initially the treatment group difference favors the Exubera group. However, after 3 months, the treatment group difference favors the comparator. Towards the end of the treatment period, there is a further separation of the curves, favoring the comparator. At 12 months, the Exubera group demonstrated a decline from baseline DLCO of 1.802 mL/min/mmHg while the comparator group demonstrated a decline from baseline DLCO of 0.145mL/min/mmHg. However, it should be noted that the 12 month PFT data is based upon 12 subjects.

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8.1.1.2.3 Conclusions

Exubera has an effect on pulmonary function in subjects without underlying lung disease. Thus, the Agency requested the Applicant prospectively assess the effects of Exubera in subjects with asthma. Data regarding the pulmonary safety of Exubera in subjects with asthma comes from two sources: the ongoing Study 1028 and a cohort of retrospectively identified subjects with asthma in the controlled phase 2 and 3 studies. Of these two sources, Study 1028 provides the best source of data because Study 1028 was specifically designed to prospectively assess the effects of Exubera in subjects with asthma. However, because of the limited number of subjects with 52 week data in Study 1028, the safety of Exubera in subjects with asthma cannot adequately be assessed.

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

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

The interim PFT data from Study 1028 suggest that subjects treated with Exubera demonstrated a greater mean decline from baseline FEV_1 than the comparator group. The treatment group difference for change from baseline post-bronchodilator FEV_1 stabilized from the early weeks of the study until Week 26. However, by Week 52, the treatment group difference for change from baseline FEV_1 had increased further favoring the comparator. At Week 52, the Exubera group had a mean decline from baseline post-bronchodilator FEV_1 of 278mL, while the comparator group had a mean decline from baseline post-bronchodilator FEV_1 of 122mL. However, the 52 week data is based upon PFT data from only 27 subjects. The pre-bronchodilator FEV_1 showed a similar pattern as the post-bronchodilator FEV_1.

The interim PFT data from Study 1028 suggest that the Exubera group demonstrated a greater decline from baseline post-bronchodilator DLCO than subjects in the comparator group at most time points. The mean treatment group difference was not consistent throughout the treatment period. Towards the end of the treatment period, there was an

increase in the separation of the treatment groups, further favoring the comparator. 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. It should be noted that the 52 week data in Study 1028 is based upon only 27 subjects. The post-bronchodilator DLCO showed a similar pattern as the pre-BD DLCO.

Asthma control was assessed by the Asthma Control Questionnaire, which is a patient reported outcomes instrument measuring asthma control. The instrument includes 6 questions and FEV_1. The questions are on a scale of 0 to 6, with higher scores reflecting poor control. At Week 52, the 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. Again, it should be noted that the 52 week data in Study 1028 is based upon only 27 subjects.

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

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

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

8.1.1.3 Chronic Obstructive Pulmonary Disease (COPD)

8.1.1.3.1 Prospectively Defined COPD – Study 1030
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 <u>COPD</u>. In this study, COPD is defined according to the following criteria:

- Prior smokers with a 10 pack year or more smoking history and either:
  - o Fixed airflow obstruction as determined at screening to include a post-BD FEV_1/FVC <70% and FEV_1<80% predicted

    and/or
  - o A 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
  - o Less than 10 pack year smokers or never smokers who otherwise meet above criteria are considered on an individual case basis
- Post-bronchodilator FEV_1, FVC, or DLCO within range of 50-120% predicted

Subjects with poorly controlled, unstable, or steroid-dependent COPD and subjects who require chronic oxygen therapy were excluded.

Eligible subjects undergo a 3 week run in period. Then subjects are randomized to Exubera or continuation of the run-in regimen for a 52 week 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.

Pulmonary function testing is 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. In addition, 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). Study 1030 also includes the administration of the BDI/TDI and asthma control questionnaire during the treatment period as well as a CXR at screening and Week 52.

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.

<u>Results</u>
Approximately 67 subjects out of a planned 250 have been randomized in Study 1030, 35 to the Exubera and 32 to the subcutaneous arm. Fifteen subjects in each treatment group have completed the study. The mean age of the subjects is 63 years of age and the majority of the subjects (85%) have type 2 diabetes.

Comment: At the time of the original submission, 26-week data was submitted on some subjects. The Applicant submitted a safety update on April 26, 2005, and this section contains information from the interim report submitted in the safety update. The safety

*update contains some information on subjects with asthma who have been exposed to
Exubera for one year.*

The Exubera group had more respiratory SAEs (4) than the SC insulin group (0). The
respiratory SAEs in the Exubera group were pneumonia, COPD exacerbation (2), and
URI. 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
and AECOPD) accounted for about half of the temporary discontinuations in the Exubera
treatment group. A similar number of subjects in each treatment group reported
respiratory AEs as shown below in Table 60. Increased cough, bronchitis, dyspnea, and
voice alteration were more common in the Exubera group than in the SC insulin group.

Table 60 Number of Subjects with Respiratory Adverse Events in Study 217-1030 – Interim Results		
	Exubera n = 35	SC Insulin n = 37
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**
Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 77, 82-83		

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 1 subject with 1 event, while the SC insulin group had none. The number of subjects

requiring systemic corticosteroid treatment was slightly higher in the 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 177-179].
*Reviewer's Comment: In general, there were more non-severe and severe COPD exacerbations 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 as shown in Table 61. It should be noted that the Week 52 data is based upon PFT data from 28 subjects.

Table 61 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 47 displays the change from baseline post- bronchodilator FEV_1 in Study 1030.

**Figure 47 Mean Change from Baseline in Post-Bronchodilator FEV$_1$ (L)
in Study 1030 – Interim Results (Mean +/-SD)**
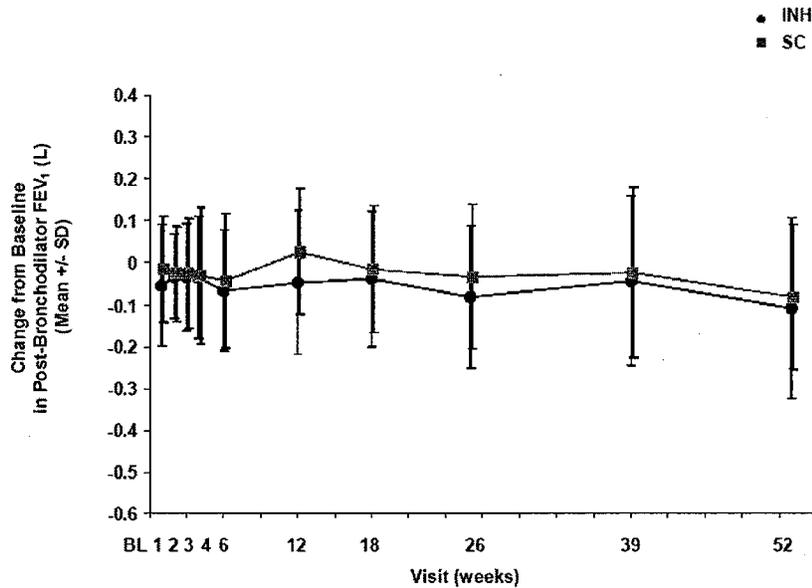
Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 36

*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 48 Mean Change from Baseline in Pre-Bronchodilator FEV$_1$ (L)
in Study 1030 – Interim Results (Mean +/- SD)**
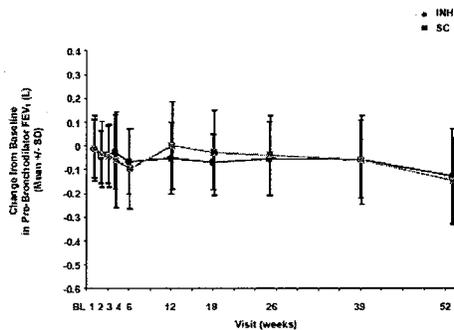
Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 38

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.

