Table 3: Analysis Population for Type 2 Data

PFT	Study	Treatment Duration (in weeks)	Number of Subjects		Overall		
			INH	Comparator	Week	INH	Comparator
DLco	103	12	27	28	12	644	530
	104	12	33	36	24	896	866
	108	24	146	147	36	305	301
	109	12	205	98	48	750	719
	110	12	74	67	65	445	418
	1001	24, 48, 65, 78, 91, 104, 110, 116	221	202	78	445	418
	1002	24, 48, 65, 78, 91, 104, 110, 116	224	216	91	445	418
	1029	12, 24, 36, 48	305	301	104	445	418
					110	445	418
					116	445	418
FEV	103	12	28	28	12	798	682
	104	12	33	36	24	926	890
	108	12, 24	149	149	36	777	741
	109	12	207	99	48	777	741
	110	12	75	68	65	471	439
	1001	24, 36, 48, 65, 78, 91, 104, 110, 116	232	209	78	471	439
	1002	24, 36, 48, 65, 78, 91, 104, 110, 116	239	230	91	471	439
	1029	12, 24, 36, 48	306	302	104	471	439
					110	471	439
					116	471	439
FRC	103	12	28	28	12	643	527
	104	12	30	33	24	911	877
	108	24	149	148	36	762	729
	109	12	206	99	48	762	729
	110	12	73	66	65	456	428
	1001	24, 36, 48, 65, 78, 91, 104, 110, 116	226	205	78	456	428
	1002	24, 36, 48, 65, 78, 91, 104, 110, 116	230	223	91	456	428
	1029	12, 24, 36, 48	306	301	104	456	428
					110	456	428
FVC	103	12	28	28	12	798	682
	104	12	33	36	24	925	889
	108	12, 24	149	149	36	776	740
	109	12	207	99	48	776	740
	110	12	75	68	65	470	438
	1001	24, 36, 48, 65, 78, 91, 104, 110, 116	231	208	78	470	438
	1002	24, 36, 48, 65, 78, 91, 104, 110, 116	239	230	91	470	438
	1029	12, 24, 36, 48	306	302	104	470	438
					110	470	438
					116	470	438
TLC	103	12	28	28	12	649	532
	104	12	33	36	24	922	885
	108	24	149	149	36	773	736
	109	12	207	99	48	773	736
	110	12	75	68	65	467	435
	1001	24, 36, 48, 65, 78, 91, 104, 110, 116	232	208	78	467	435
	1002	24, 36, 48, 65, 78, 91, 104, 110, 116	235	227	91	467	435
	1029	12, 24, 36, 48	306	301	104	467	435
					110	467	435
					116	467	435

3.2.2 DETAILED REVIEW OF POOLED TYPE 1 AND POOLED TYPE 2 STUDIES

For the purposes of evaluating the pulmonary safety of INH, protocols were grouped and their data pooled according to study completion status and the population under study. The first part of this section will focus mainly on the pooled Type 1 data, and the second part of this section will focus of Pooled Type 2 data. One of the goals of this section is to discuss and evaluate overall pulmonary safety of Exubera on adults with either Type 1 or Type 2 diabetes mellitus. This will include pooled analysis of the pulmonary function tests, pooled discussion of the respiratory adverse events, and lastly, the relations between the pulmonary function tests and antibody titers, as well as with the insulin dosing. Note that my interpretations of findings are based wholly on statistical interpretation of the results. **I defer all clinical interpretations to Dr. Seymour's review.** This section is divided into two parts based on the type of diabetes.

I. Type 1 Data

Study Design:

The design of all the controlled Phase 2/3 studies in both male and female age 18 – 65 years with Type 1 diabetes mellitus are open-label, randomized, parallel group, outpatients studies with a 4-week run-in period (Table 4). Following a 4-week baseline period during which all patients received subcutaneous (SC) insulin, subjects were randomized to either three months, six months, 1 year, or 2 years (depending on the study protocol) treatment period with either inhaled (INH) with or without subcutaneous basal insulin, or subcutaneous short-acting or long-acting (SC) insulin. Subjects underwent battery of pulmonary function tests (including spirometry, lung volumes and diffusion capacity) at the run-period (for baseline values), weeks 12, 24, 36, 48, 60, 72, 84, or 96, or end of study, depending on the length of the trial, as well as at months 1, 3, or 6, post-study completion or discontinuation (Study 1022).

Demographic Characteristics:

Demographic characteristics of subjects in the pooled Type 1 data are comparable between the two treatment groups. Majority of the subjects was white. There appears to be more males in each of the treatment group across all studies. The male subjects were heavier and taller than females in each of the treatment group. Age appears to be comparable between males and females (Table 5).

Respiratory Adverse Events:

Respiratory adverse events by individual studies are presented in Table 6. In the pooled analysis, the number of subjects with respiratory events was higher in the inhaled insulin group compared to the comparator group (Figure 1). Using preferred COSTART term and severity for all-causality adverse events, the proportion of subjects with respiratory system adverse events was generally slightly higher in the inhaled insulin group than the comparator groups, particularly increased cough (INH 28% vs. Comparator 8%). There were also more subjects in the inhaled insulin group with dyspnea, rhinitis, respiratory disorder, pharyngitis, and sinusitis than the comparator group (Figure 2). The most common respiratory system adverse event was respiratory tract infection and this was comparable between the two treatment groups.

Almost all respiratory system adverse events were either mild or moderate in severity. There are a total of 11 subjects out of 698 (2%) who **permanently discontinued** due to respiratory events (Table 7). These events include increased cough, respiratory disorder, sinusitis, sputum increased, dyspnea, rhinitis, pharyngitis, laryngitis, and asthma. Most of these events were considered mild to moderate except for one subject with severe asthma and one subject with severe cough increased. None permanently discontinued in the comparator group

Table 4: Study Design of Adult Type 1 (DM) Data

Study	Design	Treatment groups	PFT measurements Treatment Duration (in weeks)	Number of Subjects	
				INH	Comparator
102	Open-label, randomized, parallel group	Pre-meal (TID) INH plus bedtime SC Ultralente vs. conventional Subcutaneous insulin (SC), BID or TID	12	35	37
106	Open-label, randomized, parallel group	Pre-meal (TID) INH plus bedtime SC Ultralente vs. conventional Subcutaneous insulin (SC), BID	24	135	134
107	Open-label, randomized, parallel group	Pre-meal (TID) INH plus NPH injectible insulin in AM and at bedtime vs. conventional Subcutaneous insulin (SC), BID	24	102	105
1022	Open-label, randomized, parallel group	Pre-meal (TID) INH plus either SC Ultralente at bedtime, insulin glargine at bedtime, or NPH injectible insulin in AM and at bedtime vs. conventional SC at BID or TID plus either SC Ultralente at bedtime, insulin glargine at bedtime, or NPH injectible insulin in AM and at bedtime	12, 24, 36, 48, 60, 72, 84, 96 Washout period: 6 weeks and 12 weeks after month 24.	290	290
1026	Prospective, open-label, randomized, parallel group	Pre-meal (TID) INH insulin plus Insuman Basal (NPH) BID vs. pre-meal (TID) SC Insuman rapid plus Insuman Basal (NPH) BID	12, 24	23	22
1027	Open-label, randomized, parallel group	Pre-meal (TID) INH plus either SC Ultralente at bedtime, insulin glargine at bedtime, or NPH injectible insulin in AM and at bedtime vs. conventional SC at BID or TID plus either SC Ultralente at bedtime, insulin glargine at bedtime, or NPH injectible insulin in AM and at bedtime	12	99	103

Source: Study Report 217-102, 106, 107, 1022, 1026, 1027

Table 5: Mean Demographic Characteristics of Adults Type 1 Data (SD)

Variables	Inhaled Insulin		Comparator	
	Male	Female	Male	Female
No. of Subjects*	385	302	377	315
Age (years)	38 (10.4)	38 (10.9)	38 (10.5)	37 (11.4)
Race (White)	341 (89%)	265 (88%)	344 (91%)	287 (91%)
Weight (kg)	83 (12.4)	66 (9.3)	81 (11.9)	67 (9.9)
Height (cm?)	179 (7.5)	164 (6.5)	178 (7.7)	164 (6.5)
BMI	26 (2.9)	25 (3.1)	26 (2.9)	25 (3.4)

* No. of Subjects are slightly smaller than the total number who were randomized in the studies. Includes only subjects who were treated and have PFT measurements.

Table 6: Number of subjects (%) with Respiratory adverse events for all Adults Type 1 DM Subjects: All Causality

	Study 102		Study 106		Study 107		Study 1022		Study 1026		Study 1027	
	INH	Comp	INH	Comp	INH	Comp	INH	Comp	INH	Comp	INH	Comp
No. of Subjects	35	37	137	136	103	105	290	290	23	22	110	116
Total Respiratory	19 (54)	18 (49)	95 (69)	84 (62)	77 (75)	61 (58)	242 (83)	202 (70)	11 (48)	12 (55)	71 (65)	51 (44)
Asthma	0	1 (3)	1 (1)	2 (1)	2 (2)	0	3 (1)	4 (1)			1 (1)	1 (1)
Bronchiolitis							1 (0)	0				
Bronchitis	0	1 (3)	4 (3)	4 (3)	3 (3)	3 (3)	9 (3)				3 (3)	2 (2)
Cough Increased	5 (14)	3 (8)	33 (24)	7 (5)	21 (20)	4 (4)	99 (34)	36 (12)	1 (4)		34 (31)	9 (8)
Dyspnea			4 (3)	1 (1)	3 (3)	1 (1)	17 (6)	2 (1)				
Edema Pharynx							18 (6)	2 (1)			2 (2)	
Epistaxis			4 (3)	1 (1)	1 (1)	0	0		4 (17)	0	0	1 (1)
Hyperventilation					0	1 (1)	4 (1)	1 (0)			1 (1)	0
Hypoventilation								1 (0)			1 (1)	0
Laryngitis	1 (3)	0	2 (1)	1 (1)			4 (1)	1 (0)			1 (1)	1 (1)
Lung Edema							0	1 (0)				
Nasal Polyp							1 (0)	1 (0)				
Pharyngitis	5 (14)	5 (14)	22 (16)	19 (14)	25 (24)	19 (18)	52 (18)	45 (16)	1 (4)	3 (14)	18 (16)	12 (10)
Pleural Disorder				3 (2)	2 (2)	0	1 (0)	0				
Pneumonia							3 (1)	4 (1)				
Respiratory Disorder	3 (9)	1 (3)	10 (7)	8 (6)	6 (6)	3 (3)	22 (8)	13 (5)			4 (4)	2 (2)
Respiratory Distress Syndrome							0	1 (0)				
Respiratory Tract Infection	8 (23)	12 (32)	54 (39)	50 (37)	46 (45)	36 (34)	146 (50)	142 (49)	7 (30)	11 (50)	29 (26)	28 (24)
Rhinitis	3 (9)	2 (5)	18 (13)	15 (11)	9 (9)	8 (8)	51 (18)	33 (11)			15 (14)	9 (8)
Sinusitis	3 (9)	1 (3)	11 (8)	7 (5)	7 (7)	10 (10)	37 (13)	27 (9)	2 (9)	0	4 (4)	3 (3)
Sputum Increased			5 (4)	4 (3)	4 (4)	0	14 (5)	1 (0)			4 (4)	3 (3)
Voice Alteration							1 (0)	1 (0)				
Yawn							1 (0)	1 (0)				

Source: Study Report 217-102, 106, 107, 1022, 1026, 1027

Figure 1: Percentage of Subjects with at least one respiratory adverse events in the Individual and Pooled Studies in Controlled Phase 2/3 Type 1 Adults by Treatment Groups
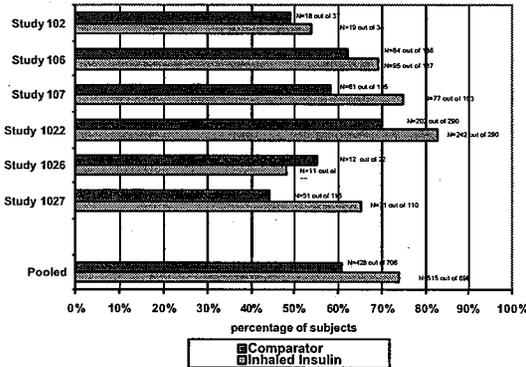
Figure 2: Respiratory Adverse Events by Treatment Group, Pooled Type 1 Controlled Phase 2/3 Studies
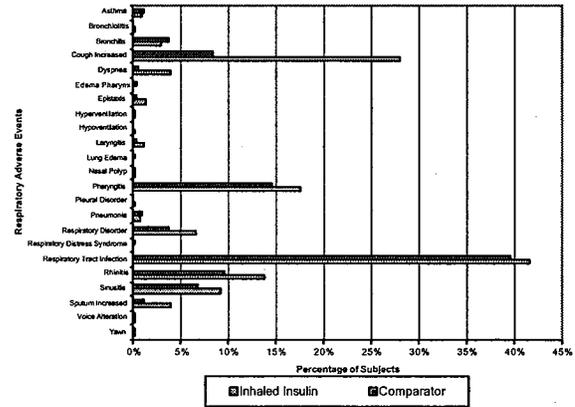

Table 7: Respiratory Adverse Events Resulting in Permanent Discontinuation from Individual Study

Study	Treatment Group	Subject	Severity	Adverse Event Preferred COSTART/Investigator Term
106	INH	5055 6135	Mild	Cough Increased
107	INH	5102 7141	Moderate	Respiratory Disorder including cough, wheezing and pulmonary obstruction
1022	INH	1005 241	Mild	Sinusitis
			Mild	Sputum Increased/Productive Cough
		1017 949	Mild	Cough Increased/Dry Cough
		1025 1425	Moderate	Dyspnea/Shortness of Breath
		1047 2728	Mild	Cough increased
			Mild	Dyspnea
			Mild	Respiratory Disorder/Decreased DLco
			Mild	Rhinitis/Nasal congestion
		5074 3085	Moderate	Cough increased/dry cough
			Moderate	Dyspnea/Shortness of breath
			Moderate	Asthenia/Weak Feeling
		5156 3797	Mild	Cough increased
			Moderate	Pharyngitis/sore throat
1027	INH	1004 154	Severe	Cough Increased/Cough
			Mild	Laryngitis
			Mild	Pharyngitis/Throat Irritation
		1006 249	Severe	Asthma/Reactive airways disease
		1006 251	Moderate	Cough increased/non-productive cough

Source: Study Report 217-102, 106, 107, 1022, 1026, 1027

Chest X-ray and Thoracic High Resolution Computed Tomography (HRCT)

In the four Type 1 DM clinical studies with chest X-ray (Studies 106, 107, 1022, 1027), only a very small proportion of subjects who had chest X-rays taken at final observation had abnormal findings compared to baseline. However, it appears that the incidences of change in chest x-ray results between baseline and last observation were numerically greater in the INH than the comparator treatment groups (INH 12, Comparator 9).

In terms of HRCT, only selected sites, from the two Type 1 DM clinical studies (Study 106 and Study 107), had HRCT scan. It appears that there is only one subject in the inhaled insulin group with more abnormal HRCT, while there are four (three from Study 106 and one from Study 107) in the comparator group who had more abnormal HRCT scan. Summary of the abnormal HRCT scan is also available upon request.

Pulmonary Function Test:

One of the main objectives of the Phase 2/3 clinical studies was to determine the safety and potential (early) effects of INH insulin on lung function as measured by pulmonary function tests (PFT). This was achieved by comparing the treatment effect (change from baseline) of inhaled insulin to the comparator group over time, as well as the response rates over time. The applicant defined response as the decline in PFT results relative to a baseline intra-subject variation criterion; the response rate was the percentage of evaluable subjects who met the response criteria.

In Type 1 Adults studies, pulmonary function was monitored in Studies 102, 106, 107 using non-standardized methodologies available in local PFT laboratories. These studies were short-term studies, usually 3 or 6 months of exposure. Pulmonary function has also been monitored in studies (1026, 1027, and updated 2-year data of Study 1022), in which standardized pulmonary testing equipment, testing procedures, and centralized data analysis were used to measure PFTs.

As noted earlier, to simplify the discussion of pulmonary safety, subjects are grouped based on the treatment actually received. Subjects treated with INH with or without subcutaneous basal insulin, or oral anti-diabetic agents (OAs) are considered to be INH- treated subjects. Subjects treated with subcutaneous short-acting (SC) insulin or with OAs alone are considered to be Comparator-treated subjects. All subjects with Type 1 DM received basal insulin in addition to INH or SC insulin.

To begin, comparison of the mean baseline values between the two treatment groups and the percent predicted at baseline are presented in Table 8 (for the individual and pooled studies). It appears that mean baseline values are comparable between the treatment groups across all the individual and pooled studies and all five pulmonary function tests. Other than Study 102, the % predicted mean values at baseline are also comparable between the treatment groups across the individual and pooled studies and five different pulmonary function tests. In Study 102, it appears that the mean percent predicted value at baseline of the comparator is slightly higher than that of the inhaled insulin group (e.g. 7% higher in DLco, 3% higher in TLC).

Table 8: Baseline PFT Measurements and Percent Predicted Mean Values at Baseline in Controlled Phase 2/3 Studies in Adults Type 1Diabetes
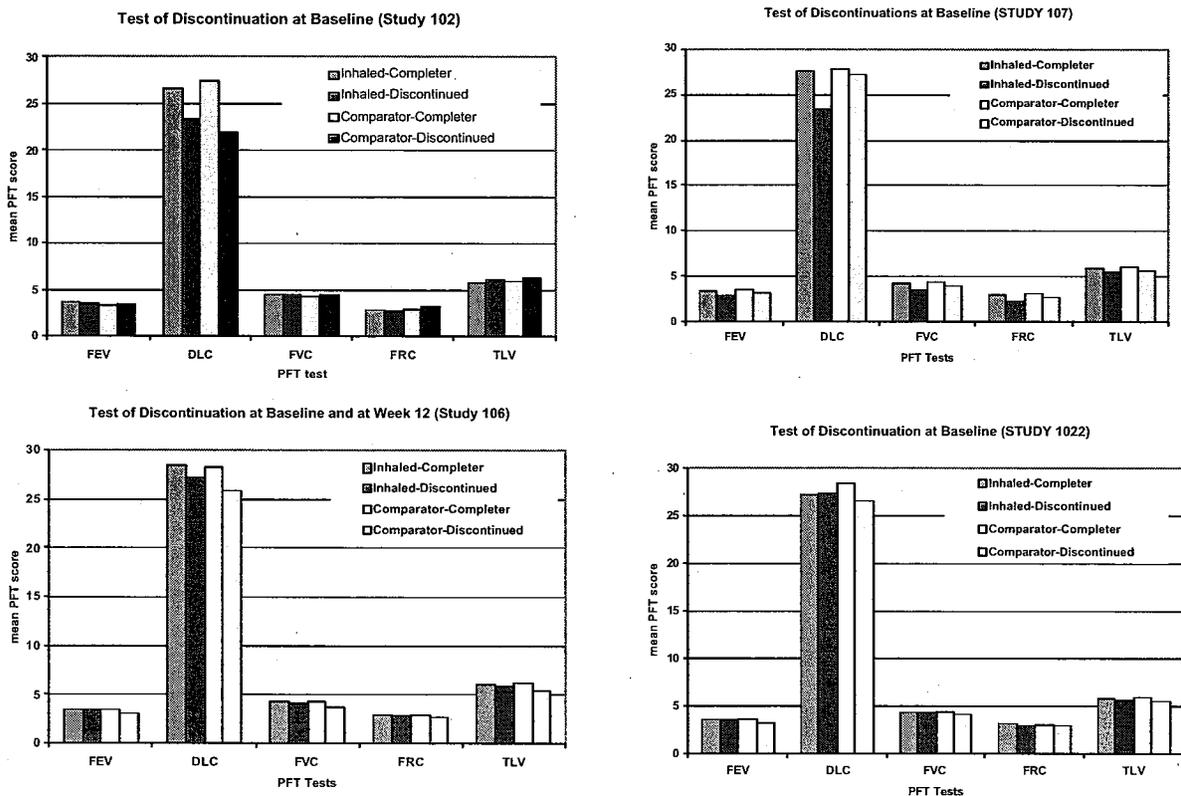
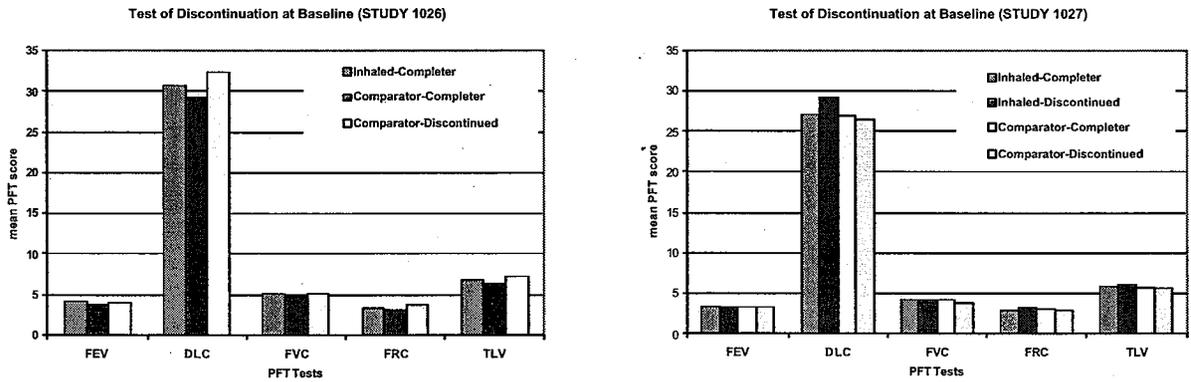| Study	Variables	N*	INH Mean % Predicted (SD)	Mean (SD)	N*	Comparator Mean % Predicted (SD)	Mean (SD)
102	FEV1	35	98.04 (11.5)	3.58 (0.8)	37	97.80 (14.7)	3.37 (0.7)
	FVC	35	97.63 (12.1)	4.43 (1.1)	37	99.74 (14.5)	4.27 (1.0)
	DLco	35	93.57 (7.7)	26.50 (7.7)	37	100.37 (19.8)	27.17 (7.4)
	FRC	35	85.92 (19.2)	2.83 (0.9)	35	88.47 (16.7)	2.90 (0.8)
	TLC	35	93.3 (13.1)	5.83 (1.5)	35	96.17 (11.1)	5.87 (1.2)
106	FEV1	136	98.29 (12.5)	3.50 (0.8)	135	97.15 (13.6)	3.47 (0.8)
	FVC	136	99.42 (12.2)	4.32 (1.0)	135	98.90 (14.2)	4.31 (1.1)
	DLco	135	97.71 (16.9)	28.34 (6.8)	134	98.17 (17.5)	28.08 (6.4)
	FRC	136	92.26 (21.9)	2.98 (1.0)	135	91.56 (20.4)	2.98 (0.8)
	TLC	136	98.85 (12.0)	6.05 (1.4)	135	99.34 (13.0)	6.09 (1.4)
107	FEV1	103	96.60 (12.4)	3.39 (0.8)	105	98.03 (15.0)	3.48 (0.8)
	FVC	103	97.39 (12.7)	4.23 (1.0)	105	98.19 (14.5)	4.32 (1.1)
	DLco	102	96.55 (15.0)	27.48 (7.0)	105	96.74 (16.4)	27.72 (7.3)
	FRC	103	92.82 (21.4)	3.00 (0.9)	104	93.71 (24.4)	3.06 (0.9)
	TLC	103	97.48 (12.6)	5.93 (1.3)	105	97.84 (15.1)	6.02 (1.4)
1022	FEV1	290	92.99 (10.8)	3.49 (0.8)	290	93.25 (10.8)	3.48 (0.8)
	FVC	290	93.94 (10.8)	4.35 (0.9)	290	94.24 (10.2)	4.32 (1.0)
	DLco	290	94.48 (13.1)	27.95 (6.2)	290	92.38 (12.6)	27.28 (6.5)
	FRC	290	-	3.00 (0.8)	290	-	3.04 (0.8)
	TLC	290	94.56 (11.3)	5.84 (1.3)	290	95.36 (10.9)	5.82 (1.3)
1026	FEV1	23	100.66 (11.5)	4.10 (0.7)	22	98.62 (10.4)	3.83 (0.8)
	FVC	23	100.73 (11.5)	5.12 (1.0)	22	100.93 (10.1)	4.84 (1.1)
	DLco	23	97.48 (13.6)	30.72 (5.4)	22	98.50 (12.9)	29.70 (6.9)
	FRC	23	97.48 (13.6)	3.29 (0.7)	22	98.50 (12.9)	3.16 (0.8)
	TLC	23	102.63 (9.6)	6.81 (1.2)	22	102.56 (10.4)	6.49 (1.5)
1027	FEV1	99	92.35 (11.2)	3.70 (0.8)	103	91.14 (10.4)	3.30 (0.7)
	FVC	99	93.66 (10.7)	4.24 (1.0)	103	92.69 (11.1)	4.17 (0.9)
	DLco	99	93.91 (12.8)	27.22 (6.7)	103	94.29 (13.0)	26.92 (5.8)
	FRC	99	-	2.96 (0.9)	103	-	2.98 (0.9)
	TLC	99	95.59 (10.5)	5.83 (1.3)	103	94.43 (10.9)	5.75 (1.3)
Pooled	FEV1	686	95.01 (11.8)	3.48 (0.8)	692	94.84 (12.5)	3.45 (0.8)
	FVC	686	92.11 (21.0)	4.34 (1.0)	692	92.47 (21.1)	4.31 (1.0)
	DLco	684	95.40 (14.4)	27.87 (6.6)	691	95.07 (15.0)	27.52 (6.6)
	FRC	686	95.92 (11.7)	2.99 (0.9)	689	96.03 (12.4)	3.02 (0.9)
	TLC	686	96.20 (11.7)	5.93 (1.3)	690	96.65 (12.2)	5.92 (1.3)

* N is based on the number of subjects who had a mean baseline score. N for the % Predicted Value may be smaller

To understand those subjects who discontinued from the study, comparison of their mean baseline PFT scores and those of subjects' who completed the study are presented graphically (Figure 3). It appears that the mean baseline PFT scores of subjects who completed the study and who discontinued the study are comparable across the five individual studies and consistently on at least 4 of the 5 PFT measurements. In Study 102, it appears that the mean baseline DLco scores are different between subjects who completed and who discontinued in both treatment groups. However, because the number of subjects who discontinued in Study 102 is small (INH=2, SC=2), no conclusion can be made by these differences. Similarly, in Study 107, although there was a difference in mean baseline DLco score between the completers and those subjects who discontinued in the inhaled insulin group, the number of subjects who discontinued is small to warrant any claim of imbalance. I also explored the mean PFT values from the last-visit-before-drop-out between subjects who completed and subjects who did not, and found similar conclusion that there is no difference between the two in both treatment groups (figures not shown).

Overall, these examinations suggest that subjects who discontinued may not influence the results of the PFT analysis. In other words, results using observed cases will be comparable to results taken from imputed data. This will be explored further in the pooled analysis.

Figure 3: Test of Discontinuation at Baseline in Controlled Phase 2/3 Adult Type 1 Studies

Test of Discontinuation at Baseline (STUDY 1026)

mean PFT score

☒ Inhaled-Completer
☒ Comparator-Completer
☐ Comparator-Discontinued

FEV   DLC   FVC   FRC   TLV
PFT Tests

Test of Discontinuation at Baseline (STUDY 1027)

mean PFT score

☒ Inhaled-Completer
☒ Inhaled-Discontinued
☐ Comparator-Completer
☐ Comparator-Discontinued

FEV   DLC   FVC   FRC   TLV
PFT Tests

As noted in the Analysis section, missing PFT measurements were not imputed in the pooled analysis by the applicant. Instead, the applicant conducted a mixed model repeated measures (MMRM) analysis to simultaneously estimate the mean change from baseline for each treatment group and its corresponding treatment differences at each assessment time point. The variance-covariance structure chosen by the applicant was the Spatial Power form, which assumes higher correlation between neighboring time points than more distant time points. From these estimates, treatment group differences (Inhaled Insulin – Comparator) and associated 95% confidence intervals in change from baseline PFTs were estimated at each assessment time point.

To explore whether using Observed Cases only (Pooled – Observed) will provide a sensible estimate of the treatment difference, I conducted two different types of sensitivity analysis. These two types of analysis were then compared to unadjusted (using the Generalized Linear Model method) treatment difference. One type of sensitivity analysis was simple LOCF imputation and analyzed using the GLM method, and the other was the mixed model repeated measures (MMRM) the applicant used. In the MMRM model, I used the model[1] the applicant proposed. Note that you will find in the discussion of individual PFT measurements that the Applicant's unadjusted MMRM model and the covariate-adjusted MMRM model yielded comparable results (Table 17, Table 19, Table 21, Table 23, and Table 25) , thus alleviating our concern that the results of these sensitivity analyses may not be applicable to the applicant's primary model (i.e. Covariate-adjusted MMRM). Furthermore, I used four different covariance structures[2] to determine how appropriate the selection of Spatial Power is. All these exploratory analyses were done before the new update for Study 1022 was submitted by the applicant, so the analyses were done with four timepoints only (weeks 12, 24, 36, and 48/52).

The following figures (Figure 4 to Figure 8) are the results of the individual and pooled studies for each PFT measurements. It includes pooled observed using GLM model, the imputed data (LOCF), and the analysis using Mixed Model Repeated Measures. From the figures, it appears that results from the observed cases are consistent with results from imputation and from using Mixed Model Repeated Measures. This is true regardless of the variance-covariance structure. From careful examination of the information criterion (AIC, BIC, AICC) and the -2xResidual (or REML) Log Likelihood, it appears that the unstructured covariance is the most appropriate choice for the data, since it minimized the information criterion value (AIC, BIC, AICC) in its -2 times the residual log-likelihood form. Therefore, unstructured covariance model is the preferred model (Table 9). Note that in theory, the greater the residual log likelihood, the better the fit of the model. Therefore, the smaller the -2 times the residual log-likelihood, the better the fit of the model.

