The following table examines insulin binding activity among patients who had severe hypoglycemic events, and among those who did not. Severe hypoglycemic events were defined as events requiring the assistance of another person, or events in which the blood glucose was ≤36 mg/dL.

Table 7.1.3.3.2.4.2 Mean End-of-Study Insulin Binding Activity for Patients who Did and Did Not have Severe Hypoglycemic Events, Type 1 Patients (Exoterix® Assay, µU/mL)

	total n	Mean End-of-Study Insulin Binding Activity (SD)
Inhaled insulin patients with severe hypoglycemic events	71	255.6 (309.3)
Inhaled insulin patients who did not have severe hypoglycemic events	367	254.3 (777.3)
Inhaled insulin patients overall	438	254.5 (722.4)
SQ patients who had severe hypoglycemic events	92	17.9 (39.7)
SQ patients who did not have severe hypoglycemic events	345	24.1 (126.2)
SQ pts overall	437	22.8 (113.7)

Analysis by Dr. Mele, Biostatistics
Source datasets: insulin antibody datasets, hypoglycemia dataset; includes data from Studies 104, 107-110, 1001, 1002, 1009, 1022, 1026-1030

Although one cannot make strong inferences from an analysis of a subset of an outcome variable, these data do not appear to demonstrate obvious differences in insulin binding activity for patients who had severe hypoglycemic events.

7.1.3.3.2.5 Characteristics of Patients with Highest Insulin Binding Activity

The applicant identified all patients in studies using the Esoterix® antibody assay who had insulin binding activity of >2,000 µU /mL. For those studies in which the Mayo assay had been used, the applicant used residual sera when available to re-examine antibody levels using the Esoterix® assay. A total of 37 patients were identified who had insulin binding activity of >2,000 µU/mL. The following table summarizes their characteristics.

Table 7.1.3.3.2.5 Summary Characteristics of Patients with Insulin Binding Activity >2,000 µU/mL by Esoterix® Assay

Pt ID	Tx	Age	Sex	DM Type	Pk[3] IBA[4] in µU/mL	Day[1] of Pk IBA	AE	Study Day(s) of AE(s)	Last A1c (%)[2]	Early W/D?	Comment
111-5005-7684	Inh	43	F	1	3,624	719 (1)	Breast lump	170	6.8	yes (Day 720, insuff clin response)	8-10 hypoglycemic events per week at time of study w/d
							Resp infxn	256			
							Cough	571			
							Flu	697			
111-5007-7331	Inh	52	F	1	3,008	389	Cough	58, 515	7.9	no	8 severe hypoglycemic events
							Severe URI	426			
							Expiratory wheezing	522			
							Foot fracture	457			
111-5013-6609	Inh	41	F	1	2,348	711	No resp or allergic AEs; no SAEs	n/a	8.3	no	Screening HbA1c 6.7%
111-5025-6591	Inh	22	F	1	4,895	737	URI	530	7.3	no	
							Flu	919			
111-5030-6883	Inh	53	F	1	2,602	714	Allergic bronchiolitis	502	6.3	no	13 severe hypoglycemic events
							Bibasilar rales	614			
							Right upper lung nodule	628			
							Anterior mediastinal soft tissue density	628			
							Benign granuloma left inferior lung	615			
							Benign granuloma left medial lung	615			
							URI	879			
							Hypoglycemia, LOC, hypothermia	7			
							Hypoglycemia, unconsciousness	111			
							Hypoglycemia, altered LOC	92			
111-5045-1383	Inh	46	M	2	3,416	503 (104)	Severe CHF	503 (97)	9.7	yes (same day as pk IBA; for CHF)	First IBA >2,000 was 2,024 (45 days after inh ins d/c; total days inh ins = 503).
							Decline in DLco	459			
							URI	468			
111-5047-6555	Inh	38	F	1	3,240	741	Decline in DLco	77	7.0		First IBA >2,000 was 2,348 (inh ins day 544)
							URI	598			
							Influenza with hospitalization	654			

Table 7.1.3.3.2.5 Summary Characteristics of Patients with Insulin Binding Activity >2,000 µU/mL by Esoterix® Assay

Pt ID	Tx	Age	Sex	DM Type	Pk[3] IBA[4] in µU/mL	Day[1] of Pk IBA	AE	Study Day(s) of AE(s)	Last A1c (%)[2]	Early W/D?	Comment
111-5048-6241	Inh	60	M	1	2,810	700 (27)	Pneumonia	572	7.9		First IBA >2,000 was 2,596 on day 673 of inh ins; two severe hypoglycemic events
							Cough	846			
111-5051-6870	Inh	25	F	1	2,470	375	URI	13	8.2		
							Flu	162			
							Decline in DLco	186			
111-5056-7711	Inh	51	M	1	2,057	946	Decline in DLco	511	9.0		2 severe hypoglycemic episodes
							Dermatitis face and arms	842			
							Cough	44			
							Decreased FEF2575	252			
							Mixed obstructive/ restrictive lung disease	1135			
							URI	536			
							Flu	787			
							Unstable angina	877			
111-5059-6683	Inh	44	M	1	2,184	180	Decline in DLco	382	8.4	yes (Day 382, same day as decline in DLco, reason given = insuff clin response)	
111-5079-3321	Inh	10	F	1	2,937	355	Decline in DLco	172	8.1		
							URI	103			
111-5079-3324	Inh	10	F	1	2,838	624	URI	258, 531, 678	9.9	yes (Day 689- "subject decided not to go into the PFT Trends amendment part of the study")	8 severe hypoglycemic episodes; episode of DKA
111-5079-3402	Inh	10	F	1	3,608	449	URI	23, 100, 132, 335, 456, 555, 567, 601	8.4		
							Expiratory wheezing	337, 566			
							Decreased expiratory reserve volume	337			
							Cough	335			
111-5084-3354	Inh	9	M	1	3,300	664	Productive cough	91	7.7		
							URI	140, 366, 395, 818			
111-5089-7567	Inh	12	F	1	3,248	806	Cough	58	12.2	yes (Day 82 elev HbA1c)	

Table 7.1.3.3.2.5 Summary Characteristics of Patients with Insulin Binding Activity >2,000 µU/mL by Esoterix® Assay

Pt ID	Tx	Age	Sex	DM Type	Pk[3] IBA[4] in µU/mL	Day[1] of Pk IBA	AE	Study Day(s) of AE(s)	Last A1c (%)[2]	Early W/D?	Comment
111-5089-7570	Inh	16	F	1	2,426	724	Onset of reactive airway disease	263	10.8		
111-5091-3007	Inh	10	F	1	4,092	371	"Cold symptoms"	383, 477, 513, 553, 605	9.2		
111-5091-3010	Inh	10	F	1	2,140	443	Viral respiratory tract infection	123, 172, 185, 193, 204, 323, 509	8.9		
							Cough	1			
111-5092-3023	Inh	7	F	1	2,101	629	Decline in DLco	86	8.0	yes (Day 671, "frequent visits too difficult to arrange")	
							URI	151, 216, 338, 567			
							Cough	171			
111-5092-3043	Inh	9	F	1	2,272	351	URI	78, 290	6.6		1 severe hypoglycemic event
							Cough	86			
111-5096-6335	Inh	13	M	1	4,972	179	Bilat eyelid swelling	48	8.9	yes (Day 403- "interested in pump")	
							URI	7, 72, 176			
111-5127-7774	Inh	43	F	1	2,382	345	Decline in total lung capacity	344	7.6	yes (Day 523, inconvenience of inhaler)	
							Chest tightness	3			
							Cold	9, 24, 151, 319			
							Audible wheeze	51			
1022-1001-0005	Inh	36	M	1	4,108	71	URI	10	9.0	yes (Day 71, insuff clin response)	2 severe hypoglycemic events
							Hypoglycemia SAE	10			
							Hypoglycemia SAE	58			
1022-1008-0420	Inh	32	F	1	2,840	370	Flu	256	8.5		1st IBA >2,000 = 2,700 on inh ins day 279
1022-1010-0537	Inh	47	M	1	3,156	359	Cough	23	5.7		1 hypoglycemia SAE
							Hypoglycemia SAE	215			
1022-1015-0833	Inh	54	M	1	2,776	266	Dyspnea on exertion	184	7.7		
1022-	SQ	59	F	1	2,192	363	URI	171, 247	6.7		

Table 7.1.3.3.2.5 Summary Characteristics of Patients with Insulin Binding Activity >2,000 µU/mL by Esoterix® Assay

Pt ID	Tx	Age	Sex	DM Type	Pk[3] IBA[4] in µU/mL	Day[1] of Pk IBA	AE	Study Day(s) of AE(s)	Last A1c (%)[2]	Early W/D?	Comment
1022-1248											
1022-1025-1425	Inh	54	F	1	27,286	14 (34)	URI	10	7.9	yes (Day 14, shortness of breath)	IBA Day 0 = 3,514 IBA Day 14 = 6,056 IBA Post-Tx Day 9 = 12,245 IBA Post-Tx Day 34 at left IBA Post-Tx Day 257 = 5,280
							Shortness of breath	14			
1022-1041-2369	Inh	23	F	1	2,340	352	Cold	1	9.6		1 severe hypoglycemic event
1022-5074-3082	Inh	51	F	1	2,063	51	Hypoglycemia SAE	4	9.5		29 severe hypoglycemic events (23 between 0100 and 0600)
1022-5154-3679	Inh	60	F	1	2,317	84	Cold	66	7.5	yes (Day 167, reason not specified)	1st Ab >2,000 = 2,067 on inh ins day 41
							Cough	85			
1027-1006-0251	Inh	27	F	1	2,456	28	URI	6, 22	9.6	yes (Day 52, reactive airways disease)	
							Severe reactive airways disease, bronchospasm	32			
							Decline in DLco	21			
1027-1012-0503	Inh	27	M	1	3,394	49	URI	8	7.2	yes (Day 49 of inh ins, due to cough)	
							Bronchitis	29			
							Cough	45			
1029-1016-0484	SQ	62	F	2	4,016	92	Flu	357	8.1		1st IBA >2,000 was 2,123 on tx day 46
							URI	54, 71			
1029-1043-2260	Inh	56	M	2	2,830	261			9.4		
1029-1101-4270	Inh	62	M	2	7,296	43	Wheezing	51	8.4		
							Cough	24			

1 # days of study treatment; if treatment stopped prior to peak insulin binding activity, includes # days off treatment in parentheses
2 last recorded on-treatment study HbA1c
3 Highest insulin binding activity measured by Esoterix® assay; pts who had previous measurements by Mayo assay may have had an earlier peak by that assay, but only one measurement on residual sera by Esoterix® assay, or insufficient residual sera for Esoterix®
4 Insulin binding activity

The majority of patients (89%) who had measured insulin binding activity >2,000 μU/mL by the Esoterix® assay were Type 1 patients (33 Type 1 vs 4 Type 2). In the overall Phase 2/3 study population, 1,209/2,787 patients (43%) had Type 1 diabetes. Pediatric patients comprised 33% (11/33) of the Type 1 patients with high antibody titres. In the overall Phase 2/3 study population, 291/1,209 (24%) of the Type 1 patients were children. Among Type 1 patients with high antibody titres, 24/33 (73%) were female. In the overall Phase 2/3 Type 1 population, 405/918 (44%) were female.

A total of 67 severe hypoglycemic events were reported in 9 patients out of the 33 Type 1 patients who had Esoterix® insulin binding activity >2,000 μU/mL. These 9 patients represent 27.3% of the group of Type 1 patients who had high insulin binding activity. In the overall controlled Type 1 Phase 2/3 patient population, 121/698 patients (17.3%) had one or more severe hypoglycemic events. Total exposure among the 33 Type 1 patients who had high Exoterix® insulin binding activity was 618.1 months; the event rate for severe hypoglycemic events was 0.11 events per month. When excluding the 29 events that occurred in a single patient, this event rate becomes 0.06 events per month of exposure. In the overall Type 1 Phase 2/3 patient population, there were 6,138 severe hypoglycemic events over 5,626.7 patient-months, for an event rate of 1.09 events/1,000 months of exposure. When considering severe hypoglycemic events on a per patient basis, these events appear to have been more common in patients who had high insulin binding activity than among the general study population. When considering severe hypoglycemic events on a person-time basis, these events do not appear to have occurred more commonly per unit of patient-time for patients with high insulin binding activity than for patients in the general study population.

7.1.3.3.2.6 Was there evidence that these antibodies could neutralize the action of insulin?

The applicant reports that they made extensive attempts to develop a neutralizing antibody bioassay, but were unable to do so.

The development of neutralizing antibodies might be signaled by an increase in insulin requirement after antibodies appear. In order to look at this question with available data, Ms. Mele examined insulin binding activity and insulin doses in Study 107, the intensive control trial in Type 1 diabetics. The assumption was made that titration would be complete by month 3, with only minor increases in mean total daily insulin requirement after that. The assumption was also made that insulin antibodies would have appeared by that time, and that any effect they would have on neutralization of insulin action would be present. Insulin binding activity in inhaled insulin patients across the development program generally increased most rapidly during the first 6 months of treatment. Dr. Mele looked for a correlation between the change in insulin dose from Month 3 to Month 6, and insulin binding activity. Her analysis revealed no correlation.

The applicant analyzed for associations between insulin binding activity and overall doses of insulins (short- and long- acting), and found no association.

7.1.3.3.2.7 Was there evidence that these antibodies could have other effects on insulin pharmacodynamics or overall glycemic control?

The majority of patients (89%) who had measured insulin binding activity >2,000 μU/mL by the Esoterix® assay were Type 1 patients (33 Type 1 vs 4 Type 2). In the overall Phase 2/3 study population, 1,209/2,787 patients (43%) had Type 1 diabetes. Pediatric patients comprised 33% (11/33) of the Type 1 patients with high antibody titres. In the overall Phase 2/3 study population, 291/1,209 (24%) of the Type 1 patients were children. Among Type 1 patients with high antibody titres, 24/33 (73%) were female. In the overall Phase 2/3 Type 1 population, 405/918 (44%) were female.

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The applicant analyzed for associations between insulin binding activity and overall doses of insulins (short- and long- acting), and found no association.

7.1.3.3.2.7 Was there evidence that these antibodies could have other effects on insulin pharmacodynamics or overall glycemic control?

The applicant provided scatter plots of insulin binding activity vs indices of glycemic control. No significant association was demonstrated between insulin binding activity and HbA1c, postprandial glucose, fasting glucose, or insulin requirement.

7.1.3.3.2.8 What happened to insulin binding activity after discontinuation of inhaled insulin?

In Study 1027, discontinuation of inhaled insulin therapy resulted in a decrease in insulin binding activity, although they did not return to baseline levels by 12 weeks of followup.

Table 7.1.3.3.2.8 Change from Baseline in Insulin Binding Activity During and After Study Drug Administration in Study 1027

	Baseline and Change from Baseline Serum Antibody Level (µU/mL)* (N) [SD]			
	Mean		Median	
Time Point	INH	SC	INH	SC
Baseline values	**17.1 (97) [40.6]**	**17.4 (99) [54.4]**	**2.4**	**2.7**
Change from baseline				
Comparative phase				
Week 1	-0.5 (90) [5.8]	-0.1 (89) [8.9]	0.0	0.0
Week 2	5.3 (87) [22.7]	-1.1 (85) [6.0]	0.0	0.0
Week 4	28.7 (94) [79.6]	0.2 (89) [5.3]	5.6	0.0
Week 8	93.2 (97) [356.0]	3.2 (96) [25.3]	15.0	0.0
Week 12	112.9 (91) [218.1]	2.9 (95) [19.4]	28.0	0.0
Follow-up phase†				
Week 2	83.1 (87) [163.7]	2.3 (88) [21.1]	27.0	0.0
Week 4	61.8 (84) [122.6]	3.8 (92) [25.5]	19.5	0.0
Week 8	42.2 (85) [74.7]	4.1 (92) [25.3]	19.0	0.0
Week 12	33.3 (85) [61.7]	5.2 (93) [33.9]	13.0	0.0

*Values less than the limit of quantitation (2.1 µU/mL) were imputed as 1.05 µU/mL.
†All subjects received subcutaneous insulin as the only short-acting insulin during the follow-up phase.
N=number of subjects evaluated for antibody levels at baseline and the noted time point, SD=standard deviation, INH=inhaled insulin, and SC=subcutaneous short-acting insulin.
Source: Study 1027 Tables 12.1.1.3, 12.1.2.3, and 12.1.2.4

Source: Applicant's Table 5, Section 5.3.5.3.2

7.1.3.3.2.9 Summary of Insulin Antibody Observations

For both Type 1 and Type 2 diabetics, inhaled insulin was associated with higher end-of-study insulin binding activity, and with greater changes from baseline in insulin binding activity, than those seen with comparator agents. Type 1 diabetics had greater changes than Type 2 patients. Among Type 1 diabetics, pediatric patients had higher insulin binding activity and greater change from baseline than adults. Among Type 1 patients, females had higher insulin binding activity and greater changes from baseline than did males. Among Type 2 patients, patients who

were age 65 years or older tended to have higher values in longer studies, and in studies using the quantitative Esoterix® assay, mean insulin binding activity appeared to correlate with age group up to age 74 years. Seroconversion from an undetectable level of insulin binding activity at the beginning of study to detectable levels of insulin binding activity at end-of-study was much more common among inhaled insulin patients (Type 1 and Type 2) than among comparator patients. Type 1 diabetics had significantly higher rates of seroconversion than Type 2 diabetics. Among Type 1 diabetics, rates of seroconversion were higher among pediatric patients than among adult patients.

