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)

Inhaled Insulin			
	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-inhaled insulin 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 inhaled insulin. However, as discussed in the Methods Section 5.1.8.1, the design is flawed in that the study population prior to randomization is likely enriched with subjects who responded favorably to inhaled insulin and tolerated inhaled insulin. Subjects who did not tolerate inhaled insulin or had a decline in pulmonary function may have been discontinued from the study. In addition, subjects were on inhaled insulin for various lengths of time prior to randomization into the discontinuation phase.

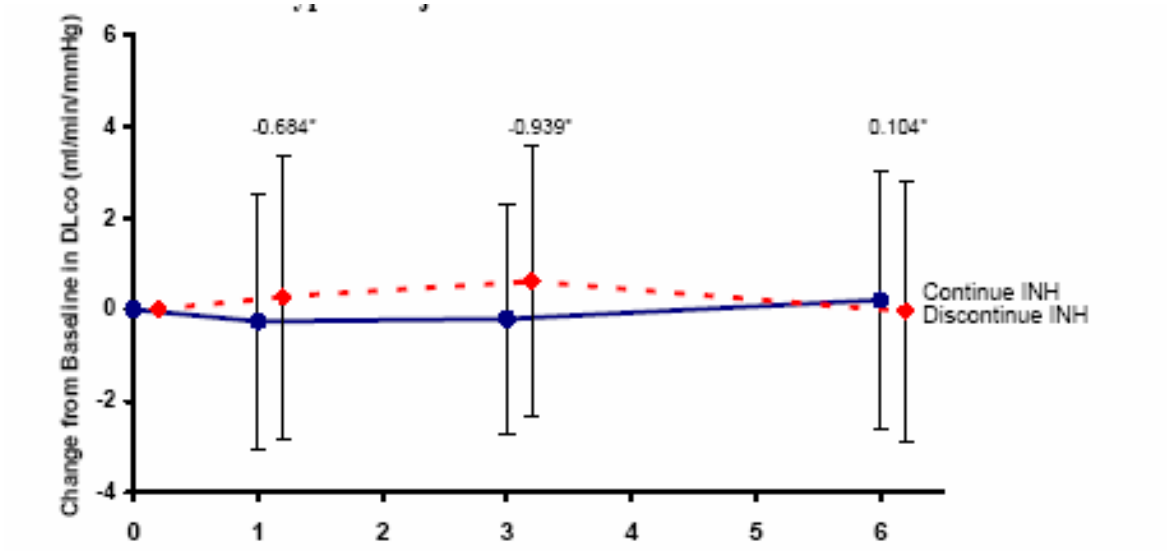
The mean observed DLCO and mean change from "baseline" DLCO in the discontinuation phase are shown in Table 44 and Figure 36 below. The results show subjects who continued on inhaled insulin had an increase in DLCO at Month 6 and subjects who discontinued inhaled insulin initially had an increase in 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 inhaled insulin and is not the true baseline prior to study medication exposure. Thus, this "baseline" is in quotes to distinguish it from the true pre-study medication baseline.

Table 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)**

Inhaled Insulin						
	Continued Inhaled Insulin			Discontinued Inhaled Insulin		
DLCO (mL/min/mmHg)	Observed	Change from "Baseline"		Observed	Change from "Baseline"	
	Mean (SD)	N	Mean (SD)	Mean (SD)	N	Mean (SD)
"Baseline"*	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 inhaled insulin
**Primary analysis set includes all randomized subjects who had a baseline FEV_1 measurement and a post-baseline measurements and received study drug for at least 50% of the duration of the controlled segment
Source: N21868/N_000/2004-12-27/clinstat/111.pdf, pg 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 inhaled insulin for an additional 6 months after the discontinuation phase. In this follow up phase inhaled insulin was discontinued. In subjects with type 2 diabetes ≥ 18 years of age, at 6 months the DLCO decreased 0.39mL/min/mmHg from the last DLCO value on inhaled insulin [N21868/N_000/2004-12-27/clinstat/111.pdf, pg 181].

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

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

5.1.8.3.2.6 Conclusions of the Effect of Inhaled Insulin on DLCO in Type 2 Diabetes

Subjects with type 2 diabetes treated with inhaled insulin 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 2/3 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 inhaled insulin group. Thus, the effect of inhaled insulin on DLCO did not appear to progress over 2 years of treatment.

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

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

Reversibility of the effect of long term inhaled insulin 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 inhaled insulin. 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.

5.1.8.3.3 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 inhaled insulin on pulmonary function.

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

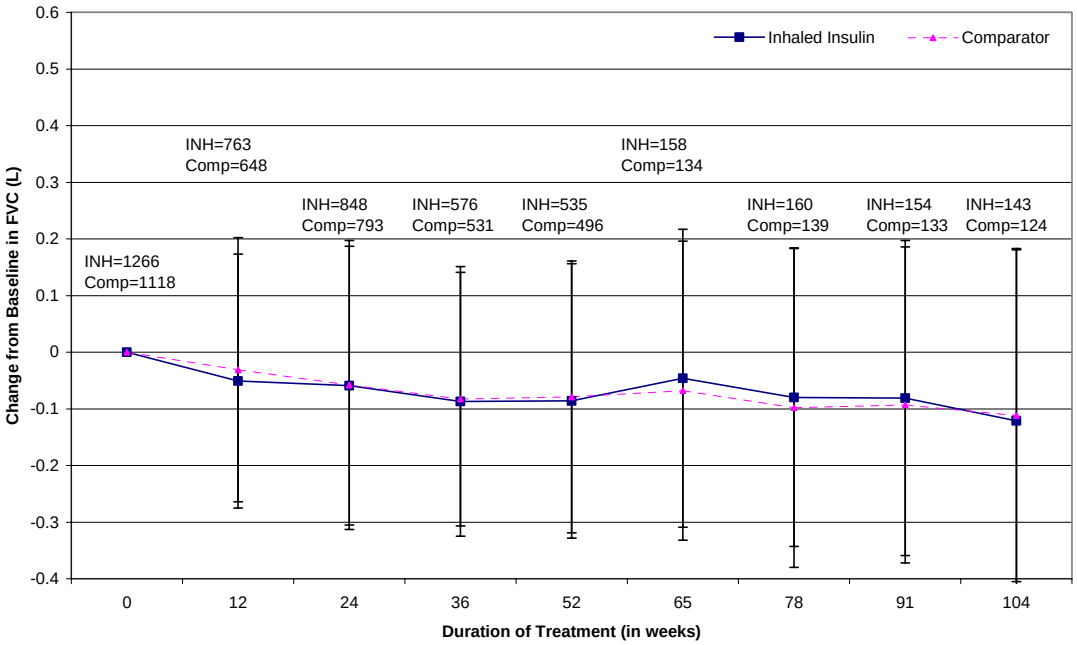
Table 45 Mean Change from Baseline and Mean Treatment Group Difference for Additional Pulmonary Function Tests in Controlled Phase 2/3 Studies in Type 2 Diabetes (Adults)

	Mean Observed Change from Baseline (N)		Mean Treatment Group Difference	
	Inhaled Insulin	Comparator	Treatment Group Difference Unadjusted (95% CI)	Treatment Group Difference Adjusted* (95% CI)
FVC				
Week 12	-0.051 (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)

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

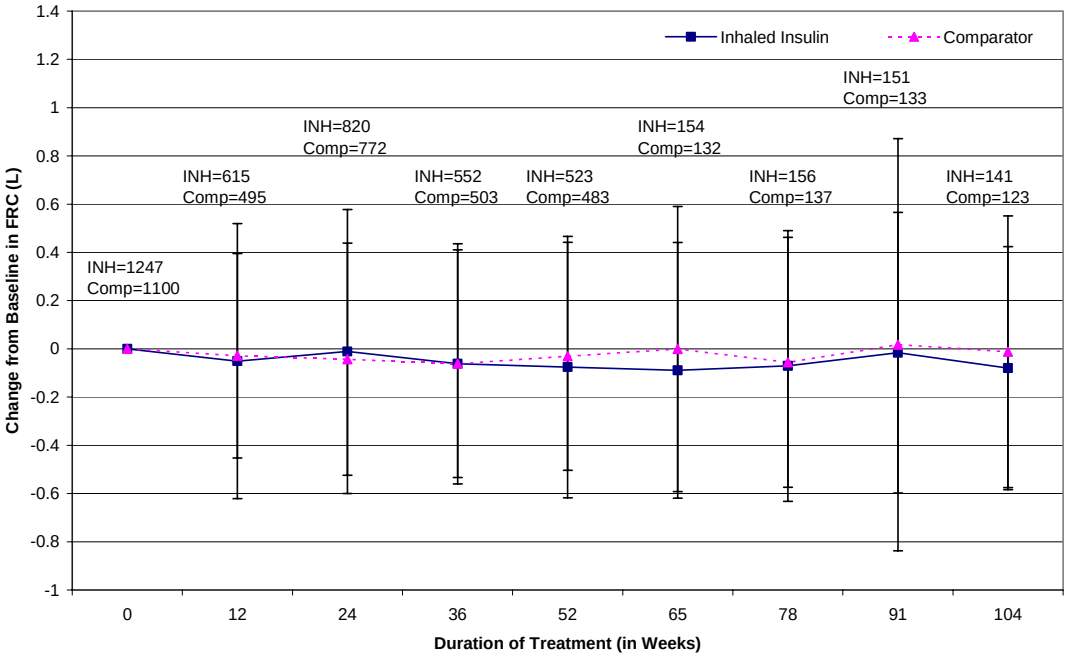
The following figures display the mean change from baseline FVC, FRC, and TLC for the pooled adult controlled phase 2/3 studies in type 2 diabetes.