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[1] Model • Treatment group, categorical variable • Visit, categorical variable
[2] Variance-Covariance Structures: Unstructured (UN), Spatial Power (SP), First-order Autoregressive (AR1), and Compound Symmetry (CS)

However, since the result from Spatial Power model is not extremely different compared to the unstructured covariance model, the applicant's choice is acceptable. Therefore, the result is not sensitive to the choice of covariance structures, as well as to the use of observed data only.

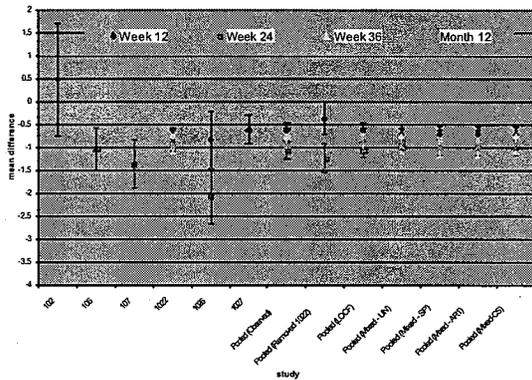Figure 4: Treatment Difference in DLco (mL/min/mmHg) in Controlled Phase 2/3 Studies in Adults Type 1 Diabetes

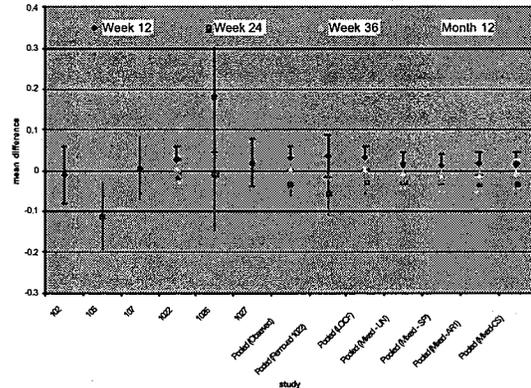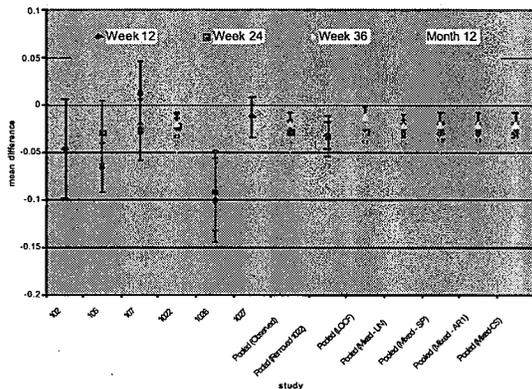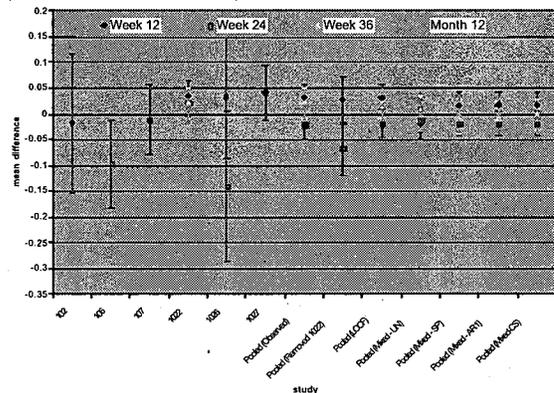Figure 5: Treatment Difference in FEV1 (L) in Controlled Phase 2/3 Studies in Adults Type 1Diabetes

Figure 6: Treatment Difference in FVC (L) in Controlled Phase 2/3 Studies in Adults Type 1Diabetes

Figure 7: Treatment Difference in FRC (L) in Controlled Phase 2/3 Studies in Adults Type 1Diabetes

Figure 8: Treatment Difference in TLC (L) in Controlled Phase 2/3 Studies in Adults Type 1Diabetes
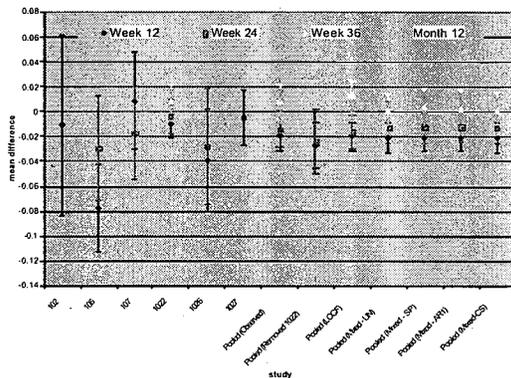
Table 9: Comparison of Covariance Models in Pooled Adult Type 1 Data

PFT	Variance-Covariance Structure	AIC	AICC	BIC	-2RLL
DLC	Spatial Power	12550.0	12550.0	12570.9	12542.0
	Unstructured	12419.7	12419.8	12497.9	12389.7
	AR(1) (no random)	12546.5	12546.5	12556.9	12542.5
	Compound	12428.5	12428.5	12438.9	12424.5
FEV	Spatial Power	-3135.1	-3135.1	-3114.2	-3143.1
	Unstructured*	-3235.8	-3235.8	-3235.8	-3235.8
	AR(1) no random	-3133.9	-3133.9	-3123.5	-3137.9
	Compound	-3232.3	-3232.3	-3221.9	-3236.3
FRC	Spatial Power	2691.8	2691.8	2712.7	2683.8
	Unstructured	2531.9	2532.1	2610.1	2501.9
	AR(1) no random	2697.0	2697.0	2707.4	2693.0
	Compound	2557.4	2557.4	2567.8	2553.4
FVC	Spatial Power	-2122.9	-2122.9	-2102	-2130.9
	Unstructured	-2330.4	-2330.2	-2252.1	-2360.4
	AR(1) no random	-2125.3	-2125.3	-2114.8	-2129.3
	Compound	-2226.8	-2226.8	-2216.4	-2230.8
TLC	Spatial Power	2274.7	2274.7	2295.6	2266.7
	Unstructured	2053.9	2054.0	2132.1	2023.9
	AR(1) no random	2272.3	2272.3	2282.7	2268.3
	Compound	2082.5	2082.6	2093.0	2078.5

* requests an unstructured R matrix be estimated from the sum-of-squares-and-crossproducts matrix of the residuals since it appears that the default REML estimate is too slow and not converging.

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The following tables are results for each five PFT measurement across different clinical studies in adult Type 1 diabetes. As noted previously, some studies are short term (12 weeks) studies, while others like Study 1022 are longer term studies. An update for Study 1022 that includes the second year data was provided by the applicant in April (data provided in July). This new dataset is included in this review.

Note that a positive value for the difference in mean change indicates a result in favour of inhaled insulin; a negative value indicates a result in favour of oral agents:

The mean changes from baseline in FVC, TLC, and for most part in FRC were small and comparable between the groups (Table 11, Table 14, and Table 13, respectively). There was a trend towards a greater mean decline from baseline in DLco in the inhaled insulin group, and this observation is consistent across the individual studies except on Study 102, in which the sample size is fairly small (Table 12). This is also supported by the confidence intervals for these changes. Although the mean changes from baseline in FEV1 measure were small, there is some indication that decline was slightly greater in the inhaled insulin group compared to the comparator group and this observation is supported for most part by the confidence interval for these changes (Table 12). Re-analysis of Study 1022 to include adjusted treatment difference showed the same conclusion with the unadjusted treatment different (Table 15).

Table 10: Mean Change from Baseline in FEV1 Score and Treatment Group Difference by Individual Studies of Adults Type 1 Diabetes

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Unadjusted Difference	95% CI
102	Week 12	33	-0.08 (0.2)	35	-0.03 (0.2)	-0.046	-0.148, 0.056
106	Week 12	131	-0.08 (0.2)	120	-0.015 (0.2)	-0.066	0.119, -0.014
	Week 24	121	-0.11 (0.2)	124	-0.08 (0.3)	-0.029	-0.094, 0.035
107	Week 12	98	-0.05 (0.3)	99	-0.06 (0.2)	0.013	-0.051, 0.078
	Week 24	100	-0.11 (0.2)	96	-0.09 (0.2)	-0.026	-0.088, 0.035
1022	Week 12	277	-0.04 (0.1)	263	-0.01 (0.1)	-0.026	-0.046, -0.006
	Week 24	260	-0.06 (0.1)	273	-0.03 (0.1)	-0.024	-0.046, -0.001
	Week 36	247	-0.06 (0.1)	264	-0.04 (0.1)	-0.022	-0.046, 0.002
	Week 48	240	-0.08 (0.1)	259	-0.04 (0.1)	-0.044	-0.069, -0.020
	Week 60	235	-0.10 (0.2)	250	-0.05 (0.2)	-0.047	-0.075, -0.019
	Week 72	226	0.09 (0.2)	230	-0.06 (0.2)	-0.029	-0.057, -0.000
	Week 84	217	-0.12 (0.2)	224	-0.06 (0.1)	-0.052	-0.082, -0.023
	Week 96	208	-0.12 (0.2)	216	-0.08 (0.2)	-0.041	-0.072, -0.010
1026	Week 12	23	-0.10 (0.1)	21	0.01 (0.1)	-0.101	-0.188, -0.015
	Week 24	23	-0.07 (0.2)	19	0.02 (0.1)	-0.091	-0.174, -0.007
1027	Week 12	96	-0.07 (0.1)	97	-0.05 (0.1)	-0.012	-0.054, 0.029

Table 11: Mean Change from Baseline in FVC Score and Treatment Group Difference by Individual Studies of Adults Type 1 Diabetes

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Unadjusted Difference	95% CI
102	Week 12	33	-0.08 (0.2)	35	-0.07 (0.4)	-0.011	-0.153, 0.132
106	Week 12	131	-0.08 (0.3)	120	0.00 (0.3)	-0.078	-0.147, -0.009
	Week 24	121	-0.09 (0.3)	124	-0.06 (0.4)	-0.029	-0.111, 0.052
107	Week 12	98	-0.04 (0.3)	99	-0.05 (0.2)	0.008	-0.068, 0.085
	Week 24	100	-0.09 (0.3)	96	-0.08 (0.2)	-0.017	-0.090, 0.056
1022	Week 12	277	-0.03 (0.1)	263	-0.02 (0.1)	-0.011	-0.033, 0.011
	Week 24	260	-0.05 (0.2)	273	-0.04 (0.1)	-0.003	-0.029, 0.023
	Week 36	247	-0.04 (0.2)	240	-0.06 (0.2)	0.007	-0.019, 0.034
	Week 48	264	-0.05 (0.1)	259	-0.06 (0.1)	-0.002	-0.028, 0.024
	Week 60	235	-0.07 (0.2)	250	-0.07 (0.2)	-0.003	-0.032, 0.027
	Week 72	226	-0.07 (0.2)	230	-0.08 (0.2)	0.014	-0.016, 0.045
	Week 84	217	-0.09 (0.2)	224	-0.08 (0.2)	-0.008	-0.041, 0.025
	Week 96	208	-0.09 (0.2)	216	-0.09 (0.2)	-0.001	-0.036, 0.034
1026	Week 12	23	-0.02 (0.1)	21	0.02 (0.1)	-0.039	-0.120, 0.042
	Week 24	23	-0.04 (0.2)	19	-0.01 (0.1)	-0.028	-0.120, 0.064
1027	Week 12	96	-0.08 (0.2)	97	-0.07 (0.1)	-0.005	-0.049, 0.039

Table 12: Mean Change from Baseline in DLco Score and Treatment Group Difference by Individual Studies of Adults Type 1 Diabetes

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Unadjusted Difference	95% CI
102	Week 12	33	-2.10 (4.3)	35	-2.59 (5.5)	0.488	-1.906, 2.882
106	Week 24	119	-1.69 (3.6)	120	-0.65 (3.5)	-1.042	-1.947, -0.137
107	Week 24	98	-1.69 (3.7)	95	-0.32 (3.6)	-1.372	-2.405, -0.338
1022	Week 12	276	-1.08 (1.7)	264	-0.29 (1.7)	-0.793	-1.081, -0.504
	Week 24	260	-1.17 (2.1)	273	-0.28 (1.8)	-0.899	-1.236, -0.563
	Week 36	246	-1.12 (2.1)	266	-0.41 (1.9)	-0.714	-1.060, -0.368
	Week 48	239	-1.37 (2.1)	257	-0.40 (2.2)	-0.964	-1.343, -0.584
	Week 60	234	1.15 (2.2)	249	-0.42 (2.2)	-0.723	-1.112, -0.334
	Week 72	226	-1.22 (2.3)	230	-0.44 (2.2)	-0.783	-1.197, -0.370
	Week 84	216	-1.34 (2.5)	224	-0.58 (2.1)	-0.765	-1.189, -0.341
	Week 96	206	-1.32 (2.3)	216	-0.74 (2.4)	-0.582	-1.036, -0.128
1026	Week 12	23	0.14 (2.4)	21	1.00 (1.7)	-0.850	-2.119, 0.419
	Week 24	23	-0.11 (1.9)	19	1.96 (1.8)	-2.066	-3.223, -0.910
1027	Week 12	95	-1.36 (2.4)	97	-0.74 (1.8)	-0.618	-1.223, -0.013

Table 13: Mean Change from Baseline in FRC Score and Treatment Group Difference by Individual
Studies of Adults Type 1 Diabetes

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Unadjusted Difference	95% CI
102	Week 12	32	-0.01 (0.5)	32	-0.07 (0.4)	-0.011	-0.153, 0.132
106	Week 24	118	0.03 (0.6)	118	0.15 (0.6)	-0.112	-0.275, 0.051
107	Week 24	99	-0.04 (0.5)	95	-0.04 (0.5)	0.005	-0.143, 0.154
1022	Week 12	276	-0.05 (0.4)	262	-0.08 (0.4)	0.031	-0.030, 0.091
	Week 24	260	-0.08 (0.4)	270	-0.07 (0.4)	-0.010	-0.075, 0.054
	Week 36	247	-0.07 (0.4)	265	-0.07 (0.4)	0.00003	-0.067, 0.067
	Week 48	240	-0.12 (0.4)	257	-0.11 (0.4)	-0.012	-0.085, 0.060
	Week 60	233	-0.15 (0.4)	249	-0.12 (0.4)	-0.026	-0.101, 0.049
	Week 72	226	-0.16 (0.4)	230	-0.12 (0.4)	-0.037	-0.111, 0.037
	Week 84	213	-0.19 (0.4)	223	-0.15 (0.4)	-0.035	-0.118, 0.048
	Week 96	204	-0.14 (0.4)	216	-0.11 (0.5)	-0.037	-0.122, 0.048
1026	Week 12	23	0.05 (0.4)	21	-0.13 (0.4)	0.179	-0.087, 0.445
	Week 24	23	-0.09 (0.4)	19	-0.08 (0.5)	-0.010	-0.275, 0.254
1027	Week 12	95	-0.17 (0.4)	96	-0.19 (0.4)	0.019	-0.098, 0.135

Table 14: Mean Change from Baseline in TLC Score and Treatment Group Difference by Individual
Studies of Adults Type 1 Diabetes

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Unadjusted Difference	95% CI
102	Week 12	33	0.03 (0.5)	35	0.05 (0.6)	-0.018	-0.284, -0.247
106	Week 24	120	-0.01 (0.7)	121	0.09 (0.6)	-0.097	-0.261, 0.067
107	Week 24	99	-0.05 (0.5)	96	-0.03 (0.5)	-0.011	-0.145, 0.122
1022	Week 12	276	-0.00 (0.3)	262	-0.03 (0.3)	0.033	-0.022, 0.087
	Week 24	259	0.02 (0.3)	270	-0.01 (0.3)	0.024	-0.032, 0.080
	Week 36	246	0.02 (0.3)	265	-0.01 (0.4)	0.021	-0.038, 0.079
	Week 48	240	0.00 (0.3)	257	-0.01 (0.4)	0.011	-0.050, 0.072
	Week 60	232	-0.01 (0.4)	249	-0.03 (0.4)	0.028	-0.039, 0.095
	Week 72	225	-0.00 (0.4)	229	-0.01 (0.4)	0.006	-0.063, 0.075
	Week 84	213	-0.04 (0.4)	223	-0.04 (0.3)	0.004	-0.063, 0.070
	Week 96	204	0.01 (0.4)	216	-0.01 (0.4)	0.018	-0.057, 0.092
1026	Week 12	23	0.03 (0.4)	21	-0.01 (0.4)	0.033	-0.202, 0.268
	Week 24	23	-0.07 (0.5)	19	0.07 (0.5)	-0.140	-0.423, 0.143
1027	Week 12	95	-0.00 (0.4)	96	-0.04 (0.3)	0.041	-0.061, 0.143

Table 15: Unadjusted and Adjusted Treatment Group Difference in PFT Measurements in Adults Type 1 Diabetes (Study 1022)

PFT	Week	Unadjusted		Adjusted	
		Difference	95% CI	Difference	95% CI
FEV1	12	-0.026	-0.046, -0.006	-0.021	-0.044, 0.002
	24	-0.024	-0.046, -0.001	-0.017	-0.040, 0.006
	36	-0.022	-0.046, 0.002	-0.014	-0.038, 0.009
	48	-0.044	-0.069, -0.020	-0.038	-0.062, -0.014
	60	-0.047	-0.075, -0.019	-0.041	-0.066, -0.017
	72	-0.029	-0.057, -0.000	-0.027	-0.052, -0.002
	84	-0.052	-0.082, -0.023	-0.046	-0.071, -0.020
	96	-0.041	-0.072, -0.010	-0.034	-0.060, -0.008
FVC	12	-0.011	-0.033, 0.011	-0.004	-0.030, 0.021
	24	-0.003	-0.029, 0.023	0.005	-0.020, 0.031
	36	0.007	-0.019, 0.034	0.016	-0.010, 0.042
	48	-0.002	-0.028, 0.024	0.006	-0.020, 0.033
	60	-0.003	-0.032, 0.027	0.004	-0.023, 0.031
	72	0.014	-0.016, 0.045	0.021	-0.006, 0.048
	84	-0.008	-0.041, 0.025	0.000	-0.028, 0.028
	96	-0.001	-0.036, 0.034	0.003	-0.025, 0.032
DLco	12	-0.793	-1.081, -0.504	-0.687	-1.023, -0.352
	24	-0.899	-1.236, -0.563	-0.782	-1.118, -0.446
	36	-0.714	-1.060, -0.368	-0.614	-0.957, -0.272
	48	-0.964	-1.343, -0.584	-0.837	-1.185, -0.488
	60	-0.723	-1.112, -0.334	-0.623	-0.977, -0.270
	72	-0.783	-1.197, -0.370	-0.576	-0.938, -0.214
	84	-0.765	-1.189, -0.341	-0.639	-1.007, -0.271
	96	-0.582	-1.036, -0.128	-0.501	-0.878, -0.125
FRC	12	0.031	-0.030, 0.091	0.003	-0.061, 0.067
	24	-0.010	-0.075, 0.054	-0.026	-0.090, 0.039
	36	0.00003	-0.067, 0.067	-0.018	-0.083, 0.048
	48	-0.012	-0.085, 0.060	-0.033	-0.100, 0.034
	60	-0.026	-0.101, 0.049	-0.039	-0.106, 0.029
	72	-0.037	-0.111, 0.037	-0.047	-0.116, 0.022
	84	-0.035	-0.118, 0.048	-0.053	-0.124, 0.017
	96	-0.037	-0.122, 0.048	-0.050	-0.123, 0.022
TLC	12	0.033	-0.022, 0.087	0.024	-0.033, 0.081
	24	0.024	-0.032, 0.080	0.016	-0.042, 0.073
	36	0.021	-0.038, 0.079	0.012	-0.047, 0.070
	48	0.011	-0.050, 0.072	0.006	-0.054, 0.065
	60	0.028	-0.039, 0.095	0.027	-0.033, 0.088
	72	0.006	-0.063, 0.075	0.004	-0.057, 0.066
	84	0.004	-0.063, 0.070	-0.005	-0.068, 0.058
	96	0.018	-0.057, 0.092	0.011	-0.053, 0.076

Unadjusted Model – Treatment
Adjusted - includes: Treatment, Pooled Center, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

In the following discussion, the results from the pooled analysis on each of the PFT measurements will be summarized.

Forced Expiratory Volume in 1 second (FEV₁)

From the individual studies, there appears to be small declines in mean FEV1 among INH- and comparator-treated subjects over 12, 24 weeks, up to 96 weeks (2 years) of exposure, with small but consistent treatment group differences favoring the comparator (Table 10). This was supported for most part by the confidence interval for these changes. Note that the treatment group differences for FEV1 remained fairly constant and did not increase.

In the pooled data set, similar treatment group differences in mean change from baseline in FEV1 favoring comparator therapy are apparent among adult subjects with type 1 after 3 months of therapy. The treatment group differences remained fairly constant and only increased slightly after their first post-baseline measurement and these differences remained comparable at subsequent time points, which the applicant claims, supports the effect of INH on FEV1 is not progressive (Table 16, Table 17; Figure 9). The results were fairly robust when the adjusted model was used. Thus, the treatment differences were of a magnitude of about 40 mL for FEV1 at the end of the study.

Note that since all of the data in the pooled studies after week 24 are from Study 1022, the results from the Pooled analysis and from Study 1022 are fairly consistent

Figure 9: Mean Change from Baseline in FEV₁ (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes
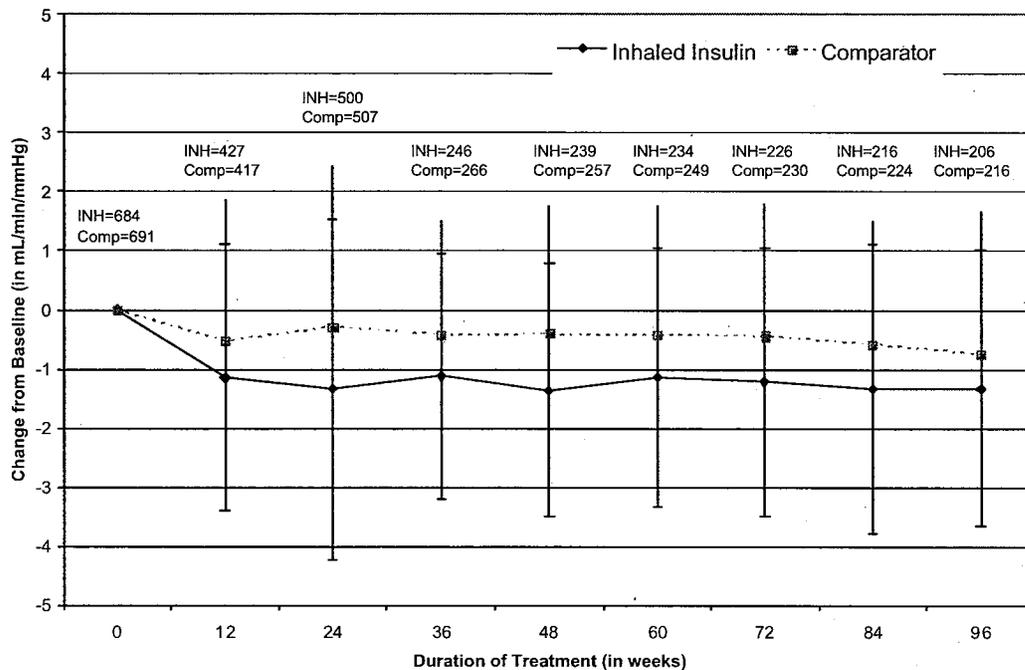
Table 16: Mean Change from Baseline in FEV1 Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	686	3.484	0.786				
	Week 12	658	3.434	0.782	-0.056	0.175	-0.029	-0.047, -0.011
	Week 24	504	3.442	0.772	-0.080	0.182	-0.029	-0.052, -0.006
	Week 36	247	3.473	0.740	-0.059	0.142	-0.022	-0.046, 0.002
	Week 48	240	3.465	0.733	-0.080	0.143	-0.044	-0.069, -0.020
	Week 60	235	3.450	0.760	-0.095	0.159	-0.047	-0.075, -0.019
	Week 72	226	3.457	0.742	-0.090	0.153	-0.029	-0.057, -0.0004
	Week 84	217	3.446	0.755	-0.116	0.167	-0.052	-0.082, -0.023
	Week 96	208	3.465	0.749	-0.118	0.168	-0.041	-0.072, -0.010
Comparator	Baseline	692	3.454	0.776				
	Week 12	635	3.436	0.783	-0.027	0.163		
	Week 24	512	3.442	0.789	-0.052	0.193		
	Week 36	264	3.432	0.789	-0.037	0.134		
	Week 48	259	3.432	0.770	-0.036	0.135		
	Week 60	250	3.424	0.767	-0.047	0.154		
	Week 72	230	3.426	0.800	-0.062	0.154		
	Week 84	224	3.423	0.777	-0.064	0.147		
	Week 96	216	3.400	0.788	-0.077	0.157		

Table 17: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FEV1 Score in Controlled Phase 2/3 Studies in Type 1 Adults

Week	Unadjusted Difference	95% CI	Adjusted* Difference	95% CI	Adjusted** Difference	95% CI
12	-0.029	-0.047, -0.011	-0.029	-0.047, -0.011	-0.028	-0.046, -0.011
24	-0.029	-0.052, -0.006	-0.027	-0.047, -0.008	-0.027	-0.046, -0.008
36	-0.022	-0.046, 0.002	-0.022	-0.048, 0.003	-0.021	-0.047, 0.004
48	-0.044	-0.069, -0.020	-0.045	-0.073, -0.017	-0.043	-0.071, -0.016
60	-0.047	-0.075, -0.019	-0.047	-0.076, -0.018	-0.046	-0.074, -0.017
72	-0.029	-0.057, -0.0004	-0.033	-0.063, -0.003	-0.032	-0.061, -0.002
84	-0.052	-0.082, -0.023	-0.051	-0.081, -0.020	-0.049	-0.079, -0.019
96	-0.041	-0.072, -0.010	-0.039	-0.071, -0.008	-0.038	-0.069, -0.007

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

The proportions of subjects who had reduction in FEV1 from baseline at each timepoint (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions are presented in Figure 10. Inspection of these graphs suggests that there are apparent differences in the proportion of subjects who had reduction in FEV1 from baseline between the two treatment groups in favor of the comparator group. Note however, that these reductions are generally very small. In fact, only a small proportion of subjects (1% maximum) had reduction of more than 15%. Except for Week 36, there also appears to be an increasing proportion of subjects in the inhaled insulin group who had any reduction in FEV1 from baseline over time, while the comparator group remained fairly constant except at Week 96/104.