Insulin antibodies appeared to be predominantly IgG, and tended to have a low affinity, high capacity binding profile.

There were no apparent associations between insulin binding activity and occurrence of allergic events or severe hypoglycemic events. There were no apparent associations between insulin binding activity and indices of glycemic control, such as HbA1c, postprandial glucose and fasting glucose. Evidence was not found of a neutralizing effect of these antibodies on the action of insulin; there was no association between insulin binding activity and requirements for either long- or short- acting insulin at last observation. In Study 107, there was no evidence of an association between insulin binding activity and changes in insulin requirements from months 3 to 6 of study.

After discontinuation of inhaled insulin, insulin binding activity appeared to decline, but had not returned to baseline by 12 weeks after discontinuation.

Although inhaled insulin patients demonstrate a brisk increase in insulin antibody levels as reflected by insulin binding activity, studies to date do not demonstrate a clinical correlate of this finding.

7.1.3.3.3 Serious Herniae and Rupture Events

Because cough was a very common adverse event among inhaled insulin patients, the clinical reviewer examined events which could result from increased intrathoracic and intraabdominal pressure, such as herniae and suture rupture events. Numbers of these events are summarized in the following table:

Table 7.1.3.3.3 Incidence of Serious Herniae and Serious Rupture Events

	Inh Ins	SQ	OA
Adult Type 1 Diabetics, Controlled Ph 2/3	2 (0.2 events/100 pts)	0	n/a
Adult Type 1 Diabetics, All Ph 2/3	1 (<0.1 event/100 pt-yrs)	0	n/a
Adult Type 2 Diabetics, Controlled Ph 2/3	4 (0.3 events/100 pts)	2 (0.4 events/100 pts)	1 (0.2 events/100 pts)
Adult Type 2 Diabetics, All Ph 2/3	6 (<0.1 event/100 pt-yrs)	4 (<0.1 event/100pt-yrs)	1 (<0.1 event/100 pt-yrs)
Pediatric Type 1 Diabetics	0	0	n/a

Serious herniae and serious rupture events did not occur with greater frequency among patients receiving inhaled insulin than among patients receiving comparator treatments.

7.1.4 Other Search Strategies

Please see Section 7.1.2 for explorations for patterns of serious adverse event groupings for events related to severe hypoglycemia consequences, and cardiovascular adverse events.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Protocols specified that all observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to study drug, were to be recorded as adverse events.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Narratives were not available for individual cases of common adverse events. When information on nonserious adverse events was included in narratives for serious adverse events, pulmonary events, or high antibody titres, event categorization appeared appropriate.

7.1.5.3 Incidence of common adverse events

In controlled Phase 2/3 studies in Type 1 diabetics, the overall incidence of adverse events was similar between inhaled insulin patients and SQ patients, with 99.4% and 98.7% of patients, respectively, experiencing some type of adverse event. In controlled Phase 2/3 studies in Type 2 patients, adverse events occurred with nearly equal frequency between inhaled insulin patients [93.7% with event(s)] and SQ patients [96.7% with event(s)]. Among Type 2 patients treated with oral agents, 81.7% experienced an adverse event. This lower rate among oral-agent treated patients is due to a lower rate of hypoglycemia among these patients than among inhaled insulin or SQ patients.

7.1.5.4 Common adverse event tables

The following tables include common adverse events; separate tables are provided for adult Type 1, adult Type 2, and pediatric Type 1 patients.

7.1.5.4.1 All-causality Common Adverse Events Occurring in ≥ 1% of Type 1 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 698 n (%)	SQ n = 705 n (%)
Body as a whole	Abdominal pain	23 (3.3)	29 (4.1)
	Abscess	4 (0.6)	10 (1.4)
	Accidental injury	77 (11.0)	80 (11.3)
	Allergic reaction	31 (4.4)	23 (3.3)
	Asthenia	81 (11.6)	85 (12.1)
	Back pain	38 (5.4)	37 (5.2)
	Chest pain	24 (3.4)	9 (1.3)

7.1.5.4.1 All-causality Common Adverse Events Occurring in ≥ 1% of Type 1 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 698 n (%)	SQ n = 705 n (%)
	Fever	8 (1.1)	5 (0.7)
	Flu syndrome	105 (15.0)	107 (15.2)
	Headache	105 (15.0)	110 (15.6)
	Infection	25 (3.6)	27 (3.8)
	Malaise	8 (1.1)	11 (1.6)
	Neck pain	5 (0.7)	10 (1.4)
	Pain	36 (5.2)	34 (4.8)
Cardiovascular	Hypertension	20 (2.9)	14 (2.0)
	Migraine	12 (1.7)	13 (1.8)
	Palpitation	10 (1.4)	5 (0.7)
	Syncope	3 (0.4)	7 (1.0)
	Tachycardia	14 (2.0)	12 (1.7)
	Vasodilation	10 (1.4)	9 (1.3)
Digestive	Constipation	5 (0.7)	9 (1.3)
	Diarrhea	50 (7.2)	35 (5.0)
	Dry mouth	16 (2.3)	2 (0.3)
	Dyspepsia	23 (3.3)	15 (2.1)
	Gastritis	10 (1.4)	6 (0.9)
	Gastroenteritis	34 (4.9)	36 (5.1)
	Gingivitis	3 (0.4)	9 (1.3)
	Increased appetite	27 (3.9)	41 (5.8)
	Nausea	58 (8.3)	46 (6.5)
	Tooth caries	5 (0.7)	7 (1.0)
	Tooth disorder	15 (2.1)	22 (3.1)
	Vomiting	33 (4.7)	26 (3.7)
Hemic and lymphatic	Anemia	2 (0.3)	10 (1.4)
	Bruise	6 (0.9)	11 (1.6)
Metabolic and nutritional	Hyperglycemia	13 (1.9)	3 (0.4)
	Hypoglycemia	676 (96.8)	677 (96.0)
	Peripheral edema	15 (2.1)	12 (1.7)
Musculoskeletal	Arthralgia	43 (6.2)	32 (4.5)
	Arthrosis	8 (1.1)	1 (0.1)
	Bone fracture accidental	21 (3.0)	17 (2.4)
	Bone pain	9 (1.3)	16 (2.3)
	Myalgia	9 (1.3)	16 (2.3)
	Synovitis	4 (0.6)	9 (1.3)
	Tenosynovitis	10 (1.4)	15 (2.1)
Nervous	Agitation	8 (1.1)	2 (0.3)
	Anxiety	49 (7.0)	39 (5.5)
	Carpal tunnel syndrome	7 (1.0)	9 (1.3)
	Confusion	25 (3.6)	36 (5.1)
	Depression	9 (1.3)	23 (3.3)
	Dizziness	58 (8.3)	51 (7.2)
	Hypertonia	2 (0.3)	7 (1.0)
	Hypesthesia	22 (3.2)	25 (3.5)
	Insomnia	23 (3.3)	14 (2.0)
	Nervousness	18 (2.6)	18 (2.6)
	Paresthesia	22 (3.2)	15 (2.1)
	Somnolence	11 (1.6)	10 (1.4)
	Thinking abnormal	16 (2.3)	13 (1.8)
	Tremor	122 (17.5)	127 (18.0)
Respiratory	Asthma	7 (1.0)	8 (1.1)
	Bronchitis	20 (2.9)	27 (3.8)
	Cough increased	196 (28.1)	59 (8.4)
	Dyspnea	27 (3.9)	4 (0.6)
	Epistaxis	9 (1.3)	2 (0.3)
	Laryngitis	8 (1.1)	3 (0.4)

7.1.5.4.1 All-causality Common Adverse Events Occurring in ≥ 1% of Type 1 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 698 n (%)	SQ n = 705 n (%)
	Pharyngitis	123 (17.6)	103 (14.6)
	Pneumonia	5 (0.7)	7 (0.1)
	Respiratory disorder	45 (6.4)	27 (3.8)
	Respiratory tract infection	290 (41.5)	279 (39.6)
	Rhinitis	96 (13.8)	67 (9.5)
	Sinusitis	64 (9.2)	48 (6.8)
	Sputum increased	27 (3.9)	8 (1.1)
Skin and appendages	Fungal dermatitis	7 (1.0)	11 (1.6)
	Herpes simplex	6 (0.9)	9 (1.3)
	Nail disorder	10 (1.4)	11 (1.6)
	Pruritis	2 (0.3)	9 (1.3)
	Rash	18 (2.6)	15 (2.1)
	Skin ulcer	1 (0.1)	7 (1.0)
	Sweating	60 (8.6)	74 (10.5)
Special senses	Abnormal vision	22 (3.2)	19 (2.7)
	Conjunctivitis	13 (1.9)	9 (1.3)
	Ear pain	8 (1.1)	11 (1.6)
	Otitis media	4 (0.6)	8 (1.1)
	Retinal disorder	6 (0.9)	11 (1.6)
Urogenital	Dysmenorrhea	6 (1.9)	7 (2.2)
	Menorrhagia	1 (0.3)	4 (1.3)
	Menstrual disorder	6 (1.9)	2 (0.6)
	Urinary tract infection	23 (3.3)	31 (4.4)
	Vaginitis	10 (3.2)	16 (5.0)

Source: Applicant's Table 4.1.2.1.1, ISS

Hypoglycemia was the most common adverse event among Type 1 patients, and occurred with equal frequency in inhaled insulin and SQ group patients. Cough was a common adverse event, and occurred with significantly greater frequency among inhaled insulin patients (196/698, 28.1%) than among SQ patients (59/705, 8.4%). Other respiratory adverse events (dyspnea, respiratory disorder) also occurred with greater frequency among inhaled insulin patients. Nasopharyngeal adverse events (epistaxis, pharyngitis, rhinitis, sinusitis) occurred at a higher frequency in inhaled insulin groups (310/698, 44.4%) than in SQ groups (220/705, 31.2%). Adverse event terms related to accidents occurred with equal frequency between groups. The event term "allergic reaction" occurred with slightly greater numeric frequency in inhaled insulin patients (31/698, 4.4%) than among SQ patients (23/705, 3.3%).

The following table lists adverse events occurring with a frequency at least 2% greater in inhaled insulin patients compared to SQ patients.

Table 7.1.5.4.2 Adverse Events Occurring with a Frequency at least 2% Greater in Inhaled Insulin Patients Compared to SQ Patients, Type 1 Patients, Controlled Phase 2 and Phase 3 Trials, Cut-off 23 Aug 03

COSTART Body System	COSTART Event Term	Inh Ins n = 698 n (%)	SQ n = 705 n (%)
Body as a whole	Chest pain	24 (3.4)	9 (1.3)
Digestive	Diarrhea	50 (7.2)	35 (5.0)
	Dry mouth	16 (2.3)	2 (0.3)
Respiratory	Cough increased	196 (28.1)	59 (8.4)
	Dyspnea	27 (3.9)	4 (0.6)
	Pharyngitis	123 (17.6)	103 (14.6)
	Respiratory disorder	45 (6.4)	27 (3.8)
	Rhinitis	96 (13.8)	67 (9.5)
	Sinusitis	64 (9.2)	48 (6.8)
	Sputum increased	27 (3.9)	8 (1.1)

Source: Applicant's Table 4.1.2.1.1, ISS

The following table lists common adverse events occurring in Type 2 patients in controlled Phase 2/3 trials.

7.1.5.4.3 All-causality Common Adverse Events Occurring in ≥ 1% of Type 2 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 SME = 12186 n (%)	SQ n = 488 SME = 4868 n (%)	OA n = 644 SME = 6452 n (%)
Body as a whole	**Abdominal pain**	49 (3.8)	16 (3.3)	40 (6.2)
	Abscess	13 (1.0)	8 (1.6)	5 (0.8)
	Accidental injury	98 (7.7)	55 (11.3)	41 (6.4)
	Allergic reaction	30 (2.3)	12 (2.5)	12 (1.9)
	Asthenia	155 (12.1)	65 (13.3)	59 (9.2)
	Back pain	97 (7.6)	53 (10.9)	40 (6.2)
	Cellulitis	16 (1.3)	6 (1.2)	5 (0.8)
	Chest pain	56 (4.4)	15 (3.1)	21 (3.3)
	Fever	17 (1.3)	4 (0.8)	10 (1.6)
	Flu syndrome	165 (12.9)	62 (12.7)	59 (9.2)
	Headache	164 (12.8)	33 (6.8)	67 (10.4)
	Infection	24 (1.9)	15 (3.1)	19 (3.0)
	Malaise	25 (2.0)	3 (0.6)	20 (3.1)
	Neck pain	13 (1.0)	7 (1.4)	4 (0.6)
	Neoplasm	11 (0.9)	6 (1.2)	2 (0.3)
	Pain	89 (7.0)	40 (8.2)	35 (5.4)
Cardiovascular	**Angina pectoris**	12 (0.9)	2 (0.4)	16 (2.5)
	Atrial fibrillation	3 (0.2)	5 (1.0)	1 (0.2)
	Hypertension	106 (8.3)	39 (8.0)	49 (7.6)
	Palpitation	16 (1.3)	9 (1.8)	10 (1.6)
	Tachycardia	21 (1.6)	9 (1.8)	5 (0.8)
	Vasodilation	10 (0.8)	7 (1.4)	3 (0.5)
Digestive	**Constipation**	22 (1.7)	4 (0.8)	16 (2.5)
	Diarrhea	88 (6.9)	28 (5.7)	68 (10.6)
	Dry mouth	32 (2.5)	2 (0.4)	9 (1.4)
	Dyspepsia	61 (4.8)	27 (5.5)	31 (4.8)
	Flatulence	12 (0.9)	3 (0.6)	13 (2.0)
	Gastritis	16 (1.3)	6 (1.2)	12 (1.9)
	Gastroenteritis	33 (2.6)	16 (3.3)	13 (2.0)
	Gingivitis	15 (1.2)	6 (1.2)	6 (0.9)
	Increased appetite	54 (4.2)	22 (4.5)	20 (3.1)
	Nausea	79 (6.2)	25 (5.1)	33 (5.1)