Figure 38 Mean Change from Baseline FVC (L) by Time in Adult Phase 2/3 Controlled Studies in Type 2 Diabetes



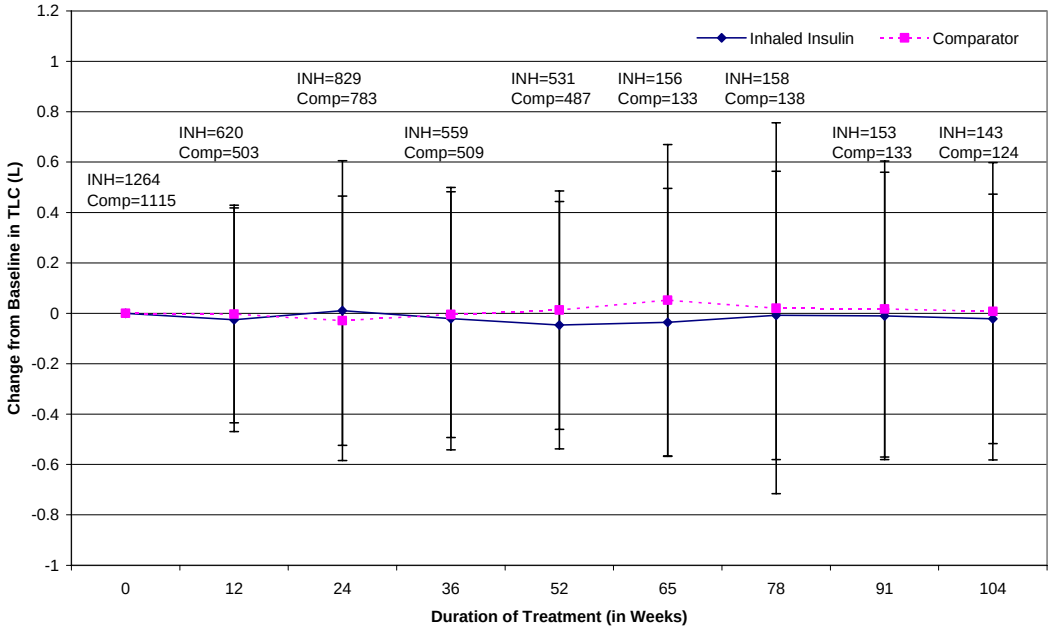
Source: Dr. Joan Buenconsejo's Biometrics Review

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



Source: Dr. Joan Buenconsejo's Biometrics Review

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



Source: Dr. Joan Buenconsejo's Biometrics Review

The Applicant determined the treatment group difference for FEV_1/FVC%, residual volume (RV), and forced expiratory flow 25-75% ($FEF_{25-75\%}$) at 24 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 2/3 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.

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

	Mean Observed Change from Baseline (N)		Mean Treatment Group Difference
	Inhaled Insulin	Comparator	Treatment Group Difference (95% CI) Adjusted by Applicant[+]
FEV_1/FVC (%)			
Month 3	-0.640 (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			

5.1.8.4 Subgroup Analyses for Pulmonary Function Tests

The Biometrics reviewer performed subgroup analyses to assess the effect of age, race, and sex on the mean change from baseline FEV_1, FVC, DLCO, TLC, and FRC in the adult controlled phase 2/3 studies. In type 1 and type 2 diabetes, no consistent association between age or sex and the mean change from baseline FEV_1, FVC, TLC, DLCO, and FRC was noted. Because there were a limited number of non-caucasian subjects, no conclusions can be made upon the subgroup analyses for race.
Reviewer's Comments: Refer to Dr. Buenconsejo's Biometric Review for further details.

5.1.8.5 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 2/3 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, inhaled insulin 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 from baseline 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 inhaled insulin 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 inhaled insulin, 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 the change in 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 inhaled insulin dose or the cumulative inhaled insulin dose.

In Study 1022, subjects were exposed to study medication for up to one year, which was the cut off for 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 inhaled insulin dose or the cumulative inhaled insulin 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 inhaled insulin dose or the cumulative inhaled insulin dose.

5.1.9 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.

The Applicant pooled the phase 2/3 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 inhaled insulin group had a slightly greater incidence of significant changes in CXR from baseline to last observation as shown in Table 47.

Table 47 Significant Changes in Chest X-Rays Between Baseline & Last Observation Adult Controlled Phase 2/3 Studies			
Number (%) of subjects with significant change from baseline [Number examined]			
	Inhaled Insulin	**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]

Source: [N21868/N_000/2004-12-27/summary-clin-safety.pdf, pg 2704-2705]

The CXR changes from baseline for the individual studies were reviewed. In general, the most common CXR changes from baseline were nodular density, opacity, nodule, atelectasis, cardiomegaly, and enhanced vasculature/pulmonary edema. Consistent with the pooled data, the individual studies indicated that the inhaled insulin group had more changes from baseline than the comparator group. Nodules/opacities/densities were more common in the inhaled insulin group than in the comparators. However, the clinical significance of this finding is unclear since the text for the CXR listing was often questionable nodular density or questionable nipple shadow. In addition, for most cases, follow up information (CT scan, additional CXR) demonstrated a resolution of the findings.

In summary, the CXR data in the pooled phase 2/3 adult controlled clinical studies demonstrates that there were more significant changes from baseline CXR in the inhaled insulin treatment group. This was true in both type 1 and type 2 diabetes. The most common new significant changes on CXR were nodular density, opacity, nodule, atelectasis, cardiomegaly, and enhanced vasculature or pulmonary edema. However, the clinical significance of this finding is unclear since the text for the CXR listing was often questionable nodular density or questionable nipple shadow. In addition, for most cases, follow up information (CT scan, additional CXR) demonstrated a resolution of the findings.

5.1.10 High Resolution Computed Tomography (HRCT)

5.1.10.1 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 inhaled insulin, to assess the pulmonary safety of inhaled insulin, the Agency recommended that the Applicant obtain HRCT data from approximately 50 subjects on inhaled insulin 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 inhaled insulin and 63 subjects treated with SC insulin. The Applicant has controlled HRCT data at 24 months on 51 subjects treated with inhaled insulin 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.

5.1.10.2 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 inhaled insulin group. There were 53 subjects in the inhaled insulin 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 inhaled insulin 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 inhaled insulin 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 48 displays a summary of the HRCT data in Studies 106, 107, and 108.

Table 48 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	Inhaled Insulin 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 of the 116 subjects did not undergo 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

- Inhaled insulin (3)
  - Linear density in lingula
  - Dependent density in basis not consistent with fibrosis
  - New dependent density, unlikely to be fibrosis
- SC insulin (4)
  - New right basilar atelectasis
  - Dependent subpleural density
  - ? New scar or atelectasis in lingual
  - Increased reticular subpleural reticular

Abnormal HRCT at baseline and more abnormal HRCT findings at last observation

- Inhaled insulin (1)
  - Persistent linear scar right base; new linear density, probably atelectasis
- SC insulin (2)
  - Lung nodule unchanged; linear density in right lower lobe is thicker
  - Increased right middle lobe subpleural lines and bands

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

5.1.10.3 One and Two Year HRCT Data

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." This section includes the partial two year HRCT results from Study 1029. The Applicant noted that not all two-year HRCT data is in the database at the time of the June 22, 2005, submission.

The HRCT data from Study 1029 does not suggest an increase in abnormal HRCT findings at Month 24 in the inhaled insulin group. At Month 24 there were 51 subjects in the inhaled insulin group and 53 subjects in the SC insulin group who underwent the HRCT substudy in Study 1029. In both treatment groups approximately 65-68% of subjects had normal HRCTs at baseline and Month 12. At Month 24, the percentage of subjects with normal HRCT was less in the inhaled insulin group compared to the SC group; however, there were a similar number of subjects with normal HRCT at baseline

and abnormal findings at Month 24 in both treatment groups, 6 in the inhaled insulin group and 5 in the SC insulin group. In subjects with abnormal HRCTs at baseline, there were 3 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. Table 49 displays a summary of the HRCT data in Study 1029.

Table 49 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**	**Inhaled Insulin N=96**	**SC Insulin N=96**	**Inhaled Insulin N=51**	**SC Insulin N=53**	**Inhaled Insulin N=98**	**SC Insulin N=96**
Yes	Yes	65 (67.7)	62 (64.6)	28 (54.9)	37 (69.8)	64 (65.3)	63 (65.6)
	No	4 (4.2)	13 (13.5)	6 (11.8)	5 (9.4)	7 (7.1)	12 (12.5)
No	Yes	6 (6.3)	5 (5.2)	3 (5.9)	4 (7.5)	8 (8.2)	6 (6.3)
	No	21 (21.9)	16 (16.7)	14 (27.5)	7 (13.2)	19 (19.4)	15 (15.6)
	No significant change	20 (20.8)	11 (11.5)	14 (27.5)	5 (9.4)	19 (19.4)	10 (10.4)
	More abnormal	0	3 (3.1)	0	0	0	1 (1.0)
	Less abnormal	1 (1.0)	2 (2.1)	0	1 (1.9)	0	3 (3.1)

Source: [N21868/N_000/2005-06-22/partial_2y_hrct_data.pdf, pg. 1]

Reviewer's Comment: The Agency requested HRCT data on at least 50 subjects on inhaled insulin and 50 subjects on comparator for at least 2 years treatment duration.

Of interest are the subjects who had normal HRCT at baseline and had abnormal HRCT at Month 24. There were no subjects who had an abnormal HRCT at baseline and more abnormal findings 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_000/2005-06-22/partial_2y_hrct_data.pdf, pg. 5-24].

HRCTs WNL at baseline and not WNL at Month 24

- Inhaled insulin (6)
  - RML and lingular subpleural nodules
  - Increased bibasilar density, probably atelectasis
  - Mildly increased bibasilar density, probably atelectasis
  - Bibasilar density, probably atelectasis
  - Minimal basilar atelectasis/fibrosis
  - Subpleural linear scar
- SC insulin (5)
  - Bibasilar fibrosis vs. atelectasis
  - Increased atelectasis vs. early fibrosis
  - New RML nodule
  - Minimal lingular atelectasis/scar
  - 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 inhaled insulin group. However, it should be noted that the study is ongoing and enrollment is not complete at the time of this review.

5.1.10.4 "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 inhaled insulin.

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. 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 inhaled insulin. Thus, it is difficult to draw any conclusions from the "for cause" HRCT data because it is not controlled data.

5.1.10.5 Conclusions

HRCT scans were obtained to assess for parenchymal lung changes associated with inhaled insulin 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 104 subjects, and "for cause" HRCT data in 48 subjects. The controlled HRCT data does not suggest an increase in abnormal findings associated with inhaled insulin use compared to SC insulin at 24 weeks or 24 months.

6 Special Populations

6.1 Underlying Lung Disease

6.1.1 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 inhaled insulin. To specifically evaluate the safety and efficacy of inhaled insulin 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 2/3 studies *retrospectively identified* as meeting criteria compatible with mild to moderate asthma or COPD. According to the Sponsor, 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 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, a diagnosis of 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: According to the inclusion criteria, subjects with chronic bronchitis without obstructive physiology could have enrolled in Study 1030.*

The integrated ULD Cohort combines the 1028/1030 Cohort and the Controlled ULD Cohort. Table 50 displays the number of subjects in each of the proposed ULD Cohorts.