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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 62, 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 62 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			

Appears This Way
On Original

Figure 49 Mean Change from Baseline Post-Bronchodilator DLCO (mL/min/mmHg) in Study 1030 (Mean +/- SD)
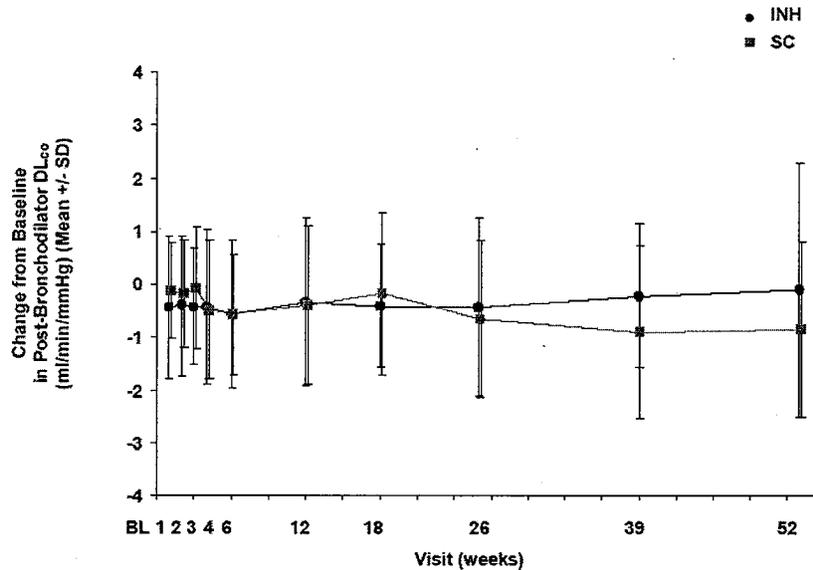
Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 41

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 in Figure 52.

Figure 50 Mean Change from Baseline Pre-Bronchodilator DLCO in Study 1030- Interim Results
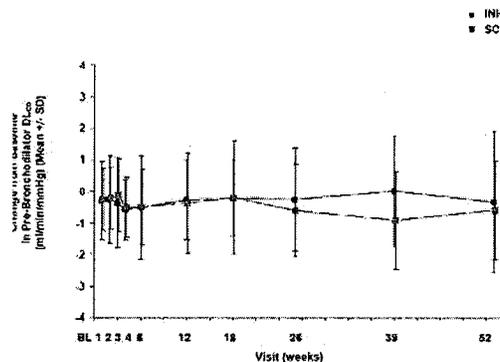
Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 42

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.

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. The interim results of Study 1030 were reviewed. While 67 subjects have been randomized, 35 to the Exubera and 32 to the subcutaneous arm, PFT data is available for only 30 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 limited data about the long term effect of Exubera on pulmonary safety in subjects with COPD.

More SAEs occurred in the SC insulin group than in the Exubera group. However, the Exubera group had more respiratory SAEs (4 – pneumonia, COPD exacerbation (2), and URI) than the SC insulin group (0). Respiratory adverse events were reported in a similar number of subjects in each treatment groups. Increased cough, bronchitis, dyspnea, and voice alteration were more common in the Exubera group than in the SC insulin 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 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 1 subject with 1 event, while the SC insulin group had none. The number of subjects requiring systemic corticosteroid treatment was slightly higher in the 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.

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.

8.1.1.3.2 Retrospectively Defined COPD

As discussed above in the Methods Section 8.1.1.1, the Applicant _retrospectively identified_ 101 subjects with COPD in the Controlled ULD Cohort. This section will include a brief review of the pertinent findings in the 101 subjects retrospectively identified with COPD in the controlled phase 2 and 3 studies.
Reviewer's Comment: As discussed earlier, the Agency informed the Applicant that an analysis of data from subjects retrospectively determined to have underlying lung disease was not acceptable to assess the safety of Exubera.

Of the 101 subjects retrospectively identified with COPD, 50 were treated with Exubera and 51 were treated with comparator. Approximately 80% of the subjects had type 2 diabetes and 20% had type 1 diabetes. The mean age of the subjects was 57-61 years of age and the baseline percent predicted FEV_1 was >80% in the majority of subjects. Only 13% of subjects were noted to take "respiratory medications" prior to the treatment period [N21868/N_000/2004-12-26/clinstat/pulm.pdf, pg 1180-1183].
Reviewer's Comment: Only 13% of subjects with retrospectively identified COPD were noted to take respiratory medications prior to the treatment period. The Applicant suggests that these subjects were primarily in the early stage of COPD.

Reviewer's Comment: Although 101 subjects were identified with retrospectively diagnosed COPD, PFT data for 12 months exposure to Exubera is available for only 51 subjects.

There were no respiratory deaths in subjects retrospectively identified with COPD. Thirteen subjects were noted to have serious adverse events (7 in the Exubera group and 6 in the comparator group). Two of the SAEs in the Exubera group were respiratory, epistaxis and vocal cord polyp. The number of subjects with overall AEs and respiratory AEs was similar between treatment groups. Bronchitis, increased cough, dyspnea, epistaxis, pharyngitis, respiratory disorder, sinusitis, and sputum increased were reported in more than one subject and in a higher percentage of subjects in the Exubera group than subjects in the comparator group as shown below in Table 63 [N21868/N_000/2004-12-26/clinstat/pulm.pdf, pg 247, 1185-1191].

Table 63 Number of Subjects with Respiratory Adverse Events in Subjects Retrospectively Identified with COPD		
	Exubera n = 50	Comparator n = 51
Any adverse event	48 (96%)	47 (92.2%)
Respiratory	17 (70.8%)	20 (66.7%)
Asthma, including asthma exacerbation	1 (2.0%)	3 (5.9%)
Bronchitis	**2 (4.0%)**	**0**
Cough increased	**13 (26.0%)**	**1 (2.0%)**
Dyspnea	**3 (6.0%)**	**2 (3.9%)**
Epistaxis	**3 (6.0%)**	**0**
Laryngitis	0	1 (2.0%)
Pharyngitis	**4 (8.0%)**	**2 (3.9%)**
Pneumonia	0	1 (2.0%)
Respiratory disorder (includes COPD exacerbation)	**5 (10.0%)**	**2 (3.9%)**
Respiratory tract infection	14 (28.0%)	17 (33.3%)
Rhinitis	0	4 (7.8%)
Sinusitis	**3 (6.0%)**	**1 (2.0%)**
Sputum increased	**3 (6.0%)**	**0**
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 207-208		

Baseline FEV_1 was lower in the Exubera group than in the comparator group. Initially, the Exubera group demonstrated a greater decline from baseline FEV_1 than subjects in the comparator group as shown below in Table 64. However, after 6 months, the comparator group demonstrated a greater decline from baseline FEV_1 through 12 months. At 12 months, the Exubera group demonstrated a decline from baseline FEV_1 of 13mL while the comparator group demonstrated a decline from baseline FEV_1 of 37mL.

Table 64 Mean Change from Baseline FEV_1 (L) in Subjects Retrospectively Identified with COPD		
FEV_1 (L)	Mean Change from Baseline FEV_1 (N)	
	Exubera	Comparator
Baseline	2.650 (47)	2.888 (48)
3 Months	-0.026 (38)	-0.002 (39)
6 Months	-0.019 (34)	-0.012 (36)
9 Months	-0.017 (22)	-0.043 (27)
12 Months	-0.013 (25)	-0.037 (26)
24 Months	-0.190 (3)	0.060 (3)
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 475		

The treatment group difference can be visualized in Figure 51 below. The mean treatment group difference is not consistent throughout the treatment period. Initially the treatment group difference favors the comparator; however, after 6 months, the treatment group difference favors the Exubera group.