7.1.5.4.3 All-causality Common Adverse Events Occurring in ≥ 1% of Type 2 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 SME = 12186 n (%)	SQ n = 488 SME = 4868 n (%)	OA n = 644 SME = 6452 n (%)
	Tooth disorder	24 (1.9)	10 (2.0)	16 (2.5)
	Vomiting	32 (2.5)	15 (3.1)	23 (3.6)
Endocrine	Goiter	2 (0.2)	7 (1.4)	3 (0.5)
Hemic and lymphatic	Anemia	12 (0.9)	3 (0.6)	9 (1.4)
Metabolic and nutritional	Hypercholesterolemia	11 (0.9)	5 (1.0)	7 (1.1)
	Hyperlipemia	24 (1.9)	8 (1.6)	22 (3.4)
	Hypoglycemia	794 (62.2)	360 (73.8)	185 (28.7)
	Peripheral edema	71 (5.6)	28 (5.7)	27 (4.2)
	Weight gain	23 (1.8)	5 (1.0)	7 (1.1)
Musculoskeletal	Arthralgia	84 (6.6)	41 (8.4)	39 (6.1)
	Arthritis	24 (1.9)	21 (4.3)	13 (2.0)
	Arthrosis	17 (1.3)	5 (1.0)	9 (1.4)
	Bone fracture accidental	26 (2.0)	11 (2.3)	10 (1.6)
	Leg cramps	9 (0.7)	10 (2.0)	12 (1.9)
	Myalgia	27 (2.1)	16 (3.3)	17 (2.6)
	Tenosynovitis	20 (1.6)	4 (0.8)	8 (1.2)
Nervous	Agitation	7 (0.5)	8 (1.6)	2 (0.3)
	Anxiety	53 (4.2)	33 (6.8)	15 (2.3)
	Carpal tunnel syndrome	10 (0.8)	6 (1.2)	6 (0.9)
	Confusion	17 (1.3)	18 (3.7)	2 (0.3)
	Depression	36 (2.8)	22 (4.5)	23 (3.6)
	Dizziness	140 (11.0)	63 (12.9)	38 (5.9)
	Hypesthesia	24 (1.9)	23 (4.7)	10 (1.6)
	Insomnia	29 (2.3)	14 (2.9)	12 (1.9)
	Muscular hypertonia	8 (0.6)	5 (1.0)	1 (0.2)
	Nervousness	33 (2.6)	16 (3.3)	4 (0.6)
	Neuropathy	24 (1.9)	11 (2.3)	16 (2.5)
	Paresthesia	55 (4.3)	8 (1.6)	19 (3.0)
	Somnolence	25 (2.0)	7 (1.4)	10 (1.6)
	Tremor	212 (16.6)	93 (19.1)	58 (9.0)
	Vertigo	23 (1.8)	1 (0.2)	5 (0.8)
Respiratory	Asthma	25 (2.0)	8 (1.6)	3 (0.5)
	Bronchitis	61 (4.8)	17 (3.5)	26 (4.0)
	Cough increased	268 (21.0)	36 (7.4)	24 (3.7)
	Dyspnea	42 (3.3)	9 (1.8)	9 (1.4)
	Epistaxis	15 (1.2)	2 (0.4)	5 (0.8)
	Pharyngitis	119 (9.3)	43 (8.8)	38 (5.9)
	Pneumonia	11 (0.9)	6 (1.2)	4 (0.6)
	Respiratory disorder	65 (5.1)	41 (8.4)	11 (1.7)
	Respiratory tract infection	357 (28.0)	166 (34.0)	127 (19.7)
	Rhinitis	103 (8.1)	46 (9.4)	19 (3.0)
	Sinusitis	65 (5.1)	41 (8.4)	15 (2.3)
Skin and appendages	Dermatitis	2 (0.2)	5 (1.0)	1 (0.2)
	Fungal dermatitis	18 (1.4)	3 (0.6)	1 (0.2)
	Herpes zoster	14 (1.1)	2 (0.4)	1 (0.2)
	Nail disorder	16 (1.3)	18 (3.7)	4 (0.6)
	Pruritus	24 (1.9)	3 (0.6)	12 (1.9)
	Rash	51 (4.0)	21 (4.3)	13 (2.0)
	Skin disorder	11 (0.9)	8 (1.6)	3 (0.5)
	Skin ulcer	14 (1.1)	9 (1.8)	5 (0.8)
	Sweating	146 (11.4)	60 (12.3)	42 (6.5)
Special senses	Abnormal vision	52 (4.1)	20 (4.1)	18 (2.8)
	Cataract	20 (1.6)	2 (0.4)	7 (1.1)
	Conjunctivitis	16 (1.3)	8 (1.6)	8 (1.2)
	Ear disorder	9 (0.7)	6 (1.2)	2 (0.3)

7.1.5.4.3 All-causality Common Adverse Events Occurring in ≥ 1% of Type 2 Patients, Controlled Phase 2/3 Studies, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 SME = 12186 n (%)	SQ n = 488 SME = 4868 n (%)	OA n = 644 SME = 6452 n (%)
	Ear pain	12 (0.9)	7 (1.4)	3 (0.5)
	Otitis media	8 (0.6)	9 (1.8)	2 (0.3)
	Retinal disorder	48 (3.8)	7 (1.4)	34 (5.3)
Urogenital	Cystitis	6 (0.5)	6 (1.2)	6 (0.9)
	Impotence	15 (1.9)	2 (0.7)	11 (3.0)
	Menstrual disorder	1 (0.2)	1 (0.6)	3 (1.1)
	Metrorrhagia	0	0	4 (1.4)
	Prostatic disorder	8 (1.0)	0	3 (0.8)
	Urinary tract infection	50 (3.9)	25 (5.1)	24 (3.7)
	Vaginitis	13 (2.7)	1 (0.6)	9 (3.2)

Source: Applicant's Table 4.1.2.1.2, Section 2.7.4

Hypoglycemia was the most common adverse event term, and occurred most commonly in SQ patients (360/488, 73.8%). Inhaled insulin patients had a lower rate of hypoglycemic events than SQ patients, but had a higher rate than OA patients [inh ins = 794/1277 (62.2%), OA = 185/644 (28.7%)]. Cough was also very common, and occurred with significantly higher frequency among inhaled insulin patients than among comparator patients (inh ins 21.0%, SQ 7.4%, OA 3.7%). Accident and injury terms occurred numerically more frequently among SQ patients than among other groups. Several respiratory events (e.g. asthma, bronchitis, dyspnea) had a somewhat higher frequency among inhaled insulin patients than among comparator patients; please see Dr. Seymour's pulmonary review for discussion. Headache and paresthesia occurred at a slightly higher numeric rate in inhaled insulin groups than in comparator groups.

The following table includes those events which occurred in Type 2 inhaled insulin patients at a frequency >2% higher than the frequency seen in a comparator group.

Table 7.1.5.4.4 All-causality Adverse Events Occurring in Inhaled Insulin Patients at a Frequency >2% Higher than the Frequency Seen in a Comparator Group, Type 2 Controlled Phase 2/3 Trials, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 n (%)	SQ n = 488 n (%)	OA n = 644 n (%)
Body as a whole	Asthenia	155 (12.1)	65 (13.3)	59 (9.2)
	Flu syndrome	165 (12.9)	62 (12.7)	59 (9.2)
	Headache	164 (12.8)	33 (6.8)	67 (10.4)
Digestive	Dry mouth	32 (2.5)	2 (0.4)	9 (1.4)
Metabolic and nutritional	Hypoglycemia	794 (62.2)	360 (73.8)	185 (28.7)
Nervous	Dizziness	140 (11.0)	63 (12.9)	38 (5.9)
	Nervousness	33 (2.6)	16 (3.3)	4 (0.6)
	Paresthesia	55 (4.3)	8 (1.6)	19 (3.0)
	Tremor	212 (16.6)	93 (19.1)	58 (9.0)
Respiratory	Cough increased	268 (21.0)	36 (7.4)	24 (3.7)
	Pharyngitis	119 (9.3)	43 (8.8)	38 (5.9)
	Respiratory disorder	65 (5.1)	41 (8.4)	11 (1.7)
	Respiratory tract infection	357 (28.0)	166 (34.0)	127 (19.7)
	Rhinitis	103 (8.1)	46 (9.4)	19 (3.0)
	Sinusitis	65 (5.1)	41 (8.4)	15 (2.3)

Table 7.1.5.4.4 All-causality Adverse Events Occurring in Inhaled Insulin Patients at a Frequency >2% Higher than the Frequency Seen in a Comparator Group, Type 2 Controlled Phase 2/3 Trials, Cut-off 23 Aug 04

COSTART Body System	COSTART Event Term	Inh Ins n = 1277 n (%)	SQ n = 488 n (%)	OA n = 644 n (%)
Skin and appendages	Rash	51 (4.0)	21 (4.3)	13 (2.0)
	Sweating	146 (11.4)	60 (12.3)	42 (6.5)
	Retinal disorder	48 (3.8)	7 (1.4)	34 (5.3)
	Vaginitis	13 (2.7)	1 (0.6)	9 (3.2)
Source: Applicant's Table 4.1.2.1.2, Section 2.7.4				

The following table lists common adverse events occurring in pediatric patients.

Table 7.1.5.4.5 All-causality Common Adverse Events Occurring in ≥ 1% of Pediatric Patients, Controlled Phase 2/3 Studies, Cut-off 1 Aug 03

COSTART Body System	COSTART Event Term	Inh Ins n = 153 n (%)	SQ n = 148 n (%)
Body as a whole	Abdominal pain	17 (11.1)	11 (7.4)
	Accidental injury	23 (15.0)	27 (18.2)
	Allergic reaction	6 (3.9)	3 (2.0)
	Appl/inj/incis/insertion site pain	6 (3.9)	3 (2.0)
	Asthenia	35 (22.9)	33 (22.3)
	Back pain	7 (4.6)	5 (3.4)
	Chest pain	5 (3.3)	0
	Face edema	1 (0.7)	5 (3.4)
	Fever	2 (1.3)	3 (2.0)
	Flu syndrome	19 (12.4)	18 (12.2)
	Headache	45 (29.4)	35 (23.6)
	Infection	9 (5.9)	14 (9.5)
	Infection fungal	2 (1.3)	1 (0.7)
	Pain	6 (3.9)	5 (3.4)
Cardiovascular	Migraine	1 (0.7)	2 (1.4)
	Pallor	1 (0.7)	3 (2.0)
	Vasodilation	2 (1.3)	2 (1.4)
Digestive	Anorexia	2 (1.3)	1 (0.7)
	Diarrhea	1 (0.7)	4 (2.7)
	Dry mouth	3 (2.0)	0
	Dyspepsia	2 (1.3)	4 (2.7)
	Flatulence	0	2 (1.4)
	Gastritis	4 (2.6)	2 (1.4)
	Gastroenteritis	3 (2.0)	6 (4.1)
	Gastrointestinal disorder	3 (2.0)	2 (1.4)
	Increased appetite	12 (7.8)	11 (7.4)
	Nausea	14 (9.2)	5 (3.4)
	Tooth disorder	1 (0.7)	2 (1.4)
	Vomiting	17 (11.1)	13 (8.8)
Hemic and lymphatic	Bruise	7 (4.6)	5 (3.4)
	Lymphadenopathy	4 (2.6)	3 (2.0)
Metabolic and nutritional	Albuminuria	2 (1.3)	0
	Hyperglycemia	2 (1.3)	1 (0.7)
	Hyperlipemia	0	2 (1.4)
	Hypoglycemia	152 (99.3)	146 (98.6)
	Ketosis	7 (4.6)	6 (4.1)
	Lipodystrophy	2 (1.3)	4 (2.7)
Musculoskeletal	Arthralgia	8 (5.2)	4 (2.7)
	Bone fracture accidental	9 (5.9)	2 (1.4)

Table 7.1.5.4.5 All-causality Common Adverse Events Occurring in ≥ 1% of Pediatric Patients, Controlled Phase 2/3 Studies, Cut-off 1 Aug 03

COSTART Body System	COSTART Event Term	Inh Ins n = 153 n (%)	SQ n = 148 n (%)
	Myalgia	2 (1.3)	1 (0.7)
	Myasthenia	2 (1.3)	0
Nervous	Anxiety	2 (1.3)	1 (0.7)
	Confusion	8 (5.2)	2 (1.4)
	Convulsion	0	2 (1.4)
	Depression	1 (0.7)	2 (1.4)
	Dizziness	22 (14.4)	14 (9.5)
	Hypertonia	1 (0.7)	2 (1.4)
	Hypesthesia	4 (2.6)	0
	Nervousness	2 (1.3)	2 (1.4)
	Paresthesia	3 (2.0)	1 (0.7)
	Somnolence	2 (1.3)	6 (4.1)
	Thinking abnormal	0	2 (1.4)
	Tremor	51 (33.3)	49 (33.1)
Respiratory	Asthma	3 (2.0)	5 (3.4)
	Cough increased	48 (31.4)	14 (9.5)
	Dyspnea	5 (3.3)	0
	Epistaxis	3 (2.0)	3 (2.0)
	Laryngitis	0	2 (1.4)
	Pharyngitis	34 (22.2)	31 (20.9)
	Pneumonia	0	2 (1.4)
	Respiratory disorder	12 (7.8)	10 (6.8)
	Respiratory tract infection	59 (38.6)	57 (38.5)
	Rhinitis	24 (15.7)	31 (20.9)
	Sinusitis	5 (3.3)	11 (7.4)
	Sputum increased	2 (1.3)	2 (1.4)
Skin and appendages	Acne	3 (2.0)	2 (1.4)
	Fungal dermatitis	1 (0.7)	2 (1.4)
	Herpes simplex	1 (0.7)	2 (1.4)
	Maculopapular rash	2 (1.3)	1 (0.7)
	Nail disorder	2 (1.3)	1 (0.7)
	Pruritus	2 (1.3)	1 (0.7)
	Rash	7 (4.6)	6 (4.1)
	Skin benign neoplasm	3 (2.0)	4 (2.7)
	Skin disorder	1 (0.7)	3 (2.0)
	Skin hypertrophy	1 (0.7)	5 (3.4)
	Sweating	14 (9.2)	5 (3.4)
Special senses	Abnormal vision	5 (3.3)	2 (1.4)
	Blepharitis	0	2 (1.4)
	Conjunctivitis	4 (2.6)	6 (4.1)
	Ear disorder	2 (1.3)	0
	Ear pain	6 (3.9)	2 (1.4)
	Otitis media	10 (6.5)	5 (3.4)
Urogenital	Dysmenorrhea	3 (3.9% of ♀)	2 (2.9% of ♀)
	Penis disorder	1 (1.3% of ♂)	1 (1.3% of ♂)
	Urinary tract infection	3 (2.0)	0
	Vaginitis	1 (1.3% of ♀)	1 (1.4% of ♀)

Source: Applicant's Table 4.1.1.1.1.1.2, Section 2.7.4, ISS

The following adverse event terms occurred at a frequency at least 2% higher among pediatric inhaled insulin patients than among SQ patients:

Table 7.1.5.4.6 Adverse Events Occurring at a Frequency at Least 2% Greater in Inhaled Insulin Patients than in SQ Patients, Type 1 DM, <18 Years of Age

COSTART Body System	COSTART Event Term	Inh Ins n = 153 n (%)	SQ n = 148 n (%)
Body as a whole	Abdominal pain	17 (11.1)	11 (7.4)
	Headache	45 (29.4)	35 (23.6)
Digestive	Dry mouth	3 (2.0)	0
	Nausea	14 (9.2)	5 (3.4)
	Vomiting	17 (11.1)	13 (8.8)
Musculoskeletal	Arthralgia	8 (5.2)	4 (2.7)
	Bone fracture accidental	9 (5.9)	2 (1.4)
Nervous	Confusion	8 (5.2)	2 (1.4)
	Dizziness	22 (14.4)	14 (9.5)
	Hypesthesia	4 (2.6)	0
Respiratory	Cough increased	48 (31.4)	14 (9.5)
Skin and appendages	Sweating	5 (3.3)	2 (1.4)
Special senses	Ear pain	6 (3.9)	2 (1.4)
	Otitis media	10 (6.5)	5 (3.4)

Source: Applicant's Table 4.1.1.1.1.1.2, ISS

Overall hypoglycemic event rates (for serious and nonserious events) did not differ between pediatric inhaled insulin and SQ patients. The adverse event term seen with the greatest excess frequency for inhaled over SQ was cough. Nausea, headache and dizziness also occurred numerically more frequently in inhaled insulin patients than in SQ patients.

When combining ear terms, adverse events related to the ear occurred more frequently in children in inhaled insulin groups than in SQ groups. The terms ear pain, ear disorder and otitis media had a combined event rate of 18/153 (11.8%) in the inhaled insulin patients vs 7/148 (4.7%) in SQ patients. This difference could be due to chance; however, the Eustachian tube in children provides an anatomically more direct route to the middle ear than does the Eustachian tube of the adult. Data provided do not permit evaluation of mechanisms, such as entry of inhalation powder into the middle ear via the Eustachian tube, Eustachian tube inflammation, or forceful entry of oral secretions into the Eustachian tube with the inhalation maneuver.

7.1.5.5 Identifying common and drug-related adverse events

Common adverse events which seem likely to be related to inhaled insulin use include cough; nasopharyngeal adverse events such as pharyngitis, rhinitis and sinusitis; and certain respiratory adverse events such as dyspnea. Adverse events related to the ear seem to be related to inhaled insulin use in children.

7.1.5.6 Additional analyses and explorations

Dr. Seymour's pulmonary review discusses respiratory adverse events. Additional analyses for rhinitis and sinusitis follow, as these events appear related to inhaled insulin use.

The following table examines the incidence of rhinitis and sinusitis by age.