Table 50 Applicant's Proposed Underlying Lung Disease (ULD) Cohorts

	Asthma		COPD		Neither Disorder	
	Inhaled Insulin	Comparator	Inhaled Insulin	Comparator	Inhaled Insulin	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 inhaled insulin. The Agency requested controlled data from prospective studies in subjects with underlying lung disease.

6.1.2 Asthma

6.1.2.1 Prospectively Defined Asthma - Study 1028

Protocol

Study 217-1028 is an ongoing phase 3, open-label, 15 month, parallel group study of inhaled insulin 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 FEV1 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 inhaled insulin 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 inhaled insulin 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. Eleven inhaled insulin 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 contained some information on subjects with asthma who have been exposed to inhaled insulin for one year.

There was one respiratory related SAE, asthma exacerbation, in each treatment group. The number of subjects with respiratory related 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 related 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 inhaled insulin group than in the SC insulin group as shown below in Table 51. More subjects discontinued from the inhaled insulin group due to adverse events (5) than the comparator group (0). The most common adverse event leading to discontinuation was asthma.

Table 51 Number of Subjects with Respiratory Related Adverse Events in Study 217-1028 – Interim Results

	Inhaled Insulin 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 inhaled insulin group. There were 25 (35%) subjects with asthma AEs in the inhaled insulin 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 inhaled insulin group than in the SC insulin group. The inhaled insulin 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 inhaled insulin group had 11 subjects with 15 events, while the SC insulin group had 9 subjects with 10 events. In the inhaled insulin 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 inhaled insulin 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 mean decline from baseline FEV_1 (pre-bronchodilator) was greater in the inhaled insulin group than in the SC insulin group at almost all time points as shown below in Table 52. At Week 52, the inhaled insulin group had a mean decline from baseline of 296mL, while the comparator group had a mean decline from baseline of 113mL. However, it should be noted that the number of subjects is quite small at Week 52.

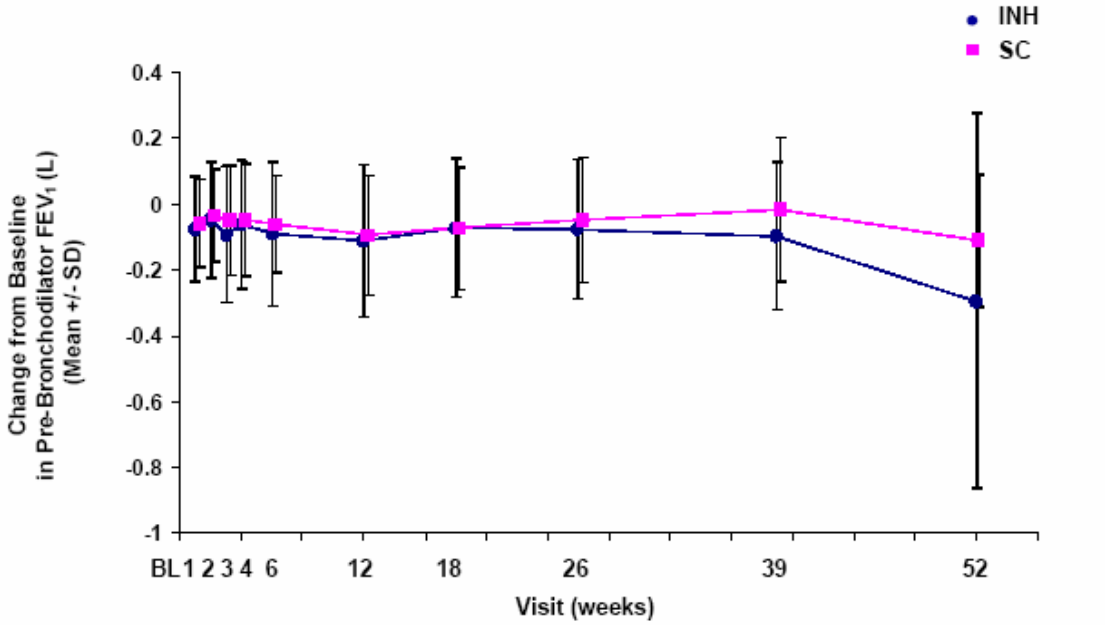
Table 52 Mean Change from Baseline FEV_1 (Pre-Bronchodilator FEV_1) and Mean Treatment Group Difference in Study 1028 – Interim Results

FEV_1 in Liters	Mean Change from Baseline FEV_1 (N)		Mean Treatment Group Difference (95% CI) Unadjusted
	Inhaled Insulin	Comparator	
Baseline	2.376 (70)	2.608 (65)	
Week 1	-0.076 (64)	-0.059 (59)	-0.017 (-0.069, 0.036)
Week 2	-0.050 (63)	-0.035 (54)	-0.015 (-0.074, 0.043)
Week 3	-0.093 (62)	-0.050 (58)	-0.043 (-0.111, 0.024)
Week 4	-0.064 (58)	-0.049 (61)	-0.015 (-0.082, 0.051)
Week 6	-0.091 (61)	-0.063 (62)	-0.029 (-0.096, 0.038)
Week 12	-0.112 (46)	-0.095 (49)	-0.018 (-0.101, 0.066)
Week 18	-0.072 (42)	-0.075 (48)	0.004 (-0.080, 0.087)
Week 26	-0.077 (33)	-0.049 (42)	-0.028 (-0.122, 0.066)
Week 39	-0.099 (17)	-0.019 (29)	-0.080 (-0.216, 0.056)
Week 52	-0.296 (10)	-0.113 (17)	-0.183 (-0.493, 0.127)

Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 38; 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 group difference increased as shown below in Figure 41.

Figure 41 Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) in Study 1028 - Interim Results



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

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 inhaled insulin group with >20% decrease from baseline FEV_1 and in the SC insulin group there were 2 subjects with 15-20% decrease from baseline FEV_1.

Reviewer's Comment: the Applicant also measured post-bronchodilator FEV_1 and in general the change from baseline in post-bronchodilator FEV_1 produces a similar pattern as the figure above. However, the unadjusted mean treatment group difference in change from baseline post-bronchodilator FEV_1 at Week 52 is -157mL, which is slightly less than the -183mL treatment group difference using the pre-bronchodilator FEV_1.

The Applicant also measured pre and post-insulin (10min and 60min) FEV_1 at certain visits. The mean pre and post-insulin FEV_1 data suggest a decrease in mean FEV_1 at 10 minutes post-dose; however, the FEV1 returns to pre-dose at 60 minutes post-dose as shown below in Table 53.

Table 53 Mean Observed FEV1 Pre- and Post-Inhaled Insulin Dose in Study 1028

	Inhaled Insulin		
FEV1 in liters	Pre-Dose	10 Minutes Post-Dose	60 Minutes Post-Dose
	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	2.361 (0.8)	2.352 (0.8)	2.354 (0.8)
Week 9	2.328 (0.9)	2.265 (0.9)	2.322 (0.9)
Week 51	2.340 (0.8)	2.297 (0.7)	2.328 (0.8)
Source: N21868/N_000/2005-04-26/clinstat/diabetes/type1/1027.pdf, pg 149-151			

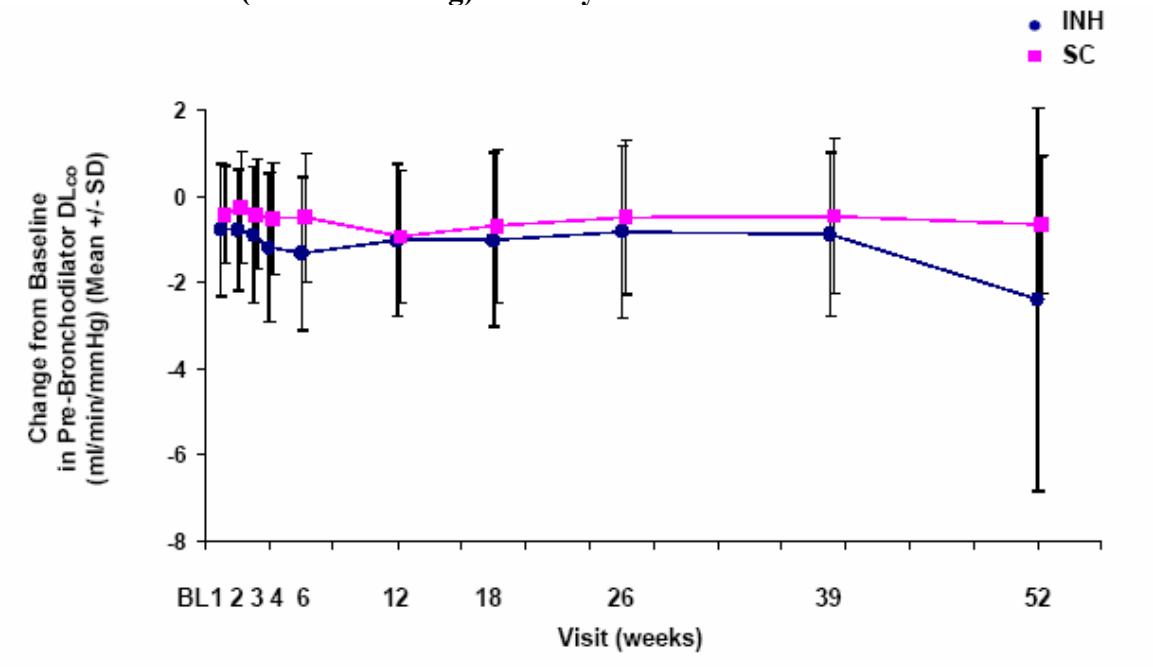
The decline from baseline DLCO (pre-bronchodilator) was greater in the inhaled insulin group than in the SC insulin group at all time points as shown below in Table 54. At Week 52, the inhaled insulin group had a mean decline from baseline of -2.394mL/min/mmHg, while the comparator group had a mean decline from baseline of -0.646mL/min/mmHg. However, it should be noted that the number of subjects is quite small at Week 52.