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Figure 51 Mean Change from Baseline FEV₁ (L) in Subjects Retrospectively Identified with COPD

Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 1040

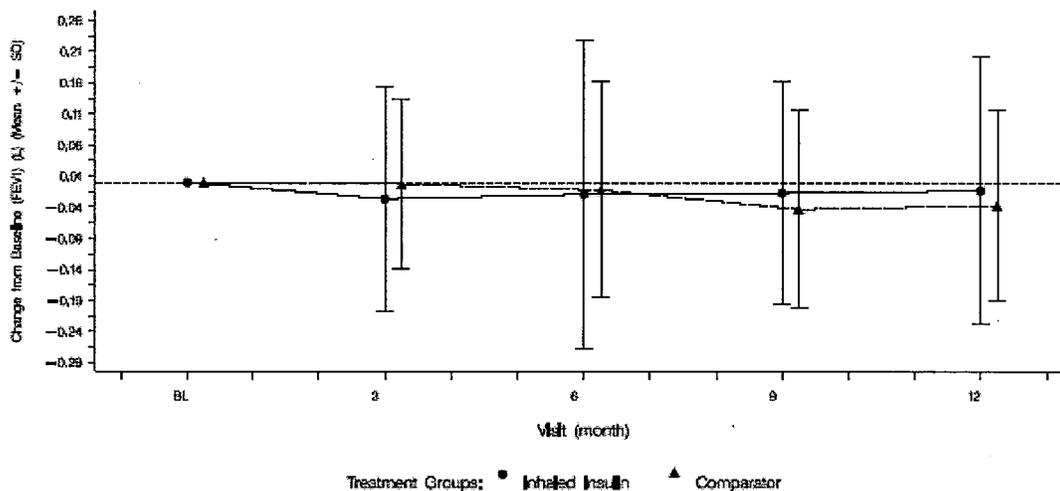The mean baseline DLCO was lower in the Exubera group than in the comparator group. The Exubera group demonstrated a greater decline from baseline DLCO than subjects in the comparator group throughout the treatment period as shown below in Table 65. After 12 months, the Exubera group demonstrated a decline from baseline DLCO of 1.407 mL/min/mmHg while the comparator group demonstrated a decline from baseline DLCO of 1.146mL/min/mmHg.

Table 65 Mean Change from Baseline DLCO (mL/min/mmHg) in Subjects Retrospectively Identified with COPD		
DLCO (mL/min/mmHg)	Mean Change from Baseline DLCO (N)	
	Exubera	Comparator
Baseline	25.444 (45)	27.051 (46)
3 Months	-0.920 (31)	-0.208 (34)
6 Months	-0.506 (32)	0.175 (34)
9 Months	-1.406 (16)	-1.191 (21)
12 Months	-1.407 (24)	-1.146 (24)
24 Months	-1.198 (3)	3.550 (1)
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 481		

The treatment group difference can be visualized in Figure 52 below. The mean treatment group difference favors the comparator throughout the treatment period. Towards the end of the treatment period, the treatment group difference decreases and remains relatively stable between 9 and 12 months.

Figure 52 Mean Change from Baseline DLCO (mL/min/mmHg) in Subjects Retrospectively Identified with COPD
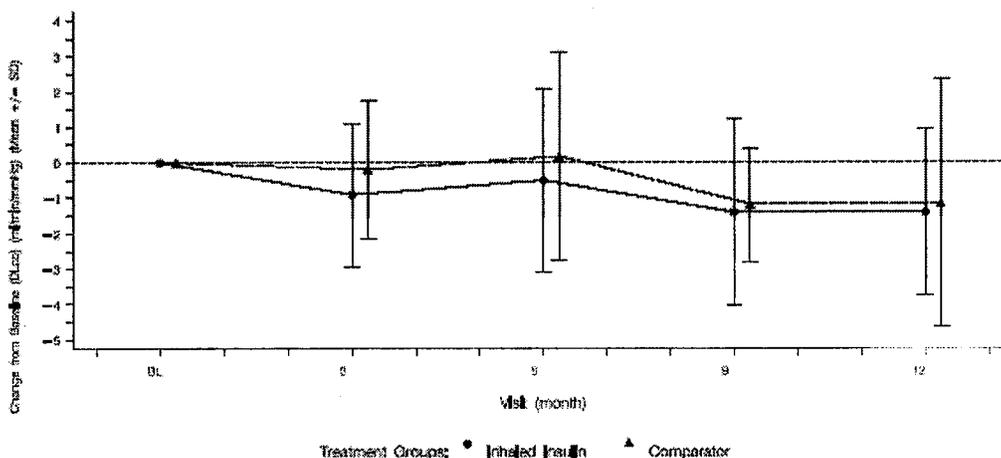
Source: N21868/N_000/2004-12-27/clinstat/pulm.pdf, pg 1061

Conclusions for Retrospectively Defined COPD
The data from the 101 subjects retrospectively identified with asthma provides limited information about the long term safety of Exubera in subjects with COPD.

In subjects retrospectively identified with COPD, the number of subjects with overall AEs, SAEs, and respiratory AEs was similar between treatment groups. Two of the SAEs in the Exubera group were respiratory, epistaxis and vocal cord polyp. Bronchitis, increased cough, dyspnea, epistaxis, pharyngitis, respiratory disorder, sinusitis, and sputum increased were reported in more than one subject and in a higher percentage of subjects in the Exubera group than subjects in the comparator group.

Baseline FEV$_1$ was lower in the Exubera group than in the comparator group. Initially, the Exubera group demonstrated a greater decline from baseline FEV$_1$ than subjects in the comparator group. However, after 6 months, the comparator group demonstrated a greater decline from baseline FEV$_1$ through 12 months. At 12 months, the Exubera group demonstrated a decline from baseline FEV$_1$ of 13mL while the comparator group demonstrated a decline from baseline FEV$_1$ of 37mL.

Baseline DLCO was lower in the Exubera group than in the comparator group. The Exubera group demonstrated a greater decline from baseline DLCO than subjects in the comparator group throughout the treatment period. After 12 months, the Exubera group demonstrated a decline from baseline DLCO of 1.407 mL/min/mmHg while the comparator group demonstrated a decline from baseline DLCO of 1.146mL/min/mmHg.

8.1.1.3.3 Conclusions

Exubera has an effect on pulmonary function in subjects without underlying lung disease. Thus, the Agency requested the Applicant prospectively assess the effects of Exubera in subjects with COPD. Data regarding the pulmonary safety of Exubera in subjects with

COPD comes from two sources: the ongoing Study 1030 and a cohort of retrospectively identified subjects with COPD in the controlled phase 2 and 3 studies. Of these two sources, Study 1030 provides the best source of data because Study 1030 was specifically designed to prospectively assess the effects of Exubera in subjects with COPD. However, because of the limited number of subjects with 52 week data in Study 1030, the safety of Exubera in subjects with COPD cannot adequately be assessed.

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

The total number of both non-severe (systemic corticosteroids, antibiotics, or oxygen) and severe (requiring hospitalization >24 hours) COPD exacerbations was higher in the 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 1 subject with 1 event, while the SC insulin group had none. The number of subjects requiring systemic corticosteroid treatment was slightly higher in the 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.