Table 7.1.5.6 Incidence of Rhinitis and Sinusitis by Age, Controlled Phase 2/3 Studies

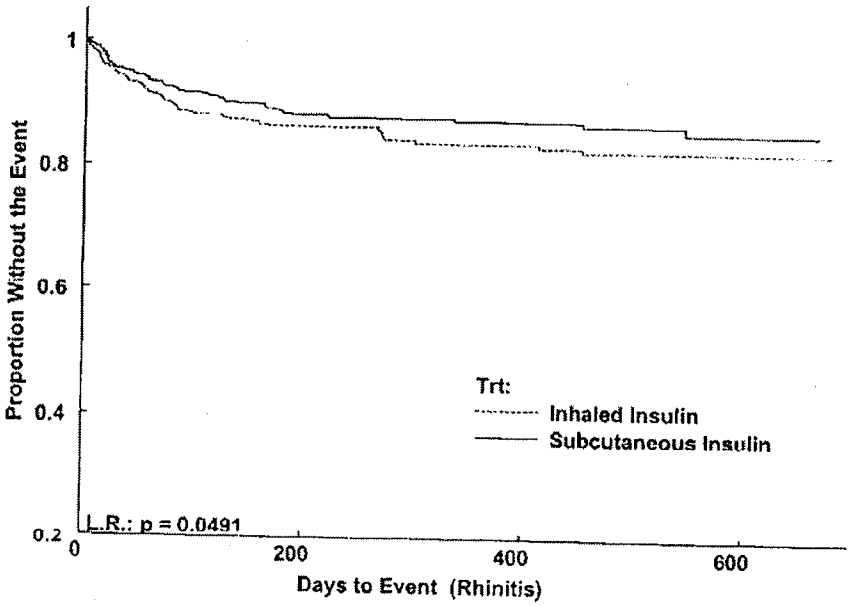
Age Group	Adverse Event	Inh Ins Grp # events (# events per 100 patients in tx grp in this age range)	SQ Grp # events (# events per 100 patients in tx grp in this age range)	OA Grp # events (# events per 100 patients in tx grp in this age range)
<18 years (Type 1)	Rhinitis	24 (20.9)	31 (20.9)	N/A
	Sinusitis	5 (3.3)	11 (7.4)	N/A
18-44 years (Type 1)	Rhinitis	72 (14.2)	52 (10.2)	N/A
	Sinusitis	44 (8.7)	37 (7.3)	N/A
18-44 years (Type 2)	Rhinitis	14 (10.9)	14 (18.7)	2 (2.8)
	Sinusitis	10 (7.7)	12 (16.0)	5 (6.9)
45-64 years (Type 1)	Rhinitis	24 (12.6)	15 (7.7)	N/A
	Sinusitis	20 (10.5)	11 (5.6)	N/A
45-64 years (Type 2)	Rhinitis	73 (8.6)	25 (8.3)	14 (3.3)
	Sinusitis	43 (5.0)	24 (7.9)	9 (2.1)
65-74 years (Type 1)	Rhinitis	0	0	N/A
	Sinusitis	0	0	N/A
65-74 years (Type 2)	Rhinitis	14 (5.3)	7 (6.9)	3 (2.5)
	Sinusitis	12 (4.5)	5 (4.9)	1 (0.8)
≥75 years (Type 2)	Rhinitis	2 (6.7)	0	0
	Sinusitis	0	0	0

Source: Applicant's Table 4.1.3.1.2, ISS; applicant's Table 4.1.1.1.1.1.2, Section 2.7.4, ISS

There is no clear relationship between age and incidence of rhinitis or sinusitis in patients exposed to inhaled insulin. For Type 1 diabetics, the highest incidence of rhinitis occurred in pediatric patients, but the incidence was equal between inhaled insulin and SQ patients. In Type 1 diabetics aged 45-64 years, rhinitis occurred more commonly among inhaled insulin patients (12.6%) than among SQ patients (7.7%). Among Type 1 diabetics treated with inhaled insulin, the highest incidence of sinusitis occurred in the age 45-64 years category, and sinusitis occurred more frequently among inhaled insulin patients in this age group than among SQ patients in this age group. Among Type 2 patients, the age category with the highest incidence of rhinitis among inhaled insulin patients was 18-44 years, but rhinitis occurred at a higher rate among SQ patients in this age group. In the age 45-64 years group of Type 2 diabetics, rhinitis occurred at a slightly higher rate among inhaled insulin patients than patients in other treatment groups. In Type 2 diabetics, the highest incidence of sinusitis among inhaled insulin patients occurred in the age 18-44 years group. There was no age group of Type 2 diabetics where the incidence of sinusitis in the inhaled insulin group exceeded the incidence of sinusitis in both other treatment groups.

Dose dependency was not demonstrated for either rhinitis or sinusitis. Time to event did not differ between inhaled insulin and comparator patients for sinusitis. However, inhaled insulin patients who developed rhinitis did so sooner than SQ patients who developed rhinitis. This is illustrated in the following Kaplan-Meier plot by Dr. Mele of Biostatistics.

Figure 7.1.5.6 Kaplan-Meier Plot for Time to Event for Rhinitis



Log-Rank chi Square = 3.871, p = 0.0491

7.1.6 Less Common Adverse Events

The clinical reviewer examined all adverse event terms in the Phase 2/3 databases (crt/datasets/ALLPH23/ae1.xpt through crt/datasets/ALLPH23/ae14.xpt) to identify relatively rare events that could be of significant concern. These events were presented in Tables 7.1.6.1 and 7.1.6.2 of the Advisory Committee briefing packet initial clinical review. On 23 Aug 05, in an email from Mr. Brian Green of Pfizer to Dr. Oluchi Elekwachi of DMEDP, Pfizer stated that an artifact of their data collection technology may have resulted in overcounting of some of these events. On 14 Sep 05, the clinical reviewer requested of Mr. Green that Pfizer provide updated information regarding actual numbers of these events across the development program.
On 3 Oct 05, Mr. Brian Green sent an email with revised data for these events of concern. The following table lists events of note, and compares the incidence of these events on a person-time basis between inhaled insulin groups (all Phase 2/3) and comparator groups (controlled Phase 2/3). Comparison between the full Phase 2/3 population for inhaled insulin and the controlled Phase 2/3 population for comparator groups has limitations, and cannot be used to firmly establish a higher incidence of any of these events among inhaled insulin patients. Because many inhaled insulin patients had a much longer duration of exposure than any comparator patient, inhaled insulin group patients may have been more likely to develop events that increase in incidence with aging.

Table 7.1.6.1 Rare but Potentially Clinically Significant Adverse Events, All Phase 2/3 Trials of Inhaled Insulin, with Comparison to Controlled Phase 2/3 Trials Incidence Among Comparator Agents

Body System	Applicant's Text Term for Event (PREFTEXT Column in Databases)	Inh Ins # events/ events per 100 pts/ events per 1,000 pt-months	SQ # events/ events per 100 pts/ events per 1,000 pt-months	OA # events/ events per 100 pts/ events per 1,000 pt-months
Eye	Eye hemorrhage	39/1.56/0.78	11/0.92/0.81	0
	Retinal detachment	3/0.12/0.06	1/0.08/0.07	0
	Retinal disorder	171/6.85/3.43	34/2.85/2.50	42/6.52/6.51
	Retinal hemorrhage	21/0.84/0.42	4/0.34/0.29	0
Hematologic	Leukopenia	9/0.36/0.18	0	0
Immune	Allergic reaction	194/7.77/3.89	44/3.69/3.22	12/1.86/1.86
Neoplasia	Bladder carcinoma	1/0.04/0.02	0	0
	Bladder neoplasm	1/0.04/0.02	0	0
	Breast carcinoma	4/0.16/0.08	3/0.25/0.22	0
	Breast neoplasm	8/0.32/0.16	6/0.05/0.44	0
	Carcinoma	3/0.12/0.06	4/0.34/0.29	0
	Carcinoma of lung	3/0.12/0.06	0	1/0.16/0.16
	Chronic myelocytic leukemia	2/0.08/0.04	0	0
	Gastrointestinal carcinoma	4/0.16/0.08	2/0.17/0.15	3/0.47/0.47
	Hepatoma	1/0.04/0.02	0	0
	Melanoma	2/0.08/0.04	0	0
	Neoplasm	48/1.92/0.96	18/1.51/1.32	2/0.31/0.31
	Prostate carcinoma	7/0.47/0.22	1/0.14/0.13	1/0.28/0.29
	Renal carcinoma	1/0.04/0.02	0	0
	Skin carcinoma	12/0.48/0.24	0	3/0.47/0.47
	Thyroid carcinoma	1/0.04/0.02	0	0
Vascular	Arterial thrombosis	3/0.12/0.06	0	0

Source: Tables ae.evt.count.1a and ae.evt.count.1b, email from Mr. Brian Green, Pfizer Regulatory Affairs, 3 Oct 05

The event term "retinal hemorrhage" occurred slightly more frequently per unit of patient-time over all Phase 2/3 trials than the term occurred per unit of patient time in comparator groups in the controlled Phase 2/3 trials. Events termed "allergic reaction" occurred at a somewhat higher frequency per unit of patient-time among inhaled insulin patients in the population of all Phase 2/3 trials than among comparator patients in the controlled Phase 2/3 trials. Concern exists for the development of undesirable immune responses to inhaled insulin. Malignant neoplasms did not occur with a greater frequency in inhaled insulin patients per unit of patient-time than in comparator patients.

The clinical reviewer attempted to examine cases of leukopenia and arterial thrombosis among inhaled insulin patients. The applicant had not provided narratives for any of these cases, and none of the study reports discussed events of leukopenia or arterial thrombosis. On 9 Jun 05, the clinical reviewer requested narratives or case report forms for cases of arterial thrombosis. On 14 Jul 05, Mr. Brian Green sent an email with narratives for these patients. Two of these patients (patient IDs 1001-0056-0122 and 1002-0143-8030) had worsening of underlying lower extremity peripheral vascular disease. The third patient (ID 108-5005-8067) experienced an event of "moderate occlusion bilateral distal superficial femoral arteries" and was referred to a vascular surgeon. This event continued for over a year, until the patient discontinued study due to bronchitis. Inhaled insulin does not appear to be associated with an increased risk for arterial thrombosis.

The following database information was available for inhaled insulin group patients with reported events of leukopenia:

7.1.6.3 Characteristics of Inhaled Insulin Patients with Reported Events of Leukopenia

Patient ID	Baseline WBC	First WBC <4.1 x 10^3 cells/ mm^3	Study Day of First WBC <4.1	Lowest WBC	Study Day of Lowest WBC	Last WBC	Study Day of Last WBC	Age at Study Entry (yrs)	Gender
102-5008-0060	3.0	3.0	BL	2.6	1462	3.6	2596	26	M
106-5030-6885	3.0	3.0	BL	2.5	521	3.6	988	42	M
106-5030-6886	3.6	3.6	BL	2.3	974	2.9	1153	28	M
107-5093-7392	7.1	3.0	877	3.0	877	4.0	996	15	F
107-5033-7829	3.6	3.6	BL	3.0	596	4.2	1038	49	M
109-5071-0073	5.1	No values <4.1	N/A	4.7	804	5.8	1079	67	F
1009-5093-3366	5.7	2.9	477	2.9	477	6.2	694	9	F
1009-5093-3359	3.4	3.4	BL	2.5	676	2.5	676	8	M

Source: Datasets ALLPH23/lab11- ALLPH23/lab19, ALLPH23/lab21- ALLPH23/lab26, ALLPH23/lab110- ALLPH23/lab 123,

Most of these patients had mild baseline leukopenia, and little change from their baseline. None of these patients became absolutely neutropenic. One of the two patients who had a normal WBC at baseline and became neutropenic recovered to a normal WBC. The other of these two patients, a 15 year old female, had recovered to just below the lower limit of normal at her last recorded WBC value. These data do not suggest an association between inhaled insulin and risk for new development of leukopenia.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The applicant provided laboratory data for 51 Phase 2 and Phase 3 studies (31 clinical pharmacology and 20 clinical). Routine chemistry, hematology and urinalyses were collected for all patients. Databases provided did not always include laboratory collected outside routine clinical visits, e.g. laboratory collected at the time of an adverse event was not always included in databases.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled Phase 2 and Phase 3 studies were used for comparisons of laboratory change and abnormalities between inhaled insulin and comparator(s).

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The following tables list median changes from baseline in safety laboratory data.

Table 7.1.7.3.1.1 Median Change from Baseline to Last Observation, Safety Laboratory, Adult Type 1 Patients, Phase 2/3 Controlled Trials

			Inh Ins			SQ		
Lab Category	**Lab Test**	**Units**	**N**	**Baseline Median**	**Median Change from Baseline**	**N**	**Baseline Median**	**Median Change from Baseline**
Hematology	**Hemoglobin (Hb)**	**G/dL**	651	15.2	0	645	15.2	0
	Hematocrit (Hct)	**%**	600	45	0	592	45	0
	Red blood cell count (RBC)	**# cells x 10^6/mm^3**	271	4.8	-0.1	266	4.8	-0.1
	Platelets (PLT)	**# cells x 10^3/mm^3**	602	233	2	606	239	-3
	White blood cell count (WBC)	**# cells x 10^3/mm^3**	613	507	0	608	5.8	0
	Neutrophils	**%**	34	59.2	-2.9	35	60.5	-0.8
	Eosinophils	**%**	246	2.8	0.6	243	2.6	0.2
	Basophils	**%**	246	0.4	0	243	0.4	0
	Lymphocytes	**%**	34	29.7	2.55	35	26	0.8
	Monocytes	**%**	34	7.55	-0.1	35	7.3	0.3
	MCV	**10^{-15} L**	33	90	0	34	90	1
	MCH	**pG/cell**	33	31	-1	34	31	0
	MCHC	**G/dL**	33	34	0	34	34	-1
	Bands	**%**	1	11	-4	1	6	0
Liver Function	**Total bilirubin (Bili)**	**mg/dL**	608	0.5	0	610	0.5	0
	Albumin (Alb)	**G/dL**	609	4.2	0	613	4.2	0
	Aspartate aminotransferase (AST)	**IU/L**	609	23	1	610	22	1
	Alanine aminotransferase (ALT)	**IU/L**	608	24	1	610	23	0
Renal function	**Blood urea nitrogen (BUN)**	**mg/dL**	609	16	0	613	16	0
	Creatinine (Cr)	**mg/dL**	55	1	0	53	1	0
Electrolytes	**Sodium (Na)**	**mEq/L**	609	141	0	613	141	-1
	Potassium (K)	**mEq/L**	607	4.6	-0.1	610	4.6	0
	Chloride (Cl)	**mEq/L**	609	103	1	613	103	0
	Bicarbonate (Bicarb)	**mEq/L**	606	26	-1.4	609	26.4	-1.6
	Calcium (Ca)	**mg/dL**	610	9.5	0	614	9.6	0
	Phosphorus (P)	**mg/dL**	609	3.9	0.1	610	3.9	0.1
Lipids	**Total cholesterol (TC) (random)**	**mg/dL**	590	178.5	1	597	176	0
	Triglycerides (TG) (random)	**mg/dL**	572	68.3	2	575	67.3	1
	Low density lipoprotein (LDL) cholesterol	**mg/dL**	497	103	0	487	102	-1
	High density lipoprotein (HDL) cholesterol	**mg/dL**	578	57	-1	576	57	0
Urinalysis	**Urine white blood cells (Uwbc)**	**cells per high power field**	5	0.5	-0.5	7	1	-1
	Urine red blood cells (Urbc)	**cells per high power field**	30	0	0	31	0	0

Source: Applicant's Table 8.1.1.1, Section 2.7.4

Table 7.1.7.3.1.2 Median Change from Baseline to Last Observation, Safety Laboratory, Adult Type 2 Patients, Phase 2/3 Controlled Trials