Table 54 Mean Change from Baseline DLCO (Pre-Bronchodilator DLCO) and Mean Treatment Group Difference in Study 1028 – Interim Results

DLCO in mL/min/mmHg	Mean Change from Baseline DLCO (N)		Mean Treatment Group Difference (95% CI) Unadjusted
	Inhaled Insulin	Comparator	
Baseline	23.200 (70)	23.516 (65)	
Week 1	-0.774 (64)	-0.419 (59)	-0.355 (-0.836, 0.127)
Week 2	-0.777(63)	-0.249 (53)	-0.528 (-1.032, -0.024)
Week 3	-0.893 (61)	-0.420 (57)	-0.473 (-0.998, 0.053)
Week 4	-1.179 (58)	-0.509 (60)	-0.670 (-1.225, -0.115)
Week 6	-1.328 (59)	-0.499 (62)	-0.829 (-1.418, -0.240)
Week 12	-1.027 (45)	-0.925 (49)	-0.102 (-0.778, 0.574)
Week 18	-1.008 (41)	-0.689 (48)	-0.320 (-1.121, 0.482)
Week 26	-0.828 (32)	-0.483 (42)	-0.346 (-1.221, 0.530)
Week 39	-0.880 (17)	-0.447 (29)	-0.434 (-1.567, 0.700)
Week 52	-2.394 (10)	-0.646 (17)	-1.748 (-4.170, 0.673)
Source: N21868/N_000/2005-04-26/update/1028_interim_2005.pdf, pg 43			

In general, the mean treatment group difference was fairly stable between Week 18 and Week 39. From Week 39 to Week 52, there was a large increase in mean treatment group difference favoring the comparator as shown below in Figure 42. At Week 52, the unadjusted mean treatment group difference was -1.748 mL/min/mmHg, favoring the comparator.

Figure 42 Mean Change from Baseline in Pre-Bronchodilator DLCO (mL/min/mmHg) in Study 1028 – Interim Results



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

Reviewer's Comment: the Applicant also measured post-bronchodilator DLCO and in general the change from baseline in post-bronchodilator DLCO produces a similar pattern as the figure above. However, the unadjusted mean treatment group difference in change from baseline post-bronchodilator DLCO at Week 52 is -1.211 mL/min/mmHg, which is slightly less than the -1.748mL/min/mmHg treatment group difference using the pre-bronchodilator FEV_1.

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. It should be noted that in the inhaled insulin group there were two subjects who had a >40% decline from baseline FEV_1.

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 inhaled insulin group showed a small increase in both the subject and clinical evaluation score, while the SC insulin group showed a small decrease in both the subject and clinical evaluation score.
Reviewer's Comment: The Asthma Control Questionnaire data suggest that the inhaled insulin group reported a slight worsening of asthma control, while the SC insulin group reported an improvement in asthma control. Again, it should be noted that the 52 Week data is based upon a small number of subjects.

Conclusions

Study 217-1028 is an ongoing phase 3, open-label, 15 month, parallel group study of inhaled insulin 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 inhaled insulin 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 the 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 inhaled insulin 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 group.

The inhaled insulin group had a slightly lower baseline mean pre- and post-bronchodilator FEV_1 than the SC insulin group. The PFT data from Study 1028 indicates that subjects treated with inhaled insulin demonstrate a greater decline from baseline FEV_1 (pre-BD) than the comparator group. In general, from Week 1 through Week 18 there was a small treatment group difference usually favoring the comparator. However, by Week 52, the treatment group difference for change from baseline FEV_1 had increased further favoring the comparator. At Week 52, the inhaled insulin group had a mean decline from baseline FEV_1 of 296mL, while the comparator group had a mean decline from baseline FEV_1 of 113mL. The decline in FEV_1 at Week 52 is greater than the annual rate of decline in FEV_1 for non-smoking subjects with asthma – a decline of FEV_1 of approximately 30-33mL/year.[3] The treatment group difference (-183mL) is much greater than the treatment group difference noted at Week 52 in the pooled controlled phase 2/3/ studies, which was approximately -30 to -40mL. However, it should be noted that the 52 week data in Study 1028 is based upon only 27 subjects.

Mean baseline pre and post-bronchodilator DLCO were similar between treatment groups. The inhaled insulin group demonstrated a greater decline from baseline DLCO than subjects in the comparator group at most time points. The mean treatment group difference fluctuated during the treatment period. The mean unadjusted treatment group difference for change from baseline pre-bronchodilator DLCO fluctuated between -0.1 to -0.8mL/min/mmHg until Week 39. At Week 52, the mean treatment group difference increased further favoring the comparator (-1.75mL/min/mmHg). At Week 52, the inhaled insulin group demonstrated a decline from baseline DLCO of 2.394 mL/min/mmHg while the comparator group demonstrated a decline from baseline DLCO

of 646mL/min/mmHg. However, it should be noted that the 12 month PFT data is based upon 27 subjects.

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

6.1.2.2 Retrospectively Defined Asthma

As discussed above in the Methods Section 6.1.1, 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 includes a brief review of the pertinent findings in the 54 subjects retrospectively identified with asthma in the controlled phase 2/3 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 inhaled insulin.

Of the 54 subjects retrospectively identified with asthma, 24 were treated with inhaled insulin 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 inhaled insulin is available for only 12 subjects. Thus, these additional retrospectively identified subjects with asthma provide limited data about the long term effect of inhaled insulin on pulmonary safety in subjects with asthma.

There were no respiratory related deaths in subjects retrospectively identified with asthma. Three subjects were noted to have serious adverse events (1 in the inhaled insulin group and 2 in the comparator group). None of the SAEs were respiratory related. The number of subjects with overall AEs and respiratory related 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 inhaled insulin group than subjects in the comparator group as shown below in Table 55 [N21868/N_000/2004-12-26/clinstat/pulm.pdf, pg 1185-1191].

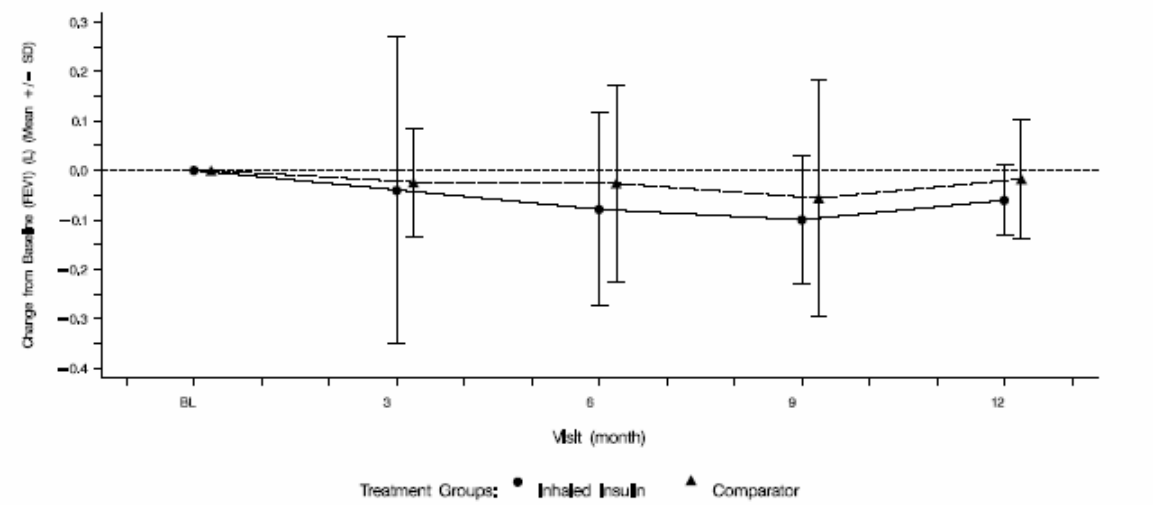
Table 55 Number of Subjects with Respiratory Related Adverse Events in Subjects Retrospectively Identified with Asthma		
	Inhaled Insulin n = 24	Comparator n = 30
Any adverse event	24 (100%)	29 (96.7%)
Respiratory	17 (70.8%)	20 (66.7%)
Asthma, including asthma exacerbation	**3 (12.5%)**	**3 (10%)**
Bronchitis	**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		

The mean baseline FEV_1 was lower in the comparator group than in the inhaled insulin group. The inhaled insulin group demonstrated a greater decline from baseline FEV_1 than subjects in the comparator group as shown below in Table 56. After 12 months, the inhaled insulin 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 56 Mean Change from Baseline FEV_1 (L) in Subjects Retrospectively Identified with Asthma		
FEV_1 (L)	Mean Change from Baseline FEV_1 (N)	
	Inhaled Insulin	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 43 below. The mean treatment group difference is fairly consistent throughout the treatment period. The treatment group difference consistently favors the comparator group.

Figure 43 Mean Change from Baseline FEV_1 (L) in Subjects Retrospectively Identified with Asthma



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

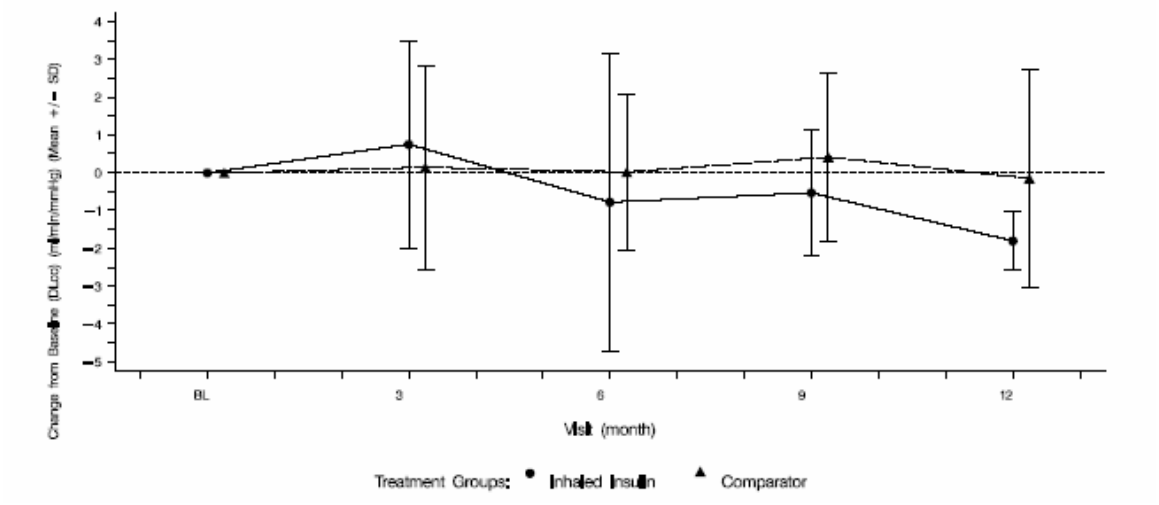
The mean baseline DLCO was lower in the comparator group than in the inhaled insulin group. The inhaled insulin group demonstrated a greater decline from baseline DLCO than subjects in the comparator group at most time points as shown below in Table 60. After 12 months, the inhaled insulin group demonstrated a decline from baseline DLCO of 1.802 mL/min/mmHg while the comparator group demonstrated a decline from baseline DLCO of 0.145mL/min/mmHg. However, it should be noted that the 12 month PFT data is based upon 12 subjects.