Figure 10: Proportion of Subjects by Percent Reduction from Baseline in FEV1 (L) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

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Percent Reduction in FEV1 (L) from Baseline at Week 60

Percent Reduction in FEV1 (L) from Baseline at Week 84

Percent Reduction in FEV1 (L) from Baseline at Week 72

Percent Reduction in FEV1 from Baseline at Week 96

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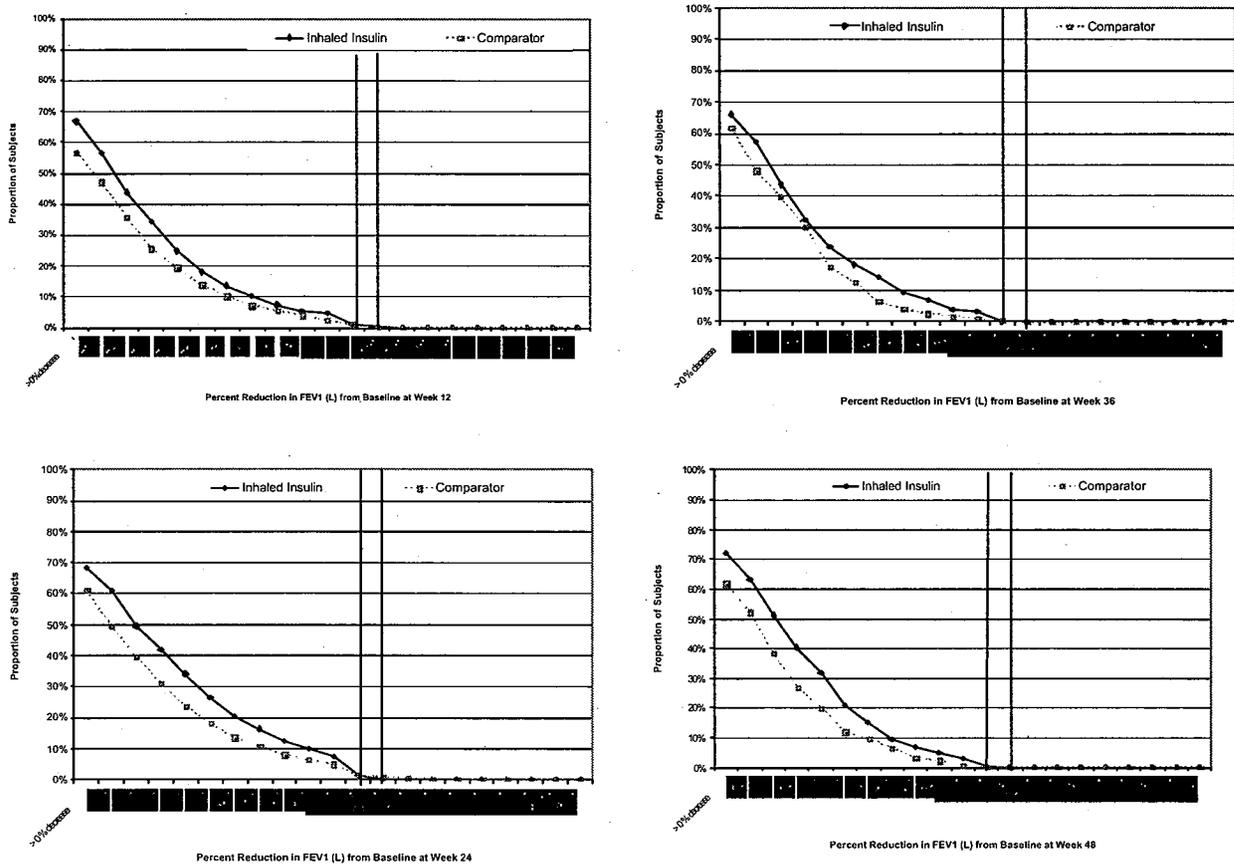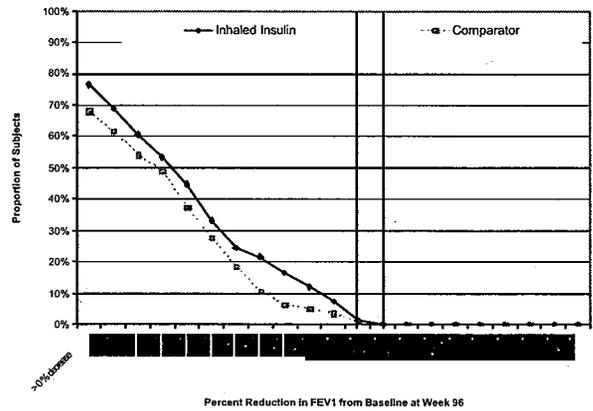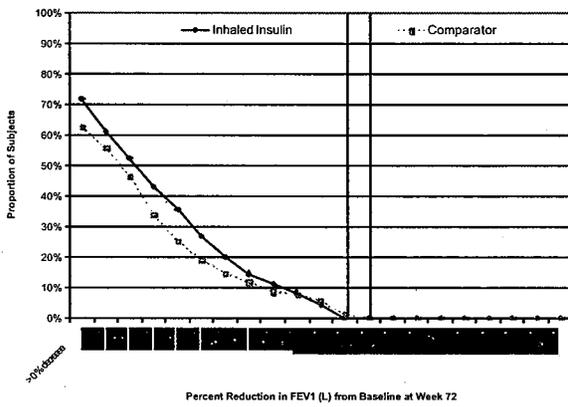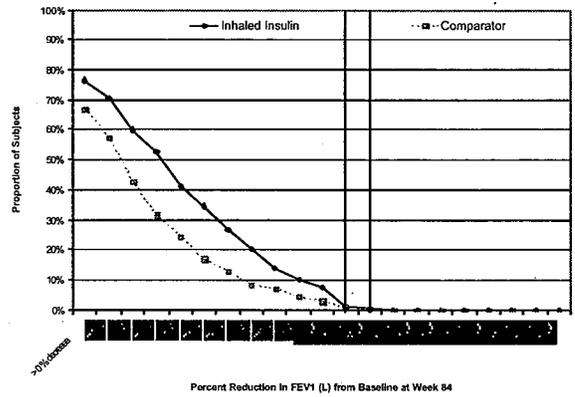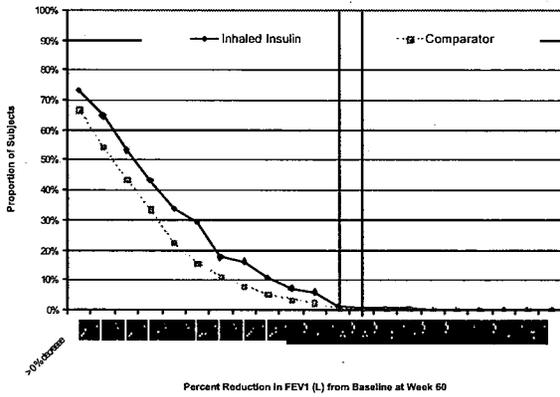
Diffusion Lung Capacity (DLco)

From the individual studies, there appears to be decline during the first 12 weeks in mean change from baseline in DLco among INH- and comparator- treated subjects, but subsequent measurements remained steady up to 96 weeks (2 years) of exposure (Table 12). In most of the individual studies, there was small but consistent treatment group differences favoring the comparator (Figure 4) and this was supported for most part by the confidence interval for these changes. Similar to the results from FEV1, the treatment group differences for Dlco remained fairly constant across time after week 12 (Week 96/104).

In the pooled data set, similar treatment group differences in mean change from baseline in DLco favoring comparator therapy are apparent among adult subjects with Type 1 diabetes after 3 months of therapy. The treatment group differences remained fairly close (ranged: -0.582 to -1.061) at subsequent time points, and had shown to be numerically smaller by the end of the study (Week 96/104), which the applicant claims, supports the effect of INH on DLco is also not progressive (Table 18, Table 19; Figure 11). The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 0.5 mL/min/mmHg for DLco at the end of the study.

All of the data in the pooled studies after week 24 are from Study 1022, therefore the results from the Pooled analysis and from Study 1022 are fairly consistent

Figure 11: Mean Change from Baseline in DLco (mL/min/mmHg) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

Table 18: Mean Change from Baseline in DLco Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Difference	Inhaled - Comparator 95% CI
Inhaled	Baseline	684	27.872	6.580				
	Week 12	427	26.733	6.284	-1.157	2.255	-0.634	-0.946, -0.321
	Week 24	500	26.898	6.257	-1.348	2.878	-1.061	-1.408, -0.715
	Week 36	246	26.998	6.064	-1.125	2.078	-0.714	-1.060, -0.368
	Week 48	239	26.931	6.004	-1.368	2.145	-0.964	-1.343, -0.584
	Week 60	234	27.170	6.178	-1.145	2.179	-0.723	-1.112, -0.334
	Week 72	226	27.070	6.029	-1.223	2.278	-0.783	-1.197, -0.370
	Week 84	216	27.083	6.053	-1.340	2.456	-0.765	-1.189, -0.341
	Week 96	206	27.089	5.974	-1.324	2.324	-0.582	-1.036, -0.128
Comparator	Baseline	691	27.521	6.552				
	Week 12	417	26.851	6.345	-0.523	2.371		
	Week 24	507	27.314	6.367	-0.286	2.730		
	Week 36	266	26.761	6.410	-0.411	1.904		
	Week 48	257	26.753	6.061	-0.404	2.152		
	Week 60	249	26.757	6.058	-0.422	2.173		
	Week 72	230	26.702	6.418	-0.439	2.218		
	Week 84	224	26.725	6.217	-0.575	2.062		
	Week 96	216	26.475	5.992	-0.742	2.415		

Table 19: Unadjusted and Sponsor-defined Adjusted Treatment Difference in DLco Score in Controlled Phase 2/3 Studies in Type 1 Adults

Week	Unadjusted Difference	Unadjusted 95% CI	Adjusted* Difference	Adjusted* 95% CI	Adjusted** Difference	Adjusted** 95% CI
12	-0.634	-0.946, -0.321	-0.707	-1.023, -0.391	-0.680	-0.976, -0.384
24	-1.061	-1.408, -0.715	-0.995	-1.294, -0.696	-0.955	-1.233, -0.677
36	-0.714	-1.060, -0.368	-0.801	-1.178, -0.424	-0.716	-1.074, -0.359
48	-0.964	-1.343, -0.584	-1.008	-1.421, -0.594	-0.893	-1.283, -0.502
60	-0.723	-1.112, -0.334	-0.786	-1.220, -0.352	-0.653	-1.060, -0.246
72	-0.783	-1.197, -0.370	-0.718	-1.168, -0.268	-0.585	-1.005, -0.165
84	-0.765	-1.189, -0.341	-0.780	-1.241, -0.319	-0.646	-1.075, -0.216
96	-0.582	-1.036, -0.128	-0.645	-1.118, -0.171	-0.513	-0.953, -0.072

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

The proportions of subjects who had reduction in DLco at baseline at each timepoints (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions are presented in Figure 12. Inspection of these graphs suggests that there are apparent differences in the proportion of subjects who had reduction in DLco from baseline between the two treatment groups in favor of the comparator group. Although these reductions are generally very small (most subjects had at most 10% reduction), there are more subjects in the inhaled insulin group that had at least 15% reduction compared to the comparator group. The difference appears to be constant across different time intervals except for Week 96/104 in which there appears to be an upward shift (increase) in the proportion of subjects with any reduction in the comparator group. The reason for such increase is unknown.

Figure 12: Proportion of Subjects by Percent Reduction from Baseline in DLco (mL/min/mmHg) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

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percent reduction in DLco (in mL/min/mmHg) from Baseline at Week 60

Percent Reduction in DLco (mL/min/mmHg) from Baseline at Weke 84

Percent Reduction in DLco (mL/min/mmHg) from Baseline at Week 72

Percent Reduction in DLco (mL/min/mmHg) from Baseline at Week 96

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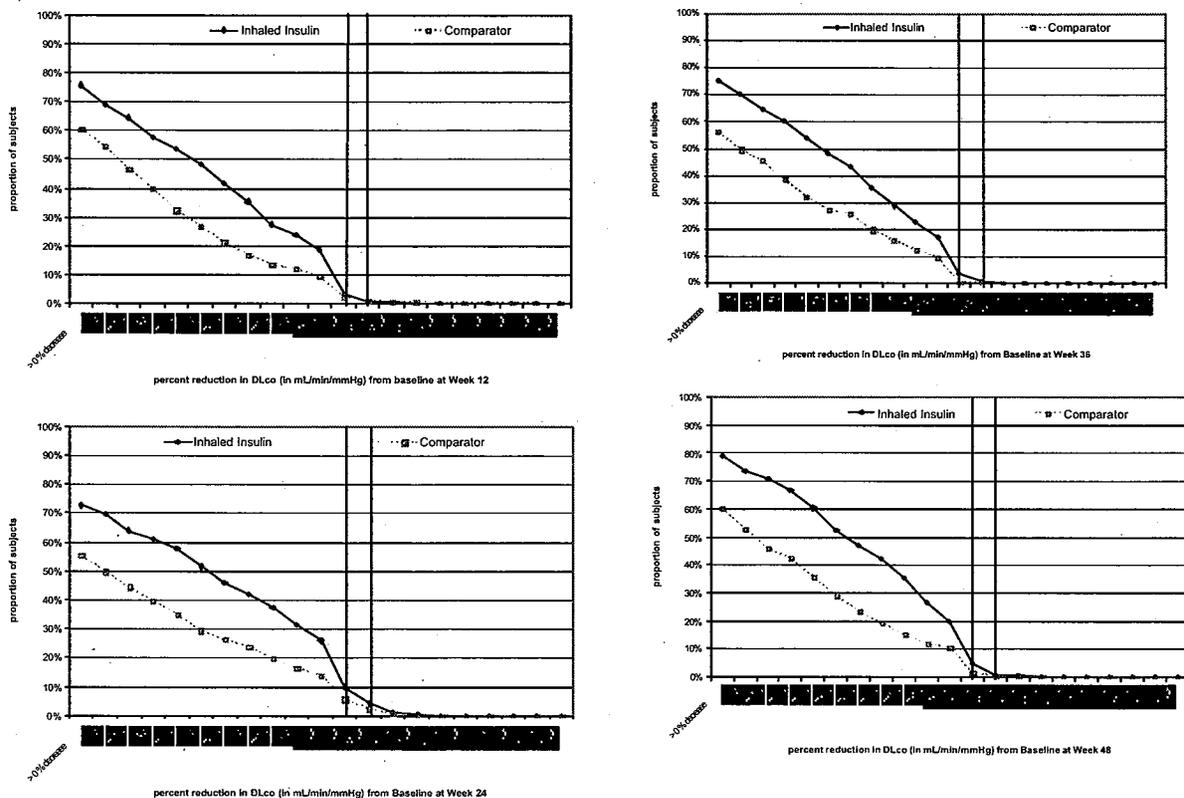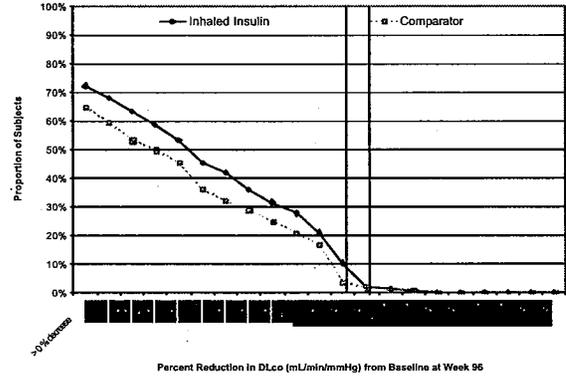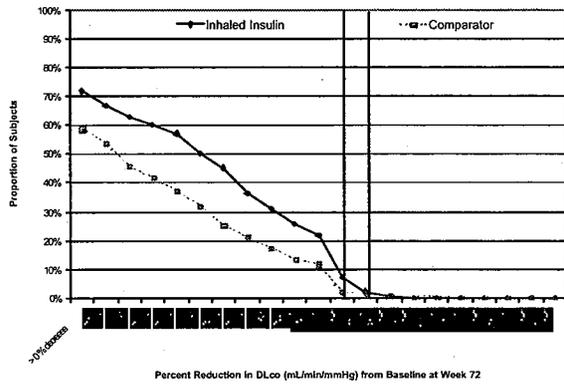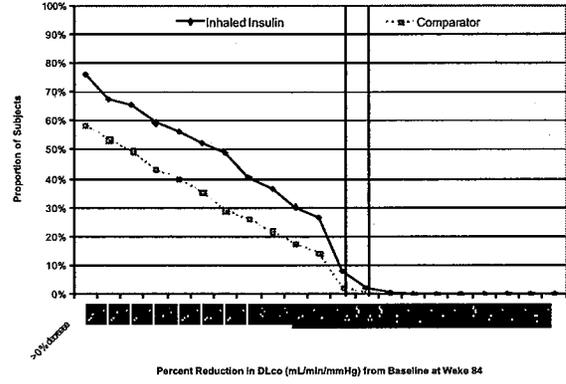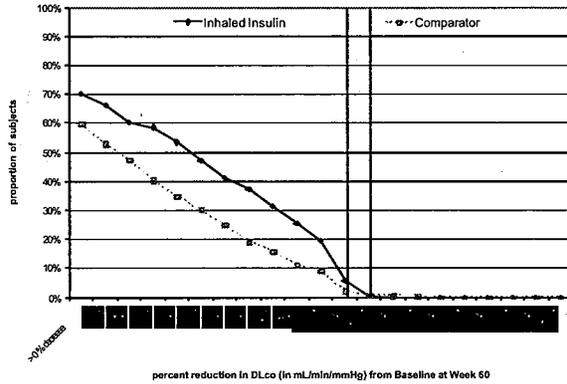
Forced Vital Capacity (FVC)

As seen from the individual studies, there appears to be a very small decline during the first 12 weeks in mean change from baseline in FVC among INH- and comparator- treated subjects, but measurements remained steady up to 96 weeks (2 years) of exposure (Table 11). Treatment group differences were comparable between inhaled insulin group and the comparator group in the sense that all 95% confidence intervals included the zero difference, but numerically favored the comparator (Figure 6).

Similar conclusions can be drawn from the pooled data set. Treatment group differences were small and fairly consistent between the two treatment groups (Figure 13; Table 20, Table 21). The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 1 mL for FVC at the end of the study. All of the data in the pooled studies after week 24 are from Study 1022, therefore the results from the Pooled analysis and from Study 1022 are fairly consistent.

The proportions of subjects who had reduction in FVC at baseline at each time points (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. In general, there are no differences in the proportion of subjects who had reduction in FVC from baseline between the two treatment groups. Furthermore, almost none had reduction of more than 15%.

Figure 13: Mean Change from Baseline in FVC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

Mean Change from Baseline in FVC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

Table 20: Mean Change from Baseline in FVC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

| Treatment		N	Observed Mean	Observed SD	Change from Baseline Mean	Change from Baseline SD	Inhaled - Comparator Difference	Inhaled - Comparator 95% CI
Inhaled	Baseline	686	4.338	1.006				
	Week 12	658	4.296	0.996	-0.051	0.212	-0.020	-0.043, 0.002
	Week 24	504	4.308	0.980	-0.065	0.226	-0.013	-0.041, 0.014
	Week 36	247	4.333	0.917	-0.044	0.163	0.007	-0.019, 0.034
	Week 48	240	4.336	0.919	-0.058	0.151	-0.002	-0.028, 0.024
	Week 60	235	4.326	0.936	-0.071	0.164	-0.003	-0.032, 0.027
	Week 72	226	4.335	0.923	-0.066	0.159	0.014	-0.016, 0.045
	Week 84	217	4.328	0.936	-0.089	0.184	-0.008	-0.041, 0.025
	Week 96	208	4.355	0.926	-0.086	0.182	-0.001	-0.036, 0.034
Comparator	Baseline	692	4.307	1.004				
	Week 12	635	4.293	1.003	-0.030	0.199		
	Week 24	512	4.291	1.027	-0.052	0.227		
	Week 36	264	4.256	0.983	-0.051	0.145		
	Week 48	259	4.254	0.968	-0.056	0.145		
	Week 60	250	4.244	0.961	-0.068	0.166		
	Week 72	230	4.240	0.992	-0.081	0.175		
	Week 84	224	4.251	0.980	-0.080	0.166		
	Week 96	216	4.239	0.986	-0.085	0.183		

Table 21: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FVC Score in Controlled Phase 2/3 Studies in Type 1 Adults

| Week	Unadjusted Difference	Unadjusted 95% CI	Adjusted* Difference	Adjusted* 95% CI	Adjusted** Difference	Adjusted** 95% CI
12	-0.020	-0.043, 0.002	-0.021	-0.043, 0.001	-0.021	-0.042, 0.000
24	-0.013	-0.041, 0.014	-0.012	-0.035, 0.011	-0.012	-0.035, 0.010
36	0.007	-0.019, 0.034	0.003	-0.027, 0.033	0.004	-0.026, 0.033
48	-0.002	-0.028, 0.024	-0.004	-0.037, 0.029	-0.003	-0.035, 0.029
60	-0.003	-0.032, 0.027	-0.004	-0.038, 0.030	-0.003	-0.036, 0.030
72	0.014	-0.016, 0.045	0.014	-0.021, 0.049	0.015	-0.019, 0.050
84	-0.008	-0.041, 0.025	-0.005	-0.042, 0.031	-0.004	-0.040, 0.031
96	-0.001	-0.036, 0.034	-0.002	-0.039, 0.035	-0.001	-0.037, 0.035

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

Forced Residual Capacity (FRC)

As seen from the individual studies, there appears to be a slow but steady decline over time in mean change from baseline in FRC among INH- and comparator- treated subjects (Table 13). Treatment group differences were comparable between inhaled insulin group and the comparator group in the sense that all 95% confidence intervals included the zero difference, but numerically favored the comparator (Figure 7).

Similar conclusions can be drawn from the pooled data set. Treatment group differences were comparable between the two treatment groups. There appears to be a small separation between the two groups after Week 48 (Table 22, Table 23; Figure 14). The treatment differences were slightly bigger in the adjusted model, but they are still in the same direction as the unadjusted (i.e. favoring the comparator group). Thus, the treatment differences were of a magnitude of about 40 – 60 mL for FRC at the end of the study (taking into account the adjusted model).

All of the data in the pooled studies after week 24 are from Study 1022 therefore the results from the Pooled analysis and from Study 1022 are fairly consistent.

Figure 14: Mean Change from Baseline in FRC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

Table 22: Mean Change from Baseline in FRC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

Treatment		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	686	2.991	0.861				
	Week 12	426	2.935	0.860	-0.066	0.389	0.033	-0.019, 0.086
	Week 24	500	2.976	0.818	-0.044	0.472	-0.031	-0.091, 0.029
	Week 36	247	2.929	0.831	-0.070	0.375	0.00003	-0.067, 0.067
	Week 48	240	2.900	0.833	-0.120	0.413	-0.012	-0.085, 0.060
	Week 60	233	2.881	0.801	-0.147	0.416	-0.026	-0.101, 0.049
	Week 72	226	2.880	0.816	-0.156	0.397	-0.037	-0.111, 0.037
	Week 84	213	2.833	0.823	-0.186	0.434	-0.035	-0.118, 0.048
	Week 96	204	2.902	0.818	-0.143	0.429	-0.037	-0.122, 0.048
Comparator	Baseline	689	3.020	0.857				
	Week 12	411	2.926	0.845	-0.099	0.384		
	Week 24	502	3.036	0.900	-0.013	0.497		
	Week 36	265	2.982	0.857	-0.070	0.391		
	Week 48	257	2.935	0.762	-0.107	0.407		
	Week 60	249	2.930	0.810	-0.121	0.419		
	Week 72	230	2.933	0.820	-0.119	0.409		
	Week 84	223	2.916	0.817	-0.151	0.449		
	Week 96	216	2.974	0.822	-0.107	0.455		

Table 23: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FRC Score in Controlled Phase 2/3 Studies in Type 1 Adults

Week	Unadjusted Difference	95% CI	Adjusted* Difference	95% CI	Adjusted** Difference	95% CI
12	0.033	-0.019, 0.086	0.014	-0.042, 0.070	0.002	-0.051, 0.055
24	-0.031	-0.091, 0.029	-0.030	-0.082, 0.023	-0.046	-0.095, 0.004
36	0.00003	-0.067, 0.067	-0.016	-0.083, 0.051	-0.032	-0.096, 0.032
48	-0.012	-0.085, 0.060	-0.029	-0.103, 0.044	-0.045	-0.115, 0.025
60	-0.026	-0.101, 0.049	-0.033	-0.110, 0.043	-0.048	-0.121, 0.024
72	-0.037	-0.111, 0.037	-0.040	-0.119, 0.039	-0.055	-0.129, 0.019
84	-0.035	-0.118, 0.048	-0.044	-0.125, 0.037	-0.061	-0.137, 0.015
96	-0.037	-0.122, 0.048	-0.041	-0.124, 0.041	-0.058	-0.136, 0.020

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

Meanwhile, the proportions of subjects who had reduction in FRC at baseline at each time points (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. Inspection of each individual graph (by time points) suggests that at Week 12, there was no difference in the reduction profile of subjects in the inhaled insulin group and the comparator group. However, at Week 48 and onwards, the curves began to separate, and shows that there was some evidence of greater proportion of subjects in the inhaled insulin group who had a greater reduction in FRC compared to the comparator. Although reductions in FRC score were generally small, there were quite a few in both treatment groups (almost 20% in each group) that had reduction of more than 15% (Figure 15).

Figure 15: Proportion of Subjects by Percent Reduction from Baseline in FRC (L) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes
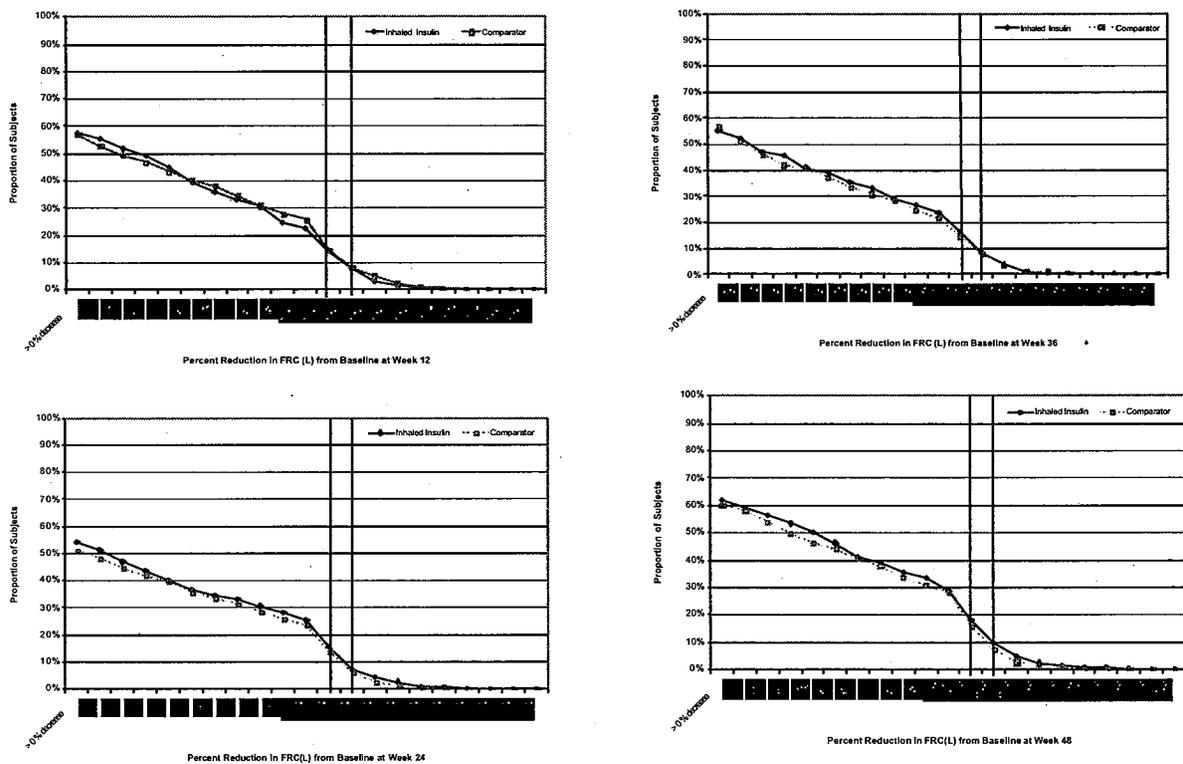
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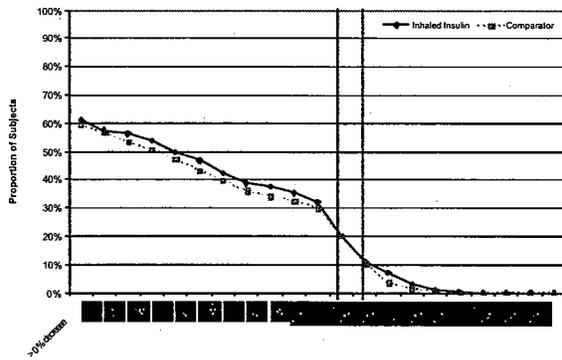
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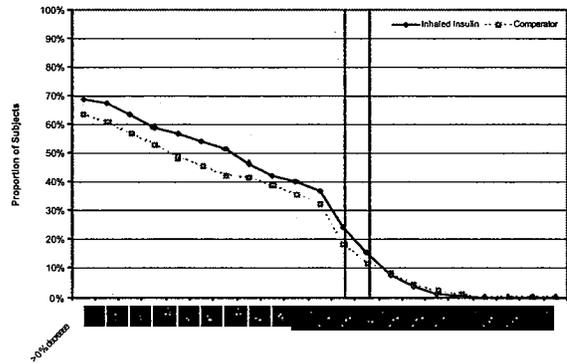
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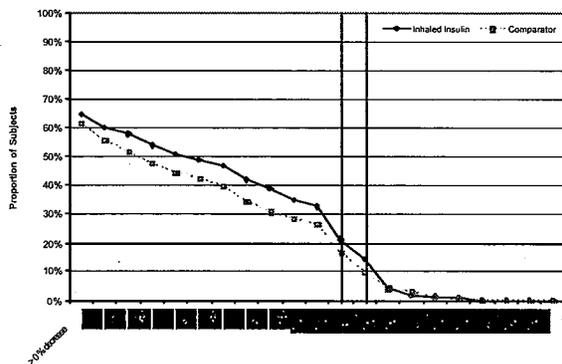
Percent Reduction in FRC(L) from Baseline at Week 72
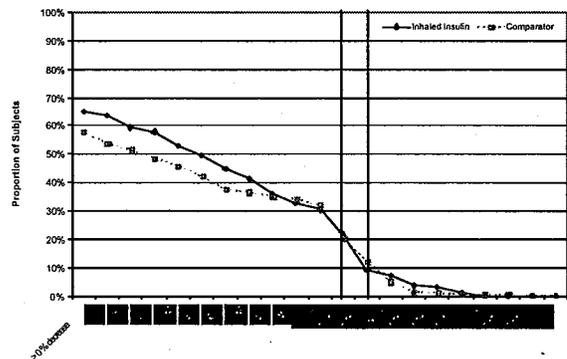
Percent Reduction in FRC(L) from Baseline at Week 96

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Total Lung Capacity (TLC)

As seen from the individual studies, there appears to be minimal to no decline in mean change from baseline in TLC among INH-treated group, while there appears to be very small decline in the comparator-treated subjects. These observations were consistent over time up to 96 weeks (2 years) of exposure (Table 14). In the individual studies, treatment group differences were comparable between the inhaled insulin group and the comparator group, but it slightly favored the inhaled insulin group particularly in Studies 1022, 1026 and 1027 (Figure 8).

Similar conclusions can be drawn from the pooled data set. Treatment group differences were comparable between the two treatment groups (Figure 16), but from Table 24 and Table 25, there is a small numerical difference between the two groups favoring the inhaled insulin group except at Week 24. This appears to be not statistically meaningful and the differences could be due to random variation. The treatment differences shifted slightly in the adjusted model favoring the comparator group at Weeks 36, 48, 72, and 84. Since the actual differences are very small, this shift is not surprising at all. Thus, the treatment differences were of a magnitude of about 6 - 18 mL for TLC by the end of the study favoring the inhaled insulin group (taking into account the adjusted model).

All of the data in the pooled studies after week 24 are from Study 1022, therefore the results from the Pooled analysis and from Study 1022 are fairly consistent except at Week 24. The small difference at Week 24 could be due to Studies 106 and 107 that have Week 24 data and showed a more favorable comparator group. Nonetheless, it appears that treatment difference in TLC slightly favored the inhaled insulin group.