The interim PFT data from Study 1030 indicate that subjects in 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. At Week 52, the mean treatment group difference for change from baseline pre-bronchodilator FEV_1 favored the Exubera group (17mL). It should be noted that the Week 52 data is based upon PFT data from 30 subjects.

For DLCO, 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.

Retrospectively Identified Subjects with COPD

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

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

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

8.2 Pediatrics

The Applicant is not seeking an indication in subjects less than 18 years of age in this Application. However, some information regarding the pulmonary safety of Exubera in the pediatric population was submitted in this NDA. The pediatric data comes from two sources: Study 1009, which was a study in six to eleven year old males and females with type 1 diabetes mellitus and a cohort of subjects <18 years of age in Studies 106 and 107. These studies provide some information regarding the safety of Exubera, but the amount of information is not enough to draw definitive conclusions regarding the safety of Exubera in the pediatric population. The pulmonary safety results of Study 1009 will be briefly reviewed here.
Reviewer's Comment: For a detailed review of Study 1009, refer to Section 10.10.1.

Study 217-1009 was an open-label, multicenter, 3-month, parallel group study in 120 six to eleven year old males and females with type 1 diabetes mellitus. The mean age was 9 years and the majority of subjects were Caucasian.

In contrast to the adult studies, more subjects reported respiratory adverse events in the SC insulin group than in the Exubera group. However, increased cough, asthma, and dyspnea were reported in more subjects in the Exubera group than in the SC insulin group. All of the respiratory adverse events were mild in severity. None of the SAEs were respiratory. Of the respiratory AEs more common in the Exubera group, increased cough was the most common. 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. According to the pulmonary narratives, one subject in the Exubera group discontinued due to increased cough.

Reviewer's Comment: Of note, one respiratory SAE was noted in a 13 year old male (Subject 50826090) in Study 111 (extension of Study 106, 107, 108). The subject had a routine CXR at the 12 month visit, which showed a large right pleural effusion, with an infiltrate in the right lung. Previous CXRs were normal. A thoracentesis was performed, which showed an exudative effusion. The effusion re-accumulated, requiring a second thoracentesis and eventually a pleuro-peritoneal shunt. The subject underwent an extensive work-up; however, the cause of the effusion could not be identified. The pleuro-peritoneal shunt was eventually removed. The most recent HRCT revealed a small right residual pleural effusion.

PFTs were measured at baseline and Week 12. Baseline pulmonary function was well-matched between treatment groups. A review of the mean change from baseline FEV_1, FVC, TLC, $FEF_{25-75\%}$, and PEFR suggests that neither group had a decline in mean values at 12 weeks. Both treatment groups showed a decline from baseline DLCO. The Exubera group demonstrated a larger decrease from baseline DLCO than the SC insulin group as shown in Table 66. A categorical analysis of the change in pulmonary function testing suggests that the Exubera group had more subjects with >10% decrease in DLCO and $FEF_{25-75\%}$ than the SC insulin group.

Table 66 Mean Change from Baseline Pulmonary Function Tests in Study 217-1009

PFT	Exubera			Subcutaneous Insulin		
	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
$FEF_{25-75\%}$	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

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

Reviewer's Comment: Because Study 1009 is only 12 weeks duration with PFTs measured at two time points, it is difficult to draw any conclusions regarding PFT trends.

In summary, Study 1009 provides some information regarding the safety of Exubera, but the amount of information is not enough to draw definitive conclusions regarding the pulmonary safety of Exubera in the pediatric population.

8.3 Advisory Committee Meeting

An Endocrine and Metabolic Drugs Advisory Committee (EMDAC) meeting was held on September 8, 2005, to discuss this NDA. The EMDAC panel included 3 pulmonologists. Several questions were asked of the committee regarding pulmonary safety. The questions are shown below followed by a summary of the responses and/or voting. In depth discussions were held during the meeting regarding pulmonary safety. The details of the discussion are located in the official transcript of the September 8, 2005, EMDAC meeting [www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4169T1.pdf].

Questions
The following questions were asked of the committee regarding pulmonary safety:

4a. Are there sufficient data to assess the pulmonary safety of Exubera in patients without underlying lung disease?
    i. If yes, do the data suggest an acceptable pulmonary safety profile in patients without underlying lung disease.
    ii. If no, what additional information is needed?
4b. Are there sufficient data to assess the pulmonary safety of Exubera in patients with underlying lung disease?
    i. If yes, do the data suggest an acceptable pulmonary safety profile in patients with underlying lung disease.
    ii. If no, what additional information is needed?
5a. Comment on clinical concerns and recommendations about the use of Exubera in the setting of pulmonary pathology or exogenous factors affecting pulmonary function:
    i. Viral upper respiratory infection
    ii. Asthma
    iii. COPD
    iv. Smoking

Responses to Questions
The following is a summary of the responses to the above questions.
- 4a. - 9 yes votes (unanimous)
- 4b. – 5 no, 4 yes votes. The following additional information was suggested by the panel to assess the pulmonary safety profile in patients with underlying lung disease.
  - Completion of Study 1028 and 1030
  - A larger number of patients exposed
  - A long-term study in patients with interstitial lung disease
  - A substantially larger study in patients with COPD over a spectrum of COPD that reflects the population that will likely use Exubera. Categorical analysis of those patients with large drops in their DLCO and FEV_1 stratified by their baseline lung function.

        o   Consideration of a withdrawal period to assess reversibility at the end of Study 1028 and 1030.

  ➤ 5a. The following general comments/concerns were provided by the committee members.

        o   Limited data regarding respiratory infection

        o   Limited information of how the PK and PD may vary with variable lung function in asthma

        o   Limited information regarding dose response to smoking/passive smoking

        o   Limited information regarding real world use of the device

        o   No information on the effects of acute asthma exacerbations and use of Exubera

        o   No information of the effects of inhaled corticosteroids

        o   Skilled, qualified personnel should perform baseline spirometry

Additional comments

The following additional concerns/comments regarding pulmonary safety were raised by the EMDAC members during the course of the meeting:

- Non-smokers could be enrolled in the ongoing COPD study (1030)

Reviewer's Comment: The Applicant indicated that there were no non-smokers in Study 1030 thus far.

- Stratify decline in FEV_1 by baseline FEV_1
- Categorical analysis of significant drops stratified by baseline FEV_1
- The effects of continued use of Exubera on the microangiopathic process in the lungs of diabetic patients

8.4 PostMarketing Risk Management Plan

The Applicant submitted a revised Risk Management Plan (RMP) on August 2, 2005, and submitted draft protocols of two proposed postmarketing studies on October 10, 2005. With regards to pulmonary safety, the RMP proposed by the Applicant includes the following 4 objectives in **bold** [N21868/N _000/2005-08-02/RMPpdf.pdf, pg 48-53].

_2_ Page(s) Withheld

_X_ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

9 Overall Assessment

9.1 Conclusions

NDA# 21-868 contains adequate information to assess the pulmonary safety of Exubera in subjects with type 1 and type 2 diabetes who do not have significant underlying lung disease. However, while the currently available database is deemed adequate to assess pulmonary safety for marketing, if the application is to be approved, we recommend that the Applicant continue to further assess the long-term pulmonary safety of Exubera in the post-marketing period. In addition, the following limitations of the pulmonary safety database should be noted. First, NDA# 21-868 does not contain adequate information to assess the pulmonary safety of Exubera in subjects with underlying lung disease, such as asthma and COPD. Second, there are a limited amount of data in non-Caucasian subjects. Finally, the pulmonary safety of Exubera beyond two years exposure has not been studied in a controlled fashion. For a detailed summary of the pulmonary safety, refer to the Executive Summary.