Table 57 Mean Change from Baseline DLCO (mL/min/mmHg) in Subjects Retrospectively Identified with Asthma

DLCO (mL/min/mmHg)	Mean Change from Baseline DLCO (N)	
	Inhaled Insulin	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 44 below. The mean treatment group difference is not consistent throughout the treatment period. Initially the treatment group difference favors the inhaled insulin 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 44 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

The data from the 54 subjects retrospectively identified with asthma provides limited information about the long term safety of inhaled insulin in subjects with asthma.

In subjects retrospectively identified with asthma, the number of subjects with overall AEs and respiratory related 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 inhaled insulin group than subjects in the comparator group.

Baseline FEV_1 was lower in the comparator group than in the inhaled insulin group. The inhaled insulin 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 inhaled insulin 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 inhaled insulin group. The inhaled insulin 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 inhaled insulin 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. After 12 months, the inhaled insulin group demonstrated a mean decline from baseline DLCO of 1.802 mL/min/mmHg while the comparator group demonstrated a mean 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.

6.1.2.3 Conclusions

Inhaled insulin has an effect on pulmonary function in subjects without underlying lung disease. Thus, the Agency requested the Applicant prospectively assess the effects of inhaled insulin in subjects with asthma. Data regarding the pulmonary safety of inhaled insulin in subjects with asthma comes from two sources: the ongoing Study 1028 and a cohort of retrospectively identified subjects with asthma in the controlled phase 2/3 studies. Of these two sources, Study 1028 provides the best source of data because Study 1028 was specifically designed to prospectively assess the effects of inhaled insulin in subjects with asthma. The Applicant also retrospectively identified 54 subjects with asthma who participated in the controlled phase 2/3 studies. Data from the retrospectively identified cohort is less robust because the diagnosis of asthma is based upon a subject reported history and was not confirmed.

Study 1028

Study 217-1028 is an ongoing 15 month controlled study which provides 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 with respiratory AEs. In general, the types of respiratory AEs noted in subjects with asthma were similar to AEs noted in subjects without asthma. Of the respiratory AEs reported in Study 1028, increased cough and respiratory tract infection were the AEs with the greatest difference between treatment groups favoring the comparator. In addition, dyspnea, pharyngitis, respiratory disorder, respiratory tract infection, and voice alteration were more common in the inhaled insulin group than in the SC insulin group.

Asthma AEs were more common in the comparator group. The protocol specified the 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 inhaled insulin group than in the SC insulin group. However, the number of subjects requiring systemic corticosteroid treatment was similar between treatment groups.

The PFT data from Study 1028 indicates that subjects treated with inhaled insulin demonstrate a greater decline from baseline pre-bronchodilator FEV_1 than the comparator group. In general, from Week 1 through Week 18 there was a small treatment group difference usually favoring the comparator. However, by Week 52, the treatment group difference for change from baseline FEV_1 (pre-BD) had increased further favoring the comparator. At Week 52, the inhaled insulin group had a mean decline from baseline FEV_1 of 296mL, while the comparator group had a mean decline from baseline FEV_1 of 113mL. The decline in FEV_1 at Week 52 is greater than the annual rate of decline in FEV_1 for non-smoking subjects with asthma – a decline of FEV_1 of approximately 30-33mL/year.[3] The treatment group difference at Week 52 (-183mL) is much greater than the treatment group difference noted at Week 48 in the pooled controlled phase 2/3/

studies, which was approximately -30 to -40mL. It should be noted that the 52 week data in Study 1028 is based upon only 27 subjects.

The PFT data from Study 1028 suggests that subjects treated with inhaled insulin demonstrate a greater decline from baseline DLCO (pre-BD) than the comparator group. Baseline pre and post-bronchodilator DLCO were similar between treatment groups. The inhaled insulin group demonstrated a greater decline from baseline DLCO than subjects in the comparator group at most time points. The mean treatment group difference fluctuated during the treatment period. The mean unadjusted treatment group difference for change from baseline pre-bronchodilator DLCO fluctuated between -0.1 to -0.8mL/min/mmHg until Week 39. At Week 52, the mean treatment group difference increased further favoring the comparator (-1.75mL/min/mmHg). At Week 52, the inhaled insulin group demonstrated a decline from baseline DLCO of 2.394 mL/min/mmHg while the comparator group demonstrated a decline from baseline DLCO of 646mL/min/mmHg. However, it should be noted that the 12 month PFT data is based upon 27 subjects.

Asthma control was assessed by the Asthma Control Questionnaire. At Week 52, the inhaled insulin group showed a small increase in both the subject and clinical evaluation score suggesting a decline in asthma control, while the SC insulin group showed a small decrease in both the subject and clinical evaluation score, suggesting an improvement in asthma control. Again, it should be noted that the 52 week data in Study 1028 is based upon only 27 subjects.

Retrospectively Identified Subjects with Asthma

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

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

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

6.1.3 Chronic Obstructive Pulmonary Disease (COPD)

6.1.3.1 Prospectively Defined COPD – Study 1030

Protocol

Study 217-1030 is an ongoing phase 3, open-label, 15 month, parallel group study of inhaled insulin versus SC insulin in 250 males and females with diabetes mellitus (type 1 or type 2) who have COPD. In this study, COPD is defined according to the following criteria:

- Prior smokers with a 10 pack year or more smoking history and either:
  - Fixed airflow obstruction as determined at screening to include a post-BD $FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ predicted
    and/or
  - 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
  - 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 inhaled insulin or continuation of the run-in regimen (SC insulin) 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. COPD is rigorously defined and subjects are followed with frequent pulmonary function tests. However, the Applicant specified the post-bronchodilator FEV_1 and DLCO as primary efficacy variables. Because the PFTs in the majority of the Applicant's studies were performed without bronchodilators, the focus of the results section is on the pre-bronchodilator FEV_1 and DLCO. The post-bronchodilator FEV_1 and DLCO are also briefly discussed.

Results

Approximately 67 subjects out of a planned 250 have been randomized in Study 1030, 35 to the inhaled insulin 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 inhaled insulin for one year.

The inhaled insulin group had more respiratory related SAEs (4) than the SC insulin group (0). The respiratory SAEs in the inhaled insulin group were pneumonia, COPD exacerbation (2), and URI. One subject from each arm discontinued due to an AE. The subject in the inhaled insulin arm discontinued due to a respiratory related AE, COPD exacerbation. Temporary discontinuations were more common in the inhaled insulin group. Respiratory AEs (pneumonia and AECOPD (3)) accounted for about half of the temporary discontinuations in the inhaled insulin treatment group. A similar number of subjects in each treatment group reported respiratory AEs as shown below in Table 58. Increased cough, bronchitis, dyspnea, and voice alteration were more common in the inhaled insulin group than in the SC insulin group.

Table 58 Number of Subjects with Respiratory Related Adverse Events in Study 217-1030 – Interim Results

	Inhaled Insulin 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 inhaled insulin group than in the SC insulin group. The inhaled insulin group had 10 subjects who had 14 non-severe COPD exacerbations and the SC insulin group had 4 subjects who had 9 non-severe COPD exacerbations. For severe COPD exacerbations, the inhaled insulin group had 1 subject with 1 event, while the SC insulin group had none. The number of subjects requiring systemic corticosteroid treatment was slightly higher in the inhaled insulin group. The inhaled insulin group had 5 subjects requiring 6 systemic corticosteroid rescues, while the SC insulin group had 3 subjects requiring 5 systemic corticosteroid rescues [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 inhaled insulin group.

In terms of pulmonary function, the inhaled insulin group has a slightly higher mean 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 observed decline in pre-bronchodilator FEV_1 stabilized from Week 6 to Week 39 in the inhaled insulin group. However, at Week 52, a larger decline in pre-bronchodilator FEV_1 was noted. The decline in pre-bronchodilator FEV_1 was not consistent in the SC insulin group. At Week 52, there was a larger decline in pre-BD FEV_1 in the SC insulin group (145mL) than the inhaled insulin group (127mL) as shown in Table 59.

Table 59 Mean Change from Baseline FEV_1 (Pre-Bronchodilator FEV_1) in Study 1030 – Interim Results

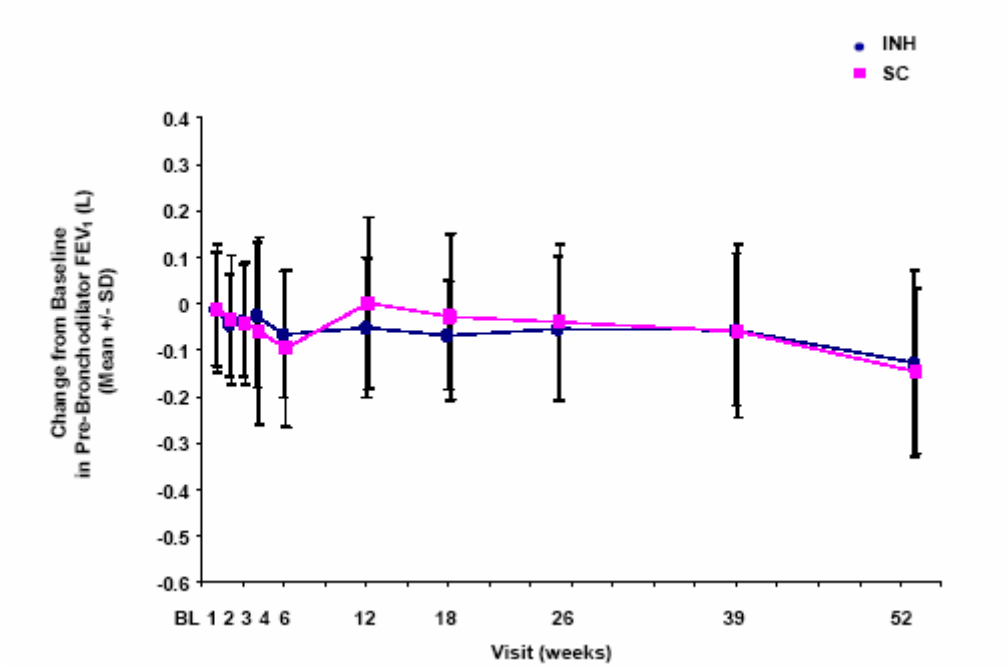
FEV_1 in Liters	Mean Change from Baseline FEV_1 (N)		Mean Treatment Group Difference (95% CI) Unadjusted
	Inhaled Insulin	Comparator	
Baseline	2.088 (35)	2.051 (32)	
Week 1	-0.012 (32)	-0.010 (29)	-0.001 (-0.068, 0.065)
Week 2	-0.045 (29)	-0.035 (30)	-0.010 (-0.076, 0.055)
Week 3	-0.036 (28)	-0.041 (31)	0.006 (-0.060, 0.071)
Week 4	-0.024 (30)	-0.058 (30)	0.034 (-0.059, 0.128)
Week 6	-0.066 (30)	-0.096 (27)	0.030 (-0.051, 0.111)
Week 12	-0.052 (29)	-0.002 (29)	-0.054 (-0.142, 0.035)
Week 18	-0.068 (29)	-0.028 (24)	-0.040 (-0.122, 0.042)
Week 26	-0.054 (27)	-0.039 (21)	-0.015 (-0.109, 0.079)
Week 39	-0.056 (21)	-0.059 (21)	0.003 (-0.108, 0.113)
Week 52	-0.127 (15)	-0.145 (15)	0.017 (-0.125, 0.159)

Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 35-37

In general, the mean treatment group difference did not follow a consistent pattern throughout the treatment period. For the first 6 weeks, the treatment group difference favored the inhaled insulin group. After Week 6, the treatment group difference favored the comparator group. At Week 39, there was no treatment group difference. At Week 52, the treatment group difference (17 mL) again favored the inhaled insulin group;

however, the number of subjects with data towards the end of the treatment period decreases. Figure 45 displays the change from baseline pre- bronchodilator FEV_1 in Study 1030.