Figure 16: Mean Change from Baseline in TLC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

Table 24: Mean Change from Baseline in TLC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 1 Adults

Treatment		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	686	5.927	1.316				
	Week 12	427	5.901	1.322	0.004	0.356	0.031	-0.017, 0.079
	Week 24	501	5.963	1.283	-0.007	0.459	-0.019	-0.076, 0.037
	Week 36	246	5.870	1.248	0.016	0.317	0.021	-0.038, 0.079
	Week 48	240	5.888	1.253	0.0006	0.342	0.011	-0.050, 0.072
	Week 60	232	5.897	1.261	-0.005	0.400	0.028	-0.039, 0.095
	Week 72	225	5.901	1.238	-0.002	0.385	0.006	-0.063, 0.075
	Week 84	213	5.853	1.240	-0.035	0.361	0.004	-0.063, 0.070
	Week 96	204	5.953	1.239	0.012	0.358	0.018	-0.057, 0.092
Comparator	Baseline	690	5.916	1.334				
	Week 12	412	5.822	1.282	-0.027	0.352		
	Week 24	506	5.971	1.383	0.012	0.452		
	Week 36	265	5.816	1.302	-0.005	0.350		
	Week 48	257	5.810	1.260	-0.010	0.353		
	Week 60	249	5.799	1.279	-0.033	0.350		
	Week 72	229	5.824	1.300	-0.007	0.361		
	Week 84	223	5.822	1.295	-0.039	0.348		
	Week 96	216	5.878	1.292	-0.006	0.414		

Table 25: Unadjusted and Sponsor-defined Adjusted Treatment Difference in TLC Score in Controlled Phase 2/3 Studies in Type 1 Adults

Week	Unadjusted Difference	95% CI	Adjusted* Difference	95% CI	Adjusted** Difference	95% CI
12	0.031	-0.017, 0.079	0.014	-0.037, 0.065	0.008	-0.042, 0.057
24	-0.019	-0.076, 0.037	-0.019	-0.066, 0.029	-0.029	-0.074, 0.018
36	0.021	-0.038, 0.079	-0.007	-0.069, 0.055	-0.016	-0.077, 0.044
48	0.011	-0.050, 0.072	-0.004	-0.071, 0.063	-0.013	-0.078, 0.053
60	0.028	-0.039, 0.095	0.024	-0.046, 0.094	0.016	-0.052, 0.083
72	0.006	-0.063, 0.075	0.005	-0.068, 0.077	-0.004	-0.073, 0.066
84	0.004	-0.063, 0.070	-0.002	-0.076, 0.072	-0.011	-0.083, 0.060
96	0.018	-0.057, 0.092	0.017	-0.059, 0.092	0.006	-0.067, 0.079

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

The proportions of subjects who had reduction in TLC at baseline at each time points (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. Inspection of each individual graphs (by time points) suggests that the reduction profile of subjects is more in favor of the inhaled insulin group than the comparator group, particularly at the end of the study (Figure 17). Note however that these differences in proportions of subjects with some reductions in TLC score were generally small. There were only a few subjects in both treatment groups that had reduction of more than 15%.

Figure 17: Proportion of Subjects by Percent Reduction from Baseline in TLC (L) at Week 96 in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

Percent Reduction in TLC (L) from Baseline at Week 96
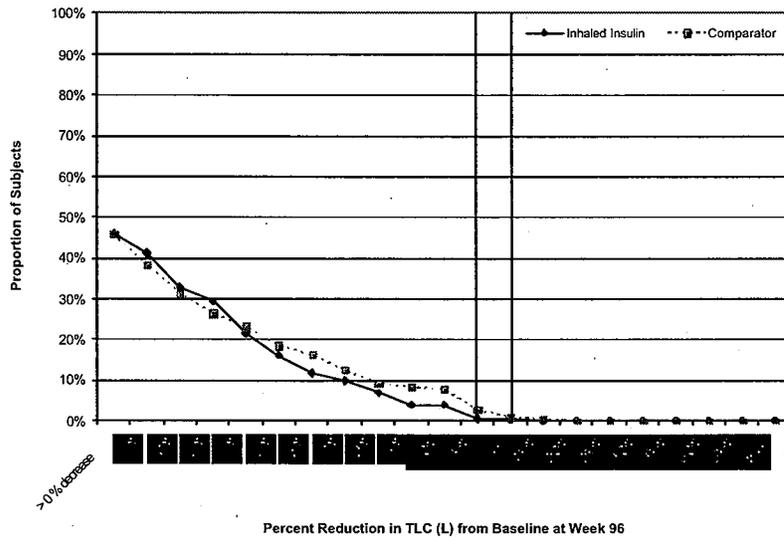
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Pulmonary Function Test and Antibody Titer

One of the requests from Dr. Seymour is to assess at the relationship between the change in pulmonary function tests and the antibody titer. To explore this relation, I evaluated the change from baseline of PFT measurements with the antibody titer at that specific week using both the Pooled Data and Study 1022 (one-year interim) for this exercise. A regression line, to assess the relationship between the change from baseline of PFT measurements and the antibody titer, was plotted for the inhaled insulin-treated group. Note that since there is no increase in the antibody titer in the comparator group, no regression line was drawn. Correlation coefficients were calculated to indicate how the antibody titers are related to the change in PFT measurements. A negative correlation (or slope) implies decreased lung function with increased antibody titers, while a positive correlation (slope) implies increased (better) lung function with decreased antibody titers. All plots are presented in Appendix I, Sections A – E.

There is no evidence of any strong correlation between the change from baseline in pulmonary function tests and antibody titers. There might be some small negative correlation in terms of DLco, FRC, and TLC, but the correlations were not large enough to warrant a concern. Alternatively, there appears to be some small positive correlation in terms of FEV1 and FVC, but again these are small. It does not appear that the correlation increases or decreases over time, however there were numerically larger correlation at Week 36. As expected, the figures and the correlation coefficients are the same in the Pooled Study and Study 1022 after Week 24. There were slight differences in the direction and the magnitude at Week 24, but this could be due to more samples/studies in the population that have Week 24 data.

Pulmonary Function Test and Insulin Dose

Another request from Dr. Seymour is to look at the relationship between the change in pulmonary function tests and the dosing. The focus of interest is on short-acting drug. To explore this relationship, I looked at the change from baseline of PFT measurements with subject-reported average daily insulin doses by week. Average daily dose, according to the applicant, is calculated based on the average dose between the day of the previous visit and the day before the present visit. I also looked at the relationship between the change from baseline of PFT measurements and the subject's cumulative daily insulin doses by visit window. The cumulative dose was calculated based on the cumulative average daily insulin doses accounting for the number of days in the study. I looked at both Study 106 and Study 1022 (one-year interim) for this exercise. Because of the different study drugs (particularly on the comparator group) that the subjects were treated to, it is hard to look at the pooled data. Scatterplots and regression lines were drawn, and correlation coefficients were calculated. All plots for Study 1022 (one-year interim) for all five pulmonary function tests are presented in Appendix I, Sections G – AA.

Overall, it appears that there is no strong correlation between the change from baseline in any of the pulmonary function test and the average total or cumulative total daily dose in both inhaled insulin and comparator insulin. However, it is important to note that in DLco after Week 24, change from baseline in any of the pulmonary function test and the average total or cumulative total daily dose in the inhaled insulin group appears to be negatively correlated, but the correlation is not strong enough to warrant any claim. Meanwhile, the comparator-treated group appears to show a negative correlation between the change from baseline in FRC and the average total or cumulative total daily dose. It does not appear that the correlation increases or decreases over time.

II.   Type 2 Data

Study Design:

The design of all the controlled Phase 2/3 studies in both male and female ages 18 and older with Type 2 diabetes mellitus are open-label, randomized, parallel group, outpatients studies with a 4-week run-in period (Table 26). Following a 4-week baseline period during which all patients received subcutaneous (SC) insulin or oral agents, subjects were randomized to either three months, six months, 1 year, or 2 years (depending on the study protocol) treatment period with either inhaled (INH) with or without subcutaneous basal insulin, or subcutaneous short-acting or long-acting (SC) insulin, or oral agents. Subjects underwent battery of pulmonary function tests (including spirometry, lung volumes and diffusion capacity) at the run-period (for baseline values), weeks 6, 12, 24, 36, 48, 60, 72, 84, or 96, or end of study, depending on the length of the trial, as well as at 6 weeks and 12 weeks post-study completion (Studies 1001 and 1002).

Table 26: Study Design of Adult Type 2 (DM) Data

Study	Design	Treatment groups	PFT measurements Treatment Duration (in weeks)	Number of Subjects	
				INH	Comparator
103	Open-label, randomized, parallel group	Pre-meal (TID) INH plus bedtime SC Ultralente vs. conventional Subcutaneous insulin (SC), BID or TID	12	28	28
104	Open-label, randomized, parallel group 2-day in-patient instruction	Pre-meal (TID) INH plus usual OA vs. usual oral agent (either sulfonylurea and/or metformin therapy)	12	33	36
108	Open-label, randomized, parallel group	Pre-meal (TID) INH plus a single bedtime Ultralente injection vs. control SC insulin of mixed regular and NPH insulin, BID	24	149	149
109	Open-label, randomized, parallel group	Pre-meal (TID) INH , or Pre-meal (TID) INH plus usual OA vs. usual oral agent (s)	12	207	99
110	Open-label, randomized, parallel group	Diet and exercise plus pre-meal (TID) INH insulin vs. diet and exercise plus rosiglitazone 4 mg, BID	12	75	68
1001-1002	Open-label, randomized, parallel group	Pre-meal (TID) INH vs. metformin (A2171001) or glibenclamide (A2171002)	24, 36, 48, 60, 72, 84, 96, Washout period: 6 weeks and 12 weeks	471	441
1029	Open-label, randomized, parallel group	Pre-meal (TID) INH insulin plus SC (either Ultralente or NPH) vs. BID or TID SC insulin plus either Ultralente, NPH or glargine	12, 24, 36, 48	314	311

Source: Study Report 217-103, 104, 108, 109, 110, combined 1001 and 1002, and 1029

Demographic Characteristics:

Demographic characteristics of subjects in the pooled Type 2 data are comparable between the two treatment groups. Majority of the subjects was white. There appears to be more males in each of the treatment group across all studies. The male subjects were heavier and were taller than females in each of the treatment group. Age appears to be comparable between males and females (Table 27).

Table 27: Demographic Characteristics of Adults Type 2 Data

Variables	Inhaled Insulin		Comparator	
	Male	Female	Male	Female
No. of Subjects*	791	478	660	461
Age (years)	57 (9.3)	57 (9.6)	56 (9.9)	56 (10.4)
Race (White)	647 (82%)	391 (82%)	552 (84%)	359 (78%)
Weight (kg)	92 (15.5)	81 (13.9)	91 (15.0)	82 (15.5)
Height (cm?)	176 (7.4)	161 (6.6)	175 (7.3)	162 (7.2)
BMI	30 (4.2)	31 (4.7)	30 (4.2)	31 (5.1)

* No. of Subjects are slightly smaller than the total number who were randomized in the studies. Includes only subjects who were treated and have PFT measurements.

Respiratory Adverse Events:

Respiratory adverse events by individual studies are presented in Table 28. In the pooled study, the number of subjects with respiratory events, as expected, was higher in the inhaled insulin group compared to the comparator group (Figure 18). Using preferred COSTART term and severity for all-causality adverse events, the proportion of subjects with respiratory system adverse events was generally slightly higher in the inhaled insulin group than the comparator groups, particularly on increased cough (INH 21% vs. Comparator 5%). There were also more subjects with dyspnea, rhinitis, pharyngitis, and sputum increased (Figure 19). The most common respiratory system adverse event was respiratory tract infection and this was comparable between the two treatment groups.

Almost all respiratory system adverse events were either mild or moderate in severity. There are a total of 28 subjects out of 1277 (2%) who **permanently discontinued** due to respiratory events in the inhaled insulin group, while 2 out of 1132 (0.1%) in the comparator group (Table 29). These events include asthma, bronchitis, carcinoma of the lung, increased cough, dyspnea, respiratory disorder, sputum increased, pharyngitis, and respiratory tract infection. Most of these events were considered mild to moderate except two subjects with severe asthma, one with severe cough, one with severe bronchitis, one with severe carcinoma of the lung, and one with severe shortness of breath in the inhaled insulin group, and finally, in the comparator group, one subject had severe carcinoma of the lung and one had severe respiratory tract infection.

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Table 28: Number of subjects (%) with Respiratory adverse events for all Adults Type 2 DM Subjects: All Causality

	Study 103		Study 104		Study 108		Study 109		Study 110		Study 1029		Study 1001 – 1002	
No. of Subjects	INH 28	Comp 28	INH 33	Comp 36	INH 149	Comp 149	INH 207	Comp 99	INH 75	Comp 68	INH 314	Comp 311	INH 471	Comp 441
Total Respiratory	20 (71)	15 (54)	17 (52)	14 (39)	94 (63)	68 (46)	107 (52)	30 (30)	35 (47)	26 (38)	247 (79)	196 (63)	219 (46)	149 (34)
Apnea													1 (0)	0
Asthma	1 (4)	0			5 (3)	1 (1)	1 (0)	0			12 (4)	7 (2)	6 (1)	3 (1)
Atelectasis					0	1 (1)								
Bronchiectasis					0	1 (1)								
Bronchiolitis					0	1 (1)								
Bronchitis	0	2 (7)			4 (3)	4 (3)	4 (2)	2 (2)	2 (3)	1 (2)	26 (8)	11 (4)	25 (5)	23 (5)
Cough Increased	12 (43)	1 (4)	5 (15)	3 (8)	32 (22)	4 (3)	27 (13)	2 (2)	6 (8)	1 (2)	115 (37)	31 (10)	1 (0)	1 (0)
Dyspnea	1 (4)	0			9 (6)	1 (1)	2 (1)	0	3 (4)	1 (2)	13 (4)	8 (3)	71 (15)	18 (4)
Edema Pharynx											1 (0)	0	14 (3)	8 (2)
Emphysema					0	1 (1)								
Epistaxis					2 (1)	0	2 (1)	1 (1)	2 (3)	0	6 (2)	2 (1)	1 (0)	0
Hemoptysis					1 (1)	0							3 (1)	4 (1)
Hyperventilation														
Hypoventilation														
Laryngitis			0	1 (3)	0	1 (1)	1 (0)	0			4 (1)	1 (0)		
Lung Disorder							1 (0)	0			2 (1)	1 (0)	2 (0)	1 (0)
Lung Edema					1 (1)	0								
Nasal Polyp													0	1 (0)
Pharyngitis	7 (25)	2 (7)	3 (9)	3 (8)	14 (9)	11 (7)	18 (9)	7 (7)	4 (5)	2 (3)	37 (12)	30 (10)		
Pleural Disorder											0	1 (0)	36 (8)	26 (6)
Pneumonia					1 (1)	4 (3)					2 (1)	2 (1)		
Respiratory Disorder	4 (14)	4 (14)	2 (6)	1 (3)	8 (5)	8 (5)	11 (5)	3 (3)	5 (7)	1 (2)	25 (8)	29 (9)	8 (2)	4 (1)
Respiratory Distress Syndrome					0	1 (1)							10 (2)	6 (1)
Respiratory Tract Infection	4 (14)	7 (25)	5 (15)	8 (22)	48 (32)	40 (27)	49 (24)	19 (19)	19 (25)	19 (28)	130 (41)	119 (38)		
Rhinitis	4 (14)	5 (18)	4 (12)	1 (3)	13 (9)	13 (9)	17 (8)	2 (2)	5 (7)	3 (4)	40 (13)	28 (9)	102 (22)	81 (18)
Sinusitis	2 (7)	0	3 (9)	2 (6)	6 (4)	7 (5)	9 (4)	2 (2)	5 (7)	2 (3)	31 (10)	34 (11)	20 (4)	13 (3)
Sputum Increased	0	1 (4)			6 (4)	0	5 (2)	0	1 (1)	0	9 (3)	3 (1)	9 (2)	9 (2)
Voice Alteration					3 (2)	0	3 (1)	0	1 (1)	0	3 (1)	0	13 (3)	3 (1)
Yawn														

Source: Study Report 217-103, 104, 108, 109, 110, combined 1001 and 1002, and 1029

Figure 18: Percentage of Subjects with at least one Respiratory Adverse Events in the Individual and Pooled Controlled Phase 2/3 Studies in Type 2 Adults by Treatment Groups
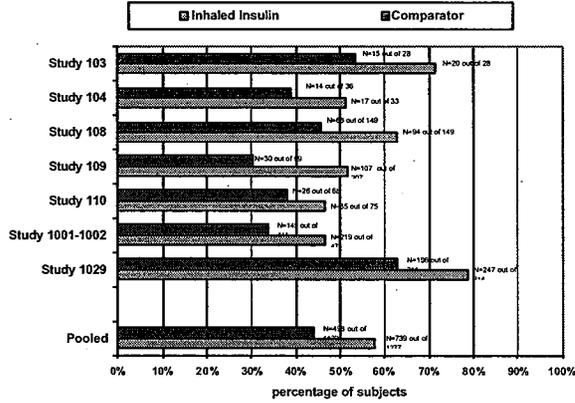
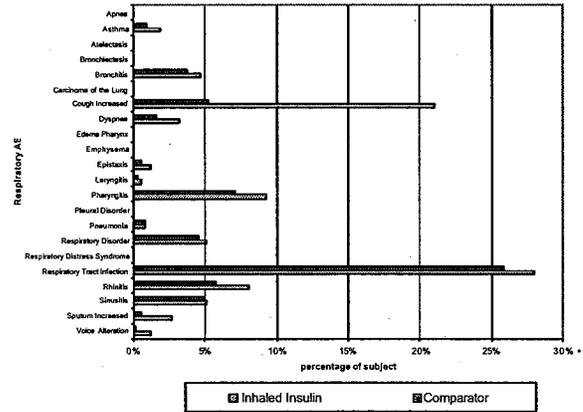Figure 19: Respiratory Events by Treatment Group, Pooled Type 2 Controlled Phase 2/3 *Studies*

Table 29: Respiratory Adverse Events Resulting in Discontinuation from Individual Study

Study	Treatment Group	Subject	Severity	Adverse Event Preferred COSTART/Investigator Term
103	INH	5002 0002	Moderate	Increased Cough
109	INH	5026 0133	Mild	Respiratory Tract Infection
109	INH + 0A	5043 0031	Severe	Dyspnea/Shortness of Breath
110	INH	5103 1426	Moderate	Bronchitis
1001	INH	0018 0060	Mild	Cough increased
1001	INH	0049 0107		Bronchitis
1001	INH	0141 2043	Mild	Asthma
1002	INH	0037 5063		Asthma
1002	INH	0047 7049		Cough Increased
1002	INH	0048 5005		Cough Increased
1002	INH	0074 5150		Cough Increased
1002	INH	0108 6285		Dyspnea
1002	INH	0110 6223		Respiratory Tract Infection, Sputum Increased
1002	INH	0119 5236	severe	Carcinoma of the lung
1002	INH	0134 5269		Cough Increased
1002	INH	0141 8036		Cough Increased
1002	INH	0142 7408		Cough increased, dyspnea
1002	OA	0083 5165	severe	Carcinoma of the lung
1029	INH	1025 1913	Severe	Asthma
1029	INH	1029 788	Mild	Cough Increased
1029	INH	1045 2319	Severe	Asthma, possible bronchospasm, (reaction to INH)
				Cough Increased
			Moderate	Respiratory Tract Infection
			Moderate	
1029	INH	1065 2783	Mild	Cough Increased
			Mild	Respiratory disorder
1029	INH	1068 1197	Moderate	Asthma
1029	INH	1083 3445	Moderate	Asthma/Bronchospasm
			Moderate	Cough Increased
			Moderate	Dyspnea
1029	INH	1085 3552	Moderate	Dyspnea
1029	INH	1105 4681	Mild	Pharyngitis
1029	INH	1113 5158	Mild	Asthma

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Chest X-ray

In the six Type 2 DM clinical studies with chest X-ray (Studies 108, 109, 110, 1001, 1002 and 1029), only a very small proportion of subjects who had chest X-rays taken at final observation had abnormal findings compared to baseline. However, it appears that the incidences of change in chest x-ray results between baseline and last observation were greater numerically in the INH than the comparator treatment groups (INH 46, Comparator 25).

In terms of HRCT, only selected sites, from the two Type 2 DM clinical studies (Study 108 and Study 1029), had HRCT scan. It appears that there is only six subjects in the inhaled insulin group with more abnormal HRCT, while there are 11 (2 from Study 108 and 9 from Study 1029) in the comparator group who had more abnormal HRCT scan.

Pulmonary Function Test:

In Type 2 Adults studies, pulmonary function was monitored in Studies 103, 104, 108, 109, 110, 1001, and 1002 using non- standardized methodologies available in local PFT laboratories. These studies were short-term studies, usually 3 or 6 months of exposure, except for 1001 and 1002 which are two-year studies. Pulmonary function has also been monitored in Study 1029 in which standardized pulmonary testing equipment, testing procedures, and centralized data analysis were used to measure PFTs.

As noted earlier, to simplify the discussion of pulmonary safety, subjects are grouped based on the treatment actually received. Subjects treated with INH with or without subcutaneous basal insulin, or oral antidiabetic agents (OAs) are considered to be INH- treated subjects. Subjects treated with subcutaneous short-acting (SC) insulin or with OAs alone are considered to be Comparator-treated subjects.

To begin, comparison of the mean baseline values between the two treatment groups and the percent predicted at baseline are presented in

Table *30*. It appears that mean baseline values and the % predicted mean values at baseline are comparable between the treatment groups across all pulmonary function tests. . It also appears that the % predicted mean values at baseline are also comparable (with +/- 3% difference) between the treatment groups across the individual studies and five different pulmonary function tests. Note however, that I found one questionable % predicted value in Study 109 on DLco (Subject 109 50600668). That subject's % predicted value is 1302.9 at baseline and 1346.1 at week 12.

Note that twenty four weeks data for Studies 1001 and 1002 were submitted separately by the applicant. In addition, the applicant also submitted the two-year combined safety report for Studies 1001 and 1002. Comparison of these two datasets yield inconsistent number of subjects and slight inconsistent in the baseline and week 24 data. However, the inconsistencies in the baseline and % predicted value were not substantial enough to warrant further exploration beyond asking the applicant's reasoning for such discrepancies. The applicant responded to an information request regarding this discrepancy. One reason they provided was that one site (site 0133) was removed from Study 1001 and no further explanation was provided as to the reason. After discussing with Dr. Sally Seymour and Dr. Jon T. Sahlroot, we decided to go ahead and analyze the Combined 1001-1002 data since that data is more complete.

Table 30: Baseline PFT Measurements and Percent Predicted Mean Values at Baseline in Pooled Controlled Phase 2/3 Studies in Adults Type 2 Diabetes

Study	Variables	N	INH Mean % Predicted (SD)	Mean (SD)	N	Comparator Mean % Predicted (SD)	Mean (SD)
103	FEV1	27	94.25 (15.0)	3.08 (0.7)	26	97.85 (15.3)	3.04 (0.9)
	FVC	27	91.15 (13.0)	3.80 (1.0)	26	94.16 (13.4)	3.72 (1.1)
	DLco	26	95.00 (16.6)	25.37 (7.1)	27	98.21 (23.2)	24.46 (8.3)
	FRC	27	81.09 (21.9)	2.65 (1.0)	27	79.44 (17.2)	2.52 (0.9)
	TLC	27	92.04 (14.4)	5.70 (1.5)	27	92.04 (13.5)	5.48 (1.5)
104	FEV1	32	94.04 (14.0)	3.09 (0.8)	36	91.45 (12.3)	3.20 (0.8)
	FVC	32	92.19 (12.4)	3.81 (1.0)	36	89.49 (11.1)	3.94 (1.0)
	DLco	33	99.14 (17.8)	25.98 (7.3)	36	102.17 (13.5)	26.96 (6.4)
	FRC	30	80.17 (19.4)	2.61 (0.9)	33	79.81 (22.0)	2.58 (0.9)
	TLC	33	91.27 (13.7)	5.60 (1.4)	36	92.09 (12.1)	5.89 (1.4)
108	FEV1	149	93.53 (14.6)	2.84 (0.7)	149	95.88 (15.5)	2.98 (0.7)
	FVC	149	92.27 (13.2)	3.59 (0.8)	149	94.87 (15.8)	3.73 (0.9)
	DLco	149	90.78 (15.3)	23.55 (5.2)	147	92.35 (14.9)	24.10 (5.4)
	FRC	149	83.92 (19.2)	2.71 (0.8)	148	87.76 (19.6)	2.83 (0.8)
	TLC	149	94.62 (12.5)	5.72 (1.2)	149	96.59 (13.9)	5.84 (1.2)
109	FEV1	207	96.72 (13.1)	2.99 (0.7)	99	96.87 (15.1)	2.97 (0.7)
	FVC	207	94.86 (13.0)	3.78 (0.9)	99	94.79 (12.7)	3.72 (1.0)
	FRC	206	87.21 (21.1)	2.84 (0.8)	97	83.75 (18.5)	2.70 (0.8)
	DLco	205	101.91 (86.1)	24.98 (6.2)	98	97.16 (17.9)	25.12 (6.6)
	TLC	207	97.41 (13.4)	5.93 (1.2)	99	97.13 (12.7)	5.80 (1.3)
Manual Combined 1001-1002	FEV1	461	100.47 (15.0)	2.90 (0.7)	430	100.18 (15.1)	2.89 (0.7)
	FVC	460	99.40 (14.1)	3.55 (0.9)	429	99.79 (13.8)	3.56 (0.9)
	FRC	446	94.37 (22.6)	2.89 (0.9)	419	95.81 (21.6)	2.87 (0.9)
	DLco	435	100.92 (23.0)	25.82 (6.4)	409	100.73 (21.3)	25.63 (6.3)
	TLC	457	98.31 (12.6)	5.69 (1.2)	426	98.02 (11.8)	5.64 (1.2)
Sponsor Combined 1001-1002	FEV1	471	100.36 (15.0)	2.90 (0.7)	439	100.09 (15.1)	2.89 (0.7)
	FVC	470	99.34 (14.1)	3.56 (0.9)	438	99.81 (13.8)	3.57 (0.9)
	FRC	456	94.63 (22.5)	2.90 (0.9)	428	95.92 (21.5)	2.89 (0.9)
	DLco	445	100.64 (17.9)	25.97 (6.4)	418	100.14 (18.0)	25.74 (6.3)
	TLC	467	98.27 (12.6)	5.71 (1.3)	435	97.92 (11.7)	5.65 (1.2)
110	FEV1	75	94.61 (14.9)	2.98 (0.7)	68	95.140 (17.0)	2.79 (0.7)
	FVC	75	93.47 (12.1)	3.72 (0.9)	68	93.172 (15.6)	3.46 (0.9)
	DLco	74	100.05 (16.6)	26.49 (6.3)	67	96.798 (15.1)	24.28 (6.2)
	FRC	73	88.72 (27.1)	2.78 (0.8)	66	89.272 (23.2)	2.72 (0.8)
	TLC	75	97.31 (12.2)	5.84 (1.1)	68	97.492 (14.7)	5.57 (1.2)
1029	FEV1	306	90.92 (11.7)	2.91 (0.7)	302	91.80 (12.5)	2.93 (0.7)
	FVC	306	90.29 (11.4)	3.75 (0.9)	302	30.60 (12.0)	3.77 (0.9)
	DLco	305	92.25 (14.0)	24.16 (5.6)	301	91.37 (12.6)	23.95 (5.7)
	FRC	306		2.80 (0.8)	301		2.75 (0.8)
	TLC	306	92.26 (11.4)	5.67 (1.2)	301	92.31 (11.1)	5.65 (1.3)

Table 30 (Continued):

Variables	N	INH Mean % Predicted (SD)	Mean (SD)	N	Comparator Mean % Predicted (SD)	Mean (SD)
FEV1	1267	96.05 (14.4)	2.92 (0.7)	1119	96.21 (15.0)	2.93 (0.7)
FVC	1266	94.88 (13.5)	3.66 (0.9)	1118	95.34 (14.1)	3.67 (0.9)
DLco	1234	97.41 (38.3)	25.09 (6.1)	1094	96.22 (16.5)	24.89 (6.2)
FRC	1247	89.96 (22.5)	2.82 (0.8)	1100	91.10 (21.5)	2.80 (0.8)
TLC	1264	95.87 (12.7)	5.74 (1.2)	1115	95.79 (12.5)	5.69 (1.3)

* N is based on the number of subjects who had a mean baseline score. N for the % Predicted Value may be smaller

Since there were quite a number of subjects who discontinued from each of these studies, to understand those subjects who discontinued from the study, comparison of their mean baseline PFT scores and those of subjects' who completed the study are presented graphically (Figure 20). It appears that the mean baseline PFT scores of subjects who completed the study and who discontinued the study are comparable across the seven individual studies and consistently on at least 4 of the 5 PFT measurements. In Study 103, it appears that the mean baseline DLco scores are different between subjects who completed and who discontinued in both treatment groups. However, because the number of subjects who discontinued in Study 103 is small (INH=2, SC=4), no conclusion can be made by these differences. Note that in most studies except for the longer term studies (i.e. combined 1001 and 1002 studies and Study 1029), number of discontinuations ranged between 0 to 13 in the inhaled insulin group and 0 to 10 in the comparator group. It makes sense (although not ideal) that discontinuation rates are higher in the longer term studies. In Studies 1001 and 1002, because the studies were extended twice (one in week 52 and one in week 104), the number of subjects who completed the study was smaller compared to when it started (Range of Discontinuation:
INH is around 328 out of 471 and Comparator is around 314 out of 441). Study 1029 is another long-term study in which one-year data was available for analysis. In this study, the discontinuation at Week 48/52 was around 81 out of 314 subjects in the inhaled insulin group and around 72 out of 311 (23%) in the comparator group. In spite of the large proportion of subjects who discontinued in these studies, the baseline scores between the completers and those who discontinued were still comparable in both treatment groups.

Overall, these examinations suggest that subjects who discontinued may not influence the results of the PFT analysis. In other words, results using observed cases will be comparable to results taken from imputed data. To confirm this assumption, this will explored further in the pooled analysis.