9.2 Recommendation on Regulatory Action

This review is limited to the pulmonary safety of Exubera. Non-pulmonary safety and efficacy were not addressed in this review. Therefore, the recommendation on the regulatory action on this application is deferred to the DMEP. However, the pulmonary safety findings discussed in this review and the limitations of the pulmonary safety database should be weighed in the risk/benefit analysis regarding the approval of Exubera.

9.3 Recommendation on PostMarketing Actions

The following are potential phase four commitments:
- The Applicant should reevaluate the two year HRCT data from ongoing Study 1029 by blinding the reading radiologist to treatment group and time.
- The Applicant should conduct a large controlled study designed to further assess the long term pulmonary safety of Exubera. In the absence of a specific safety signal, the most appropriate duration and size of the study are unclear. We suggest a minimum of 5000 patients in each treatment arm for duration of at least 5 years. Enrollment in this study should include a significant number of non-Caucasian patients. Ideally the study would include an assessment of FEV_1 and DLCO.
-
- The Applicant should complete Studies 1028 and 1030 to provide more data regarding the safety and efficacy of Exubera in patients with underlying lung disease.
- The Applicant should complete Studies 1022 and 1029 to provide additional pulmonary safety data for up to 5 years of Exubera exposure.

9.4 Labeling Review

A detailed labeling review was performed for this consult and a line-by-line edited label has been conveyed to the DMEP. The following are general recommendations for the Exubera product label.

- Include the following language in the Precautions section: Respiratory.

  "In clinical trials up to two years duration, patients treated with EXUBERA demonstrated a greater decline in pulmonary function, specifically the forced expiratory volume in one second (FEV$_1$) and the carbon monoxide diffusing capacity (DL$_{CO}$), than comparator treated patients. The mean treatment group difference in pulmonary function, favoring the comparator group, was noted within the first several weeks of treatment with EXUBERA, and did not progress over the two year treatment period (See ADVERSE REACTIONS: Pulmonary Function).

- Include the following language in the Precautions section: Underlying Lung Disease.

  "The use of EXUBERA in patients with underlying lung disease, such as asthma or COPD, is not recommended because the safety of EXUBERA in this population has not been established."

- Include a table of adverse events in the Adverse Reactions section to more clearly display the adverse events and the percentage of AEs in the Exubera treatment group as well as the comparator treatment groups.

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- Include the following language in the Adverse Reactions section under a new subheading of Pulmonary Function.
  "Pulmonary Function

- Include the following language in the Dosage and Administration section.

- Consider removing the information regarding treatment satisfaction in the Clinical Studies section since the studies were open-label and subject to bias.

10 Appendices

10.1 Discontinuations Due to Respiratory AEs

The following are brief summaries of subjects who discontinued Exubera therapy due to respiratory AEs in the controlled phase 2 and 3 studies.

Reviewer's Comment: Table 67 and Table 68 are based upon the Applicant's Listing of Discontinuation due to Adverse Events. The tables may not be complete as Study 1022 and 1029 are ongoing studies.

Table 67 Listing of Discontinuations due to Respiratory Adverse Events Adult Controlled Phase 2 and 3 Studies in Type 1 Diabetes					
Study #	Patient ID #	Age	Treatment	Study Day	COSTART Preferred Term Respiratory Body System
Type 1 Diabetes					
106	50556135	51	Exubera	30, 42, 68	Cough Increased
107	51027141	52	Exubera	23, 43	Asthma, Cough Increased, Dyspnea, Respiratory Disorder (pulmonary obstruction)
1022	1005241	42	Exubera	26	Sinusitis, Sputum increased
1022	1007359	41	Exubera	491	Respiratory distress syndrome (bronchial hyperactivity)
1022	1017949	28	Exubera	92, 252	Cough Increased
1022	10251425	54	Exubera	22	Dyspnea
1022	10472728	31	Exubera	2, 42, 85	Cough Increased, Dyspnea, Respiratory Disorder (decreased DLCO)
1022	50743085	58	Exubera	141, 162	Cough Increased, Dyspnea
1022	51563797	34	Exubera	17, 57	Pharyngitis, Cough Increased
1027	1004154	48	Exubera	57	Cough Increased, Laryngitis, Pharyngitis
1027	1006251	27	Exubera	7, 23, 43	Respiratory Tract Infection, Asthma
1027	1012503	28	Exubera	46	Cough Increased

Source: [N21868/N_000/2004-12-27/summary_clin_safety.pdf, pg 2384-2419]

Table 68 Listing of Discontinuations due to Respiratory Adverse Events Adult Controlled Phase 2 and 3 Studies in Type 2 Diabetes					
Study #	Patient ID #	Age	Treatment	Study Day	COSTART Preferred Term Respiratory Body System
Type 2 Diabetes					
1001	00180060	62	Exubera	78, 311	Cough Increased
1001	00490107	56	Exubera	61	Bronchitis
1001	01412043	44	Exubera	546, 548	Asthma
1002	00255050	46	Exubera	2	Respiratory Disorder (lung pain)
1002	00375063	69	Exubera	276, 303, 359, 459	Asthma
1002	00477049	35	Exubera	342, 367	Cough Increased

Table 68 Listing of Discontinuations due to Respiratory Adverse Events Adult Controlled Phase 2 and 3 Studies in Type 2 Diabetes					
Study #	Patient ID #	Age	Treatment	Study Day	COSTART Preferred Term Respiratory Body System
1002	00485005	68	Exubera	8, 36	Cough Increased
1002	00745150	48	Exubera	179, 212, 254, 318, 338	Cough Increased
1002	01086285	64	Exubera	256, 361	Dyspnea
1002	01106223	54	Exubera	13	Respiratory tract infection, sputum increased
1002	01195236	65	Exubera	673	Carcinoma of the lung
1002	01345269	59	Exubera	15, 22	Cough Increased
1002	01417404	39	Exubera	111	Dyspnea
1002	01418036	66	Exubera	153, 163	Cough Increased
1002	01418036	66	Exubera	197, 198	Cough Increased, Dyspnea
1002	01427408	43	Exubera	600, 632, 716	Cough Increased, Dyspnea
103	50020002	60	Exubera	32, 57	Cough Increased
108	50260133	70	Exubera	1, 9, 15, 50	Respiratory tract infection
109	50430031	65	Exubera	75	Dyspnea
110	51031426	56	Exubera	3, 58	Bronchitis
1029	10251913	64	Exubera	258, 292, 298, 302	Asthma, Dyspnea
1029	1029788	65	Exubera	90	Cough Increased
1029	10452319	21	Exubera	2, 8, 21	Asthma, Respiratory Tract Infection
1029	10652783	58	Exubera	2	Cough Increased, Respiratory Disorder (irritation in the lungs)
1029	10681197	56	Exubera	296	Asthma
1029	10833445	58	Exubera	61, 72, 49, 73, 61	Asthma, Cough Increased, Dyspnea
1029	10853552	50	Exubera	45, 51	Dyspnea, Respiratory Disorder (Acute Respiratory Failure)
1029	10883612	58	Exubera	457	Cough Increased
1029	11054681	45	Exubera	100	Pharyngitis
1029	11135158	67	Exubera	149	Asthma
1002	00835165	57	Oral Agent	63	Carcinoma of the lung

Source: [N21868/N_000/2004-12-27/summary_clin_safety.pdf, pg 2394-2419]

10.2 Listing of Chest X-ray Changes from Baseline

Table 69 displays the text for the chest X-ray changes from baseline for the individual studies in the adult controlled phase 2 and 3 studies.