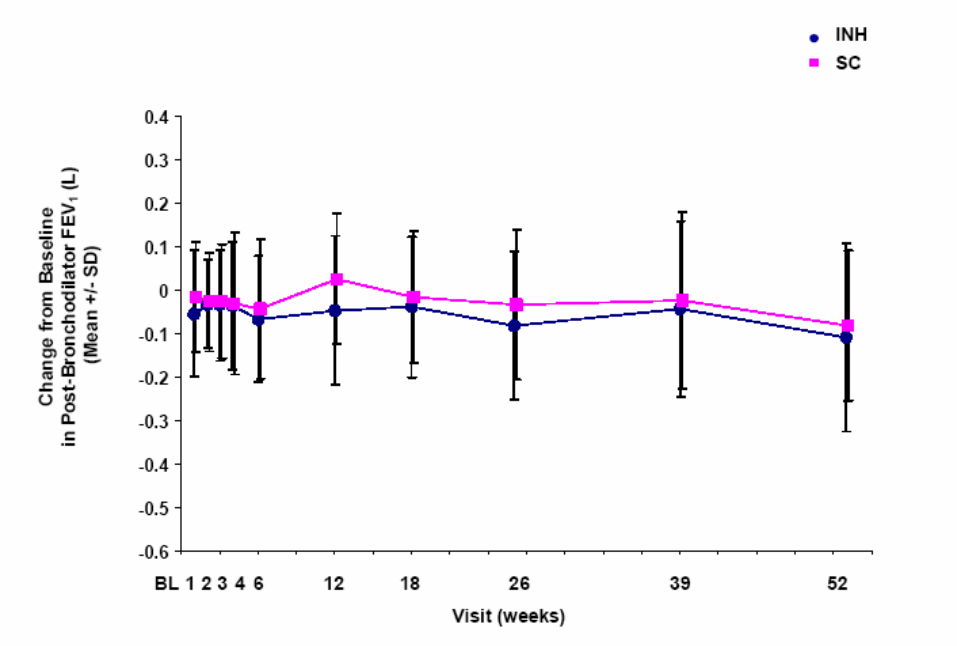
Figure 45 Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) in Study 1030 – Interim Results



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

Reviewer's Comment: The Applicant specified the post-bronchodilator FEV_1 as a primary variable. In general, for the post-bronchodilator FEV_1, the inhaled insulin group demonstrated a larger decline from baseline than the SC insulin group at each time point. At Week 52, the inhaled insulin group demonstrated a decline from baseline post-bronchodilator FEV_1 of 109mL, while the SC insulin group demonstrated a decline of 82mL. Thus, the treatment group difference for change from baseline post-bronchodilator FEV_1 at Week 52 is -27mL, favoring the comparator as shown below in Figure 46.

Figure 46 Mean Change from Baseline in Post-Bronchodilator FEV_1 (L) in Study 1030 – Interim Results



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

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-inhaled insulin mean FEV_1 was less than the pre-inhaled insulin 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-inhaled insulin measurement.

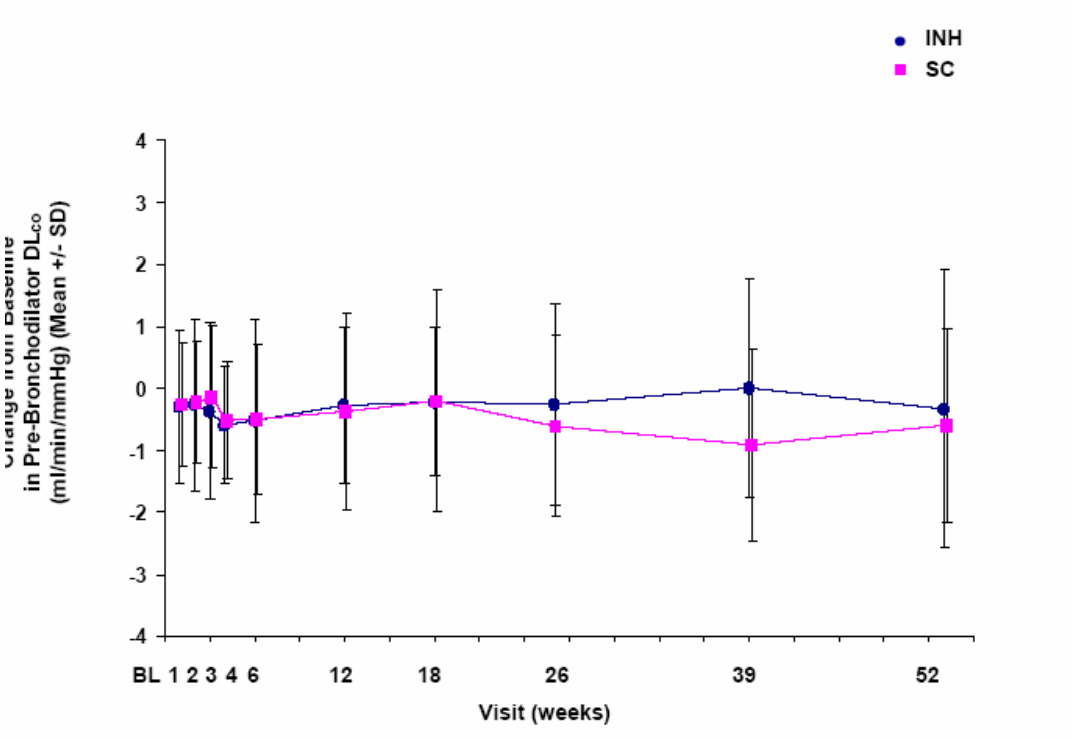
The Applicant also performed a responsiveness analysis for response to bronchodilator. Responsiveness was defined as the difference between the post-BD FEV_1 and the pre-BD FEV_1. The baseline bronchodilator responsiveness was similar between treatment groups. In general, throughout the treatment period,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

Baseline mean pre-bronchodilator DLCO and post-bronchodilator DLCO were similar between treatment groups. Both treatment groups demonstrated a decline in pre-BD DLCO. The pre-bronchodilator DLCO data did not demonstrate a consistent pattern throughout the 52 week treatment period. Initially, the inhaled insulin group demonstrated a larger decline in pre-BD DLCO; however, by Week 12, the SC insulin group demonstrated a greater decline than the inhaled insulin group as shown in Table 60. At Week 52, the inhaled insulin group demonstrated a decline from baseline pre-bronchodilator DLCO of 0.338mL/min/mmHg while the SC insulin group demonstrated a decline from baseline pre-bronchodilator DLCO of 0.606mL/min/mmHg.

Table 60 Mean Change from Baseline DLCO (Pre-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
	Inhaled Insulin	Comparator	
Baseline	19.391 (35)	19.212 (32)	
Week 1	-0.306 (32)	-0.258 (29)	-0.049 (-0.625, 0.527)
Week 2	-0.270 (29)	-0.221 (29)	-0.050 (-0.686, 0.587)
Week 3	-0.367 (27)	-0.149 (31)	-0.218 (-0.898, 0.461)
Week 4	-0.589 (29)	-0.519 (30)	-0.070 (-0.561, 0.421)
Week 6	-0.530 (29)	-0.500 (27)	-0.030 (-0.805, 0.744)
Week 12	-0.273 (27)	-0.369 (28)	0.097 (-0.679, 0.873)
Week 18	-0.226 (27)	-0.197 (24)	-0.029 (-0.879, 0.822)
Week 26	-0.258 (27)	-0.608 (21)	0.350 (-0.561, 1.261)
Week 39	-0.007 (21)	-0.916 (20)	0.909 (-0.143, 1.961)
Week 52	-0.338 (15)	-0.606 (15)	0.268 (-1.180, 1.716)
Source: N21868/N_000/2005-04-26/update/1030_interim_2005.pdf, pg 42			

From Week 26 to Week 52, the treatment group difference favored the inhaled insulin group for the change from baseline pre-bronchodilator DLCO as shown below in Figure 47. At Week 52, the mean unadjusted treatment group difference was 0.268mL/min/mmHg, favoring inhaled insulin.