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Figure 20: Test of Discontinuation at Baseline in Controlled Phase 2/3 Adult Type 2 Studies
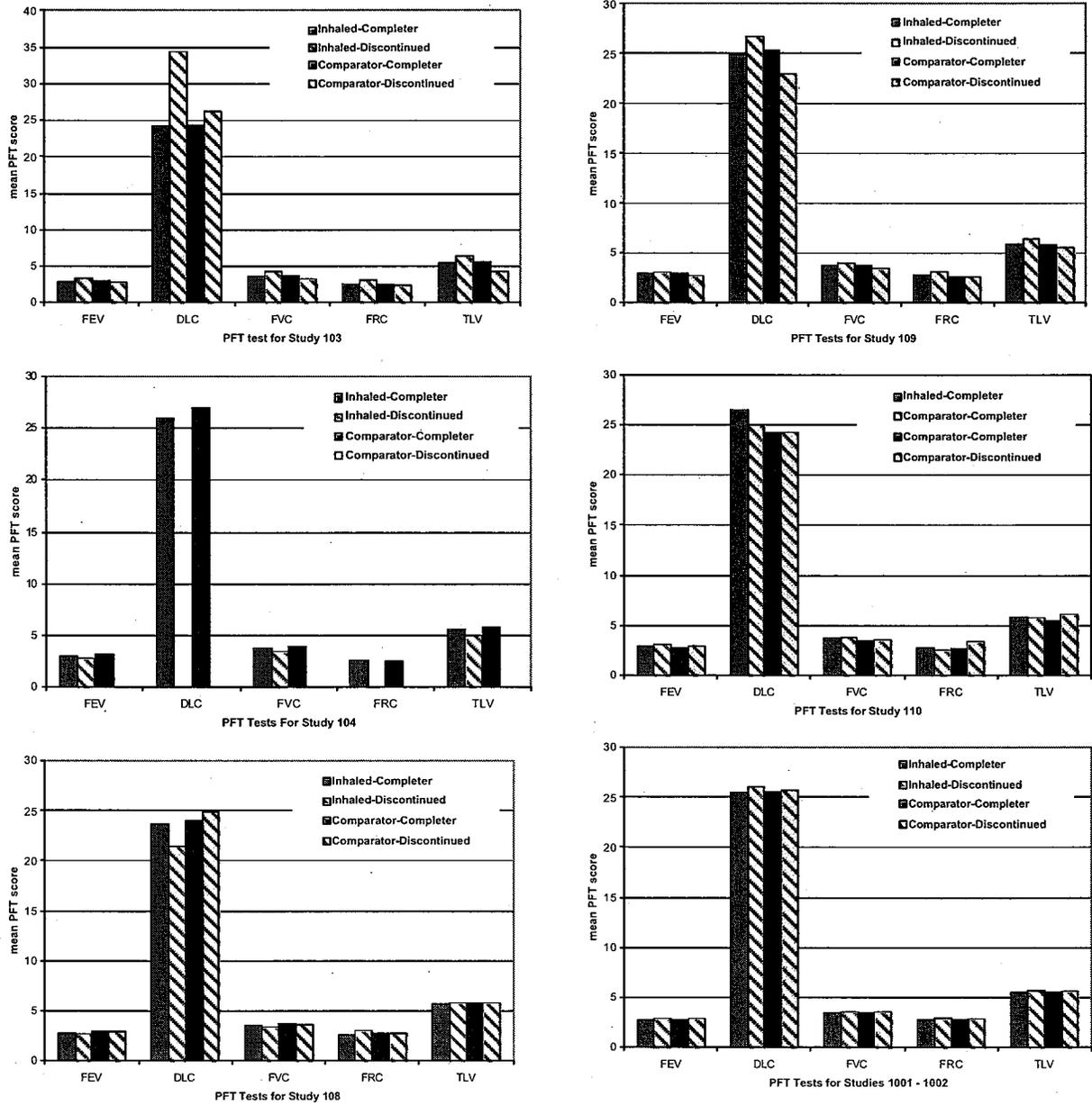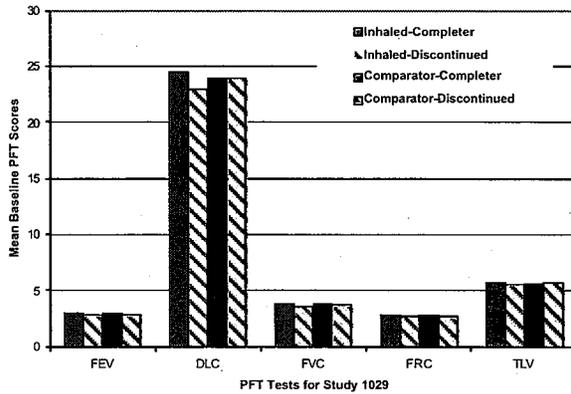
Similar to Type 1 data, I explored whether using Observed Cases only (Pooled – Observed) will provide a sensible estimate of the treatment difference, I conducted different types of mixed model repeated measures (MMRM) analysis. Similar to pooled Type 1 data, I used the unadjusted model[3] the applicant proposed. Note that you will find in the discussion of individual PFT measurements that the Applicant's unadjusted MMRM model and the covariate-adjusted MMRM model yielded comparable results (Table 39, Table 42, Table 44, Table 46 and Table 48) , thus alleviating our concern that the results of these sensitivity analyses may not be applicable to the applicant's primary model (i.e. Covariate-adjusted MMRM). Furthermore, I used four different covariance structures[4] model to determine how appropriate the selection of Spatial Power is. All these exploratory analyses were done on the pooled Type 2 data. Note that LOCF was not conducted because of the difference in duration and designs of the individual studies. I find that it is not practical to impute the data with some studies having only two timepoints, while others have eight timepoints (e.g. in Study 1001: weeks 12, 24, 36, 48, 60, 72, 85, 96).

The following figures (Figure 21 to Figure 25) are the results of the individual and pooled studies for each PFT measurements. It includes pooled observed using GLM model and the analysis using Mixed Model Repeated Measures (MMRM). From the figures, it appears that results from the observed cases are consistent with results from imputation and from using Mixed Model Repeated Measures. This is true regardless of the variance-covariance structure. From careful examination of the information criterion (AIC, BIC, AICC) and the -2xResidual (or REML) Log Likelihood, it appears that unstructured covariance is the most appropriate choice for the data, since it minimized the information criterion value (AIC, BIC, AICC) in its -2 times the residual log-likelihood form. Therefore, unstructured covariance model is the preferred model (Table 31) Note that in theory, the greater the residual log likelihood, the better the fit of the model. Therefore, the smaller the -2 times the residual log-likelihood, the better the fit of the model. However, since the result from Spatial Power model is not extremely different compared to the unstructured covariance model, the applicant's choice is acceptable. Therefore, the result is not sensitive to the choice of covariance structures, as well as to the use of observed data only.

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[3] Unadjusted Model • Treatment group, categorical variable • Visit, categorical variable

[4] Variance-Covariance Structures: Unstructured (UN), Spatial Power (SP), First-order Autoregressive (AR1), and Compound Symmetry (CS)

Figure 21: Treatment Difference in DLco
(mL/min/mmHg) in Controlled Phase 2/3
Studies in Adults Type 2 Diabetes

Figure 22: Treatment Difference in FEV1 (L) in
Controlled Phase 2/3 Studies in Adults
Type 2Diabetes

Figure 23: Treatment Difference in FVC (L) in
Controlled Phase 2/3 Studies in Adults Type
2Diabetes
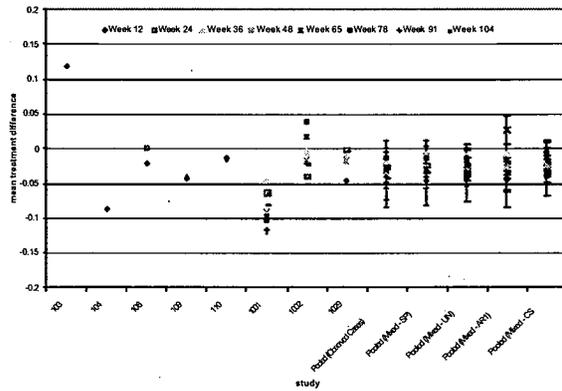
Figure 24: Treatment Difference in FRC (L) inControlled
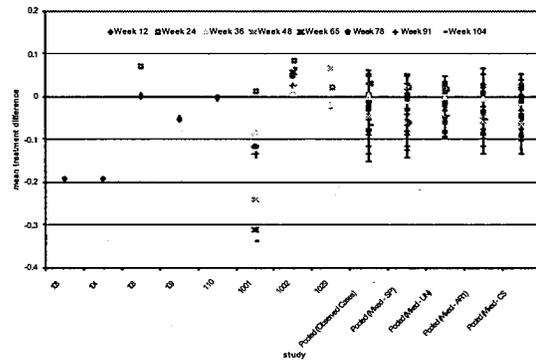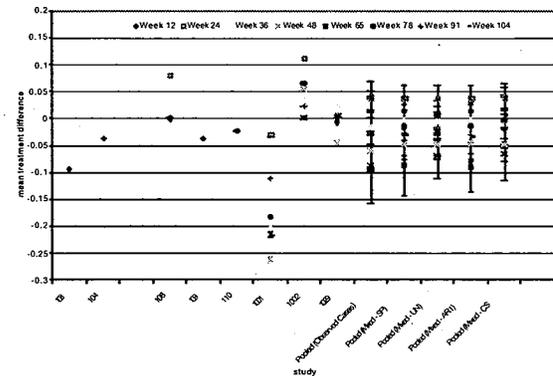Phase 2/3 Studies in Adults Type 2Diabetes

Figure 25: Treatment Difference in TLC (L) in
Controlled Phase 2/3 Studies in Adults Type
2Diabetes

Table 31: Comparison of Covariance Models in Pooled Adult Type 2 Data

PFT	Variance-Covariance Structure	AIC	AICC	BIC	-2RLL
DLC	Spatial Power	24864.7	24864.8	24887.8	24856.7
	Unstructured	24670.8	24671.1	24831.9	24614.8
	AR(1) (no random)	25045.9	25045.9	25057.4	25041.9
	Compound	24819.8	24819.8	24831.3	24815.8
FEV	Spatial Power	-3589.6	-3589.6	-3566.5	-3597.6
	Unstructured*	-3751.8	-3751.8	-3751.8	-3751.8
	AR(1) no random	-3598.0	-3598.0	-3586.4	-3602
	Compound	-3774.5	-3774.5	-3762.9	-3778.5
FRC	Spatial Power	7890.9	7890.9	7913.9	7882.9
	Unstructured*	7825.4	7825.4	7825.4	7825.4
	AR(1) no random	7913.5	7913.5	7925.1	7909.5
	Compound	7708.8	7708.8	7720.4	7704.8
FVC	Spatial Power	-1607.8	-1607.8	-1584.7	-1615.8
	Unstructured	-2020.2	-2019.8	-1812.2	-2092.2
	AR(1) no random	-1616.0	-1616.0	-1604.4	-1620.0
	Compound	-1935.5	-1935.5	-1924.0	-1939.5
TLC	Spatial Power	7615.7	7615.7	7638.8	7607.7
	Unstructured	7196.7	7197.2	7404.6	7124.7
	AR(1) no random	7615.7	7615.7	7627.2	7611.7
	Compound	7292.6	7292.6	7304.2	7288.6

* requests an unstructured R matrix be estimated from the sum-of-squares-and-crossproducts matrix of the residuals since it appears that the default REML estimate is too slow and not converging.

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The following tables are results for each five PFT measurement across different clinical studies in adult Type 2 diabetes. As noted previously, some studies are short term (12 weeks) studies, while others like Studies 1001, 1002, and 1029 are longer term studies. The analysis method for the longer term studies was slightly different from the shorter term such that it included random effects and additional covariates in the model as described in the applicant's protocol. One of the models in studies 1001 – 1002 combined was the random effects model that included covariates such as protocol, country, baseline PFT, age, gender and height at baseline in the model.

Note that a positive value for the difference in mean change indicates a result in favour of inhaled insulin; a negative value indicates a result in favour of oral agents:

The unadjusted data for the All Subjects cohort showed that mean changes from baseline in the FEV1, DLco, FVC, TLC, and FRC were small and comparable between treatment groups across different studies (Table 32 and Table 36). Although there were small decreases from baseline in both treatment groups and for most PFT measurements (except DLco), the inhaled insulin group had a slightly higher decline than the comparative group, there appears to be no clear pattern over time to warrant a concern from any of these PFT measurements, particularly from both Studies 1001-1002 and 1029. In other words, the treatment differences did not appear to progress during the 48 and 104 weeks of treatment.

In the combined studies 1001 and 1002, the unadjusted results also followed a similar pattern to that of the Week 104 Completers the applicant reported in their Study Report (Table 37). Any changes found in the Week 104 Completers were small and similar in both treatment groups. There were slight differences in the applicant's adjusted mean differences from the results I got using the same model that they used. The variance-covariance structure I applied was the Spatial Power they used in the other studies and in the Pooled data. Regardless of these differences, the results from the adjusted and unadjusted appear to be similar. The directions, in terms of the mean change from baseline in both treatment group and the treatment differences appear to be consistent.

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Table 32: Mean Change from Baseline in FEV1 score and Unadjusted Treatment Difference in
Controlled Phase 2/3 Individual Studies in Adult Type 2 DM

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Unadjusted Difference	95% CI
103	Week 12	25	0.03 (0.2)	26	-0.09 (0.2)	0.118	0.008, 0.228
104	Week 12	32	-0.12 (0.2)	36	-0.03 (0.2)	-0.087	-0.191, 0.017
108	Week 12	140	-0.07 (0.2)	141	-0.05 (0.2)	-0.021	-0.070, 0.028
	Week 24	136	-0.07 (0.2)	142	-0.07 (0.2)	0.003	-0.049, 0.055
109	Week 12	199	-0.10 (0.2)	91	-0.05 (0.2)	-0.042	-0.095, 0.011
110	Week 12	74	-0.02 (0.2)	64	-0.00 (0.2)	-0.014	-0.078, 0.050
1001-1002	Week 24	430	-0.09 (0.2)	372	-0.04 (0.2)	-0.051	-0.083, -0.018
	Week 36	312	-0.10 (0.2)	257	-0.08 (0.2)	-0.022	-0.060, 0.015
	Week 48/52	309	-0.12 (0.2)	261	-0.07 (0.2)	-0.047	-0.086, -0.008
	Week 65	158	-0.08 (0.2)	134	-0.06 (0.3)	-0.028	-0.083, 0.027
	Week 78	160	-0.12 (0.2)	139	-0.11 (0.2)	-0.013	-0.064, 0.038
	Week 91	154	-0.15 (0.2)	134	-0.10 (0.3)	-0.057	-0.112, -0.001
	Week 104	143	-0.17 (0.2)	125	-0.13 (0.2)	-0.042	-0.100, 0.017
	LOCF 104	436	-0.13 (0.3)	380	-0.10 (0.2)	-0.031	-0.065, 0.004
	6 Week Washout	149	-0.14 (0.2)	138	-0.15 (0.3)	0.008	-0.049, 0.065
	12 Week Washout	132	-0.16 (0.2)	128	-0.15 (0.2)	-0.014	-0.073, 0.044
1029	Week 12	293	-0.06 (0.1)	290	-0.01 (0.1)	-0.045	-0.068, -0.022
	Week 24	282	-0.05 (0.2)	281	-0.05 (0.2)	-0.001	-0.028, 0.026
	Week 36	265	-0.08 (0.2)	275	-0.07 (0.2)	-0.01	-0.038, 0.018
	Week 48	227	-0.09 (0.2)	235	-0.08 (0.2)	-0.017	-0.047, 0.013

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Table 33: Mean Change from Baseline in FVC score and Unadjusted Treatment Difference in Controlled Phase 2/3 Individual Studies in Adult Type 2 DM

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Difference	95% CI
103	Week 12	25	0.09 (0.2)	26	-0.10 (0.3)	0.185	0.054, 0.315
104	Week 12	32	-0.09 (0.3)	36	-0.02 (0.3)	-0.072	-0.226, 0.081
108	Week 12	140	-0.06 (0.3)	141	-0.05 (0.3)	-0.008	-0.073, 0.057
	Week 24	136	-0.05 (0.3)	142	-0.08 (0.3)	0.025	-0.048, 0.099
109	Week 12	199	-0.07 (0.3)	91	-0.03 (0.3)	-0.036	-0.100, 0.028
110	Week 12	74	-0.01 (0.3)	64	-0.00 (0.3)	-0.008	-0.093, 0.077
1001-	Week 24	430	-0.07 (0.3)	370	-0.05 (0.3)	-0.021	-0.058, 0.017
1002	Week 36	311	-0.08 (0.3)	256	-0.08 (0.3)	-0.004	-0.048, 0.041
	Week 48/52	308	-0.09 (0.3)	261	-0.06 (0.3)	-0.026	-0.072, 0.020
	Week 65	158	-0.05 (0.3)	134	-0.07 (0.3)	0.022	-0.039, 0.083
	Week 78	160	-0.08 (0.3)	139	-0.10 (0.3)	0.018	-0.044, 0.080
	Week 91	154	-0.08 (0.3)	133	-0.09 (0.3)	0.012	-0.053, 0.077
	Week 104	143	-0.12 (0.3)	124	-0.11 (0.3)	-0.010	-0.082, 0.063
	LOCF 104	436	-0.10 (0.3)	379	-0.08 (0.3)	-0.018	-0.058, 0.022
	6 Week Washout	149	-0.09 (0.3)	137	-0.14 (0.3)	0.047	-0.020, 0.113
	12 Week Washout	132	-0.12 (0.2)	127	-0.15 (0.3)	0.023	-0.045, 0.090
1029	Week 12	293	-0.06 (0.1)	290	-0.03 (0.2)	-0.031	-0.056, -0.006
	Week 24	282	-0.05 (0.2)	281	-0.06 (0.2)	0.014	-0.017, 0.044
	Week 36	265	-0.09 (0.2)	275	-0.09 (0.2)	-0.005	-0.036, 0.026
	Week 48	227	-0.09 (0.2)	235	-0.10 (0.2)	0.016	-0.018, 0.050

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Table 34: Mean Change from Baseline in DLco score and Unadjusted Treatment Difference in Controlled Phase 2/3 Individual Studies in Adult Type 2 DM

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Unadjusted Difference	95% CI
103	Week 12	25	0.09 (4.2)	24	-0.50 (3.2)	0.597	-1.552, 2.745
104	Week 12	36	-1.18 (2.7)	36	-1.26 (2.5)	0.081	-1.157, 1.318
108	Week 24	133	-1.05 (3.1)	138	-0.59 (3.4)	-0.461	-1.236, 0.314
109	Week 12	196	-0.84 (3.4)	88	-0.35 (3.0)	-0.484	-1.322, 0.354
110	Week 12	73	-0.69 (3.0)	63	-0.46 (2.7)	-0.232	-1.197, 0.733
1001-1002	Week 24 Week 36	397	-0.37 (3.7)	349	-0.33 (3.6)	-0.038	-0.564, 0.489
	Week 48/52	292	-0.74 (3.9)	254	-0.69 (3.7)	-0.049	-0.695, 0.597
	Week 65	141	-1.35 (3.7)	128	-0.78 (3.3)	-0.570	-1.416, 0.276
	Week 78	138	-1.59 (3.1)	121	-1.32 (3.1)	-0.270	-1.029, 0.489
	Week 91	139	-1.50 (3.6)	126	-1.06 (3.2)	-0.431	-1.252, 0.390
	Week 104	129	-1.53 (3.8)	116	-1.58 (3.3)	0.054	-0.846, 0.954
	LOCF 104	410	-0.84 (3.9)	360	-1.04 (3.6)	0.198	-0.332, 0.728
	6 Week Washout	132	-1.13 (3.7)	128	-1.35 (3.1)	0.214	-0.628, 1.056
	12 Week Washout	112	-1.25 (3.6)	119	-1.15 (3.4)	-0.103	-1.013, 0.806
1029	Week 12	291	-0.55 (1.6)	290	-0.26 (1.5)	-0.287	-0.539, -0.035
	Week 24	278	-0.55 (1.6)	282	-0.39 (1.8)	-0.163	-0.448, 0.122
	Week 36	265	-0.66 (1.8)	271	-0.73 (1.8)	0.071	-0.230, 0.372
	Week 48	226	-0.75 (1.9)	233	-0.49 (1.9)	-0.264	-0.612, 0.084

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Table 35: Mean Change from Baseline in FRC score and Unadjusted Treatment Difference in Controlled Phase 2/3 Individual Studies in Adult Type 2 DM

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Unadjusted Difference	95% CI
103	Week 12	25	-0.57 (1.1)	24	-0.37 (0.8)	-0.194	-0.771, 0.383
104	Week 12	30	-0.24 (0.5)	33	-0.05 (0.6)	-0.192	-0.473, 0.090
108	Week 24	133	0.05 (0.5)	137	-0.02 (0.5)	0.073	-0.043, 0.188
109	Week 12	196	-0.04 (0.6)	87	0.01 (0.4)	-0.053	-0.192, 0.086
110	Week 12	72	0.12 (0.8)	62	0.12 (0.4)	-0.004	-0.221, 0.213
1001-1002	Week 24	415	0.02 (0.7)	358	-0.03 (0.5)	0.053	-0.038, 0.143
	Week 36	288	-0.04 (0.6)	235	-0.01 (0.6)	-0.029	-0.127, 0.068
	Week 48/52	298	-0.06 (0.6)	254	0.01 (0.5)	-0.073	-0.171, 0.026
	Week 65	154	-0.09 (0.5)	132	-0.00 (0.6)	-0.088	-0.218, 0.043
	Week 78	156	-0.07 (0.6)	137	-0.06 (0.5)	-0.015	-0.140, 0.110
	Week 91	151	-0.02 (0.6)	133	0.02 (0.9)	-0.033	-0.202, 0.136
	Week 104	141	-0.08 (0.5)	123	-0.01 (0.6)	-0.068	-0.197, 0.061
	LOCF 104	424	-0.09 (0.7)	365	-0.04 (0.6)	-0.048	-0.135, 0.039
	6 Week Washout	147	-0.13 (0.6)	136	-0.05 (0.6)	-0.081	-0.215, 0.053
	12 Week Washout	130	-0.07 (0.6)	126	-0.04 (0.6)	-0.024	-0.176, 0.129
1029	Week 12	292	-0.04 (0.4)	289	-0.04 (0.3)	0.007	-0.050, 0.065
	Week 24	272	-0.09 (0.4)	277	-0.07 (0.4)	-0.023	-0.088, 0.042
	Week 36	264	-0.09 (0.4)	268	-0.11 (0.4)	0.021	-0.046, 0.088
	Week 48	225	-0.09 (0.4)	229	-0.08 (0.4)	-0.018	-0.091, 0.055

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Table 36: Mean Change from Baseline in TLC score and Unadjusted Treatment Difference in
Controlled Phase 2/3 Individual Studies in Adult Type 2 DM

Study	Visit Window	N	INHALED Change from Baseline (SD)	N	Comparator Change from Baseline (SD)	Inhaled - Comparator Unadjusted Difference	95% CI
103	Week 12	25	-0.05 (0.5)	25	0.05 (0.7)	-0.094	-0.460, 0.271
104	Week 12	32	0.02 (0.6)	36	0.05 (0.6)	-0.037	-0.332, 0.258
108	Week 24	134	0.02 (0.5)	139	-0.06 (0.6)	0.080	-0.054, 0.213
109	Week 12	197	-0.04 (0.5)	89	-0.00 (0.5)	-0.038	-0.160, 0.084
110	Week 12	74	0.01 (0.6)	64	0.04 (0.5)	-0.023	-0.211, 0.165
1001-	Week 24	423	0.04 (0.7)	367	-0.00 (0.5)	0.045	-0.045, 0.136
1002	Week 36	295	-0.01 (0.6)	241	0.06 (0.6)	-0.064	-0.168, 0.041
	Week 48/52	306	-0.01 (0.6)	258	0.07 (0.6)	-0.082	-0.176, 0.012
	Week 65	156	-0.04 (0.5)	133	0.05 (0.6)	-0.088	-0.221, 0.046
	Week 78	158	-0.01 (0.6)	138	0.02 (0.7)	-0.027	-0.177, 0.122
	Week 91	153	-0.01 (0.6)	133	0.02 (0.6)	-0.027	-0.161, 0.108
	Week 104	143	-0.02 (0.5)	124	0.01 (0.6)	-0.030	-0.160, 0.101
	LOCF 104	432	-0.01 (0.6)	375	0.01 (0.6)	-0.012	-0.098, 0.075
	6 Week Washout	148	-0.06 (0.6)	137	-0.03 (0.6)	-0.025	-0.161, 0.110
	12 Week Washout	132	-0.04 (0.6)	127	-0.04 (0.6)	0.009	-0.137, 0.154
1029	Week 12	292	-0.03 (0.3)	289	-0.02 (0.3)	-0.007	-0.061, 0.047
	Week 24	272	-0.04 (0.3)	277	-0.05 (0.4)	0.006	-0.053, 0.065
	Week 36	264	-0.04 (0.4)	268	-0.06 (0.3)	0.023	-0.039, 0.085
	Week 48	225	-0.09 (0.3)	229	-0.05 (0.3)	-0.044	-0.107, 0.019

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Table 37: Week 104 Completers, All Subjects Unadjusted and All Subjects Adjusted Treatment Group Difference in PFT Measurements in Adults Type 2 Diabetes (Studies 1001 and 1002)

PFT	Week	Week 104 Completers		Unadjusted		Adjusted	
		Differences	95% CI	Difference	95% CI	Difference	95% CI
FEV1	24	-0.068	-0.117, -0.020	-0.051	-0.083, -0.018	-0.052	-0.084, -0.020
	36	-0.011	-0.063, 0.041	-0.022	-0.060, 0.015	-0.014	-0.050, 0.022
	48	-0.023	-0.075, 0.029	-0.047	-0.086, -0.008	-0.040	-0.078, -0.003
	65	-0.032	-0.086, 0.022	-0.028	-0.083, 0.027	-0.032	-0.082, 0.018
	78	-0.020	-0.073, 0.032	-0.013	-0.064, 0.038	-0.012	-0.063, 0.039
	91	-0.058	-0.114, -0.003	-0.057	-0.112, -0.001	-0.054	-0.106, -0.002
	104	-0.042	-0.100, 0.017	-0.042	-0.100, 0.017	-0.023	-0.075, 0.030
	WOP 6	-0.008	-0.067, 0.050	0.008	-0.049, 0.065	-0.007	-0.058, 0.045
	WOP12	-0.021	-0.078, 0.035	-0.014	-0.073, 0.044	-0.036	-0.089, 0.017
FVC	24	0.002	-0.056, 0.060	-0.021	-0.058, 0.017	-0.025	-0.062, 0.011
	36	0.021	-0.037, 0.079	-0.004	-0.048, 0.041	0.001	-0.041, 0.042
	48	0.024	-0.036, 0.083	-0.026	-0.072, 0.020	-0.025	-0.068, 0.018
	65	0.020	-0.043, 0.082	0.022	-0.039, 0.083	-0.001	-0.059, 0.056
	78	0.012	-0.053, 0.076	0.018	-0.044, 0.080	0.006	-0.052, 0.065
	91	0.013	-0.052, 0.079	0.012	-0.053, 0.077	0.001	-0.059, 0.061
	104	-0.010	-0.082, 0.063	-0.010	-0.082, 0.063	-0.008	-0.068, 0.052
	WOP 6	0.037	-0.032, 0.107	0.023	-0.045, 0.090	0.026	-0.033, 0.086
	WOP 12	0.011	-0.058, 0.081	-0.038	-0.564, 0.489	-0.016	-0.077, 0.046
DLco	24	-0.407	-1.194, 0.380	-0.038	-0.564, 0.489	-0.070	-0.546, 0.406
	36						
	48	-0.364	-1.247, 0.519	-0.049	-0.695, 0.597	-0.030	-0.058, 0.519
	65	-0.564	-1.435, 0.306	-0.570	-1.416, 0.276	-0.190	-0.934, 0.0554
	78	-0.210	-0.983, 0.562	-0.270	-1.029, 0.489	-0.079	-0.853, 0.694
	91	-0.414	-1.244, 0.416	-0.431	-1.252, 0.390	-0.203	-0.977, 0.571
	104	0.054	-0.846, 0.954	0.054	-0.846, 0.954	0.189	-0.592, 0.970
	WOP 6	0.272	-0.614, 1.158	0.214	-0.628, 1.056	0.231	-0.539, 1.002
	WOP 12	-0.232	-1.193, 0.729	-0.103	-1.013, 0.806	0.031	-0.775, 0.837
FRC	24	0.044	-0.075, 0.164	0.053	-0.038, 0.143	0.046	-0.030, 0.123
	36	-0.051	-0.175, 0.074	-0.029	-0.127, 0.068	-0.061	-0.150, 0.028
	48	-0.101	-0.220, 0.018	-0.073	-0.171, 0.026	-0.099	-0.189, -0.010
	65	-0.086	-0.219, 0.046	-0.088	-0.218, 0.043	-0.113	-0.234, .0009
	78	-0.001	-0.126, 0.124	-0.015	-0.140, 0.110	-0.028	-0.151, 0.094
	91	-0.043	-0.214, 0.128	-0.033	-0.202, 0.136	-0.064	-0.188, 0.060
	104	-0.068	-0.197, 0.061	-0.068	-0.197, 0.061	-0.045	-0.171, 0.080
	WOP 6	-0.093	-0.234, 0.048	-0.081	-0.215, 0.053	-0.113	-0.236, 0.009
	WOP 12	-0.059	-0.217, 0.099	-0.024	-0.176, 0.129	-0.054	-0.182, 0.073
TLC	24	-0.043	-0.170, 0.084	0.045	-0.045, 0.136	0.043	-0.034, 0.121
	36	-0.051	-0.179, 0.078	-0.064	-0.168, 0.041	-0.047	-0.136, 0.042
	48	-0.071	-0.196, 0.054	-0.082	-0.176, 0.012	-0.062	-0.152, 0.028
	65	-0.088	-0.225, 0.049	-0.088	-0.221, 0.046	-0.098	-0.219, 0.023
	78	-0.034	-0.188, 0.119	-0.027	-0.177, 0.122	-0.024	-0.148, 0.099
	91	-0.032	-0.169, 0.104	-0.027	-0.161, 0.108	-0.024	-0.150, 0.102
	104	-0.030	-0.160, 0.101	-0.030	-0.160, 0.101	0.010	-0.116, 0.137
	WOP 6	-0.037	-0.179, 0.106	-0.025	-0.161, 0.110	-0.047	-0.171, 0.078
	WOP 12	-0.015	-0.167, 0.137	0.009	-0.137, 0.154	0.019	-0.111, 0.148

Unadjusted Model – Treatment (Week 104 Completers Only) Source:
Unadjusted Model – Treatment (All Subjects)
Adjusted - includes: Treatment, Protocol, Pooled Center, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure (All Subjects)

In the following discussion, the results from the pooled analysis on each of the PFT measurements will be summarized.