Reviewer's Comment: Some listings were not included in this table if the comment or change from baseline was not clear. In addition the line listings for the CXR changes from baseline were not submitted for the ongoing studies.

	Table 69 Summary of Chest X-Ray Changes From Baseline in Adult Controlled Phase 2 and 3 Studies		
Study Number	**Patient Number**	**Exubera**	**Comparator**
106	50606959	Nodule (F/U CT normal)	
107	50897567	Density noted on screening now resolved	
107	51037815	Nodular density ? nipple shadow (F/U CT nl)	
107	50077985		Nodular opacity (F/U CXR nl)
107	5017761		Nodular density ?nipple shadow
107	50277735		Osteopenic Vertebrae
107	50637421		Focal opacity "poor misfunction"
107	50937393		Infiltrate
108	50028593	Subsegmental volume loss	
108	50058444	Nodule	
108	50078055	Hiatal hernia	
108	50168502	?Nodular density ? granuloma (F/U CXR stable right granulomatous dz and no nodular density)	
108	50208123	Increase heart size	
108	50268345	S/P CABG, mild pulmonary edema	
108	50438113	Healing rib fracture	
108	50488427	Nodular opacity (F/U CT negative)	
108	50498599	Slight elevation of R hemidiaphragm	
108	50608437	Opacity (F/U CT old granulomatous dz)	
108	51298153	Mild heart failure	
108	50078056		Pneumonia, atelectasis
108	50478400		Nodule
108	50538374		Opacity (unchanged) and nodules
108	50608041		Infiltrate
109	50600666	Unchanged from baseline	
109	50700718	Prominent hilum – (F/U CT negative)	
109	50140392		Prominent hilum
110	51031426	Infiltrate	
110	51031441	Atelectasis (Resolved on F/U)	
110	51121369	Resolution of atelectasis	
110	51321454	? Nodule vs. nipple shadow (F/U CXR nl)	
110	51231338		Widened mediastinum, enlarged LN
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	

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Study Number	Patient Number	Exubera	Comparator
Table 69 Summary of Chest X-Ray Changes From Baseline in Adult Controlled Phase 2 and 3 Studies			
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
1027	1007299	Heart appears to be larger	
1027	1004150		Subtle parenchymal disease
Source: [N21868/N_000/2004-12-27/ Section 13, Table 20 of individual study reports; N21868/N-000/2005-07-26/response_ir_request_21jun05.pdf, pg 4]			

10.3 Listings of "For Cause" HRCT Scans

The following are synopses of some interesting findings from the "for cause" HRCT listings submitted by the Applicant. For many of the cases, there was no reason listed for obtaining the HRCT.

- 108 50538373
  - o 75 year old male on Exubera for 541 days; reason for HRCT not listed
  - o HRCT interpreted as COPD, some fibrotic honeycombing in the lower lobes bilaterally, subpleural parenchymal scarring;
  - o Follow up HRCT performed for decrease in DLCO; HRCT interpreted as mild interval progression of multiple regions of subpleural blebs and fibrosis consistent with idiopathic interstitial pneumonia, either UIP or NSIP, focal basilar cylindrical bronchiectasis
- 108 50438114

- o 39 year old male on Exubera for 511 days; reason for HRCT was shortness of breath and decreased pulmonary function testing
- o HRCT interpreted as hyperinflation with mild emphysematous changes
- 104 50130077
  - o 67 year old female on Exubera for 2005 days; reason for HRCT not listed
  - o HRCT interpreted as minimal interstitial changes from early fibrosis likely in the most inferior aspects of the RUL laterally, minimal interstitial changes at the left base medially, no significant fibrotic change, nodule, or mass
- 108 50168053
  - o 62 year old male on Exubera for 698 days; reason for HRCT not listed; 3 HRCTs performed
  - o Bronchiectasis noted on first HRCT, which was unchanged on repeat HRCTs
- 107 50297599
  - o 57 year old female on Exubera for 826 days; reason for HRCT was for nodule
  - o HRCT interpreted as 8mm nodule, which was stable on follow up 7 months later
- 109 50280694
  - o 56 year old male on Exubera for 824 days; reason for HRCT was chronic cough/asthma
  - o HRCT interpreted as several minute nodules, which were stable on follow up HRCT 10 months later; suggestion of mild bronchiectasis with mild bronchial wall thickening
- 106 50656943
  - o 35 year old female on Exubera for 682 days; reason for HRCT was bilateral hilar fullness
  - o HRCT interpreted as mediastinal adenopathy; bilateral upper lobe subpleural intralobular ill-defined nodules; suggestive of sarcoidosis
- 106 50536783
  - o 54 year old male on Exubera for 869 days; HRCT for decreased pulmonary function tests
  - o HRCT interpreted as minimal scarring or atelectasis in lung bases
- 108 50488404
  - o 59 year old male on Exubera for 826 days; reason for HRCT not listed
  - o HRCT interpreted as right lower chest pleural and parenchymal changes suggestive of fibrosis; follow-up HRCT unchanged

[N21868/N_000/2004-12-27/pulm.pdf, pg 1213-1231].

10.4 Review of Individual Study Reports – Completed Studies in Type 1 Diabetes

10.4.1   Study 217-102

Inhaled Human Insulin vs. Usual Subcutaneous Human Insulin Therapy in Subjects with Type 1 Diabetes Mellitus: A Three-Month, Open-Label, Parallel Comparative Trial with Optional One-Year Extension

10.4.1.1   Protocol

Study 217-102 was a phase 2, open-label, 3-month, parallel group study in 60 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 asthma, other respiratory disease, or suspected abnormality of oropharyngeal or pulmonary function or anatomy were excluded. Smokers (any smoking in past 6 months) were also excluded. Subjects who successfully completed the 3-month trial were eligible to received Exubera treatment in a one-year open-label protocol extension [N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, 179-181].

A screening visit was followed by a baseline lead-in period (4 weeks) during which subjects underwent pulmonary function testing. At the end of the lead-in-period, subjects were admitted to the study site for a 2-day period of instruction and dosing experience with Exubera. Eligible subjects were randomized prior to discharge to either continuation of their pre-study regimen or Exubera therapy (pre-meals) with a single bedtime SC long-acting (ultralente) insulin injection [N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, 181-187].

Safety monitoring included AEs, laboratories, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, DLCO, and resting oxygen saturation. PFT testing was performed at baseline (week -3), week 6 (spirometry only) and week 12. PFTs were performed using ATS certified methods A chest x-ray was performed at screening and at end of study (12 weeks) [N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, 193-194].

Open-Label Extension
Subjects who completed the 12-week study were eligible for the one-year, non-randomized, open-label extension. According to the protocol, each patient had the choice in the extension of using Exubera or conventional subcutaneous insulin. Each investigator was to recruit at least one patient for the conventional SC insulin regimen for every two subjects choosing Exubera. Newly recruited subjects were matched with one of the two subjects selecting Exubera therapy by age, sex, smoking history, diabetic complications, and degree of glucose control at week 12 [N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, pg 199-206].
Reviewer's Comment: From a pulmonary standpoint, the new recruits had the same inclusion/exclusion criteria listed above. However, the new recruits are not an optimal comparator group because they were not randomized and recruited specifically to receive SC insulin.

Safety monitoring during the one-year open-label extension included PFTs at baseline (screening for new recruits or week 12 for subjects completing the previous protocol), 3, 6, 9 (spirometry only), and 12 months [N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, pg 206].