			Inh Ins			SQ			OA		
Lab Category	**Lab Test**	**Units**	**N**	**BL Median**	**Median Change from BL**	**N**	**BL Median**	**Median Change from BL**	**N**	**BL Median**	**Median Change from BL**
Heme	**Hb**	**G/dL**	1185	15.3	-0.1	461	15.1	0	572	15.4	-0.1
	Hct	**%**	1126	45	-1	405	45	0	566	46	-1
	RBC	**# x 10^6/mm^3**	882	4.9	-0.1	162	4.9	-0.1	572	4.9	-0.1
	Platelets (Plt)	**# x 10^3/mm^3**	1126	231	3	395	225	-3	565	235	4
	WBC	**# x 10^3/mm^3**	1140	6.5	0	405	6.5	0	572	6.5	0
	Neutrophils	**%**	438	60.1	-0.2	161	60.6	-2	178	61.0	-2.4
	ANC[a]	**# x 10^3/mm^3**	435	3.64	0.04	0			383	3.72	0.11
	Eosinophils	**%**	438	2.7	0.3	161	2.9	0.2	178	2.9	0.5
	Basophils	**%**	438	0.4	0	161	0.4	0	178	0.4	0
	Lymphocytes	**%**	438	29.25	-0.2	161	28.3	1.4	178	28.4	1.2
	Monocytes	**%**	438	6.9	0	161	6.8	0.2	178	6.4	0.1
	MCV	**10^{-15} L**	57	89	0	25	90	0	35	91	0
	MCH	**pG/cell**	497	30	0	25	30	0	424	30	0
	MCHC	**G/dL**	57	34	0	25	34	0	35	34	0
	Bands	**%**	1	2	3	0			0		
LFT	**Total bili**	**mg/dL**	1159	0.4	0	402	0.4	0	619	0.4	0
	Total prot	**G/dL**	460	7.5	0.1	0			425	7.6	0.1
	Alb	**G/dL**	1158	4.2	-0.1	408	4.3	0	612	4.2	0
	AST	**IU/L**	1160	22	1	404	22	1	619	21	1
	ALT	**IU/L**	1160	29	-1	404	29	0	619	30	-1
	Alk Phos	**IU/L**	1155	82	-5	399	83	-3	619	80	-9
Renal	**BUN**	**mg/dL**	1132	17	1	409	18	1	590	17	0
	Cr	**mg/dL**	57	0.9	0	26	0.9	0	36	1	0
Chem	**Na**	**mEq/L**	1158	141	0	409	142	-1	612	140	1
	K	**mEq/L**	1156	4.6	0	402	4.6	-0.1	613	4.5	0
	Cl	**mEq/L**	1158	102	1	409	103.1	0	612	101	1
	Bicarb	**mEq/L**	1156	25.2	-1	406	26	-0.8	609	25	-1
	Ca	**mg/dL**	1146	9.5	0	406	9.6	-0.1	592	9.5	0.1
	P	**mg/dL**	1149	3.7	0.1	402	3.9	0	592	3.7	0.1
Lipids	**TC (random)**	**mg/dL**	705	189	-1	412	188	1	187	193	6
	TG (random)	**mg/dL**	706	143	-13	411	125	4	187	174	7
	LDL	**mg/dL**	1064	112	1	372	110	0	561	118	1
	HDL	**mg/dL**	1131	54	2	402	50	1	590	93	3
Urinalysis	**Uwbc**	**cells/ hpf**	7	1.5	-0.5	1	0.5	-0.5	7	1.5	-1.5
	Urbc	**cells/ hpf**	50	0	0	25	0	0	33	0	0

a Absolute Neutrophil Count
Source: Applicant's Table 8.1.1.2, Section 2.7.4

No significant differences between treatment groups are noted in median change from baseline for these safety laboratory values for either Type 1 or Type 2 diabetics.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following tables list numbers of patients who had shifts from a normal baseline to an abnormal value.

Table 7.1.7.3.2.1 Shifts from Normal Baseline to Abnormal Values, Type 1 Diabetics, Controlled Phase 2/3 Studies

				Inh Ins		SQ	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**
Heme	Hb	G/ dL	<0.8x BL	620	1 (0.2)	615	0
	Hct	%	<0.8x BL	583	1 (0.2)	574	0
	RBC	10^6/ mm^3	<0.75 BL	267	1 (0.4)	261	0
	Plt	10^3/ mm^3	<75	600	1 (0.2)	600	0
			>700	600	0	600	0
	WBC	10^3/ mm^3	<2.5	574	0	572	0
			>17.5	574	0	574	0
	Lymphs	%	<0.5x LLN	232	0	240	0
			>1.5x ULN	232	0	240	0
	Neutrophils	%	<0.5x LLN	239	0	239	0
			>1.2x ULN	239	0	239	0
	Eosinophils	%	>1.5x ULN	225	1 (0.4)	226	1 (0.4)
	Basophils	%	>1.0x ULN	249	2 (0.8)	247	0
	Monocytes	%	>1.0x ULN	246	3 (1.2)	245	3 (1.2)
	Bands	%	>1.0x ULN	10	0	5	1 (20)
	MCV	10^{-15}/ L	<0.9x LLN	33	0	33	0
			>1.1x ULN	33	0	33	0
	MCH	pG/ cell	<0.9x LLN	32	0	30	0
			>1.1x ULN	32	0	30	0
	MCHC	G/ dL	<0.9x LLN	33	0	33	0
			>1.1x ULN	33	0	33	0
LFTs	Total bili	mg/ dL	>1.5x ULN	593	0	589	3 (0.5)
	AST	IU/L	>3x ULN	592	2 (0.3)	595	1 (0.2)
	ALT	IU/L	>3x ULN	578	2 (0.3)	582	2 (0.3)
	Alk Phos	IU/L	>3x ULN	562	0	573	0
	Albumin	G/dL	<0.8x LLN	611	1 (0.2)	617	0
			>1.2x ULN	611	0	617	0
Renal	BUN	mg/ dL	>1.3x ULN	581	5 (0.9)	583	0
	Cr	mg/ dL	>1.3x ULN	572	5 (0.9)	583	0
Lipids	TC (random)	mg/ dL	>1.3x ULN	443	6 (1.4)	459	2 (0.4)
	TG (random)	mg/ dL	>1.3x ULN	560	7 (1.3)	563	4 (0.7)
	HDL	mg/ dL	<0.8x LLN	579	1 (0.2)	588	2 (0.3)
	LDL	mg/ dL	>1.2x ULN	422	8 (1.9)	440	5 (1.1)
Chem	Na	mEq/ L	<0.95x LLN	565	0	572	0
			>1.05x ULN	565	0	572	0
	K	mEq/ L	<0.9x LLN	581	0	583	0
			>1.1x ULN	581	2 (0.3)	583	2 (0.3)
	Cl	mEq/ L	<0.9x LLN	551	0	548	0
			>1.1x ULN	551	0	548	0
	Ca	mg/ dL	<0.9x LLN	575	1 (0.2)	581	1 (0.2)
			>1.1x ULN	575	0	581	1 (0.2)
	P	mg/ dL	<0.8x LLN	552	2 (0.4)	559	2 (0.4)
			>1.2x ULN	552	3 (0.5)	559	2 (0.4)
	Bicarb	mEq/ L	<0.9x LLN	521	5 (1.0)	544	4 (0.7)
			>1.1x ULN	521	5 (1.0)	544	4 (0.7)
UA	Sp Gr		<1.001	498	0	493	0
			>1.035	498	22 (4.4)	493	18 (3.7)
	pH		<1.0x LLN	530	0	520	0
			>1.0x ULN	530	0	520	0
	U glu (qual)		≥ 2+	276	54 (19.6)	258	64 (24.8)
	U prot (qual)		≥ 2+	530	1 (0.2)	533	0

Table 7.1.7.3.2.1 Shifts from Normal Baseline to Abnormal Values, Type 1 Diabetics, Controlled Phase 2/3 Studies

				Inh Ins		SQ	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**
	U WBC	cells/ hpf	≥ 6	449	32 (7.6)	435	34 (7.8)
	U RBC	cells/ hpf	≥ 6	334	15 (4.5)	327	14 (4.3)
	Ket (qual)		≥ 1+	483	19 (3.9)	471	41 (8.7)
	U bld (qual)		≥ 1+	554	21 (3.8)	560	28 (5.0)
	U bili (qual)		≥ 1+	33	0	35	0

Source: Applicant's Table 8.1.2.1, Section 2.7.4

Table 7.1.7.3.2.2 Shifts from Normal Baseline to Abnormal Values, Type 2 Diabetics, Controlled Phase 2/3 Studies

				Inh Ins		SQ		OA	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**	**Total N**	**n with abn (%)**
Heme	Hb	G/ dL	<0.8x BL	1122	4 (0.4)	425	4 (0.9)	553	3 (0.5)
	Hct	%	<0.8x BL	1057	2 (0.2)	382	3 (0.8)	532	2 (0.4)
	RBC	10^6/ mm^3	<0.75 BL	868	0	159	0	567	0
	Plt	10^3/ mm^3	<75	1099	0	379	0	546	0
			>700	1099	0	379	0	546	0
	WBC	10^3/ mm^3	<2.5	1105	1 (0.1)	396	1 (0.3)	553	0
			>17.5	1105	1 (0.1)	396	0	553	0
	Lymphs	%	<0.5x LLN	432	0	157	0	176	0
			>1.5x ULN	432	0	157	0	176	0
	Neutrophils	%	<0.5x LLN	432	0	158	0	178	0
			>1.2x ULN	432	0	158	0	178	0
	Eosinophils	%	>1.5x ULN	423	7 (1.7)	145	2 (1.4)	166	6 (3.6)
	Basophils	%	>1.0x ULN	446	0	161	0	180	0
	Monocytes	%	>1.0x ULN	444	3 (0.7)	160	2 (1.3)	179	2 (1.1)
	Bands	%	>1.0x ULN	8	0	5	0	4	0
	MCV	10^{-15}/ L	<0.9x LLN	458	0	23	0	396	4 (1.0)
			>1.1x ULN	458	1 (0.2)	23	0	396	0
	MCH	pG/ cell	<0.9x LLN	481	2 (0.4)	22	0	413	6 (1.5)
			>1.1x ULN	481	0	22	0	413	0
	MCHC	G/ dL	<0.9x LLN	56	0	25	0	33	0
			>1.1x ULN	56	0	25	0	33	0
	ANC		<0.8x LLN	419	9 (2.1)	0	0	370	14 (3.8)
LFTs	Total bili	mg/ dL	>1.5x ULN	1144	4 (0.3)	399	2 (0.5)	609	1 (0.2)
	AST	IU/L	>3x ULN	1115	0	390	0	583	0
	ALT	IU/L	>3x ULN	1017	3 (0.3)	370	0	530	0
	Alk Phos	IU/L	>3x ULN	1045	0	345	0	554	0
	Total prot	G/dL	>1.2x ULN	453	0	0	0	422	0
			<0.8x LLN	453	0	0	0	422	0
	Albumin	G/dL	<0.8x LLN	1158	0	406	0	610	0
			>1.2x ULN	1158	0	406	0	610	1 (0.2)
Renal	BUN	mg/ dL	>1.3x ULN	1057	35 (3.3)	362	5 (1.4)	562	24 (4.3)
	Cr	mg/ dL	>1.3x ULN	1116	4 (0.4)	367	0	611	5 (0.8)
Lipids	TC (random)	mg/ dL	>1.3x ULN	444	2 (0.5)	255	1 (0.4)	107	1 (0.9)
	TG (random)	mg/ dL	>1.3x ULN	541	17 (3.1)	331	15 (4.5)	133	9 (6.8)

Table 7.1.7.3.2.2 Shifts from Normal Baseline to Abnormal Values, Type 2 Diabetics, Controlled Phase 2/3 Studies

				Inh Ins		SQ		OA	
Lab Category	Lab Test	Units	Criteria for Abnl	Total N	n with abn (%)	Total N	n with abn (%)	Total N	n with abn (%)
	HDL	mg/dL	<0.8x LLN	1040	10 (1.0)	372	2 (0.5)	544	11 (2.0)
	LDL	mg/dL	>1.2x ULN	810	59 (7.3)	278	15 (5.4)	405	40 (9.9)
Chem	Na	mEq/L	<0.95x LLN	1131	1 (0.1)	374	0	606	2 (0.3)
			>1.05x ULN	1131	0	374	0	606	0
	K	mEq/L	<0.9x LLN	1137	1 (0.1)	386	2 (0.5)	603	0
			>1.1x ULN	1137	3 (0.3)	386	3 (0.8)	603	3 (0.5)
	Cl	mEq/L	<0.9x LLN	1100	0	351	0	612	0
			>1.1x ULN	1100	0	351	0	612	0
	Ca	mg/dL	<0.9x LLN	1121	2 (0.2)	378	0	583	1 (0.2)
			>1.1x ULN	1121	0	378	0	583	0
	P	mg/dL	<0.8x LLN	1132	4 (0.4)	372	2 (0.5)	584	0
			>1.2x ULN	1132	1 (0.1)	372	0	584	0
	Bicarb	mEq/L	<0.9x LLN	1083	35 (3.2)	365	6 (1.6)	570	22 (3.9)
			>1.1x ULN	1083	8 (0.7)	365	3 (0.8)	570	1 (0.2)
UA	Sp Gr		<1.001	627	0	379	0	167	0
			>1.035	627	6 (1.0)	379	8 (2.1)	167	10 (6.0)
	U pH		<1.0x LLN	1118	0	384	0	590	0
			>1.0x ULN	1118	0	384	3 (0.8)	590	0
	U glu (qual)		≥ 2+	635	29 (4.6)	249	23 (9.2)	351	15 (4.3)
	U prot (qual)		≥ 2+	956	8 (0.8)	326	2 (0.6)	522	1 (0.2)
	U WBC	cells/hpf	≥ 6	673	51 (7.6)	315	31 (9.8)	274	24 (8.8)
	U RBC	cells/hpf	≥ 6	488	17 (3.5)	238	12 (5.0)	235	6 (2.6)
	Ket (qual)		≥ 1+	1042	7 (0.7)	375	5 (1.3)	548	1 (0.2)
	U bld (qual)		≥ 1+	1100	11 (1.0)	388	6 (1.5)	573	7 (1.2)
	U bili (qual)		≥ 1+	57	0	26	0	36	0

1 LLN used by applicant for ANC = 1,700 cells
Source: Applicant's Table 8.1.2.2. Section 2.7.4

Among adult Type 1 and Type 2 patients who had normal laboratory at baseline, the occurrence of glycosuria was common, but did not occur more commonly among inhaled insulin patients than among comparator patients.

The following tables list the incidence of recurrent or worsening laboratory abnormalities among patients who had abnormal laboratory values at baseline.

Table 7.1.7.3.2.3 Incidence of Laboratory Abnormalities Among Adult Type 1 Diabetics with Abnormal Baseline Laboratory[1]

				Inh Ins		SQ	
Lab Category	Lab Test	Units	Criteria for Abnl	Total N	n Meeting both Criteria (%)	Total N	n Meeting both Criteria (%)
Heme	Eosinophils	%	>1.5x ULN and >1.5x BL	25	2 (8.0)	22	1 (4.5)
LFTs	ALT	IU/L	>3x ULN and >1.5x BL	33	0	33	1 (3.0)
Renal	BUN	mg/dL	>1.3x ULN and >1.3x BL	31	1 (3.2)	34	2 (5.9)

Table 7.1.7.3.2.3 Incidence of Laboratory Abnormalities Among Adult Type 1 Diabetics with Abnormal Baseline Laboratory[1]

				Inh Ins		SQ	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**
Lipids	**TC (random)**	**mg/ dL**	>1.3x ULN and >1.3x BL	152	0	143	1 (0.7)
	TG (random)	**mg/ dL**	>1.3x ULN and >1.5x BL	17	3 (17.6)	17	1 (5.9)
	HDL	**mg/ dL**	<0.8x LLN and <0.8x BL	17	1 (5.9)	12	0
	LDL	**mg/ dL**	>1.2x ULN and >1.2x BL	96	5 (5.2)	73	3 (4.1)
Chem	**Na**	**mEq/ L**	<0.95x LLN and <0.95x BL	47	1 (2.1)	45	0
	P	**mg/ dL**	>1.2x ULN and >1.2x BL	60	0	56	2 (3.6)
UA	**U glu (qual)**		≥ 2+ and >BL+1	315	28 (8.9)	335	39 (11.6)
	U prot (qual)		≥ 2+ and >BL+1	67	1 (1.5)	67	1 (1.5)
	U WBC	**cells/ hpf**	≥ 6 and ≥ 6	20	8 (40)	13	6 (46.2)
	U RBC	**cells/ hpf**	≥ 6 and ≥ 6	28	5 (17.9)	23	8 (34.8)
	Ket (qual)		≥ 1+ and >BL+1	114	2 (1.8)	129	2 (1.6)
	U bld (qual)		≥ 1+ and >BL+1	43	1 (2.3)	40	2 (5.0)

1 Table includes only tests with abnormal values while on study treatment
Source: Applicant's Table 8.1.3.1, Section 2.7.4

Table 7.1.7.3.2.4 Incidence of Laboratory Abnormalities Among Type 2 Diabetics with Abnormal Baseline Laboratory[1]