Forced Expiratory Volume in 1 second (FEV$_1$)

As seen from the individual studies, there appears to be small declines in mean FEV1 among INH- and comparator- treated subjects over 12, 24 weeks, up to 96 weeks (2 years) of exposure (Table 32), with small but consistent treatment group differences favoring the comparator (Figure 22). Some of these differences were supported by the confidence interval for these changes. Note that the treatment group differences for FEV1 remained fairly constant and did not increase. Meanwhile, although the mean change from baseline in FEV$_1$ score in the inhaled insulin group did not improve 6 weeks and 12 weeks after washout, the treatment different appears to be smaller and slightly in favor of inhaled insulin at 6 weeks after washout.

In the pooled data set, similar treatment group differences in mean change from baseline in FEV1 favoring comparator therapy are apparent among adult subjects with type 2 after 3 months of therapy. The treatment group differences remained fairly constant and only increased slightly after their first post-baseline measurement and these differences remained comparable at subsequent time points, which the applicant claims, supports the effect of INH on FEV1 is not progressive (Table 38, Table 39; Figure 26). The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 20 – 60 mL and around 30 – 40 mL at the end of study for FEV$_1$.

All of the data in the pooled studies after week 48 are from Combined Studies 1001 and 1002 therefore the results from the Pooled analysis and from the combined studies 1001 and 1002 are fairly consistent.

Figure 26: Mean Change from Baseline in FEV$_1$ (L) by Time in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes
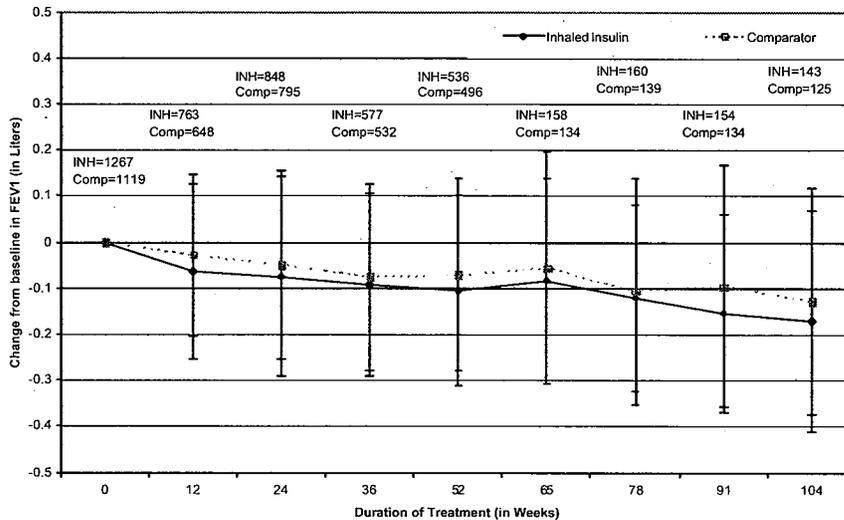
Table 38: Mean Change from Baseline in FEV1 Score and Unadjusted Treatment Group Difference in Controlled Type 2 Studies

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	1267	2.924	0.701				
	Week 12	763	2.866	0.681	-0.064	0.189	-0.036	-0.055, -0.017
	Week 24	848	2.831	0.702	-0.074	0.215	-0.025	-0.045, -0.005
	Week 36	577	2.839	0.694	-0.092	0.198	-0.017	-0.041, 0.006
	Week 48/52	536	2.819	0.691	-0.105	0.207	-0.034	-0.059, -0.009
	Week 65	158	2.784	0.687	-0.083	0.223	-0.028	-0.083, 0.027
	Week 78	160	2.736	0.691	-0.120	0.202	-0.013	-0.064, 0.038
	Week 91	154	2.706	0.668	-0.153	0.215	-0.057	-0.112, -0.001
	Week 104	143	2.663	0.676	-0.170	0.239	-0.042	-0.100, 0.017
	6 Week Washout	149	2.703	0.661	-0.139	0.214	0.008	-0.049, 0.065
	12 Week Washout	132	2.689	0.677	-0.164	0.237	-0.014	-0.073, 0.044
Comparator	Baseline	1119	2.928	0.728				
	Week 12	648	2.926	0.714	-0.028	0.176		
	Week 24	795	2.873	0.709	-0.049	0.205		
	Week 36	532	2.835	0.702	-0.075	0.202		
	Week 48/52	496	2.851	0.714	-0.071	0.209		
	Week 65	134	2.718	0.655	-0.055	0.253		
	Week 78	139	2.717	0.665	-0.106	0.246		
	Week 91	134	2.699	0.634	-0.096	0.263		
	Week 104	125	2.708	0.641	-0.128	0.247		
	6 Week Washout	138	2.707	0.670	-0.147	0.273		
	12 Week Washout	128	2.689	0.645	-0.150	0.243		

Table 39: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FEV1 Score in Controlled Phase 2/3 Studies in Type 2 Adults

Week	Unadjusted Difference	95% CI	Adjusted* Difference	95% CI	Adjusted** Difference	95% CI
12	-0.036	-0.055, -0.017	-0.044	-0.065, 0.024	-0.043	-0.063, -0.022
24	-0.025	-0.045, -0.005	-0.023	-0.042, -0.004	-0.024	-0.043, -0.005
36	-0.017	-0.041, 0.006	-0.009	-0.031, 0.014	-0.009	-0.032, 0.013
52	-0.034	-0.059, -0.009	-0.027	-0.051, -0.002	-0.028	-0.052, -0.005
65	-0.028	-0.083, 0.027	-0.029	-0.072, 0.014	-0.027	-0.067, 0.013
78	-0.013	-0.064, 0.038	-0.012	-0.058, 0.033	-0.010	-0.054, 0.033
91	-0.057	-0.112, -0.001	-0.056	-0.103, -0.009	-0.053	-0.099, -0.008
104	-0.042	-0.100, 0.017	-0.033	-0.082, 0.016	-0.031	-0.078, 0.017

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

The proportions of subjects who had reduction in FEV1 from baseline at each timepoint (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions are presented in Figure 27. Inspection of these graphs suggests that there are apparent differences in the proportion of subjects who had reduction in FEV1 from baseline between the two treatment groups in favor of the comparator group before Week 48. The treatment difference appears to diminish slowly after Week 48 particularly those who had more than 6% reduction, except at Week 84. Note however, that these reductions are generally very small. In fact, only a small proportion of subjects (1% maximum) had reduction of more than 15%, although this appears to increase especially after Week 48 in the comparator group.

Figure 27: Proportion of Subjects by Percent Reduction from Baseline in FEV1 (L) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

Percent Reduction in FEV1 (L) from Baseline at Week 12

Percent Reduction in FEV1 (L) from Baseline at Week 36

Percent Reduction in FEV1 (L) from Baseline at Week 24

Percent Reduction in FEV1 (L) from Baseline at Week 48

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Percent Reduction in FEV1 (L) from Baseline at Week 60

Percent Reduction in FEV1 from Baseline at Week 96

Percent Reduction in FEV1 (L) from Baseline at Week 72

Percent Reduction in FEV1 (L) from Baseline 6 Weeks after Washout

Percent Reduction in FEV1 (L) from Baseline at Week 84

Percent Reduction in FEV1 (L) from Baseline 12 Weeks after Washout

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70
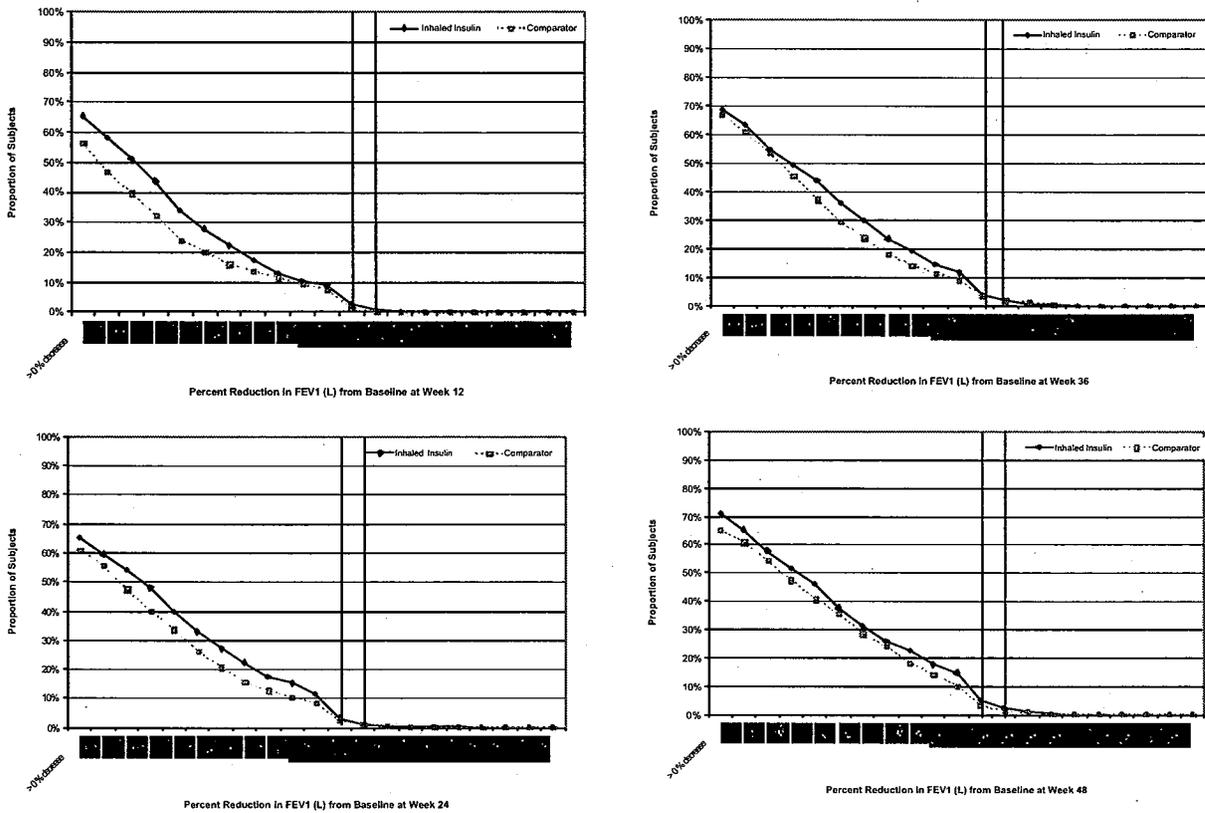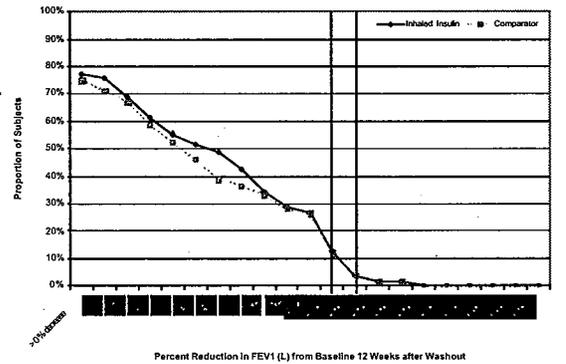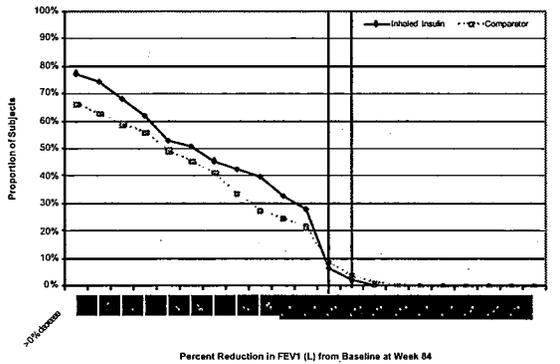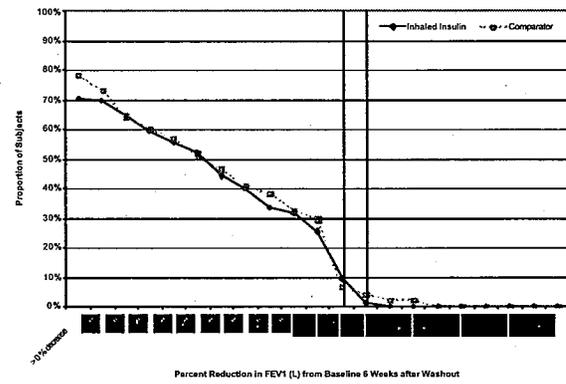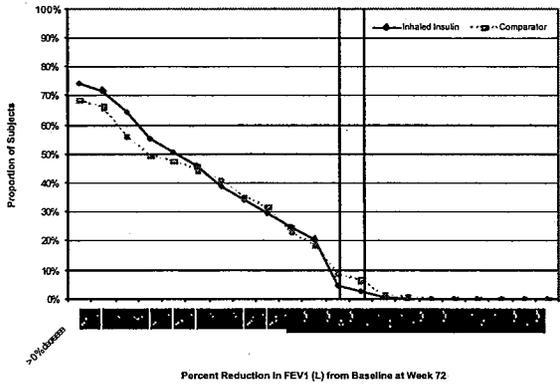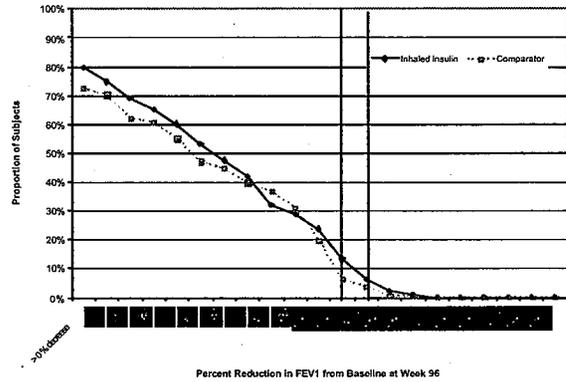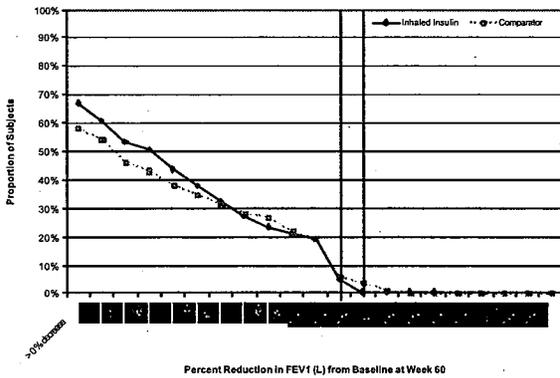
Diffusion Lung Capacity (DLco)

From the results of the individual studies, there appears to be a slow and steady decline in mean change from baseline in DLco among INH- and comparator- treated subjects up to 96 weeks (2 years) of exposure (Figure 21). In most of the individual studies, there was a consistent treatment group difference numerically favoring the comparator. However, these differences were not supported by the confidence interval. Note that one of the concerns Dr. Seymour had was in the change in direction on the treatment difference from Week 91 and Week 104 (i.e. -0.431 and 0.054, respectively) in combined studies 1001 and 1002. This phenomenon is seen also in the pooled analysis (Table 41 and Table 42). After careful exploration of the scatterplots in the between Weeks 91 and 104, I found that there were several outliers that could explain this shift in direction. Some of the extreme outliers are presented in Table 40. Removal of the two extremes (PID: 100101380278 and 100100590136) led to a negative treatment differences at Weeks 91 and 104, making them consistent. It is unknown what happened to these outliers, so removal of these subjects may not be the best way to handle this problem. Therefore, I would note of such problem, but will still include these subjects in the analysis.

Table 40: Change from Baseline in DLco at Weeks 91 and 104

PID	Treatment Group	Change from Baseline PFT at 91	Change from Baseline PFT at 104
100200477343	INH	0.5729	-7.4491
100100590133	Comparator	-0.0322	-5.2679
100201315262	INH	8.2805	-3.8506
100101380278	INH	-6.6139	10.9050
100100590136	INH	-11.7171	14.7865

Figure 28: Exploratory Analysis of the Change from Baseline in DLco at Week 91 by Change from Baseline in DLco at Week 104

Change from Baseline in DLco at Week 104

0=Comparator, 1=Inhaled Insulin
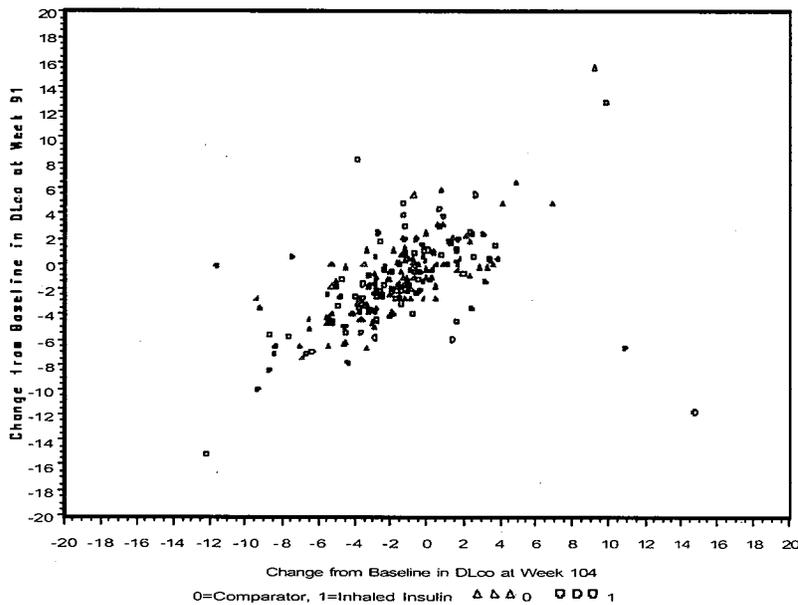
In the pooled data set, there also appears to be a slow and steady decline in mean change from baseline in DLco among INH- and comparator- treated subjects up to 96 weeks (2 years) of exposure (Table 34). Similar to the results from the individual studies, treatment group differences in mean change from baseline in DLco numerically favors the comparator therapy among adult subjects with Type 2 diabetes after 3 months of therapy, except at Weeks 36 and 96/104. Similar to the individual studies in 1001 and 1002, there is a change in direction from Weeks 91 and 104, which is the result of few outliers in the data. Meanwhile, data for Week 36 is only available in Study 1029, thus the samples are very small, and this shift in direction could again be due to some outliers. Note however, that in Study 1029, Week 24 is -0.163, Week 36 is 0.071, and Week 48 is -0.264, which in a sense are not that extreme, unlike the week 91 and 104 data. The applicant claims that the effect of INH on DLco did not appear to be progressive (Table 41, Table 42; Figure 29). Meanwhile, although the mean change from baseline in DLco score in both the inhaled insulin and the comparator groups did not improve 6 weeks and 12 weeks after washout, the treatment different appears to be smaller and slightly in favor of inhaled insulin at 6 weeks after washout. However, this observation appears to be false at 12 weeks after washout. The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 0.4 mL/min/mmHg for DLco at week 84/91.

All of the data in the pooled studies after week 48 are from combined Studies 1001 and 1002, therefore the results from the Pooled analysis and from combined studies 1001 and 1002 are fairly consistent

Figure 29: Mean Change from Baseline in DLco (mL/min/mmHg) by Time in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

Table 41: Mean Change from Baseline in DLco Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 2 Adults

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Difference	Inhaled - Comparator 95% CI
Inhaled	Baseline	1234	25.091	6.152				
	Week 12	618	24.091	6.006	-0.666	2.660	-0.278	-0.568, 0.011
	Week 24	808	24.516	6.225	-0.540	3.046	-0.145	-0.445, 0.154
	Week 36	265	23.728	5.389	-0.660	1.804	0.071	-0.230, 0.373
	Week 48/52	518	24.559	6.297	-0.742	3.203	-0.151	-0.535, 0.233
	Week 65	141	24.550	5.748	-1.352	3.730	-0.570	-1.416, 0.276
	Week 78	138	24.200	5.922	-1.588	3.088	-0.270	-1.029, 0.489
	Week 91	139	24.251	5.830	-1.495	3.563	-0.431	-1.252, 0.390
	Week 104	129	24.017	5.743	-1.529	3.791	0.054	-0.846, 0.954
	6 Week Washout	132	24.114	5.998	-1.133	3.731	0.214	-0.628, 1.056
	12 Week Washout	112	24.218	5.735	-1.253	3.610	-0.103	-1.013, 0.806
Comparator	Baseline	1094	24.892	6.172				
	Week 12	501	24.135	5.934	-0.388	2.177		
	Week 24	769	24.411	6.057	-0.395	3.012		
	Week 36	271	23.239	5.562	-0.731	1.751		
	Week 48/52	487	24.195	6.033	-0.591	2.991		
	Week 65	128	24.288	5.810	-0.782	3.270		
	Week 78	121	24.243	5.686	-1.318	3.104		
	Week 91	126	24.135	5.582	-1.063	3.185		
	Week 104	116	24.056	5.664	-1.583	3.306		
	6 Week Washout	128	24.364	5.818	-1.347	3.127		
	12 Week Washout	119	24.569	5.765	-1.149	3.402		

Table 42: Unadjusted and Sponsor-defined Adjusted Treatment Difference in DLco Score in Controlled Phase 2/3 Studies in Type 2 Adults

Week	Unadjusted Difference	Unadjusted 95% CI	Adjusted* Difference	Adjusted* 95% CI	Adjusted** Difference	Adjusted** 95% CI
12	-0.278	-0.568, 0.011	-0.251	-0.572, 0.069	-0.230	-0.540, 0.079
24	-0.145	-0.445, 0.154	-0.175	-0.456, 0.107	-0.163	-0.429, 0.104
36	0.071	-0.230, 0.373	0.089	-0.305, 0.483	0.107	-0.277, 0.490
52	-0.151	-0.535, 0.233	-0.148	-0.497, 0.202	-0.122	-0.455, 0.210
65	-0.570	-1.416, 0.276	-0.213	-0.785, 0.358	-0.180	-0.737, 0.376
78	-0.270	-1.029, 0.489	-0.116	-0.761, 0.528	-0.075	-0.696, 0.546
91	-0.431	-1.252, 0.390	-0.204	-0.876, 0.469	-0.173	-0.814, 0.468
104	0.054	-0.846, 0.954	0.167	-0.543, 0.877	0.194	-0.481, 0.869

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

The proportions of subjects who had reduction in DLco at baseline at each timepoints (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions are presented in Figure 30. Inspection of these graphs suggests that there are some differences in the proportion of subjects who had reduction in DLco from baseline between the two treatment groups in favor of the comparator group at Weeks 12 and after Week 48. But these differences are small compared to the Type 1 data. Although these reductions are generally very small (most subjects had at most 10% reduction), same as the Type 1 data, there are quite a few in the inhaled insulin group that had at least 15% reduction compared to the comparator group.

Figure 30: Proportion of Subjects by Percent Reduction from Baseline in DLco (mL/min/mmHg) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

Percent Reduction in DLco (mL/min/mmHg) from Baseline at Week 84

Percent Reduction in DLco (mL/min/mmHg) from Baseline 6 Weeks after Washout

Percent Reduction in DLco (mL/min/mmHg) from Baseline at Week 96

Percent Reduction in DLco (mL/min/mmHg) from baseline 12 Weeks after Washout
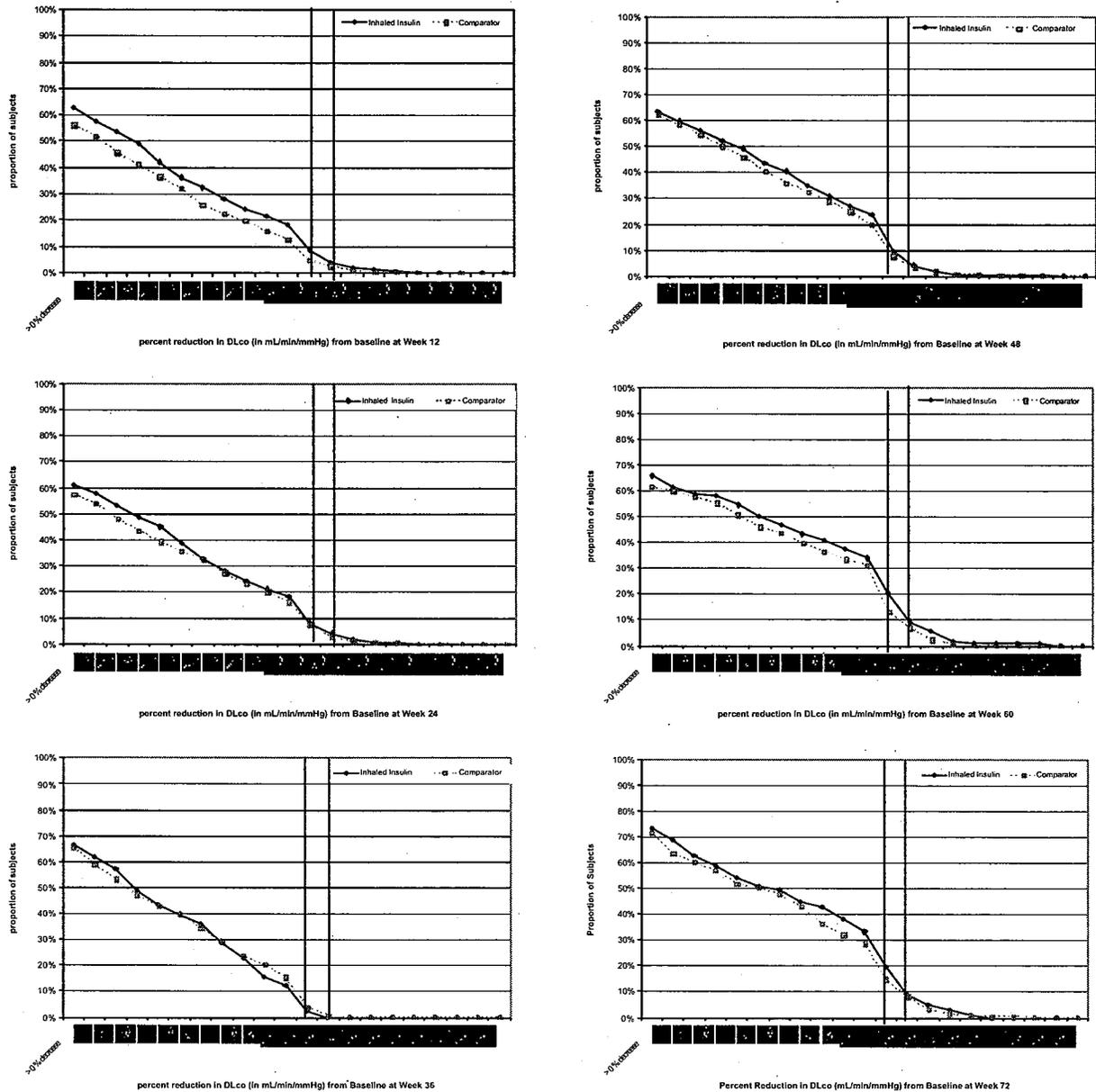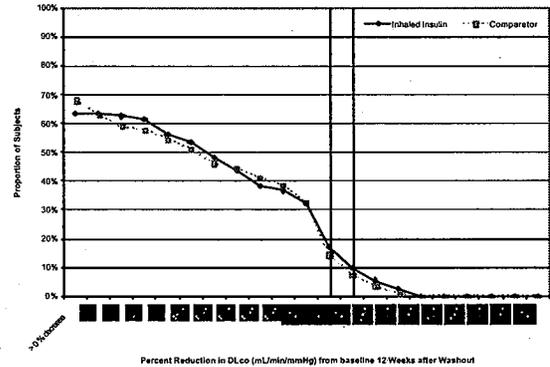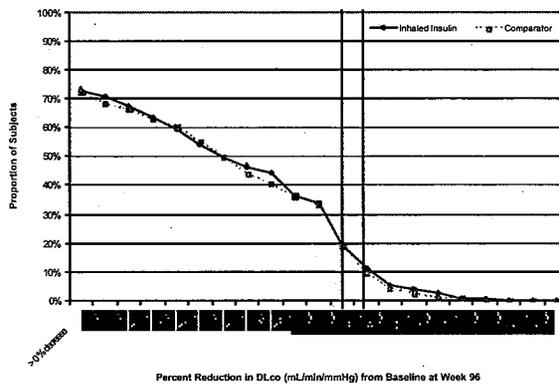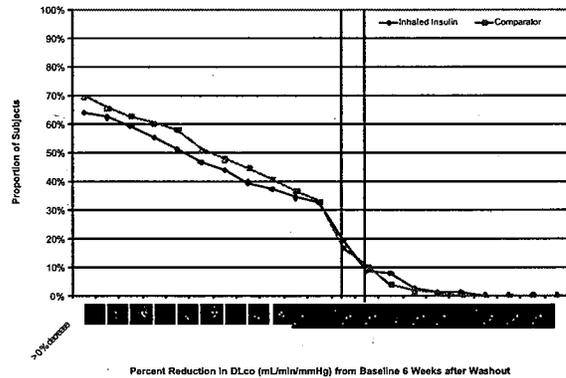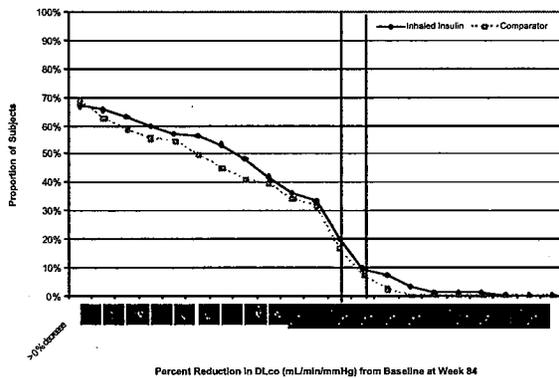
Forced Vital Capacity (FVC)

As seen from the individual studies, there appears to be a small decline that looks to be constant over time in mean change from baseline in FVC among INH- and comparator- treated subjects (Table 33). Treatment group differences were comparable between inhaled insulin group and the comparator group in the sense that all 95% confidence intervals included the zero difference (Figure 23).