10.4.1.2   Results

The 12-week study commenced on December 13, 1996, and was completed on
September 11, 1997. Ten centers participated in the study. A total of 113 subjects were
screened for the study and 72 were randomized (35 Exubera, 37 SC insulin). Subject
disposition in displayed in Table 70.

Table 70 Subject Disposition Study 217-102		
	Exubera	SC Insulin
Randomized (72)	35	37
Completed Study	35	35
Discontinued Study	0	2
Withdrew consent	0	1
Moved out of state	0	1

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, pg 27]

The mean age of the subjects was between 35 and 40 years while the mean FEV_1 percent
predicted at baseline was 98% as shown in Table 71.

Table 71 Baseline Characteristics Study 217-102			
		Exubera n = 35	SC Insulin n = 37
Gender	Male	19 (54%)	19 (51%)
	Female	16 (46%)	18 (49%)
Age	Mean	35.4	39.7
	Range	18-51	20-56
FEV_1 (% predicted)	Mean	98%	98%

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, pg 47, 148]

*Reviewer's Comment: A review of the summary of medical history of the subjects
indicates that one subject in the Exubera group reported asthma in the past
[N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, pg 50-59].*

Respiratory Adverse Events
Respiratory adverse events were slightly more common in the Exubera group than in the
SC insulin group. Respiratory disorder, pharyngitis, and sinusitis were more common in
the Exubera group than in the SC insulin group. A detailed summary of the respiratory
AEs is listed in Table 72.

Table 72 Summary of Respiratory Adverse Events for Study 217-102		
	Exubera n = 35	SC Insulin n = 37
Serious adverse events	0	0
Any adverse event	35 (100%)	37 (100%)
Respiratory	**19 (54.3%)**	**18 (48.6%)**
Asthma	0	1 (2.7%)
Bronchitis	0	1 (2.7%)
Cough increased	5 (14.3%)	5 (13.5%)
Laryngitis	1 (2.9%)	0
Pharyngitis	5 (14.3%)	5 (13.5%)
Respiratory disorder	**3 (8.6%)**	**1 (2.7%)**
Respiratory tract infection	8 (22.9%)	12 (32.4%)
Rhinitis	**3 (8.6%)**	**2 (5.4%)**
Sinusitis	**3 (8.6%)**	**2 (5.4%)**

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, pg 96, 101]

Reviewer's Comment: Hypoglycemia and tremor were the most common AEs in both treatment groups. Respiratory tract infection was the most common respiratory AE.

Pulmonary Function Tests

A review of the mean change in FEV_1, FVC, and DLCO shows that both treatment groups demonstrated a slight decrease in pulmonary function at Week 12. The Exubera group demonstrated a greater mean decrease in FEV_1 than the SC insulin group. The mean decline in FVC was similar between treatment groups. The SC insulin group experienced a greater mean decrease in DLCO compared to the Exubera group. A summary of the PFTs is displayed in Table 73.

Table 73 Summary of Pulmonary Function Tests for Study 217-102		
Mean values	Exubera n = 35	SC Insulin n = 37
Baseline FEV_1 L (% predicted)	3.58 (98%)	3.37 (98%)
FEV_1 change from baseline at week 12 L (% change)	-0.08 (-2.2%)	-0.03 (-1%)
Baseline FVC L (% predicted)	4.43 (98%)	4.27 (100%)
FVC change from baseline at week 12 L (% change)	-0.08 (-1.7%)	-0.07 (-1.5%)
DLCO mL/min/mmHg (% predicted)	26.5 (94%)	27.2 (100%)
DLCO change from baseline at week 12 mL/min/mmHg (% change)	-2.1 (-5.8%)	-2.6 (-7.7%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/102.pdf, pg 148-150]

Reviewer's Comment: A total of 8 subjects (3 Exubera, 5 SC insulin) were noted to have a 15% drop from baseline in pulmonary function tests. All of these subjects continued into the extension period and will be discussed in the extension study, Study 217-111.

Reviewer's Comment: Although oxygen saturation was specified to be collected with the PFTs, the Applicant did not report the results for the oxygen saturation in the study report.

10.4.1.3   Conclusions

Study 217-102 was an open-label, 3-month, parallel group study of Exubera versus SC insulin in 72 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 Exubera group. Respiratory adverse events which were more common in the Exubera group than in the SC insulin group were respiratory disorder, pharyngitis, and sinusitis.

A review of the mean change in FEV_1, FVC, and DLCO shows that both treatment groups demonstrated a slight decrease in pulmonary function at Week 12. The Exubera group demonstrated a greater mean decrease in FEV_1 than the SC insulin group. The mean decline in FVC was similar between treatment groups. The SC insulin group experienced a greater mean decrease in DLCO compared to the Exubera group.

10.4.2   Study 217-106

Efficacy and Safety of Inhaled Compared to Subcutaneous Insulin Therapy in Subjects with Type 1 Diabetes Mellitus: A Six-Month, Outpatient, Parallel Comparative Trial

10.4.2.1   Protocol

Study 217-106 was a phase 3, open-label, 6-month, parallel group study in 320 males and females with type 1 diabetes mellitus. Subjects with the following were excluded:
- Clinically significant abnormalities on screening CXR
- Poorly-controlled asthma, clinically significant COPD, or other significant respiratory disease
- Subjects with frankly abnormal PFTs at Week -3, defined as DLCO <75%, TLC >120% or <80%, or FEV_1<70% predicted
- Any smoking within the last 6 months

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 281-284].

A screening visit was followed by a baseline lead-in period (4 weeks) during which subjects underwent pulmonary function testing. At the end of the lead-in-period, subjects were instructed on the proper use of Exubera. Eligible subjects were then randomized to either continuation of their pre-study subcutaneous insulin regimen or Exubera therapy (pre-meals) and Ultralente SC HS [N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 285-289].

Safety monitoring included AEs, laboratories, CXR, and pulmonary function testing. PFTs included: FVC, FEV_1, $FEF_{25-75\%}$, PEFR, TLC, FRC, RV, VC, DLCO, and resting oxygen saturation. PFT testing was performed at baseline (week -3), week 12 (spirometry only), and week 24. PFTs were performed using ATS standards. If a subject had a decrease of >15% in any FEV_1, FVC, TLC, FRC, or DLCO in the absence of intercurrent illness, the PFTs were repeated. If the >15% decrease persisted, then further pulmonary evaluation, including pulmonologist consultation, CXR, or HRCT was

obtained. CXRs were performed at the beginning and end of the study
[N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 299, 306].

An HRCT substudy was included in Studies 217-106, 217-107, and 217-108.
Approximately 100 subjects were recruited prior to randomization for the HRCT
substudy at participating sites. Baseline HRCTs were obtained prior to randomization.
HRCTs were performed without contrast by taking 1 mm cuts starting 2 cm above the
carina and continuing inferiorly every 2cms for a total of 10 cuts. Enrollment continued
until at least 50 of the subjects were randomized to Exubera. Both the baseline HRCT
and 24 week HRCT were forwarded together to a central radiology site for a blinded
review. A second original set of films was kept at the investigative site. Abnormalities
noted on the baseline HRCT were discussed with a Pfizer clinician prior to
randomization. The number and percentage of new abnormalities at the end of treatment
was summarized across the 100 subjects in the substudy [N21868/N_000/2004-12-
27/clinstat/diabetes/type1/106.pdf, pg 313].