				Inh Ins		SQ		OA	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**
Heme	**Hb**	**G/ dL**	<0.8x LLN and <0.8x BL	75	1 (1.3)	38	0	22	1 (4.5)
	Hct	**%**	<0.8x LLN and <0.8x BL	82	2 (2.4)	29	0	37	1 (2.7)
	RBC	**10^6/ mm^3**	<0.75 LLN and <0.8x BL	25	1 (4.0)	4	0	8	0
	Plt	**10^3/ mm^3**	<75 and <0.8x BL	42	1 (2.4)	25	0	24	0
	WBC	**10^3/ mm^3**	<2.5 and <0.75x BL	46	1 (2.2)	16	0	22	0
	Eosinophils	**%**	>1.5x ULN and >1.5x BL	25	1 (4.0)	17	0	14	2 (14.3)
	MCV	**10^{-15}/ L**	<0.9x LLN and <0.9x BL	36	2 (5.6)	2	0	24	1 (4.2)
	MCH	**pG/ cell**	<0.9x LLN and <0.9x	17	1 (5.9)	3	0	13	1 (7.7)

Table 7.1.7.3.2.4 Incidence of Laboratory Abnormalities Among Type 2 Diabetics with Abnormal Baseline Laboratory[1]

				Inh Ins		SQ		OA	
Lab Category	**Lab Test**	**Units**	**Criteria for Abnl**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**	**Total N**	**n Meeting both Criteria (%)**
			BL						
	ANC		<0.8x LLN[2] and <0.8x BL	17	2 (11.8)	0	0	15	0
LFTs	AST	IU/L	>3x ULN and >1.5x BL	53	1 (1.9)	17	0	37	0
	ALT	IU/L	>3x ULN and >1.5x BL	151	2 (1.3)	37	0	90	1 (1.1)
Renal	BUN	mg/dL	>1.3x ULN and >1.3x BL	83	6 (7.2)	48	2 (4.2)	29	0
	Cr	mg/dL	>1.3x ULN and >1.3x BL	49	2 (4.1)	43	0	2	0
Lipids	TC (random)	mg/dL	>1.3x ULN and >1.3x BL	264	2 (0.8)	158	0	80	3 (3.8)
	TG (random)	mg/dL	>1.3x ULN and >1.5x BL	168	8 (4.8)	81	9 (11.1)	54	3 (5.6)
	HDL	mg/dL	<0.8x LLN and <0.8x BL	123	5 (4.1)	39	0	68	3 (4.4)
	LDL	mg/dL	>1.2x ULN and >1.2x BL	318	26 (8.2)	104	7 (6.7)	196	30 (15.3)
Chem	K	mEq/L	>1.1x ULN and >1.1x BL	27	1 (3.7)	19	0	11	0
	P	mg/dL	<0.8x LLN and <0.8x BL	25	0	33	0	8	1 (12.5)
	Bicarb	mEq/L	<0.9x LLN and <0.75x BL	83	0	43	1 (2.3)	40	1 (2.5)
UA	U pH		>1.0x ULN and >1.0x BL	25	9 (36.0)	23	8 (34.8)	0	0
	U glu (qual)		≥ 2+ and >BL+1	506	13 (2.6)	157	10 (0.64)	239	6 (2.5)
	U prot (qual)		≥ 2+ and >BL+1	184	1 (0.5)	81	0	66	1 (1.5)
	U WBC	cells/hpf	≥ 6 and ≥ 6	48	14 (29.2)	14	4 (28.6)	34	5 (14.7)
	U RBC	cells/hpf	≥ 6 and ≥ 6	28	7 (25.0)	22	4 (18.2)	2	1 (50.0)
	Ket (qual)		≥ 1+ and >BL+1	101	1 (1.0)	32	0	42	1 (2.4)
	U bld (qual)		≥ 1+ and >BL+1	42	1 (2.4)	19	1 (5.3)	17	1 (5.9)

1 Table includes only tests with abnormal values while on study treatment
2 ANC LLN used by applicant = 1,700 cells
Source: Applicant's Table 8.1.3.2, Section 2.7.4

Baseline glycosuria and lipid abnormalities were common in both Type 1 and Type 2 diabetics in all treatment groups; the development of a worsened degree of glycosuria or hyperlipoproteinemia was not more common among inhaled insulin patients than among comparator patients.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The applicant did not provide listings or analyses of marked laboratory outliers in the NDA submission. The following table lists marked laboratory outliers among patients taking inhaled insulin in all Phase 2 and Phase 3 trials; these were extracted by the clinical reviewer from the laboratory datasets for all Phase 2/3 trials.

Table 7.1.7.3.3: Marked Laboratory Outliers, Inhaled Insulin Patients, All Phase 2 and Phase 3 Trials

Lab Test	Normal Range and Units	Lab Value	Pt ID	Study Day	Comment
Alanine Aminotransferase, Serum	0-35 U/L	153	1001-0047-3002	372	
		145	1001-0145-1307	736	BL LFTs >3x ULN
		139	1002-0145-6299	636	
		138	1001-0131-2331	127	BL LFTs >3x ULN
Alkaline Phosphatase, Serum	30-120 U/L	614	1009-5079-3380	638	
Bicarbonate, Serum	21-30 mEq/L	40	104-5007-0026	81	
		39	1001-0141-3048	47	
		14.5	1029-1016-0483	374	
		12.8	1029-1110-4985	363	
		11.7	1022-1006-0318	365	
Bilirubin, Serum Total	0.3-1.0 mg/dL	5.7	108-5048-8401	898	
Creatinine, Serum	<1.5 mg/dL	11.5	103-5002-0092	1580	
		5.3	103-5002-0005	2584	
		4.8	108-5072-8386	870	
Eosinophil Count, Absolute	0-1,000 cells	1810	1002-0047-8321	449	
		1630	1002-0141-7398	456	
Gamma Glutamyl Transferase, Serum	1-94 U/L	304	1002-0047-7051	127	
		295	1001-0098-0198	46	Gallstones, fatty liver, permanently discontinued
		265	1001-0145-1307	736	BL LFTs >3x ULN
Glucose, Random Serum	<120 mg/dL	633	106-5064-6517	734	
		514	107-5076-7230	866	

Table 7.1.7.3.3: Marked Laboratory Outliers, Inhaled Insulin Patients, All Phase 2 and Phase 3 Trials

Lab Test	Normal Range and Units	Lab Value	Pt ID	Study Day	Comment
Hemoglobin A1c	3.8-6.4%	15.0	107-5084-7002	1335	
		14.9	106-5064-6519	288	DKA later in study
		14.6	106-5064-6103	352	DKA later in study
		4.3	1027-1016-0646	85	
Neutrophil Count, Absolute	>1,700 cells[2]	1290	1001-0046-1100	205	
		1280	1001-0141-2053	817	
		1280	1001-0002-3301	169	
		1160	1002-0027-6281	184	
		1110	1002-0135-5275	724	
		850	1002-0074-6149	828	
		540	1002-0142-7408	163	Discontinued for severe cough and dyspnea on Study Day 632
		480	1001-0145-1307	169	
Phosphorus, Serum	3-4.5 mg/dL	7.4	103-5002-0092	1599	Renal failure
		6.8	1009-5128-3004	457	
		1.7	1027-5148-1329	86	Occurred on the same day as a severe hypoglycemic episode
		1.5	106-5073-6835	530	
Platelets, Blood	150-350 x 10^3/mm^3	71K	1029-1096-4029	355	
Potassium, Serum	3.5-5.0 mEq/L	6.4	108-5071-8431	163	
		6.4	1022-1001-0009	106	
		2.9	110-5102-1361	802	
		2.8	103-5006-0047	97	
Red Blood Cells, Urine	0-2/hpf	TNTC	106-5002-6846	894	
		TNTC	107-5041-7152	504	Decline in DLco Study Day 1065
		TNTC	107-5052-7181	533	
		TNTC	107-5061-7798	554	Discontinued same day for declines in FEV1 and DLco
		TNTC	107-5066-7742	707	
		TNTC	108-5007-8550	164	
		TNTC	108-5048-8610	166	Decline in DLco Study Day 344
		TNTC	109-5072-0503	454	
		TNTC	1009-5093-3363	450	
		TNTC	1002-	547	

Table 7.1.7.3.3: Marked Laboratory Outliers, Inhaled Insulin Patients, All Phase 2 and Phase 3 Trials

Lab Test	Normal Range and Units	Lab Value	Pt ID	Study Day	Comment
			0005-6031		
		TNTC	1002-0051-5095	730	
		TNTC	1002-0101-5208	731	
Sodium, Serum	136-145 mEq/L	126	1001-0047-2002	172	
		125	1002-0056-5109	169	
		125	108-5005-8067	729	Discontinued due to bronchitis on Study Day 609 after 435 days inhaled insulin exposure
		122	1022-1008-0448	366	
White Blood Cell Count, Blood	4.5-11.0 x 10^3/mm^3	1.8	106-5013-6604	526	
		1.7	106-5065-6947	1003	
		1.7	1001-0145-1307	169	

1 Reference ranges from Harrison's Textbook of Internal Medicine, 16th Ed
2 ANC LLN used by applicant
Source: Applicant's datasets allph23/lab11 - allph23/lab19, allph23lab21 - allph23lab29, allph23lab110 - allph23lab123, allph23lab210 - allph23lab218

The clinical reviewer searched for clinical information related to these abnormalities, but most had no narrative or other information in either the individual study report or the overall safety narratives. The clinical reviewer requested further clinical information from the applicant on 16 Jun 05. On 20 Jul 05, the applicant sent, via email, a table which included additional details for some of these patients. For most of these laboratory outliers, there was no report of a recorded event which could have explained the laboratory finding. For those outliers for which a followup value was available, most unexplained abnormal values returned to the normal range.

The one type of laboratory outlier that remained somewhat concerning was low white blood cell count and/or low absolute neutrophil count. However, review of the controlled Phase 2/3 laboratory datasets revealed that similar percentages of control patients also exhibited outlier values in these ranges for white blood cell count and absolute neutrophil count (Source: crt/datasets/CNTPH23lab12 and crt/datasets/CNTPH23lab 213).

Discontinuations due to laboratory abnormalities were discussed in Section 7.1.3.

7.1.7.4 Additional analyses and explorations

Because there were no significant differences between inhaled insulin groups and comparator groups for laboratory abnormalities in controlled Phase 2/3 trials, explorations for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions, and drug-drug interactions were not applicable.

7.1.7.5 Special assessments

7.1.7.5.1 Hepatotoxicity

Transaminase elevations did not occur at a higher rate among inhaled insulin patients than among comparator patients in the controlled Phase 2/3 study population. Additional information was requested from the applicant on 16 Jun 05 regarding patient 108-5048-8401, who had an elevated bilirubin of 5.7 mg/dL on day 898, per the applicant's laboratory datasets for all Phase 2 and Phase 3 studies. The laboratory outlier table sent by the applicant on 20 Jul 05 reported that no event was recorded to coincide with this bilirubin value. However, the patient had a baseline bilirubin of 4.7 mg/dL, and his bilirubin on day 911 was 5.1 mg/dL. It appears that this patient had baseline hyperbilirubinemia that was not substantially worsened after inhaled insulin exposure. Additional information was requested from the applicant on 16 Jun 05 regarding patient 104E-5011-0034, who had a serious adverse event of jaundice and increased liver function tests. On 18 Jul 05, Mr. Brian Green sent a narrative regarding this patient via email. This 69 year old man had negative hepatitis serology, and was suspected to have a drug-induced hepatitis related to irbesartan. Discontinuation of irbesartan was followed by resolution of jaundice, but LFTs remained elevated. Several months later, the patient had a 7 mm biliary stone removed via endoscopic retrograde cholangiopancreatography. The applicant did not have data regarding resolution of the elevated LFTs. Overall, there does not appear to be a signal of hepatotoxicity for Exubera®.

7.1.7.5.2 QTc

An intensive QTc study was not performed. Electrocardiograms were performed at baseline in Phase 2 and Phase 3 studies, but routine electrocardiograms (ECGs) were not performed after baseline in Studies 1001, 1002, 102, 1026, 1027, and 1029. ECGs were not performed at specific times relative to study drug administration. From routine electrocardiograms from those studies for which postbaseline ECGs were obtained, mean changes in QTc were not significantly different between inhaled insulin and comparator patients in controlled Phase 2 and Phase 3 studies. Bazzett's correction was used for QTc.

Table 7.1.7.5.2.1 Mean Changes in QTc, Adult Population, Controlled Phase 2 and Phase 3 Studies

	Type 1 Patients		Type 2 Patients		
	Inh Ins n = 252	SQ n = 248	Inh Ins n = 907	SQ n = 167	OA n = 579
QTc BL msec (SD)	408.8 (30.8)	407.8 (24.2)	411.8 (41.6)	415.1 (24.2)	409.9 (45.8)
QTc Mean Δ from BL msec (SD)	-6.0 (30.8)	-1.0 (21.2)	1.0 (27.3)	1.0 (23.6)	2.0 (30.5)

Source: Applicant's Tables 10.1.2.2 and 10.1.2.1, ISS

From routine electrocardiograms, outlier abnormalities of the QTc interval did not occur more frequently among inhaled insulin patients than among comparator patients in controlled Phase 2 and Phase 3 studies, as illustrated in the following table.

Table 7.1.7.5.2.2 QTc Changes from Baseline with Outliers, Adult Patients, Controlled Phase 2 and Phase 3 Studies

	Type 1 Patients		Type 2 Patients		
QTc Change from Baseline	**Inh Ins n = 251 n (%)**	**SQ n = 247 n (%)**	**Inh Ins n = 898 n (%)**	**SQ n = 167 n (%)**	**OA n = 573 n (%)**
≤ 30 msec	233 (92.8)	232 (93.9)	846 (94.2)	153 (91.6)	552 (96.3)
>30 to ≤ 60 msec	15 (6.0)	14 (5.7)	44 (4.9)	11 (6.6)	16 (2.8)
>60 msec	3 (1.2)	1 (0.4)	8 (0.9)	3 (1.8)	5 (0.9)

Source: Applicant's Tables 80 and 81, ISS 2.7.4 Section 4.4

There was no difference between groups in frequency of QTc outliers by gender (source Applicant's Tables 10.1.4.1 and 10.1.4.2, ISS).

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (systolic and diastolic blood pressure, pulse) were measured at baseline and at end of study or time of study discontinuation. Body weight was a secondary endpoint in some studies, but is presented here because of its occurrence as an undesirable association with improved or intensive glycemic control.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The clinical reviewer used the controlled Phase 2 and Phase 3 populations for comparisons of frequencies of vital signs abnormalities.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Mean pulse and blood pressure did not change substantially from baseline to last observation for adult patients, and there were no significant differences between treatment groups.

Table 7.1.8.3.1.1 Mean Change from Baseline in Pulse and Blood Pressure, Adult Patients, Controlled Phase 2 and Phase 3 Studies

	Type 1		Type 2		
	Inh Ins n = 684 Mean Δ (SD)	SQ n = 687 Mean Δ (SD)	Inh Ins n = 1,243 Mean Δ (SD)	SQ n = 481 Mean Δ (SD)	OA n = 599 Mean Δ (SD)
Systolic BP (mmHg)	0.98 (13.61)	0.41 (13.50)	-1.11 (16.77)	0.53 (16.09)	-3.15 (18.29)
Diastolic BP (mmHg)	-0.15 (9.09)	-0.06 (9.21)	-1.18 (9.51)	0.05 (9.60)	-2.18 (9.90)
Pulse (bpm)	0.31 (10.48)	-0.33 (10.04)	0.09 (10.05)	-0.45 (10.24)	0.09 (9.95)

Source: Applicant's Tables 9.1.1.1 and 9.1.1.2, ISS

Among adult Type 1 diabetics in Studies 106 and 107, there was little difference between treatment groups for mean change in body weight.

Table 7.1.8.3.1.2 Mean Change from Baseline in Body Weight (kg), Adult Type 1 Patients, Studies 106 and 107, ITT Population

Study	Tx Grp	N	BL (SD)	EOS (SD)	Mean Δ (SD)	Adj Diff (95% CI)
106	Inh Ins	135	77.4 (14.9)	77.7 (14.9)	0.3 (3.1)	-0.72 (-1.48, 0.04)
	SQ	134	76.4 (13.0)	77.4 (13.7)	1.0 (3.2)	
107	Inh Ins	103	76.0 (13.6)	76.5 (14.3)	0.5 (3.5)	-0.24 (-1.07, 0.59)
	SQ	104	76.9 (14.1)	77.7 (14.7)	0.7 (2.5)	

Source: Applicant's Tables 1.7.1.1, 1.7.1.2, Section 2.7.3

Type 2 patients who were insulin-using at study entry did not gain more weight with inhaled insulin than with comparator; in Study 108, SQ patients actually gained statistically significantly more weight (1.28 kg, 95% CI 0.6-1.96). However, inhaled insulin patients who were not using insulin at study entry did have statistically significantly greater weight gain than comparator patients in several studies, as illustrated in the following table.