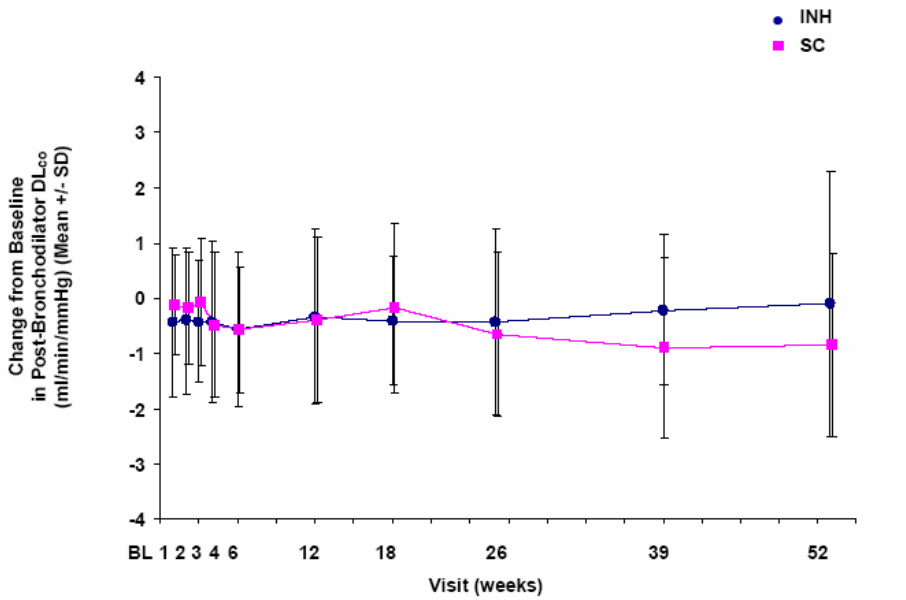
Figure 47 Mean Change from Baseline Pre-Bronchodilator DLCO in Study 1030- Interim Results



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

Reviewer's Comment: As shown below, similar to the pre-bronchodilator DLCO, the pattern of response is not consistent for the post-bronchodilator DLCO. The post-BD DLCO also suggested that at Week 52, the SC insulin group had more of a decline than the inhaled insulin group. In fact, the inhaled insulin group actually demonstrated an increase from baseline post-bronchodilator DLCO at Week 52.

Figure 48 Mean Change from Baseline Post-Bronchodilator DLCO (mL/min/mmHg) in Study 1030



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

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 inhaled insulin 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 inhaled insulin 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 inhaled insulin 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 inhaled insulin on pulmonary safety in subjects with COPD.

The inhaled insulin group had more respiratory related SAEs (4 – pneumonia, COPD exacerbation (2), and URI) than the SC insulin group (0). Respiratory related 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 inhaled insulin group than in the SC insulin group.

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

In terms of pulmonary function, the inhaled insulin 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 observed decline in pre-bronchodilator FEV_1 stabilized from Week 6 to Week 39 in the inhaled insulin group. However, at Week 52, a larger decline in pre-bronchodilator FEV_1 was noted. The decline in pre-bronchodilator FEV_1 was not consistent in the SC insulin group. At Week 52, there was a larger decline in pre-BD FEV_1 in the SC insulin group (145mL) than the inhaled insulin group (127mL). For the post-BD FEV_1, the inhaled insulin group had a larger decline than the SC insulin group throughout the 52 week treatment period. At Week 52, the mean treatment group difference for change from baseline post-BD FEV_1 was -27mL, favoring the comparator.

Mean baseline pre-bronchodilator DLCO and post-bronchodilator DLCO were similar between treatment groups. The pattern of response was not consistent throughout the 52 week treatment period. Both treatment groups demonstrated a decline in pre-BD DLCO. Initially, the inhaled insulin group demonstrated a larger decline in pre-BD DLCO; however, by Week 12, the SC insulin group demonstrated a greater decline than the inhaled insulin group. At Week 52, the inhaled insulin group demonstrated a decline from baseline pre-bronchodilator DLCO of 0.338mL/min/mmHg while the SC insulin group demonstrated a decline from baseline pre-bronchodilator DLCO of 0.606mL/min/mmHg with a treatment group difference of 0.268 mL/min/mmHg, favoring the inhaled insulin group. The post-BD DLCO also suggested that at Week 52, the SC insulin group had more of a decline than the inhaled insulin group. In fact, the inhaled insulin group actually demonstrated an increase from baseline post-bronchodilator DLCO at Week 52.

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.

6.1.3.2 Retrospectively Defined COPD

As discussed above in the Methods Section 6.1.1, the Applicant *retrospectively identified* 101 subjects with COPD in the Controlled ULD Cohort. This section includes a brief review of the pertinent findings in the 101 subjects retrospectively identified with COPD in the controlled phase 2/3 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 inhaled insulin.

Of the 101 subjects retrospectively identified with COPD, 50 were treated with inhaled insulin 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 inhaled insulin is available for only 51 subjects.

There were no respiratory related deaths in subjects retrospectively identified with COPD. Thirteen subjects were noted to have serious adverse events (7 in the inhaled insulin group and 6 in the comparator group). Two of the SAEs in the inhaled insulin group were respiratory related – epistaxis and vocal cord polyp. The number of subjects with overall AEs and respiratory related 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 inhaled insulin group than subjects in the comparator group as shown below in Table 61 [N21868/N_000/2004-12-26/clinstat/pulm.pdf, pg 247, 1185-1191].

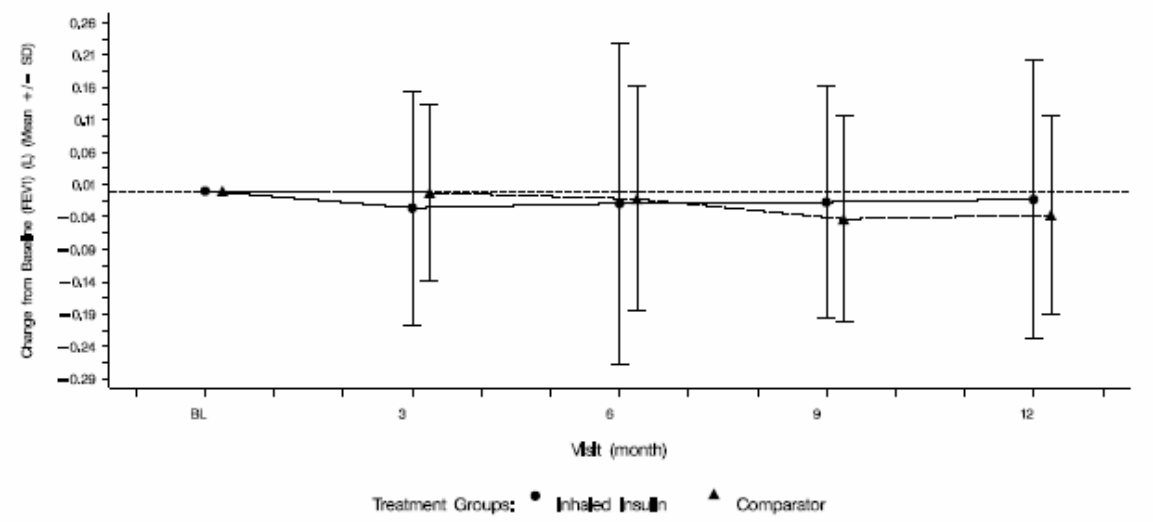
Table 61 Number of Subjects with Respiratory Related Adverse Events in Subjects Retrospectively Identified with COPD		
	Inhaled Insulin n = 50	Comparator n = 51
Any adverse event	48 (96%)	47 (92.2%)
Respiratory	17 (70.8%)	20 (66.7%)
Asthma, including asthma exacerbation	1 (2.0%)	3 (5.9%)
Bronchitis	**2 (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		

Mean baseline FEV_1 was lower in the inhaled insulin group than in the comparator group. Initially, the inhaled insulin group demonstrated a greater mean decline from baseline FEV_1 than subjects in the comparator group as shown below in Table 62. However, after 6 months, the comparator group demonstrated a greater decline from baseline FEV_1 through 12 months. At 12 months, the inhaled insulin group demonstrated a decline from baseline FEV_1 of 13mL while the comparator group demonstrated a decline from baseline FEV_1 of 37mL.

Table 62 Mean Change from Baseline FEV_1 (L) in Subjects Retrospectively Identified with COPD		
FEV_1 (L)	Mean Change from Baseline FEV_1 (N)	
	Inhaled Insulin	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 49 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 inhaled insulin group.

Figure 49 Mean Change from Baseline FEV_1 (L) in Subjects Retrospectively Identified with COPD



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

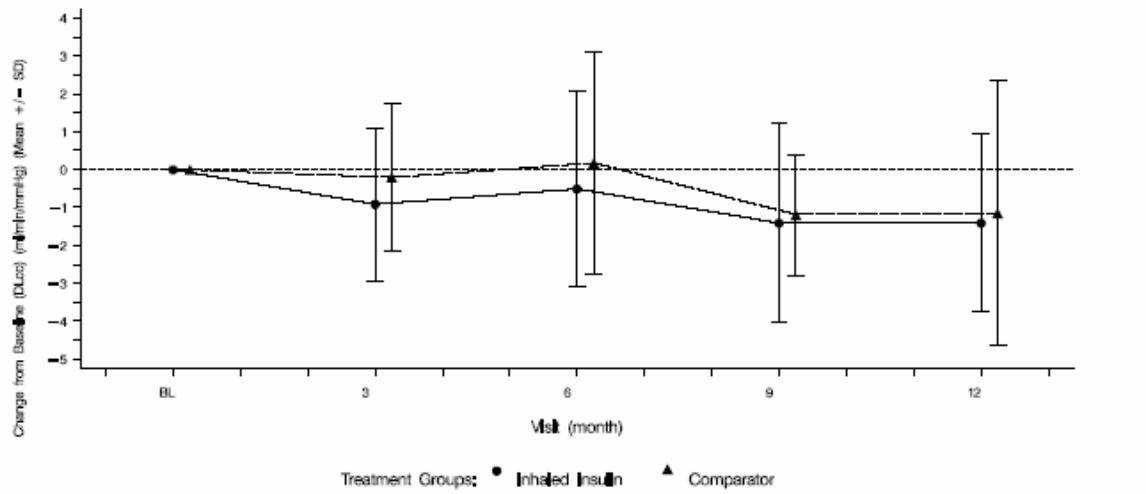
Mean baseline DLCO was lower in the inhaled insulin group than in the comparator group. The inhaled insulin group demonstrated a greater decline from baseline DLCO than subjects in the comparator group throughout the treatment period as shown below in Table 63. After 12 months, the inhaled insulin group 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 63 Mean Change from Baseline DLCO (mL/min/mmHg) in Subjects Retrospectively Identified with COPD

DLCO (mL/min/mmHg)	Mean Change from Baseline DLCO (N)	
	Inhaled Insulin	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 50 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 50 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

The data from the 101 subjects retrospectively identified with asthma provides limited information about the long term safety of inhaled insulin in subjects with COPD.

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

Baseline FEV_1 was lower in the inhaled insulin group than in the comparator group. Initially, the inhaled insulin 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 inhaled insulin 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 inhaled insulin group than in the comparator group. The inhaled insulin group demonstrated a greater decline from baseline DLCO than subjects in the comparator group throughout the treatment period. After 12 months, the inhaled insulin 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.