Similar conclusions can be drawn from the pooled data set. Treatment group differences were small and fairly consistent between the two treatment groups (Table 43, Table 44; Figure 31). The results were fairly robust when adjusted model was used. Thus, the treatment differences were of a magnitude of about 10 mL for FVC at the end of the study. In terms of the two washout data, the mean change from baseline in FVC score did not improve at 6 weeks or 12 weeks after washout in both treatment groups. However, the treatment different numerically appears to be in favor of inhaled insulin at 6 weeks and 12 weeks after washout.

All of the data in the pooled studies after week 48 are from the combined studies 1001 and 1002, therefore the results from the Pooled analysis and from the combined studies 1001 and 1002 are fairly consistent.

The proportions of subjects who had reduction in FVC at baseline at each time points (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. In general, the graphs suggest that there are no differences in the proportion of subjects who had any reduction in FVC from baseline between the two treatment groups, except at week 12 (in favor of comparator) and during the

washout phase (slightly in favor of the inhaled insulin). Only few subjects (<1%) had reduction of more than 15% during the early phase of the treatment period, but this soon increased to 5% after week 48, particularly in the comparator insulin group.

Figure 31: Mean Change from Baseline in FVC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes
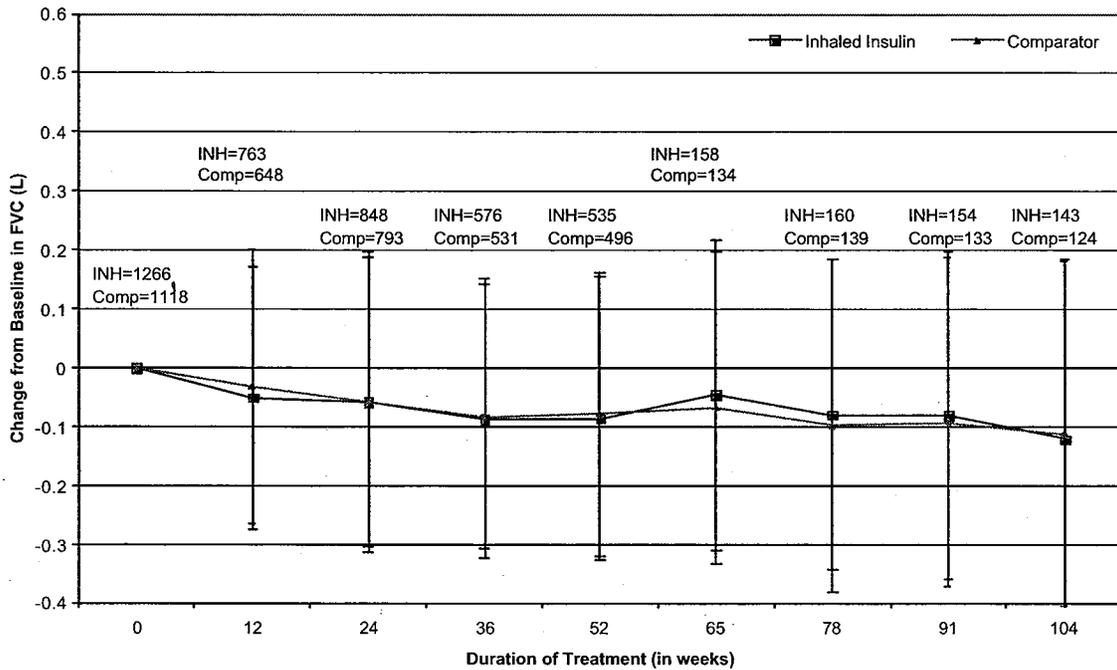
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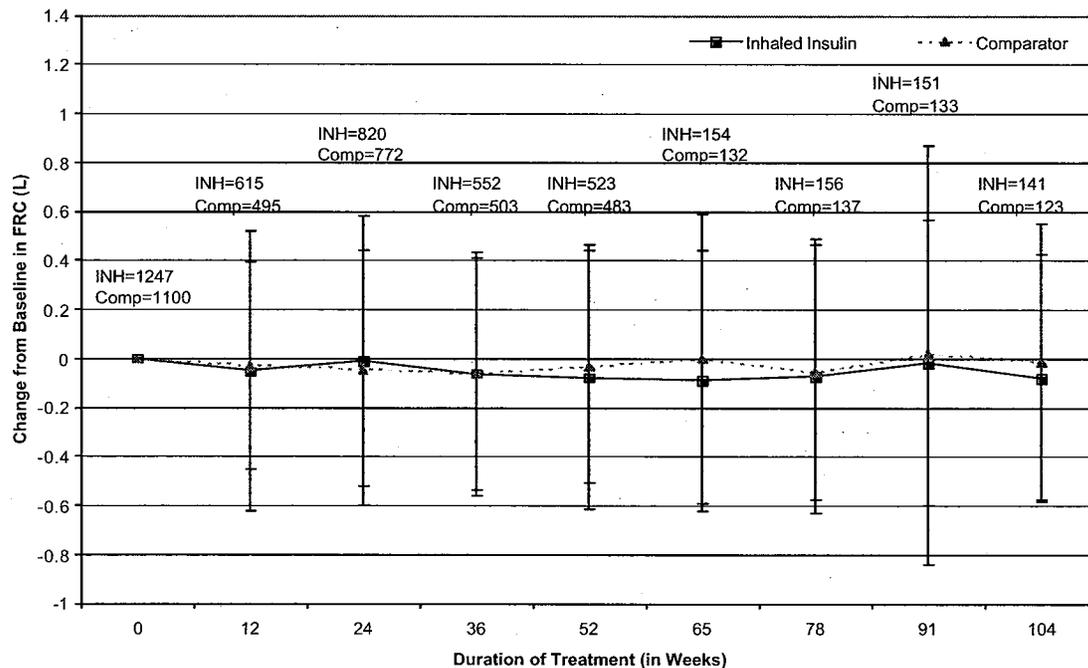
Table 43: Mean Change from Baseline in FVC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 2 Adults

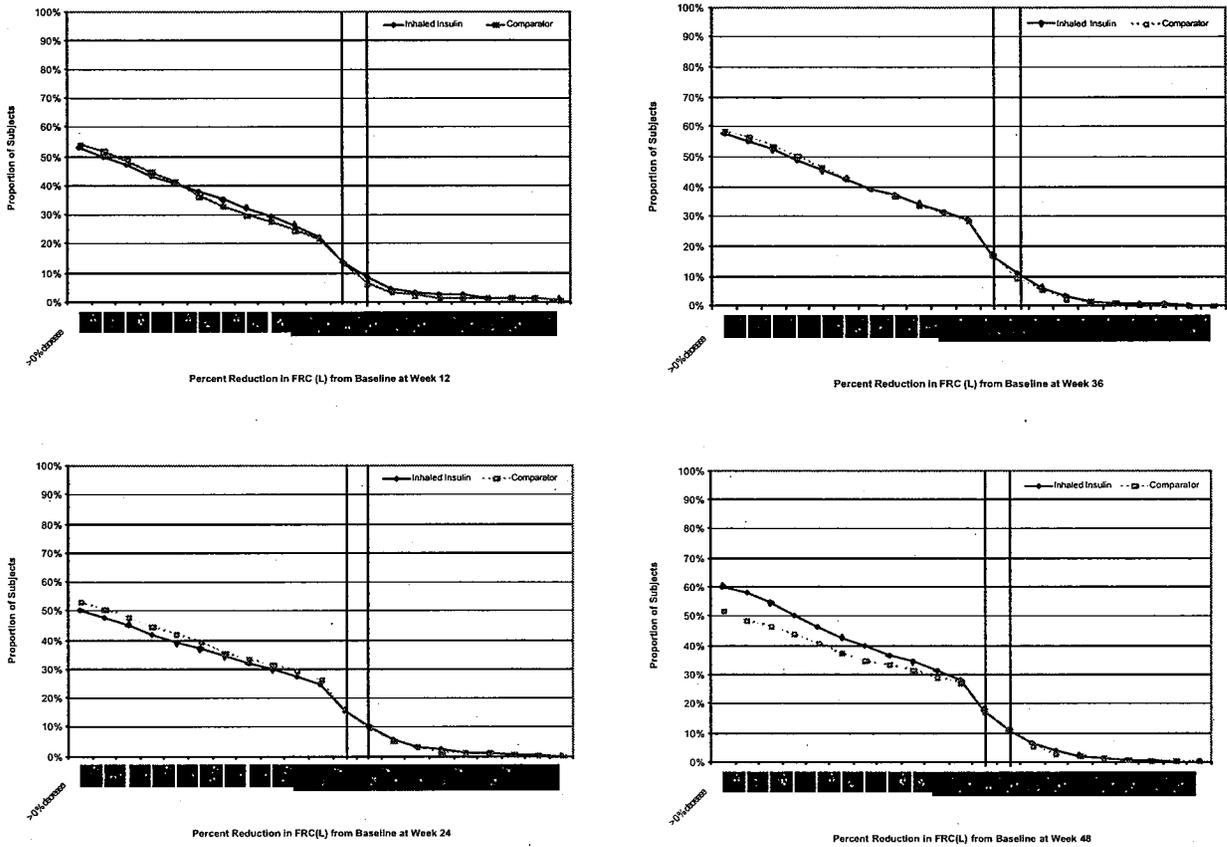| Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	1266	3.664	0.889				
	Week 12	763	3.665	0.877	-0.051	0.224	-0.020	-0.044, 0.004
	Week 24	848	3.576	0.883	-0.059	0.246	-0.001	-0.025, 0.023
	Week 36	576	3.578	0.870	-0.087	0.238	-0.004	-0.031, 0.023
	Week 48/52	535	3.575	0.871	-0.086	0.242	-0.006	-0.036, 0.023
	Week 65	158	3.458	0.830	-0.046	0.263	0.022	-0.039, 0.083
	Week 78	160	3.405	0.863	-0.080	0.263	0.018	-0.044, 0.080
	Week 91	154	3.388	0.843	-0.081	0.278	0.012	-0.053, 0.077
	Week 104	143	3.342	0.856	-0.121	0.304	-0.010	-0.082, 0.063
	6 Week Washout	149	3.358	0.846	-0.094	0.279	0.047	-0.020, 0.113
	12 Week Washout	132	3.345	0.864	-0.124	0.242	0.023	-0.045, 0.090
Comparator	Baseline	1118	3.666	0.926				
	Week 12	648	3.707	0.917	-0.031	0.233		
	Week 24	793	3.610	0.904	-0.058	0.255		
	Week 36	531	3.578	0.899	-0.083	0.224		
	Week 48/52	496	3.586	0.909	-0.079	0.240		
	Week 65	134	3.375	0.794	-0.068	0.264		
	Week 78	139	3.395	0.802	-0.098	0.282		
	Week 91	133	3.383	0.774	-0.093	0.279		
	Week 104	124	3.411	0.766	-0.112	0.293		
	6 Week Washout	137	3.402	0.804	-0.140	0.294		
	12 Week Washout	127	3.394	0.788	-0.147	0.308		

Table 44: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FVC Score in Controlled Phase 2/3 Studies in Type 2 Adults

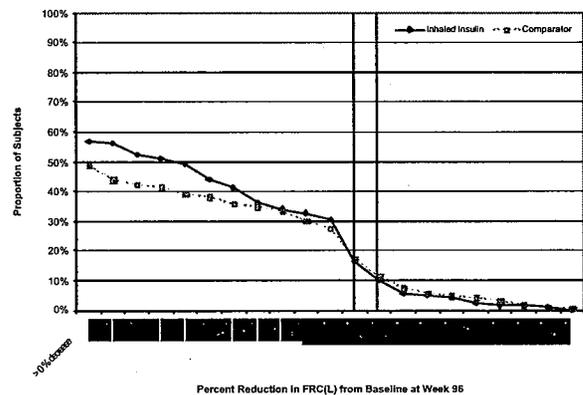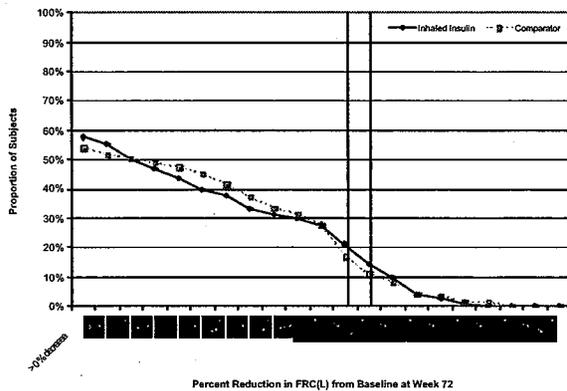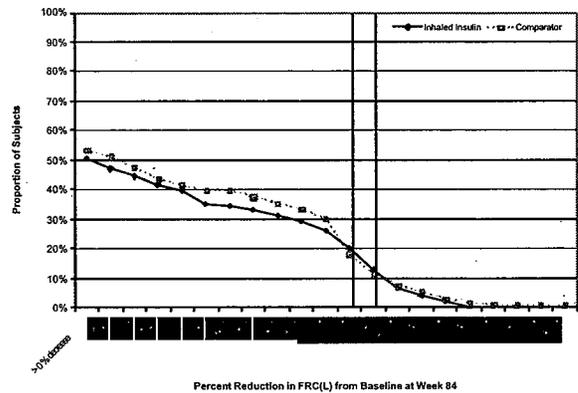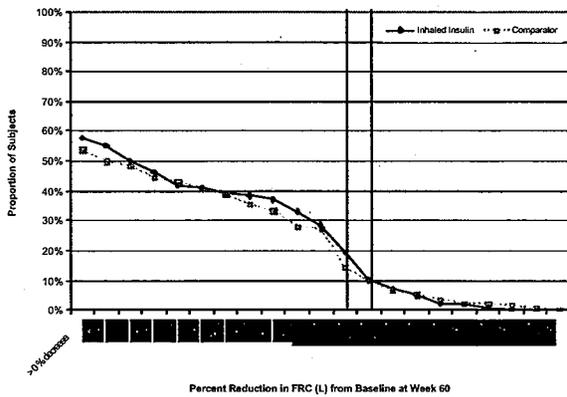| Week	Unadjusted Difference	Unadjusted 95% CI	Adjusted* Difference	Adjusted* 95% CI	Adjusted** Difference	Adjusted** 95% CI
12	-0.020	-0.044, 0.004	-0.028	-0.052, -0.004	-0.029	-0.054, -0.005
24	-0.001	-0.025, 0.023	0.002	-0.021, 0.025	-0.001	-0.024, 0.022
36	-0.004	-0.031, 0.023	0.007	-0.020, 0.034	0.003	-0.023, 0.030
52	-0.006	-0.036, 0.023	0.002	-0.027, 0.030	-0.002	-0.031, 0.026
65	0.022	-0.039, 0.083	0.009	-0.038, 0.057	-0.008	-0.039, 0.055
78	0.018	-0.044, 0.080	0.013	-0.039, 0.057	0.012	-0.040, 0.063
91	0.012	-0.053, 0.077	0.009	-0.046, 0.064	0.007	-0.047, 0.061
104	-0.010	-0.082, 0.063	-0.005	-0.063, 0.052	-0.008	-0.064, 0.049

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

Forced Residual Capacity (FRC)

As seen from the individual studies, there appears to be a very small decline that looks constant across time in mean change from baseline in FRC among INH- and comparator- treated subjects (Table 35). Treatment group differences were comparable between inhaled insulin group and the comparator group, but numerically favored the comparator group after Week 12 (Figure 24).

Similar conclusions can be drawn from the pooled data set. Treatment group differences were comparable between the two treatment groups in the sense that the confidence interval includes zero difference. There appears to be a small separation between the two groups after Week 36 (Table 45, Table 46; Figure 32). The treatment differences were slightly bigger in the adjusted model, but generally are in the same direction as the unadjusted (i.e. favoring the comparator group). Thus, the treatment differences were of a magnitude of about 0 – 90 mL for FRC (taking into account the adjusted model), and about 70 mL at the end of the study (week 96/104). In terms of the two washout data, the mean change from baseline in FRC score did not improve at 6 weeks or 12 weeks after washout in both treatment groups. The treatment difference improved a little at 12 weeks after washout, in favor of inhaled insulin.

All of the data in the pooled studies after week 48 are from the combined studies 1001 and 1002, therefore the results from the Pooled analysis and from combined studies 1001 and 1002 are fairly consistent.

Figure 32: Mean Change from Baseline in FRC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 1 Diabetes

Table 45: Mean Change from Baseline in FRC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 2 Adults

Treatment Group		Observed			Change from Baseline		Inhaled - Comparator	
		N	Mean	SD	Mean	SD	Difference	95% CI
Inhaled	Baseline	1247	2.824	0.842				
	Week 12	615	2.728	0.816	-0.051	0.570	-0.022	-0.083, 0.038
	Week 24	820	2.828	0.876	-0.011	0.589	0.032	-0.022, 0.085
	Week 36	552	2.781	0.824	-0.062	0.498	0.00002	-0.059, 0.059
	Week 48/52	523	2.772	0.838	-0.076	0.542	-0.045	-0.109, 0.018
	Week 65	154	2.744	0.690	-0.089	0.530	-0.088	-0.218, 0.043
	Week 78	156	2.729	0.741	-0.071	0.561	-0.015	-0.140, 0.110
	Week 91	151	2.768	0.726	-0.016	0.582	-0.033	-0.202, 0.136
	Week 104	141	2.716	0.783	-0.080	0.504	-0.068	-0.197, 0.061
	6 Week Washout	147	2.653	0.763	-0.130	0.572	-0.081	-0.215, 0.053
	12 Week Washout	130	2.692	0.825	-0.067	0.620	-0.024	-0.176, 0.129
Comparator	Baseline	1100	2.798	0.824				
	Week 12	495	2.692	0.825	-0.029	0.424		
	Week 24	772	2.785	0.838	-0.043	0.481		
	Week 36	503	2.751	0.842	-0.062	0.472		
	Week 48/52	483	2.789	0.858	-0.031	0.473		
	Week 65	132	2.856	0.892	-0.001	0.591		
	Week 78	137	2.811	0.898	-0.056	0.518		
	Week 91	133	2.849	1.055	0.017	0.855		
	Week 104	123	2.835	0.856	-0.012	0.563		
	6 Week Washout	136	2.860	0.895	-0.048	0.575		
	12 Week Washout	126	2.858	0.866	-0.044	0.622		

Table 46: Unadjusted and Sponsor-defined Adjusted Treatment Difference in FRC Score in Controlled Phase 2/3 Studies in Type 2 Adults

Week	Unadjusted		Adjusted*		Adjusted**	
	Difference	95% CI	Difference	95% CI	Difference	95% CI
12	-0.022	-0.083, 0.038	0.000	-0.059, 0.059	-0.009	-0.066, 0.047
24	0.032	-0.022, 0.085	0.021	-0.030, 0.072	0.011	-0.036, 0.059
36	0.00002	-0.059, 0.059	-0.012	-0.071, 0.048	-0.021	-0.078, 0.035
52	-0.045	-0.109, 0.018	-0.059	-0.123, 0.005	-0.068	-0.128, -0.009
65	-0.088	-0.218, 0.043	-0.087	-0.193, 0.019	-0.096	-0.198, 0.006
78	-0.015	-0.140, 0.110	-0.006	-0.121, 0.109	-0.018	-0.127, 0.091
91	-0.033	-0.202, 0.136	-0.054	-0.174, 0.067	-0.064	-0.177, 0.049
104	-0.068	-0.197, 0.061	-0.060	-0.186, 0.065	-0.072	-0.190, 0.046

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

The proportions of subjects who had reduction in FRC at baseline at each timepoint (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. Inspection of each individual graphs (by timepoints) suggests no difference in the reduction profile of subjects in the inhaled insulin group and the comparator group except at Weeks 48 and 96. It appears that the differences are small that a slight separation of curves may be due to random variation. Although reductions in FRC score were generally small, there were quite a few in both treatment groups (almost 20% in each group) that had reduction of more than 15% (Figure 33).

Figure 33: Proportion of Subjects by Percent Reduction from Baseline in FRC (L) at each Time Points in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

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Percent Reduction in FRC (L) from Baseline at Week 60

Percent Reduction in FRC(L) from Baseline at Week 84

Percent Reduction in FRC(L) from Baseline at Week 72

Percent Reduction in FRC(L) from Baseline at Week 96

Total Lung Capacity (TLC)

As seen from the individual studies, there appears to be minimal to no decline in mean change from baseline in TLC among INH-treated group, while there appears to be very small decline in the comparator-treated subjects. These observations were consistent over time up to 96 weeks (2 years) of exposure (Table 36). Treatment group differences were comparable between the inhaled insulin group and the comparator group in the sense that the confidence intervals include zero difference, but numerically favored the comparator insulin group in most studies, which is the opposite of what is seen in the Type 1 data (Figure 25).

Similar conclusions can be drawn from the pooled data set. Treatment group differences were comparable between the two treatment groups (Figure 34), but from Table 47 and Table 48, it appears that numerically there is a small difference between the two groups favoring the comparator insulin group except at Week 24. The treatment differences were of a magnitude of about 10 – 90 mL for TLC (taking into account the adjusted model), and about 30 mL at the end of the study (week 96/104). In terms of the two washout data, the mean change from baseline in TLC score did not improve at 6 weeks or 12 weeks after washout in both treatment groups. The treatment difference improved a little at 12 weeks after washout, in favor of inhaled insulin.

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Figure 34: Mean Change from Baseline in TLC (L) by Time in Adults Phase 2/3 Controlled Studies in Type 2 Diabetes

All of the data in the pooled studies after week 48 are from the combined studies 1001 and 1002, therefore the results from the Pooled analysis and from combined studies 1001 and 1002 are fairly consistent.

The proportions of subjects who had reduction in TLC at baseline at each timepoint (Weeks 12, 24, 36, 48, 60, 78, 84, and 96), for all the various definitions of PFT reductions were also explored. Inspection of each of the individual graphs (by time points) suggests no difference in the reduction profile of subjects in the inhaled insulin group and the comparator group except at Weeks 60, 72 and 96. It appears that the differences are small that a slight separation of curves may be due to random variation. There were only a few in both treatment groups that had reduction of more than 15%.

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Table 47: Mean Change from Baseline in TLC Score and Unadjusted Treatment Group Difference in Controlled PFT Phase 2/3 Studies in Type 2 Adults

Treatment Group		N	Observed Mean	SD	Change from Baseline Mean	SD	Inhaled - Comparator Difference	95% CI
Inhaled	Baseline	1264	5.741	1.233				
	Week 12	620	5.720	1.279	-0.026	0.444	-0.024	-0.075, 0.028
	Week 24	829	5.707	1.281	0.011	0.595	0.040	-0.014, 0.094
	Week 36	559	5.692	1.274	-0.021	0.521	-0.016	-0.077, 0.045
	Week 48/52	531	5.662	1.226	-0.047	0.491	-0.060	-0.120, -0.001
	Week 65	156	5.570	1.254	-0.036	0.532	-0.088	-0.221, 0.046
	Week 78	158	5.566	1.285	-0.008	0.572	-0.027	-0.177, 0.122
	Week 91	153	5.556	1.233	-0.010	0.570	-0.027	-0.161, 0.108
	Week 104	143	5.559	1.264	-0.022	0.495	-0.030	-0.160, 0.101
	6 Week Washout	148	5.495	1.264	-0.058	0.552	-0.025	-0.161, 0.110
	12 Week Washout	132	5.515	1.374	-0.035	0.602	0.009	-0.137, 0.154
Comparator	Baseline	1115	5.686	1.251				
	Week 12	503	5.689	1.314	-0.003	0.432		
	Week 24	783	5.644	1.262	-0.029	0.495		
	Week 36	509	5.607	1.269	-0.005	0.488		
	Week 48/52	487	5.630	1.272	0.013	0.473		
	Week 65	133	5.605	1.284	0.052	0.618		
	Week 78	138	5.626	1.307	0.020	0.736		
	Week 91	133	5.555	1.245	0.017	0.587		
	Week 104	124	5.587	1.203	0.008	0.590		
	6 Week Washout	137	5.621	1.269	-0.032	0.610		
	12 Week Washout	127	5.582	1.262	-0.043	0.584		

Table 48: Unadjusted and Sponsor-defined Adjusted Treatment Difference in TLC Score in Controlled Phase 2/3 Studies in Type 2 Adults

Week	Unadjusted Difference	95% CI	Adjusted* Difference	95% CI	Adjusted** Difference	95% CI
12	-0.024	-0.075, 0.028	-0.013	-0.070, 0.044	-0.016	-0.072, 0.040
24	0.040	-0.014, 0.094	0.037	-0.012, 0.086	0.028	-0.019, 0.076
36	-0.016	-0.077, 0.045	-0.004	-0.061, 0.054	-0.011	-0.068, 0.045
52	-0.060	-0.120, -0.001	-0.047	-0.109, 0.014	-0.055	-0.116, 0.004
65	-0.088	-0.221, 0.046	-0.087	-0.189, 0.014	-0.094	-0.194, 0.007
78	-0.027	-0.177, 0.122	-0.016	-0.127, 0.095	-0.021	-0.131, 0.088
91	-0.027	-0.161, 0.108	-0.028	-0.144, 0.089	-0.032	-0.145, 0.082
104	-0.030	-0.160, 0.101	-0.028	-0.150, 0.094	-0.028	-0.146, 0.091

Unadjusted Model – Treatment
Adjusted* - includes Treatment and Visit, by Sponsor, using Spatial Power as Variance-Covariance Structure
Adjusted** - includes: Treatment, Protocol, Visit, Baseline Measurement, Age, Gender, and Baseline Height, by Sponsor, using Spatial Power as Variance-Covariance Structure

Pulmonary Function Test and Antibody Titer

Similar to Type 1 data, I also explored the relationship between the change in pulmonary function tests and the antibody titer by week of treatment using pooled Type 2 data. A regression line, to assess the relationship between the change from baseline of PFT measurements and the antibody titer, was plotted for the inhaled insulin-treated group. Correlation coefficients were included in the graphs to indicate how the antibody titers are related to the change in PFT measurements.

In general, the graphs showed that most of the correlations are small and negative (Appendix II, Sections A – E). These may even be significant in some cases since even small correlations can be significant if the dataset is large enough. However, statistical significance, in general and especially true for correlations, is not the same as clinical significance. Therefore I find that there is no strong evidence to suggest any correlation between the change from baseline in pulmonary function tests and antibody titers. There is also no evidence of a 'correlation' trend over time in each of the PFT measurements.

Pulmonary Function Test and Insulin Dosing

The relationship between pulmonary function tests and the dosing was also explored. I looked at the change from baseline of PFT measurements with subject-reported average daily inhaled insulin doses at that specific week, as well as subject's cumulative daily insulin doses at that specific visit window using the combined 1001 and 1002 studies (see Appendix II, Sections H – L). Because of the different study drugs (particularly on the comparator group) that the subjects were treated to, I did not explore this relationship in the comparator group, or the pooled data for that matter.

Numerically the correlation coefficients are very small between the change from baseline in any of the pulmonary function test and the average total or cumulative total daily dose in the inhaled insulin group. Although most of these coefficients (from DLco, FEV1, and FVC measures) are negative, indicating some decrease in lung function with increasing dose, but these correlations are not strong enough to warrant any concern. Similarly, in FRC and TLC, change from baseline appears to be negatively correlated with insulin dose at the beginning but became positive towards Week 36 and Week 64, respectively. Again, these correlations are small and may not be clinically significant.

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4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

Analyses to assess the pulmonary safety of INH in different subpopulations based on age, race, and gender were performed using pooled Type 1 and pooled Type 2 data from controlled Phase 2/3 studies. Data were summarized for subjects with Type 1 DM and Type 2 DM using inhaled insulin or comparative insulin (i.e. subcutaneous or oral agents). Results are shown for subjects = 18 years of age. Treatment difference within each subgroups were analyzed using the unadjusted model (PROC GLM) and the mixed model repeated measures (PROC MIXED) with covariates (baseline PFT, height, visit/time, age, male, protocol/study) to be consistent with the analyses done in the pooled data. Adjusting for the categorical variable gender should not affect the results or lose degrees of freedom using MMRM when analyzing the gender subpopulations since it will just ignore the variable. Meanwhile, adjusting for the continuous variable age when analyzing the age subpopulation should make the confidence intervals tighter.

4.1 SEX, RACE AND AGE

In this review, I find that there appears to be a greater decline in pulmonary function among inhaled insulin treated group, specifically FEV1 and DLco, than the comparator groups in both Type 1 and Type 2 Diabetes. Age for Type 1 DM are categorized into two groups: 18 – 44 and = 45. Because only a minority of subjects is > 64 years of age, Dr. Seymour and I decided it best to include these subjects in the = 45 group. In Type 2 Diabetes, because subjects were a lot older than Type 1 (Table XX for Type 1 Demo; Table XX for Type 2), we decided to categorize age into three groups: 18 – 44, 45 – 64, and = 65. Since majority of subjects were white, we collapsed Blacks, Hispanics, Asians and others into the non-white group.

4.1.1 TYPE 1 DATA

It appears that majority of the subjects were between ages 18 to 44 (72%) in both treatment groups. Male subjects accounted for close to 55% in the Type 1 population in both treatment groups, while around 90% of the Type 1 population was white.

FEV_1, DLco, FVC, FRC, and TLC data for subjects with Type 1 DM are presented by age groups, gender, and race groups in Figure 35 to Figure 39. Descriptive statistics for change from baseline in each treatment groups by strata are available upon request.