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

10.4.2.2   Results

The study commenced on September 27, 1999, and was completed on September 12,
2000. Forty-one centers participated in the study (United States 33, Canada 8). A total
of 416 subjects were screened for the study and 335 were randomized, 170 to the Exubera
and 165 to the subcutaneous arm. Subject disposition is shown in Table 74. One subject
discontinued the study due to a respiratory AE, cough [N21868/N_000/2004-12-
27/clinstat/diabetes/type1/106.pdf, pg 35]

Table 74 Subject Disposition Study 217-106		
	Exubera	SC Insulin
Randomized (335)	170	165
Completed	152	151
Discontinued Study	18	14
Withdrew consent prior to tx	0	1
Adverse Event	**3**	**1**
Cough	1	0
Hypoglycemia/hypoglycemic coma	2	0
Hypoglycemia → seizure, lip lac, chipped tooth	0	1
Lack of efficacy	3	2
Other (includes protocol violation)	3	1
Subject defaulted (includes lost to F/U)	9	9

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 117, 199]
*Reviewer's Comment: Because one subject withdrew consent after randomization and
before treatment the number of the subjects in the SC insulin group will be 164, not 165.
Reviewer's Comment: A 51 yo female subject (10650556135) discontinued due to cough
on Day 68. The subject developed a mild to moderate cough related to insulin dosing*

that persisted throughout the treatment period. The investigator discontinued the subject when she asked for a cough suppressant. FVC and DLCO decreased from baseline 5.41L to 5.19L and 16.6ml/min/mmHg to 14.6 ml/min/mmHg, respectively. FEV$_1$, TLC, and CXR were unchanged
[N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg195].

The mean age of the subjects was 33 years and the majority of the subjects were Caucasian as shown in Table 75.

Table 75 Baseline Characteristics Study 217-106		Exubera n = 170	SC Insulin n = 164
Gender	Male	88 (52%)	91 (55%)
	Female	82 (48%)	73 (45%)
Age	Mean	33.5	33.9
	Range	11-63	11-64
Race	Caucasian	152 (89%)	155 (95%)
	Black	7 (4%)	3 (2%)
	Asian	2 (1%)	0
	Hispanic	9 (5%)	3 (2%)
	Other	0	3 (2%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 69]

Reviewer's Comment: A review of the summary of medical history of the subjects indicates that some subjects reported a history of asthma. For example, asthma (unspecified) was reported in the past in 14 subjects and in the present in 9 subjects. Extrinsic asthma was reported in the present in one subject [N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 73].

Respiratory Adverse Events
Respiratory adverse events were slightly more common in the Exubera group than in the SC insulin group. Respiratory tract infection, increased cough, pharyngitis, and rhinitis were the most common respiratory adverse events. Increased cough, dyspnea, epistaxis, and pharyngitis were more common in the Exubera group than in the SC insulin group. A detailed summary of the respiratory AEs are listed in Table 76. All the respiratory AEs were mild to moderate in severity.

Table 76 Number of Subjects with Respiratory Adverse Events in Study 217-106		
	Exubera n = 170	SC Insulin n = 164
Serious adverse events	6 (3.5%)	9 (5.5%)
Any adverse event	169 (99.4%)	163 (99.4%)
Respiratory	**124 (73%)**	**107 (65%)**
Asthma	1 (0.6%)	5 (3.0%)
Bronchitis	4 (2.4%)	4 (2.4%)
Cough increased	**46 (27.1%)**	**9 (5.5%)**
Dyspnea	**6 (3.5%)**	**1 (0.6%)**
Epistaxis	**6 (3.5%)**	**1 (0.6%)**
Laryngitis	2 (1.2%)	2 (1.2%)
Pharyngitis	**37 (21.8%)**	**28 (17.1%)**
Pneumonia	0	3 (1.8%)
Respiratory disorder	14 (8.2%)	13 (7.9%)
Respiratory tract infection	69 (40.6%)	63 (38.4%)
Rhinitis	26 (15.3%)	23 (14%)
Sinusitis	12 (7.1%)	10 (6.1%)
Sputum increased	5 (2.9%)	4 (2.4%)
Voice alteration	0	1 (1.6%)

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 149, 156]

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

Reviewer's Comment: Cough was reported by one subject in each treatment group during the run-in period. Therefore the number of subjects reporting cough during the treatment period was actually 45 and 8 in the Exubera group and SC insulin group, respectively.

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

An increase in cough was more common in the Exubera group than in the SC insulin group. The number of subjects reporting cough during the treatment period was 45 subjects in the Exubera group and 8 subjects in the SC insulin group. A total of 60 cough events were reported in the Exubera group compared to 8 in the SC insulin group. In both treatment groups, about half of the cough AEs were reported in the first 4 weeks and the majority of cough AEs were reported in the first 12 weeks. All of the cough events 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 5.07 weeks and 4.88 weeks for the Exubera group and SC insulin group, respectively. About 58% of subjects reporting cough in the SC insulin group had a duration of cough of 2 weeks or less [N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 55-56, 206-209].

Reviewer's Comment: It is unclear if the Applicant has a specific definition of mild, moderate, and severe cough or if cough was graded as other AEs. Other AEs were graded as mild for a trivial AE not causing any real problem to the subject, moderate for an adverse event that was a problem to the subject but did not interfere significantly with

usual activities, and severe as an adverse event that interfered significantly with usual daily activities or clinical status.

Pulmonary Function Tests

Baseline PFTs were well-matched between the treatment groups. A review of the mean change in pulmonary function at 24 weeks shows that both treatment groups demonstrated a slight decrease in FEV₁, FVC, and DLCO. However the decrease tended to be greater in the Exubera group, especially the DLCO. A summary of the PFTs is shown below in Table 77.

Table 77 Pulmonary Function Tests for Study 217-106 – Summary of Mean Change						
	Exubera			Subcutaneous Insulin		
PFT	BL	Week 24 (LOCF)	Change from BL	BL	Week 24 (LOCF)	Change from BL
FEV₁	N=169	N=166	N=166	N=164	N=157	N=157
Mean (L)	3.48	3.42	-0.067	3.43	3.42	-0.033
SD	0.81	0.79	0.237	0.80	0.78	0.30
FVC	N=169	N=166	N=166	N=164	N=157	N=157
Mean (L)	4.27	4.24	-0.029	4.23	4.25	-0.002
SD	1.03	0.99	0.301	1.05	1.04	0.355
DLCO	N=167	N=153	N=150	N=163	N=149	N=148
Mean (ml/min/mmHg)	28.44	26.75	-1.69	28.14	28.10	-0.389
SD	6.94	6.75	3.86	6.39	6.85	3.69
TLC	N=169	N=153	N=152	N=164	N=149	N=149
Mean (L)	5.87	5.91	0.04	5.90	6.07	0.118
SD	1.41	1.36	0.64	1.41	1.46	0.58

[N21868/N_000/2004-12-27/clinstat/diabetes/type1/106.pdf, pg 221-232]

Reviewer's Comment: The Applicant used the last observation carried forward (LOCF) for missing data, which is displayed in Table 77. The results for the mean change from baseline for FEV₁, TLC, and DLCO were quite similar for the Week 24 observed data and the Week 24 (LOCF) data. For FVC, the change from baseline for the 24 week for the SC insulin group was -0.011L. Thus, using the LOCF actually suggests a slightly smaller decrease in FVC for the SC insulin group.

Reviewer's Comment: Although oxygen saturation was specified to be collected with the PFTs, the Applicant did not report the results for the oxygen saturation in the study report.

A categorical analysis of the PFT data suggests that there were more subjects in the Exubera group than in the SC insulin group who had a decline in PFT parameters of more than 10%. Table 78 displays the categorical analyses of the PFTs. More subjects appeared to have a decline in DLCO than any other PFT parameter. The majority of subject with declines of >15% continued into the extension study. The results will be discussed further in Study 217-111.