Table 7.1.8.3.1.3 Mean Change from Baseline in Body Weight (kg), Type 2 Patients, Non-insulin-using at Study Entry, Controlled Phase 2 and Phase 3 ITT Populations

Study	Tx Grp	N	BL (SD)	EOS (SD)	Mean Δ (SD)	Adj Diff (95% CI)
109	Inh Ins	103	89.5 (15.8)	92.3 (15.2)	2.8 (3.6)	2.80 (1.94, 3.65)[a]
	Inh Ins + OA	101	88.6 (15.5)	91.3 (16.6)	2.7 (3.3)	2.75 (1.89, 3.61)[b]
	OA	96	88.0 (15.4)	88.0 (15.5)	-0.1 (1.9)	
110	Inh Ins	75	92.9 (17.6)	94.8 (16.1)	1.9 (3.7)	0.95 (-0.18, 2.09)
	Rosi	68	93.1 (23.9)	93.9 (23.3)	0.8 (3.7)	
1001 (6 month data, pts with BL HbA1c 8-9.5%)	Inh Ins + SU	102	79.9 (12.3)	82.3 (12.5)	2.3 (2.8)	2.67 (1.84, 3.51)
	Met + SU	93	81.9 (14.0)	81.6 (14.0)	-0.3 (2.4)	
1001 (6 month data, pts with BL HbA1c >9.5-12%)	Inh Ins + SU	112	80.8 (14.6)	84.4 (15.2)	3.5 (3.7)	3.60 (2.81, 4.39)
	Met + SU	103	79.5 (14.6)	79.4 (14.9)	0 (2.6)	
1002 (6 month data, pts with BL HbA1c 8-9.5%)	Inh Ins + Met	123	90.3 (16.6)	92.2 (16.9)	1.8 (3.7)	0.38 (-0.52, 1.27)
	Gli[c] + Met	114	88.2 (16.5)	89.7 (16.7)	1.5 (2.9)	
1002 (6 month data, pts with BL HbA1c >9.5-12%)	Inh + Met	105	88.3 (17.0)	90.9 (16.9)	2.6 (3.5)	0.26 (-0.70, 1.21)
	Gli + Met	102	87.8 (16.3)	90.2 (16.9)	2.4 (3.8)	

a Comparison of Inh Ins to OA
b Comparison of Inh Ins+OA to OA
c Glibenclamide
Source: Applicant's Table 26, Section 2.7.3.3.2.2.5

The difference in weight gain was most evident in Study 1001, in which add-on inhaled insulin was compared to add-on metformin.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The applicant did not submit analyses of vital signs data for shifts from normal to abnormal.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

The applicant did not submit outlier analyses for vital signs data.

There was no significant difference between treatment groups in the frequency of adverse events of hypotension and hypertension, as illustrated in the following table.

Table 7.1.8.3.3.1 Adverse Events of Hypotension and Hypertension, Adult Patients, Controlled Phase 2 and Phase 3 Studies

	Type 1		Type 2		
	Inh Ins n = 698 n (%)	SQ n = 705 n (%)	Inh Ins n = 1,277 n (%)	SQ n = 488 n (%)	OA n = 644 n (%)
Hypotension	0	0	4 (0.3)	0	0
Hypertension	20 (2.9)	14 (2.0)	106 (8.3)	39 (8.0)	49 (7.6)
Source: Applicant's Table 68, Section 2.1.5.3.1					

Table 7.1.7.5.2.2 QTc Changes from Baseline with Outliers, Adult Patients, Controlled Phase 2 and Phase 3 Studies

	Type 1 Patients		Type 2 Patients		
QTc Change from Baseline	**Inh Ins n = 251 n (%)**	**SQ n = 247 n (%)**	**Inh Ins n = 898 n (%)**	**SQ n = 167 n (%)**	**OA n = 573 n (%)**
≤ 30 msec	233 (92.8)	232 (93.9)	846 (94.2)	153 (91.6)	552 (96.3)
>30 to ≤ 60 msec	15 (6.0)	14 (5.7)	44 (4.9)	11 (6.6)	16 (2.8)
>60 msec	3 (1.2)	1 (0.4)	8 (0.9)	3 (1.8)	5 (0.9)

Source: Applicant's Tables 80 and 81, ISS 2.7.4 Section 4.4

There was no difference between groups in frequency of QTc outliers by gender (source Applicant's Tables 10.1.4.1 and 10.1.4.2, ISS).

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (systolic and diastolic blood pressure, pulse) were measured at baseline and at end of study or time of study discontinuation. Body weight was a secondary endpoint in some studies, but is presented here because of its occurrence as an undesirable association with improved or intensive glycemic control.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The clinical reviewer used the controlled Phase 2 and Phase 3 populations for comparisons of frequencies of vital signs abnormalities.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Mean pulse and blood pressure did not change substantially from baseline to last observation for adult patients, and there were no significant differences between treatment groups.

Table 7.1.8.3.1.1 Mean Change from Baseline in Pulse and Blood Pressure, Adult Patients, Controlled Phase 2 and Phase 3 Studies

	Type 1		Type 2		
	Inh Ins n = 684 Mean Δ (SD)	SQ n = 687 Mean Δ (SD)	Inh Ins n = 1,243 Mean Δ (SD)	SQ n = 481 Mean Δ (SD)	OA n = 599 Mean Δ (SD)
Systolic BP (mmHg)	0.98 (13.61)	0.41 (13.50)	-1.11 (16.77)	0.53 (16.09)	-3.15 (18.29)
Diastolic BP (mmHg)	-0.15 (9.09)	-0.06 (9.21)	-1.18 (9.51)	0.05 (9.60)	-2.18 (9.90)
Pulse (bpm)	0.31 (10.48)	-0.33 (10.04)	0.09 (10.05)	-0.45 (10.24)	0.09 (9.95)
Source: Applicant's Tables 9.1.1.1 and 9.1.1.2, ISS					

Among adult Type 1 diabetics in Studies 106 and 107, there was little difference between treatment groups for mean change in body weight.

Table 7.1.8.3.1.2 Mean Change from Baseline in Body Weight (kg), Adult Type 1 Patients, Studies 106 and 107, ITT Population

Study	Tx Grp	N	BL (SD)	EOS (SD)	Mean Δ (SD)	Adj Diff (95% CI)
106	Inh Ins	135	77.4 (14.9)	77.7 (14.9)	0.3 (3.1)	-0.72 (-1.48, 0.04)
	SQ	134	76.4 (13.0)	77.4 (13.7)	1.0 (3.2)	
107	Inh Ins	103	76.0 (13.6)	76.5 (14.3)	0.5 (3.5)	-0.24 (-1.07, 0.59)
	SQ	104	76.9 (14.1)	77.7 (14.7)	0.7 (2.5)	
Source: Applicant's Tables 1.7.1.1, 1.7.1.2, Section 2.7.3						

Type 2 patients who were insulin-using at study entry did not gain more weight with inhaled insulin than with comparator; in Study 108, SQ patients actually gained statistically significantly more weight (1.28 kg, 95% CI 0.6-1.96). However, inhaled insulin patients who were not using insulin at study entry did have statistically significantly greater weight gain than comparator patients in several studies, as illustrated in the following table.

Table 7.1.8.3.1.3 Mean Change from Baseline in Body Weight (kg), Type 2 Patients, Non-insulin-using at Study Entry, Controlled Phase 2 and Phase 3 ITT Populations

Study	Tx Grp	N	BL (SD)	EOS (SD)	Mean Δ (SD)	Adj Diff (95% CI)
109	Inh Ins	103	89.5 (15.8)	92.3 (15.2)	2.8 (3.6)	2.80 (1.94, 3.65)[a]
	Inh Ins + OA	101	88.6 (15.5)	91.3 (16.6)	2.7 (3.3)	2.75 (1.89, 3.61)[b]
	OA	96	88.0 (15.4)	88.0 (15.5)	-0.1 (1.9)	
110	Inh Ins	75	92.9 (17.6)	94.8 (16.1)	1.9 (3.7)	0.95 (-0.18, 2.09)
	Rosi	68	93.1 (23.9)	93.9 (23.3)	0.8 (3.7)	
1001 (6 month data, pts with BL HbA1c 8-9.5%)	Inh Ins + SU	102	79.9 (12.3)	82.3 (12.5)	2.3 (2.8)	2.67 (1.84, 3.51)
	Met + SU	93	81.9 (14.0)	81.6 (14.0)	-0.3 (2.4)	
1001 (6 month data, pts with BL HbA1c >9.5-12%)	Inh Ins + SU	112	80.8 (14.6)	84.4 (15.2)	3.5 (3.7)	3.60 (2.81, 4.39)
	Met + SU	103	79.5 (14.6)	79.4 (14.9)	0 (2.6)	
1002 (6 month data, pts with BL HbA1c 8-9.5%)	Inh Ins + Met	123	90.3 (16.6)	92.2 (16.9)	1.8 (3.7)	0.38 (-0.52, 1.27)
	Gli[c] + Met	114	88.2 (16.5)	89.7 (16.7)	1.5 (2.9)	
1002 (6 month data, pts with BL HbA1c >9.5-12%)	Inh + Met	105	88.3 (17.0)	90.9 (16.9)	2.6 (3.5)	0.26 (-0.70, 1.21)
	Gli + Met	102	87.8 (16.3)	90.2 (16.9)	2.4 (3.8)	

a Comparison of Inh Ins to OA
b Comparison of Inh Ins+OA to OA
c Glibenclamide
Source: Applicant's Table 26, Section 2.7.3.3.2.2.5

The difference in weight gain was most evident in Study 1001, in which add-on inhaled insulin was compared to add-on metformin.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The applicant did not submit analyses of vital signs data for shifts from normal to abnormal.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

The applicant did not submit outlier analyses for vital signs data.

There was no significant difference between treatment groups in the frequency of adverse events of hypotension and hypertension, as illustrated in the following table.

Table 7.1.8.3.3.1 Adverse Events of Hypotension and Hypertension, Adult Patients, Controlled Phase 2 and Phase 3 Studies

	Type 1		Type 2		
	Inh Ins n = 698 n (%)	**SQ n = 705 n (%)**	**Inh Ins n = 1,277 n (%)**	**SQ n = 488 n (%)**	**OA n = 644 n (%)**
Hypotension	0	0	4 (0.3)	0	0
Hypertension	20 (2.9)	14 (2.0)	106 (8.3)	39 (8.0)	49 (7.6)
Source: Applicant's Table 68, Section 2.1.5.3.1					

No inhaled insulin group patients were reported to have discontinued due to a change in blood pressure or pulse.

The following table lists patients identified by investigators as having had significant change in body weight. The definition for the applicant's criterion for a significant change in weight was not noted. For Type 2 patients, investigators reported more events of significant weight gain among inhaled insulin patients than among comparator patients.

Table 7.1.8.3.3.2 Adult Patients with Significant Changes in Body Weight, Controlled Phase 2 and Phase 3 Studies

Tx Grp	DM Type	Pt ID	Amt of Wt Incr (kg)[2]
Inh Ins	1	106-5051-6277	11.8
SQ	1	1022-5060-2907	NV[1]
	1	1027-1005-0208	4.5
Inh Ins	2	1001-0018-0059	5
	2	1001-0018-1057	8
	2	1001-0018-1058	6-8
	2	1001-0045-0093	6.5
	2	1001-0045-3362	5
	2	1001-0065-0157	NV
	2	1002-0045-5079	NV
	2	109-5026-0602	11.4
	2	109-5127-0161	NV
	2	110-5058-1409	NV
	2	110-5112-1371	NV
OA (glibenclamide)	2	1002-0141-8034	NV

1 No value given
2 Amount of weight gain from patient's adverse event report
Source: Applicant's Table 9.1.3.1 and 9.1.3.2, Section 2.7.4

Only one patient in all phase 2 and Phase 3 trials discontinued treatment due to weight gain, patient 1029-1033-2138, a 53 year old Type 2 diabetic woman who discontinued after 60 days on inhaled insulin treatment. Her measured weight gain was negligible, with a weight on Study Day 1 of 83.4 kg, on Study Day 30 of 84.1 kg, and on Study Day 58 of 83.6 kg.

7.1.8.4 Additional analyses and explorations

As there were few differences between treatment groups for blood pressure and pulse, additional analyses were not performed for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions or drug-drug interactions.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were performed at baseline in Phase 2 and Phase 3 studies, but they were not performed routinely after baseline in Studies 1001, 1002, 1022, 1026, 1027 and 1029. ECGs

were not performed at a specific time relative to study drug administration. QTc is discussed above in Section 7.1.7.5.2.

Pharmacologic toxicology review of preclinical data related to cardiac conduction revealed no concerns.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The controlled Phase 2 and Phase 3 studies for which ECGs were routinely performed at baseline and at least once after baseline were used for comparisons.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Among Adult Type 1 and Type 2 diabetics, there was little difference between groups for mean changes in heart rate, PR interval or QRS width.

Table 7.1.9.3.1.1 Mean Changes in ECG Parameters, Adult Type 1 Diabetics, Controlled Phase 2 and Phase 3 Studies with ECGs at Baseline and at Least Once After Baseline

Parameter (units)	Inh Ins n = 252 Mean BL (SD)	SQ n = 248 Mean BL (SD)	Inh Ins n = 252 Mean Change from BL to Last Observ (SD)	SQ n = 248 Mean Change from BL to Last Observ (SD)
Heart rate (bpm)	69.0 (11.0)	69.9 (11.4)	0 (9.6)	0 (9.2)
PR interval (msec)	148.6 (23.8)	150.6 (22.0)	2.0 (18.2)	1.0 (13.9)
QRS width (msec)	85.0 (12.5)	84.1 (12.8)	0 (8.4)	0 (10.3)

Source: Applicant's Table 10.1.2.1, Section 2.7.4

Table 7.1.9.3.1.2 Mean Changes in ECG Parameters, Type 2 Diabetics, Controlled Phase 2 and Phase 3 Studies with ECGs at Baseline and at Least Once After Baseline

Parameter (units)	Inh Ins n = 907 Mean BL (SD)	SQ n = 167 Mean BL (SD)	OA n = 579 Mean BL (SD)	Inh Ins n = 907 Mean Change from BL to Last Observ (SD)	SQ n = 167 Mean Change from BL to Last Observ (SD)	OA n = 579 Mean Change from BL to Last Observ (SD)
Heart rate (bpm)	72.3 (11.7)	72.2 (11.4)	74.0 (12.1)	1.0 (10)	0 (10.2)	0 (10.4)
PR Interval (msec)	163.4 (27.1)	159.1 (26.8)	161.9 (26.3)	1.0 (17.8)	0 (13.9)	3.0 (15.4)
QRS Width (msec)	88.6 (17.6)	87.9 (14.7)	87.6 (17.6)	1.0 (11.1)	1.0 (10.5)	1.0 (8.6)

Source: Applicant's Table 10.1.2.2, Section 2.7.4

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

were not performed at a specific time relative to study drug administration. QTc is discussed above in Section 7.1.7.5.2.

Pharmacologic toxicology review of preclinical data related to cardiac conduction revealed no concerns.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The controlled Phase 2 and Phase 3 studies for which ECGs were routinely performed at baseline and at least once after baseline were used for comparisons.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Among Adult Type 1 and Type 2 diabetics, there was little difference between groups for mean changes in heart rate, PR interval or QRS width.