In general, there appears to be a small shift in the treatment difference in FEV1, FVC, FRC, and TLC among subjects who were older (>44 years of age) in favor of the comparator group. However, this increase in treatment difference does not appear to be a cause for alarm. One possible reason for this shift could be due the natural decline of most PFT scores as one gets older, or this could also be due to unbalance sample size between the subgroups (e.g. 27% age > 44 vs. 72% age 18 - 44). There is no difference between unadjusted and adjusted model accounting for age.

In terms of race, there is no apparent difference between male and female subgroups in both unadjusted and adjusted model except on FRC score. There appears to be a gender difference in terms of FRC score which is quite difficult to explain except that this may just be random occurrence.

There also appears to be disparity in treatment difference among white and non-white subjects. This could easily be due to the enormous discrepancy in the sample size between the subgroups (e.g. 10% non-whites vs. 90% whites).

Figure 35: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race using Unadjusted and Mixed Model (Spatial Power) in FEV₁ (L) Score

Figure 38: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race in FRC (L) Score
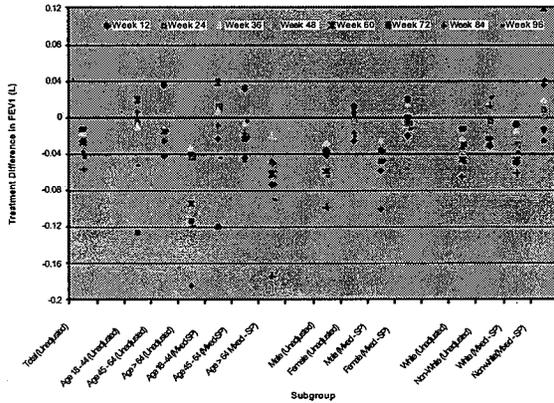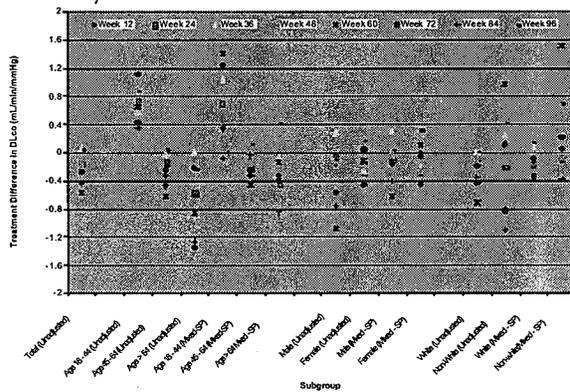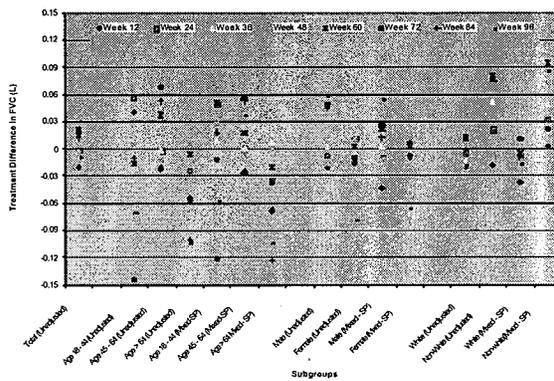

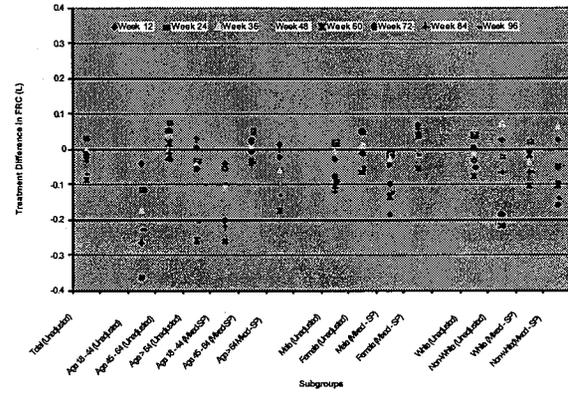Figure 36: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race in DLco (mL/min/mmHg) Score
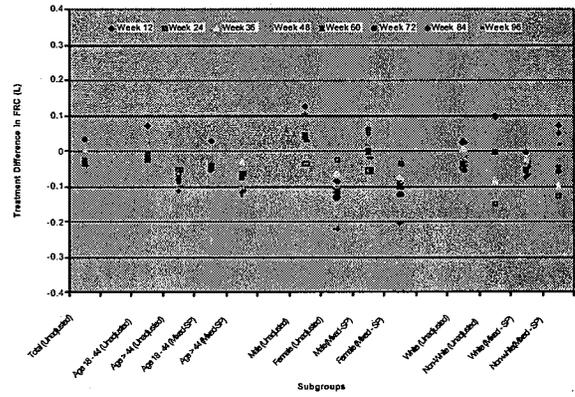
Figure 39: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race in TLC (L) Score

Figure 37: Subgroup Analyses on Pooled Type 1 Adults by Age, Gender, and Race
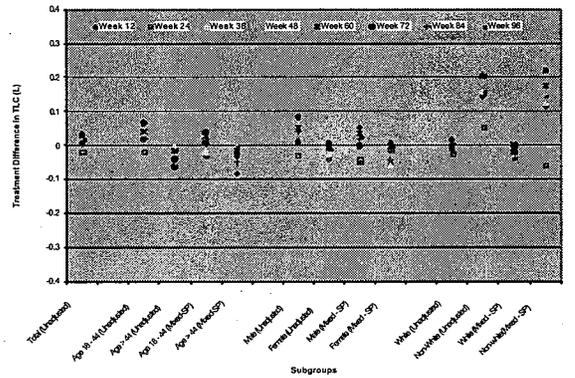
4.1.2 TYPE 2 DATA

It appears that majority of the subjects were between ages 45 to 64 (~65%) in both treatment groups. There are about 23% that were older than 64 and about 11% younger than 44. Male subjects accounted for close to 60% in the Type 2 population in both treatment groups. Almost 82% in the Type 2 population were white.

FEV_1, DLco, FVC, FRC, and TLC data for subjects with Type 2 DM are presented by age groups, gender, and race groups in Figure 40 to Figure 44.

In general, there appears to be a small shift in the treatment difference in FEV1, FVC, FRC, and TLC among subjects who were younger (<45 year of age) and older (>64 years of age) in favor of the comparator group. While subjects who are 45 to 64 years of age almost have identical treatment difference as the Type 2 pooled data. This increase in treatment difference does not appear to be a cause for alarm simply because subjects who are younger and subjects who are older accounts for only 11% and 23% respectively of the total population. Thus this shift should be cause for alarm. There is no difference between unadjusted and adjusted model accounting for age.

In terms of race, there appears to be a gender difference in terms of FEV1 and possibly TLC score, in which the average FEV1 score for the pooled Type 2 data seems to hover in the middle of the average FEV1 score of each of the gender. There is really no clear explanation as to why this occurs and this is not consistent with other PFT scores and with the Type 1 data.

There also appears to be disparity in treatment difference among white and non-white subjects. This could easily be due to the enormous discrepancy in the sample size between the subgroups (e.g. 18% non-whites vs. 82% whites).

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Figure 40: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender, and Race using Unadjusted and Mixed Model (Spatial Power) in FEV₁ (L) Score

Figure 43: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender, and Race in FRC (L) Score

Figure 41: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender, and Race in DLco (mL/min/mmHg) Score

Figure 44: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender and Race in TLC (L) Score

Figure 42: Subgroup Analyses on Pooled Type 2 Adults by Age, Gender, and Race in FVC (L) Score
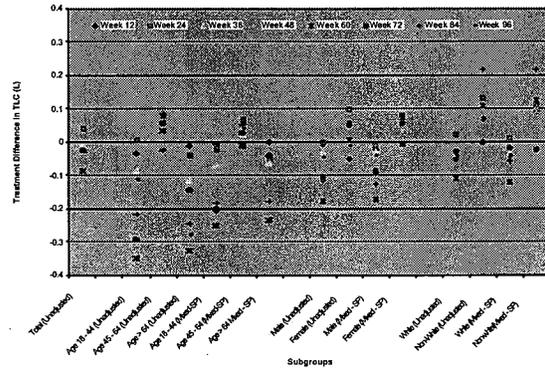
5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Overall, the quality of the data provided by the applicant was good. There were some minor data problems encountered during the re-analyses process such as discrepancies between combined and individual data (e.g. Data for Studies 1001 and 1002, Updated data for Study 1002), as well detection of outliers (Study 1001). It is difficult to understand the origin of these outliers (i.e. whether it is typographical, measurement error, or true and actual measure) such that deletion of these outliers may not be an ideal approach. Post-hoc analyses showed the removing these outliers will change the outcome for DLco at Week 104. Meanwhile, post-hoc analyses comparing the combined and the manually-combined individual studies showed no considerable differences that would affect the overall findings.

Several statistical issues were identified after reviewing this NDA submission. These issues did not affect the overall conclusion of the pulmonary safety of the inhaled insulin, but I find that it is worth noting in this review. Post-hoc analyses had been conducted to address and clarify some of these issues.

The first issue is on the study population used to evaluate the PFT measurements. This is with regards to the concern I have for the inconsistency of baseline values and consequently the number of subjects with baseline values in the pooled Type 1 and Type 2 data with the individual studies. An inquiry was made on June 7, 2005. In the response letter dated July 5, 2005, the applicant wrote:

> In Table 15, only subjects with a nonmissing baseline measurement and a nonmissing postbaseline measurement captured in at least one of the tabulated nominal visit windows contribute to the count of subjects (n) at baseline. Based on this logic, Table 15's requirement for a baseline and a post-baseline tabulated measurement can alternatively be expressed as a requirement for a non-missing change from baseline (pft_ c) at one of the tabulated visits. In some of the individual CSR tables cited, the only requirement was the presence of a nonmissing baseline value. Implicit in the calculation of change from baseline is the requirement to have both a baseline and post-baseline measurement thus explaining the observation that the change from baseline values and the treatment differences from the pooled results agree with the results from the individual CSRs.

Although the overall findings were not affected by the exclusion of subjects with no post-baseline measures, I find that it is best to capture all subjects who had PFT measures (intent-to-treat approach), instead of restricting to only subjects who had post-baseline PFT measurements. The restriction should only be applied when imputation (such as last observation carried forward) is applied. Therefore, all subjects who received at least one dose of study treatment and have a baseline PFT measurement should be evaluable for the analyses of PFT decline. Furthermore, analyses should also not be restricted to completers (Combined Studies 1001 – 1002).

The second issue is on missing PFT measurements. In some of the individual studies, missing data were imputed using last observation carried forward (LOCF), while in some individual studies, specifically designed to study PFT measures, missing data were not imputed. The applicant also did not impute missing data in the pooled population. I find that this approach is more reasonable than to impute missing data using LOCF. Most of the concern about missing data comes from subject discontinuation. Discontinuation can be due to treatment-related adverse events, lack of efficacy, lost to follow-up, protocol violation, or subject's voluntary withdrawal. Typically, there is a natural decline of PFT measures in each individual over time. LOCF approach may not account for this decline. Instead, missing data will be imputed with a PFT that is potentially higher (better) than what the actual PFT should be. If the discontinuation is due to treatment-related adverse or treatment-related lack of efficacy, then the imputed value may actually be more favorable to the study drug. To account for the natural decline of PFT measures, imputation should take into account the slope of the observed values.

As stated, the applicant did not impute missing data, in studies specifically designed to study PFT measures (long-term studies) and the pooled data. The statistical model they chose to apply is the likelihood-based mixed model repeated measures analyses (MMRM) to account for intra-subject variation. In their primary model, they pre-specified covariates that they wanted to include in the model such as the categorical variable visits/time, protocols, sex, and in some instance centers, and continuous variables such as baseline PFT measures, baseline age, and height. I find that this is a reasonable approach considering that this model takes into account missing data. The only caveat in this type of modeling is that the missing data must be Missing at Random (MAR) which is a common assumption for this type of data. Post-hoc analyses have been conducted in Type 1 data to see the effects of imputed data versus using observed cases only. Comparison was also made between unadjusted (PROC GLM by visit/week) treatment difference and adjusted (using MMRM) treatment difference. All results from different PFT measures showed no differences using either one of the approaches. The question remains as to the usefulness of conducting a more complicated modeling technique (MMRM) versus using unadjusted analysis when the results are comparable. MMRM has the added advantage of accounting for within-subject variation (as well as known and clinically relevant covariates).

The third issue is related to the mixed model approach the applicant used in their analysis and the choice of variance-covariance structure. The variance-covariance structure chosen by the applicant is the Spatial Power, which assumes higher correlation between neighboring time points than farther time points. This model appears to be reasonable particularly when there are a lot of time points. There was a concern that the results from the first-order autoregressive structure, AR(1) would be very similar with the result from the Spatial Power since the time variable in the pooled Type 1 (or Type 2) data only has a maximum of 8 timepoints. Post-hoc analyses have shown that the unstructured model generally yields a lower (more favorable) information criterion (AIC, AAIC, BIC) compared to the spatial power model. However, the difference is not large. The analyses also showed no difference between the AR(1) model and the Spatial Power model. Although the spatial power model is acceptable, I thought this concern is worth noting.

As stated earlier, these issues were not crucial, but nonetheless important. These issues were either resolved or data were re-analyzed to address these problems in the review.

5.2 CONCLUSIONS AND RECOMMENDATIONS

I conclude that the data quality and analytical techniques used by the applicant in analyzing the pulmonary safety data are acceptable.

In Pooled Type 1, I find that respiratory adverse events were higher in the inhaled insulin group compared to the comparator group, particularly on increased cough. Only 2% of the 698 subjects in the inhaled insulin group discontinued due to respiratory events. There is evidence that inhaled insulin consistently showed a greater decline in FEV$_1$ and DLco from baseline over time particularly at early timepoints compared to the comparator group. Treatment differences were of a magnitude of about 40 mL for FEV1 at the end of the study and about 0.5 mL/min/mmHg for DLco at the end of the study. Although there are declines in FRC, FVC, and TLC scores in each of the treatment groups (i.e. inhaled insulin and comparator), the treatments were comparable over time. There is no evidence of any consistent correlation between the change from baseline in pulmonary function tests and antibody titers. In terms of PFT measures and insulin dose, correlations were generally small, usually no greater in absolute value than 0.15.

In Pooled Type 2, I find that respiratory adverse events were higher in the inhaled insulin group compared to the comparator group, particularly on increased cough. Only 2% of the 1277 subjects in the inhaled insulin group and 0.1% of the 1132 subjects in the comparator discontinued due to respiratory events. There is evidence that inhaled insulin consistently showed a greater numerical decline in FEV$_1$ and DLco from baseline over time compared to the comparator group. However, the majority of these differences were not statistically significant as indicated by the confidence intervals for these changes. Treatment differences were of a magnitude of about 40 mL for FEV1 at the end of the study (same as Type 1 data) and about

0.4 mL/min/mmHg for DLco at week 84/91. A similar conclusion can be drawn for FRC, FVC, and TLC scores. Although treatment group differences slightly favored the comparator group, the differences were comparable in the sense that the confidence intervals include the zero difference. There is no evidence of consistent correlation between the change from baseline in pulmonary function tests and antibody titers. In terms of PFT measures and insulin dose, correlations were generally small, usually no greater in absolute value than 0.15.

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6 APPENDIX

I. Type 1 Study

A. Change from Baseline in DLco by Antibody Titer
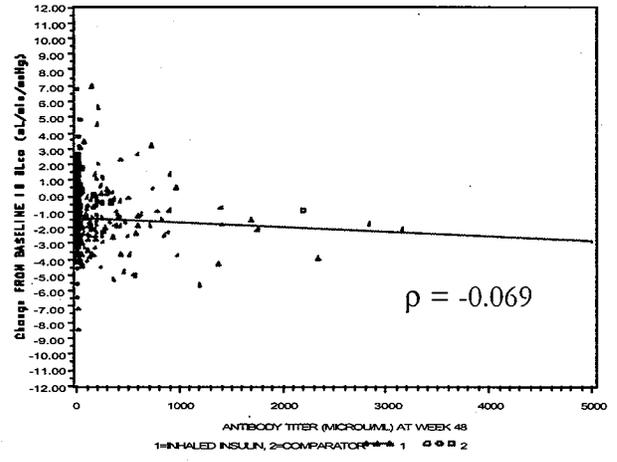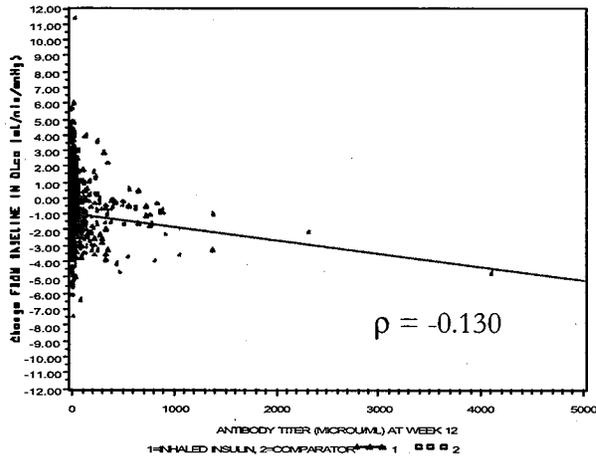
B. Change from Baseline in FEV1 by Antibody Titer
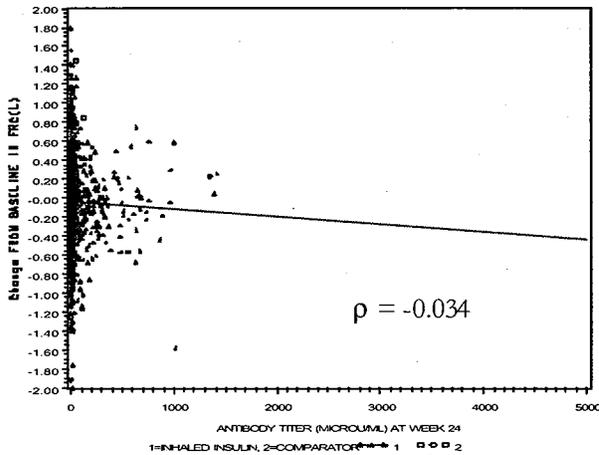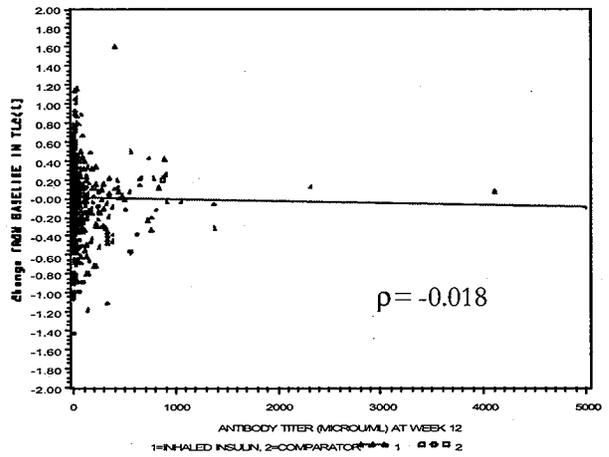
$\rho = 0.050$

$\rho = 0.041$

$\rho = 0.053$

$\rho = 0.018$
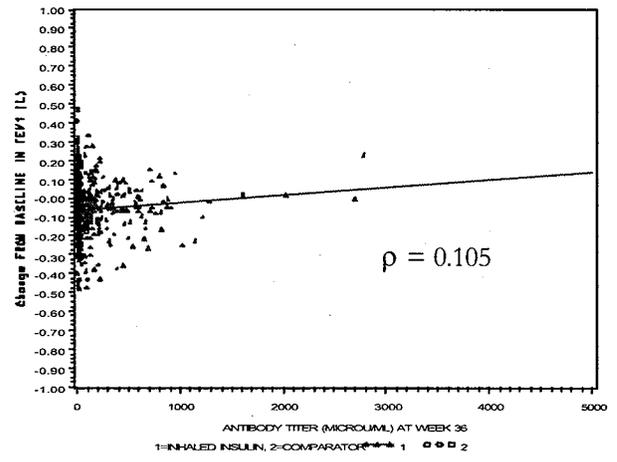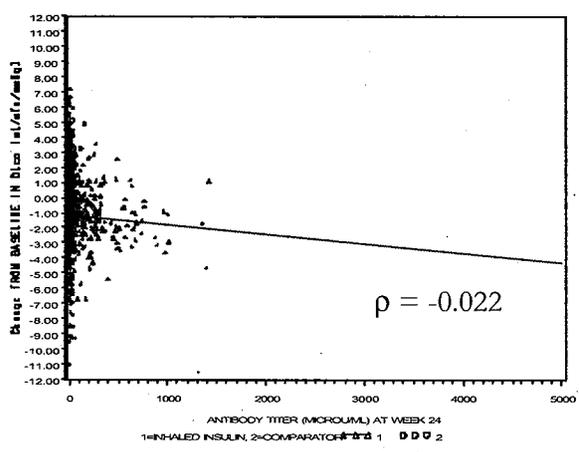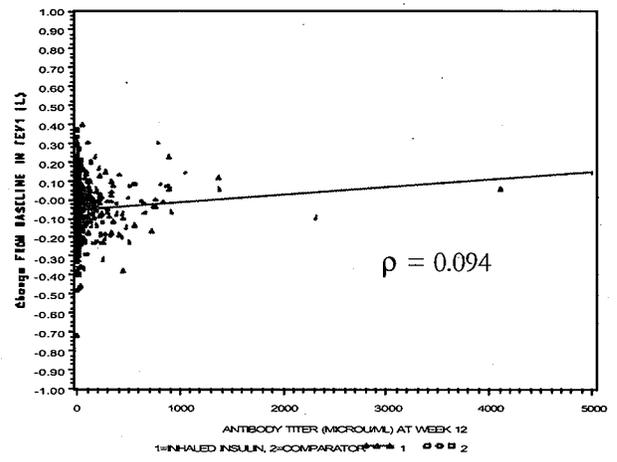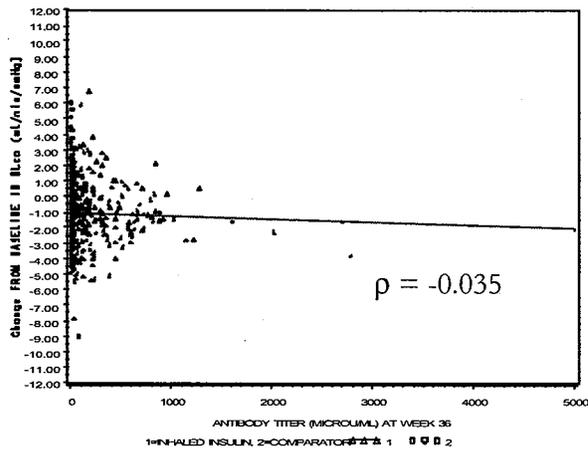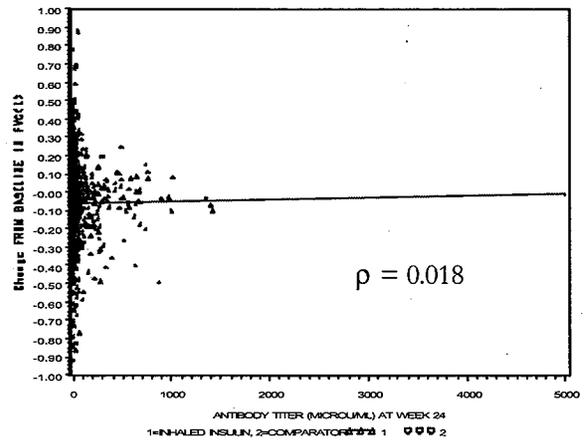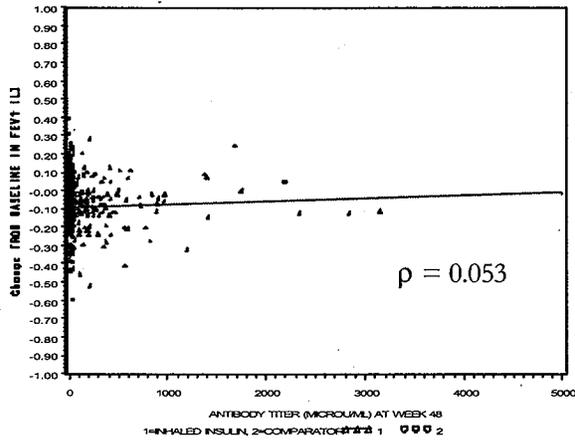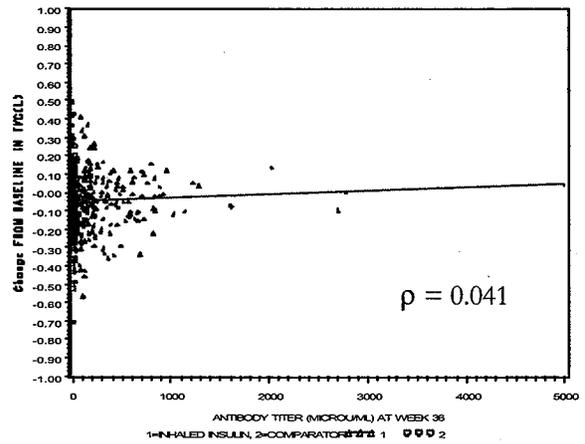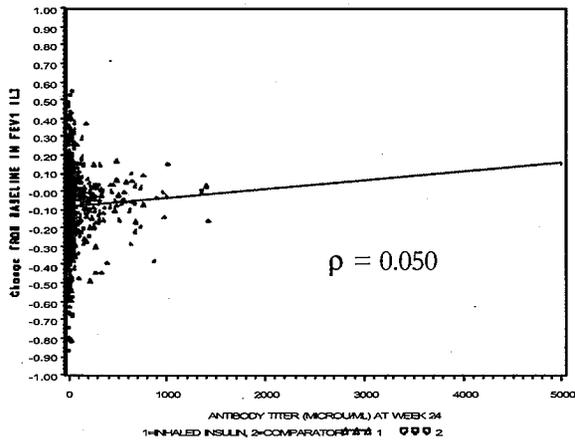
C: Change from Baseline in FVC by Antibody Titer

$\rho = 0.019$

$\rho = -0.007$
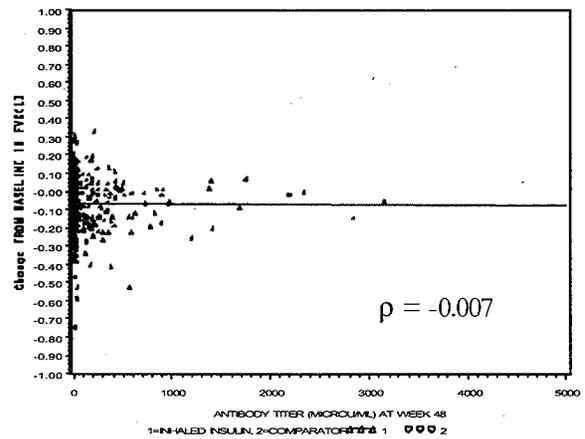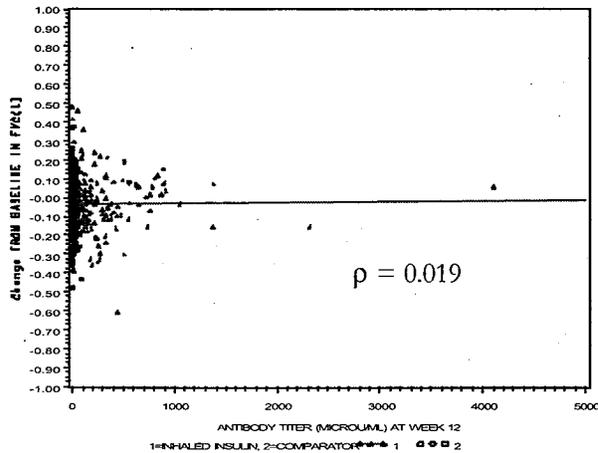
D: Change from Baseline in FRC by Antibody Titer

$\rho = 0.035$

$\rho = -0.096$
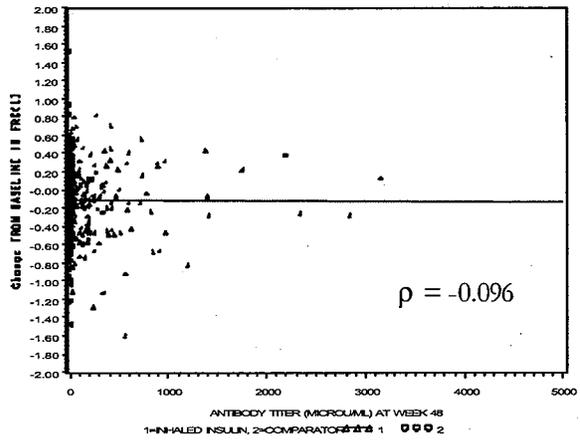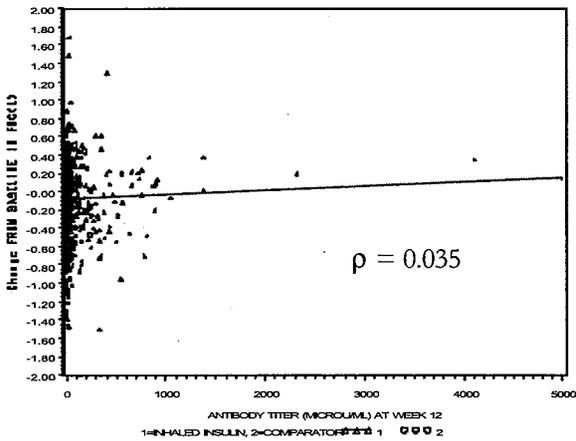
E: Change from Baseline in TLC by Antibody Titer

$\rho = -0.114$

$\rho = -0.018$

$\rho = -0.034$

$\rho = -0.234$

ρ = -0.018

ρ = -0.148

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