6.1.3.3 Conclusions

Inhaled insulin has an effect on pulmonary function in subjects without underlying lung disease. Thus, the Agency requested the Applicant prospectively assess the effects of inhaled insulin in subjects with COPD. Data regarding the pulmonary safety of inhaled insulin in subjects with COPD comes from two sources: the ongoing Study 1030 and a cohort of retrospectively identified subjects with COPD in the controlled phase 2/3 studies. Of these two sources, Study 1030 provides the best source of data because Study 1030 was specifically designed to prospectively assess the effects of inhaled insulin in subjects with COPD. The Applicant also retrospectively identified 101 subjects with COPD who participated in the controlled phase 2/3 studies. Data from the retrospectively identified cohort is less robust because the diagnosis of COPD is based upon a retrospective diagnosis of COPD (history of smoking and $FEV_1/FVC < 70\%$ at baseline).

Study 1030

Study 217-1030 is an ongoing 15 month controlled study which provides data on 72 subjects with COPD; however, 12 month PFT data is only available for 30 subjects. The results from Study 1030 indicate that the inhaled insulin group had more respiratory related SAEs (4) than the SC insulin group (0). The respiratory SAEs in the inhaled insulin group were pneumonia, COPD exacerbation (2), and URI. 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 asthma. Of the respiratory AEs reported in Study 1030, bronchitis, increased cough, dyspnea, and voice alteration were reported in more than one subject and in more subjects treated with inhaled insulin than subjects treated with the comparator.

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

The interim PFT data from Study 1030 indicates that subjects in both treatment groups demonstrate a mean decline from baseline FEV_1 (pre-BD) at Week 52. At Week 52, the inhaled insulin group had a mean decline from baseline FEV_1 of 127mL, while the comparator group had a mean decline from baseline FEV_1 of 145mL. The decline in FEV_1 at Week 52 is greater than the expected annual rate of decline in FEV_1 for subjects with COPD – a decline of FEV_1 of approximately 45mL/year.[4] At Week 52, the mean treatment group difference for change from baseline pre-BD FEV_1 favored the inhaled insulin group (17mL). For the post-BD FEV_1, the inhaled insulin group had a larger decline than the SC insulin group throughout the 52 week treatment period. The treatment group difference was -27 mL at Week 52 for the post-BD FEV_1, favoring the comparator. It should be noted that the Week 52 data is based upon 30 subjects.

Both treatment groups demonstrated a mean decline in pre-BD DLCO. Initially, the inhaled insulin group demonstrated a larger mean decline in pre-BD DLCO; however, by Week 12, the SC insulin group demonstrated a greater mean decline than the inhaled insulin group. At Week 52, the inhaled insulin group demonstrated a decline from baseline pre-bronchodilator DLCO of 0.338mL/min/mmHg while the SC insulin group demonstrated a decline from baseline pre-bronchodilator DLCO of 0.606mL/min/mmHg. Thus, at Week 52, the treatment group difference favored the inhaled insulin group. The post-BD DLCO also suggested that at Week 52 the SC insulin group had more of a decline than the inhaled insulin group. In fact, the inhaled insulin group actually demonstrated an increase from baseline post-bronchodilator DLCO at Week 52. It should be noted that the Week 52 data is based upon 30 subjects.

Retrospectively Identified Subjects with COPD
In the 101 subjects retrospectively identified with COPD, the number of subjects with overall AEs, SAEs, and respiratory related AEs was similar between treatment groups. Two of the SAEs in the inhaled insulin group were respiratory related – epistaxis and vocal cord polyp. Bronchitis, increased cough, dyspnea, epistaxis, pharyngitis, respiratory disorder, sinusitis, and sputum increased were reported in more than one subject and in a higher percentage of subjects in the inhaled insulin group than subjects in the comparator group.

The PFT data from the 101 subjects retrospectively identified with COPD indicate that the treatment group difference is not consistent during the treatment period. Initially, the inhaled insulin 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 inhaled insulin group demonstrated a decline from baseline FEV_1 of 13mL while the comparator group demonstrated a decline from baseline FEV_1 of 37mL, favoring the inhaled insulin group.

The inhaled insulin group demonstrated a greater decline from baseline DLCO than subjects in the comparator group throughout the treatment period. At 12 months, the inhaled insulin 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.

6.2 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 inhaled insulin 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 inhaled insulin, but the amount of information is not enough to draw definitive conclusions regarding the safety of inhaled insulin in the pediatric population. The pulmonary safety results of Study 1009 are briefly discussed here.

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 related adverse events in the SC insulin group than in the inhaled insulin group. However, cough increased, asthma, and dyspnea were reported in more subjects in the inhaled insulin group than in the SC insulin group. All of the respiratory adverse events were mild in severity. None of the SAEs were respiratory related. Of the respiratory AEs more common in the inhaled insulin group, increased cough was the most common. A total of 31 cough events were reported in the inhaled insulin group compared to 4 in the SC insulin group. In the inhaled insulin 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 inhaled insulin group discontinued due to increased cough.

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 inhaled insulin group demonstrated a larger decrease from baseline DLCO than the SC insulin group as shown in Table 64. A categorical analysis of the change in pulmonary function testing suggests that the inhaled insulin group had more subjects with >10% decrease in DLCO and $FEF_{25-75\%}$ than the SC insulin group.

Table 64 Mean Change from Baseline Pulmonary Function Tests in Study 217-1009

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

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 long term PFT trends.

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

Reviewer's Comment: Of note, one respiratory SAE was noted in a 13 year old male in Study 111 (extension of Study 106, 107, 108). (Study 111, Subject 50826090). 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.

7 Overall Assessment

7.1 Conclusions

Please refer to the Executive Summary for the conclusions of this consultation.

8 Appendices

8.1 Discontinuations Due to Respiratory Related AEs

The following are brief summaries of subjects who discontinued inhaled insulin therapy due to respiratory related AEs in the controlled phase 2/3 studies.

Table 65 Listing of Discontinuations due to Respiratory Adverse Events
Adult Controlled Phase 2/3 Studies in Type 1 Diabetes

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

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

Table 66 Listing of Discontinuations due to Respiratory Adverse Events
Adult Controlled Phase 2/3 Studies in Type 2 Diabetes

Study #	Patient ID #	Age	Treatment	Study Day	COSTART Preferred Term Respiratory Body System
Type 2 Diabetes					
1001	00180060	62	Inhaled Insulin	78, 311	Cough Increased
1001	00490107	56	Inhaled Insulin	61	Bronchitis
1001	01412043	44	Inhaled Insulin	546, 548	Asthma

Table 66 Listing of Discontinuations due to Respiratory Adverse Events

Adult Controlled Phase 2/3 Studies in Type 2 Diabetes

Study #	Patient ID #	Age	Treatment	Study Day	COSTART Preferred Term Respiratory Body System
1002	00255050	46	Inhaled Insulin	2	Respiratory Disorder (lung pain)
1002	00375063	69	Inhaled Insulin	276, 303, 359, 459	Asthma
1002	00477049	35	Inhaled Insulin	342, 367	Cough Increased
1002	00485005	68	Inhaled Insulin	8, 36	Cough Increased
1002	00745150	48	Inhaled Insulin	179, 212, 254, 318, 338	Cough Increased
1002	01086285	64	Inhaled Insulin	256, 361	Dyspnea
1002	01106223	54	Inhaled Insulin	13	Respiratory tract infection, sputum increased
1002	01195236	65	Inhaled Insulin	673	Carcinoma of the lung
1002	01345269	59	Inhaled Insulin	15, 22	Cough Increased
1002	01417404	39	Inhaled Insulin	111	Dyspnea
1002	01418036	66	Inhaled Insulin	153, 163	Cough Increased
1002	01418036	66	Inhaled Insulin	197, 198	Cough Increased, Dyspnea
1002	01427408	43	Inhaled Insulin	600, 632, 716	Cough Increased, Dyspnea
103	50020002	60	Inhaled Insulin	32, 57	Cough Increased
108	50260133	70	Inhaled Insulin	1, 9, 15, 50	Respiratory tract infection
109	50430031	65	Inhaled Insulin	75	Dyspnea
110	51031426	56	Inhaled Insulin	3, 58	Bronchitis
1029	10251913	64	Inhaled Insulin	258, 292, 298, 302	Asthma, Dyspnea
1029	1029788	65	Inhaled Insulin	90	Cough Increased
1029	10452319	21	Inhaled Insulin	2, 8, 21	Asthma, Respiratory Tract Infection
1029	10652783	58	Inhaled Insulin	2	Cough Increased, Respiratory Disorder (irritation in the lungs)
1029	10681197	56	Inhaled Insulin	296	Asthma
1029	10833445	58	Inhaled Insulin	61, 72, 49, 73, 61	Asthma, Cough Increased, Dyspnea
1029	10853552	50	Inhaled Insulin	45, 51	Dyspnea, Respiratory Disorder (Acute Respiratory Failure)
1029	10883612	58	Inhaled Insulin	457	Cough Increased
1029	11054681	45	Inhaled Insulin	100	Pharyngitis
1029	11135158	67	Inhaled Insulin	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]

8.2 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
  - 75 year old male on inhaled insulin for 541 days; reason for HRCT not listed
  - HRCT interpreted as COPD, some fibrotic honeycombing in the lower lobes bilaterally, subpleural parenchymal scarring;
  - 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
  - 39 year old male on inhaled insulin for 511 days; reason for HRCT was shortness of breath and decreased pulmonary function testing
  - HRCT interpreted as hyperinflation with mild emphysematous changes
- 104 50130077
  - 67 year old female on inhaled insulin for 2005 days; reason for HRCT not listed
  - 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
  - 62 year old male on inhaled insulin for 698 days; reason for HRCT not listed; 3 HRCTs performed
  - Bronchiectasis noted on first HRCT, which was unchanged on repeat HRCTs
- 107 50297599
  - 57 year old female on inhaled insulin for 826 days; reason for HRCT was for nodule
  - HRCT interpreted as 8mm nodule, which was stable on follow up 7 months later
- 109 50280694
  - 56 year old male on inhaled insulin for 824 days; reason for HRCT was chronic cough/asthma
  - 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
  - 35 year old female on inhaled insulin for 682 days; reason for HRCT was bilateral hilar fullness
  - HRCT interpreted as mediastinal adenopathy; bilateral upper lobe subpleural intralobular ill-defined nodules; suggestive of sarcoidosis
- 106 50536783
  - 54 year old male on inhaled insulin for 869 days; HRCT for decreased pulmonary function tests
  - HRCT interpreted as minimal scarring or atelectasis in lung bases

- 108 50488404
    - 59 year old male on inhaled insulin for 826 days; reason for HRCT not listed
    - 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].