Table 7.1.9.3.1.1 Mean Changes in ECG Parameters, Adult Type 1 Diabetics, Controlled Phase 2 and Phase 3 Studies with ECGs at Baseline and at Least Once After Baseline

Parameter (units)	Inh Ins n = 252 Mean BL (SD)	SQ n = 248 Mean BL (SD)	Inh Ins n = 252 Mean Change from BL to Last Observ (SD)	SQ n = 248 Mean Change from BL to Last Observ (SD)
Heart rate (bpm)	69.0 (11.0)	69.9 (11.4)	0 (9.6)	0 (9.2)
PR interval (msec)	148.6 (23.8)	150.6 (22.0)	2.0 (18.2)	1.0 (13.9)
QRS width (msec)	85.0 (12.5)	84.1 (12.8)	0 (8.4)	0 (10.3)

Source: Applicant's Table 10.1.2.1, Section 2.7.4

Table 7.1.9.3.1.2 Mean Changes in ECG Parameters, Type 2 Diabetics, Controlled Phase 2 and Phase 3 Studies with ECGs at Baseline and at Least Once After Baseline

Parameter (units)	Inh Ins n = 907 Mean BL (SD)	SQ n = 167 Mean BL (SD)	OA n = 579 Mean BL (SD)	Inh Ins n = 907 Mean Change from BL to Last Observ (SD)	SQ n = 167 Mean Change from BL to Last Observ (SD)	OA n = 579 Mean Change from BL to Last Observ (SD)
Heart rate (bpm)	72.3 (11.7)	72.2 (11.4)	74.0 (12.1)	1.0 (10)	0 (10.2)	0 (10.4)
PR Interval (msec)	163.4 (27.1)	159.1 (26.8)	161.9 (26.3)	1.0 (17.8)	0 (13.9)	3.0 (15.4)
QRS Width (msec)	88.6 (17.6)	87.9 (14.7)	87.6 (17.6)	1.0 (11.1)	1.0 (10.5)	1.0 (8.6)

Source: Applicant's Table 10.1.2.2, Section 2.7.4

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The applicant did not submit analyses of shifts from normal to abnormal for ECG data.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

The applicant did not submit analyses of ECG outliers.

One Type 2 diabetic inhaled insulin group patient, a 64 year old man (ID 103-5014-0022), discontinued treatment on Study Day 84 due to a cerebrovascular accident, bradycardia and premature ventricular contractions that had begun on Study Day 82.

7.1.9.4 Additional analyses and explorations

Because no significant differences were noted between treatment groups for ECG abnormalities, additional explorations were not performed for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions or drug-drug interactions.

7.1.10 Immunogenicity

Please see Section 7.1.3.3.2 for a discussions of the development of insulin antibodies among inhaled insulin patients, and the occurrence of allergic and immune events.

The actual drug substance used ([redacted] insulin, Aventis) did not exhibit inherent immunogenicity in Aventis Study 3002, in which 476 insulin-naïve Type 2 patients were randomized to receive either [redacted] or SQ Huminsulin® (Eli Lilly human insulin) for one year. Rates of insulin antibody development did not differ between groups.

7.1.11 Human Carcinogenicity

Malignant neoplastic adverse events in humans are discussed in Sections 7.1.2.1, 7.1.3.2 and 7.1.6. Overall, malignant neoplasms did not occur at a higher frequency in inhaled insulin patients than in comparator patients for either Type 1 or Type 2 diabetics. In controlled Phase 2 and Phase 3 trials in Type 2 diabetics, discontinuations due to neoplasia did not occur more frequently among inhaled insulin group patients than among control patients. One case of lung carcinoma occurred in the inhaled insulin groups, and one in the oral agent groups. Pulmonary neoplasms are to be discussed in Dr. Seymour's pulmonary safety review. For all Phase 2 and Phase 3 trials, controlled and uncontrolled, neoplastic adverse event terms leading to discontinuation were numerically more frequent and slightly (not statistically significantly) more frequent on a person-time basis in the inhaled insulin groups than in the control groups.

The applicant did not conduct animal carcinogenicity studies with inhaled insulin.

7.1.12 Special Safety Studies

Dr. Seymour's pulmonary safety review will include discussion of specific pulmonary safety studies; please see Section 7.1.3.3 for a discussion of insulin antibody studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The abuse potential of inhaled insulin was not evaluated by the applicant. Recreational abuse of insulin is unlikely, as it is not known to induce pleasurable effects generally associated with drugs of abuse. One accidental overdose of inhaled insulin occurred during the drug development program, resulting in hypoglycemia, but no unexpected adverse effects.

Studies 111, 1001, 1002, and 1027 included withdrawal of inhaled insulin, and substitution of subcutaneous insulin as subsequent insulin treatment. An increased incidence of hypoglycemia was noted during the initial period of replacement with subcutaneous insulin. Withdrawal of inhaled insulin was associated with increases (returns toward baseline) in FEV1 and DLco compared to inhaled insulin continuation. Withdrawal of inhaled insulin was associated with decreases (returns toward baseline) in insulin antibody levels as reflected by insulin binding activity. No withdrawal phenomena suggestive of addictive potential were reported.

Inhaled insulin does not appear to have abuse potential, but withdrawal of inhaled insulin requires an initial period of increased monitoring and careful medical supervision, with vigilance for hypoglycemia, as subcutaneous therapy is instituted.

7.1.14 Human Reproduction and Pregnancy Data

The applicant did not conduct animal reproduction studies with Exubera®.

Study 1007 was a clinical pharmacokinetic and pharmacodynamic study conducted in 10 gestational and 3 pregestational diabetic women. It was an open-label, randomized, two-period, two-treatment, crossover study. Each subject received a single morning fasting dose of either 9 U regular SQ insulin or 1 puff of 3 mg inhaled insulin, then no study insulin for 14 days (with continued usual management of their diabetes), then a single dose of cross-over study medication.

Insulin Tmax was earlier with inhaled insulin administration than with regular SQ insulin. Cmax was 83% higher with inhaled insulin than with regular SQ. $AUC_{0\text{-}360}$ was similar for both treatments.

Table 7.1.14.1 Insulin Pharmacokinetics, Study 1007, Gestational and Pregestational Pregnant Diabetics				
	Inh Ins mean (SD)	**SQ mean (SD)**	**Ratio or Difference**	**95% CI for Diff Between Grps**
AUC_{0-360} (µU-min/mL)	2435 (50)	2630 (57)	93%	55%, 155%
Cmax (µU/mL)	39.0 (57)	21.3 (57)	183%	116%, 290%
Tmax (min)	45.8 (39)	82.9 (63)	-37.1 min	-75.1 min, 1.0 min
Source: Applicant's Tables 5.2.1, 5.2.2, 5.3.1, Study 1007 report				

Insulin Tmax in this study was similar to that seen in nonpregnant diabetics in other studies, where Tmax ranged from 38-78 minutes. Fasting insulin Cmax in these women was also similar to fasting insulin Cmax seen in nonpregnant diabetics. Bioavailability of inhaled insulin relative to SQ was 10% based on geometric mean; this relative bioavailability is similar to that seen in nonpregnant women.

Mean maximum reduction of plasma glucose was similar between treatments; time to maximum reduction of glucose was numerically, although not statistically significantly, shorter with inhaled insulin than with regular insulin. The lack of statistical significance of the difference in time to maximum reduction of glucose may have been due to small sample size.

Table 7.1.14.2 Glucose Pharmacodynamics, Study 1007, Gestational and Pregestational Pregnant Diabetics				
	Inh Ins mean (SD)	**SQ mean (SD)**	**Ratio or Difference**	**95% CI for Diff Between Grps**
AUC_{0-360} (µU-min/mL)	6083 (41)	5582 (50)	109%	80%, 148%
Maximum decline in glu conc (mg/dL)	28.8 (35)	28.1 (44)	103%	81%, 130%
Time to maximum decline in glu conc (min)	210 (62)	275 (24)	-65.0 mg/dL	-142.3 mg/dL, 12.3 mg/dL
Source: Applicant's Tables 5.4, 5.5.1, Study 1007 report				

Time to maximum decline in glucose was somewhat shorter for pregnant inhaled insulin patients in this study (210 minutes) than for nonpregnant Type 2 diabetics receiving inhaled insulin in Study 1004, where the time to maximum decline in glucose was 248 minutes. The maximum decline in glucose concentration was less in these pregnant diabetics exposed to inhaled insulin than it was in nonpregnant Type 2 diabetics in Study 1004, but significant differences in baseline glucose levels and patient age limit the interpretability of this observation.

One subject was discontinued from Study 1007 after completing her first treatment (inhaled insulin). Discontinuation was due to a prolapsed umbilical cord, resulting in a Caesarian delivery. Two women had hypoglycemic episodes two hours after administration of inhaled insulin; no women became hypoglycemic after SQ insulin administration. Pregnancy outcomes were not reported.

In other studies in the clinical development program, a total of 10 women became pregnant while taking inhaled insulin, and two women became pregnant while taking SQ insulin. All patients

The applicant did not submit analyses of shifts from normal to abnormal for ECG data.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

The applicant did not submit analyses of ECG outliers.

One Type 2 diabetic inhaled insulin group patient, a 64 year old man (ID 103-5014-0022), discontinued treatment on Study Day 84 due to a cerebrovascular accident, bradycardia and premature ventricular contractions that had begun on Study Day 82.

7.1.9.4 Additional analyses and explorations

Because no significant differences were noted between treatment groups for ECG abnormalities, additional explorations were not performed for dose dependency, time dependency, drug-demographic interactions, drug-disease interactions or drug-drug interactions.

7.1.10 Immunogenicity

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The applicant did not conduct animal carcinogenicity studies with inhaled insulin.

7.1.12 Special Safety Studies

Dr. Seymour's pulmonary safety review will include discussion of specific pulmonary safety studies; please see Section 7.1.3.3 for a discussion of insulin antibody studies.

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The applicant did not conduct animal reproduction studies with Exubera®.

Study 1007 was a clinical pharmacokinetic and pharmacodynamic study conducted in 10 gestational and 3 pregestational diabetic women. It was an open-label, randomized, two-period, two-treatment, crossover study. Each subject received a single morning fasting dose of either 9 U regular SQ insulin or 1 puff of 3 mg inhaled insulin, then no study insulin for 14 days (with continued usual management of their diabetes), then a single dose of cross-over study medication.

Insulin Tmax was earlier with inhaled insulin administration than with regular SQ insulin. Cmax was 83% higher with inhaled insulin than with regular SQ. $AUC_{0\text{-}360}$ was similar for both treatments.

Table 7.1.14.1 Insulin Pharmacokinetics, Study 1007, Gestational and Pregestational Pregnant Diabetics				
	Inh Ins mean (SD)	**SQ mean (SD)**	**Ratio or Difference**	**95% CI for Diff Between Grps**
$AUC_{0\text{-}360}$ (µU-min/mL)	2435 (50)	2630 (57)	93%	55%, 155%
Cmax (µU/mL)	39.0 (57)	21.3 (57)	183%	116%, 290%
Tmax (min)	45.8 (39)	82.9 (63)	-37.1 min	-75.1 min, 1.0 min
Source: Applicant's Tables 5.2.1, 5.2.2, 5.3.1, Study 1007 report				

Insulin Tmax in this study was similar to that seen in nonpregnant diabetics in other studies, where Tmax ranged from 38-78 minutes. Fasting insulin Cmax in these women was also similar to fasting insulin Cmax seen in nonpregnant diabetics. Bioavailability of inhaled insulin relative to SQ was 10% based on geometric mean; this relative bioavailability is similar to that seen in nonpregnant women.

Mean maximum reduction of plasma glucose was similar between treatments; time to maximum reduction of glucose was numerically, although not statistically significantly, shorter with inhaled insulin than with regular insulin. The lack of statistical significance of the difference in time to maximum reduction of glucose may have been due to small sample size.

Table 7.1.14.2 Glucose Pharmacodynamics, Study 1007, Gestational and Pregestational Pregnant Diabetics				
	Inh Ins mean (SD)	**SQ mean (SD)**	**Ratio or Difference**	**95% CI for Diff Between Grps**
$AUC_{0\text{-}360}$ (µU-min/mL)	6083 (41)	5582 (50)	109%	80%, 148%
Maximum decline in glu conc (mg/dL)	28.8 (35)	28.1 (44)	103%	81%, 130%
Time to maximum decline in glu conc (min)	210 (62)	275 (24)	-65.0 mg/dL	-142.3 mg/dL, 12.3 mg/dL
Source: Applicant's Tables 5.4, 5.5.1, Study 1007 report				

Time to maximum decline in glucose was somewhat shorter for pregnant inhaled insulin patients in this study (210 minutes) than for nonpregnant Type 2 diabetics receiving inhaled insulin in Study 1004, where the time to maximum decline in glucose was 248 minutes. The maximum decline in glucose concentration was less in these pregnant diabetics exposed to inhaled insulin than it was in nonpregnant Type 2 diabetics in Study 1004, but significant differences in baseline glucose levels and patient age limit the interpretability of this observation.

One subject was discontinued from Study 1007 after completing her first treatment (inhaled insulin). Discontinuation was due to a prolapsed umbilical cord, resulting in a Caesarian delivery. Two women had hypoglycemic episodes two hours after administration of inhaled insulin; no women became hypoglycemic after SQ insulin administration. Pregnancy outcomes were not reported.

In other studies in the clinical development program, a total of 10 women became pregnant while taking inhaled insulin, and two women became pregnant while taking SQ insulin. All patients

were discontinued from study once their pregnancy was reported. The following table lists these patients and their pregnancy outcomes.

Table 7.1.14.3 Pregnancy Occurrence and Outcome, All Phase 2 and Phase 3 Studies

Patient	Trtmnt	Age	DM Type	Time on Treatment (days) Prior to DC	EGA at Time of Last Study Drug Dose	Last Known Insulin Antibody Level (Insulin Binding Activity)	Last Known HbA1c	Pregnancy Outcome
111-5059-6684	Inh Ins	29	1	243	1-2 months	14% binding	8.4%	No narrative; reported uncomplicated Caesarian delivery
111-5029-8422	Inh Ins	37	2	209	4 wks	21% binding	7.9%	No narrative; reported sp abortion at appr 14 wks after LMP, abnl fetal karyotype
111-5007-7988	Inh Ins	22	1	916	Unk	23% binding	9.2%	No narrative re pregnancy; reported sp abortion at unk gest age, 7 weeks after DC of inh ins. Pt also had recurrent severe hypoglycemia and decline in DLco
102E-5007-0073	Inh Ins	31	1	207	6 wks	Not measured	8.9%	No narrative; healthy birth by C-section at 36 weeks EGA
1022-1006-0305	Inh Ins	27	1	42	2 mos	24 µU/mL	7.8%	No narrative; reported deliv near term
106-5016-6932	Inh Ins	28	1	53	Unk	<3% binding	5.5%	Unk; subject moved out of state; no narrative
1022-1039-2253	Inh Ins	21	1	110	11 wks	20 µU/mL	9.2%	Preterm labor at 31 wks EGA; C-section at 32 weeks EGA. Neonatal cardiomegaly and macrosomia; neonatal death at age 2 days. See Section 7.1.1 (deaths) for further details
1022-1047-2730	Inh Ins	27	1	176	Unk	89 µU/mL	9.0%	Sp abortion shortly after becoming pregnant; no narrative
1022-5155-3735	Inh Ins	42	1	304	5 weeks	185 µU/mL	7.2%	Sp abortion at 10 wks EGA; no narrative
1027-1015-0600	Inh Ins	31	1	86	3 mos	31 µU/mL	5.6%	Healthy birth near term. Neonatal hypoglycemia one hour after delivery. No narrative
1022-1008-0447	SQ	29	1	SQ cont	SQ cont	4.6 µU/mL	6.9%	Birth at 37 wks EGA; LGA and neonatal hypoglycemia, Apgars 6 and 9. No narrative.
1022-1023-1306	SQ	20	1	SQ cont	SQ cont	<2 µU/mL	6.2%	Pregnancy ongoing at time of reporting; no complications. No narrative.

Source: Applicant's Table 87, ISS

The applicant did not provide narratives for most of these pregnancies. The case of neonatal death is discussed further in the Deaths section (7.1.1). Transient neonatal hypoglycemia occurred in one patient exposed to inhaled insulin; this is a common event in infants of diabetics mothers in general.

In the medical literature, clinically apparent spontaneous abortions are reported to occur in insulin-requiring diabetic women at a rate roughly twice that of the normal population of pregnant women (29.5% vs 10-15%) (Miodovnik 1988). In the Exubera® development program, 4/10 women who became pregnant while taking inhaled insulin had a spontaneous abortion. The risk for spontaneous abortion in pregnant Type 1 diabetics is increased with poor glycemic control in the first trimester; however, the threshold for increased risk occurs with initial HbA1c concentrations above 12% (Rosenn 1994). None of the inhaled insulin patients who had spontaneous abortions had HbA1cs >12%, although two had HbA1cs ≥ 9%.

In Studies 106 and 107, mean end-of-study insulin binding activities for Type 1 nonpregnant diabetic women were 32.6% binding (SD 22.46) for the semiquantitative Mayo assay, and 435.0 µU/mL (SD 1194.2) for the quantitative Esoterix® assay. None of the women in the development program who had adverse pregnancy outcomes had known insulin binding activity higher than these means. Thus, limited data do not suggest a contribution of insulin antibody formation to adverse pregnancy outcomes with inhaled insulin.

The applicant proposes Pregnancy Category C for Exubera®, with the following language for the label:

"Animal reproduction studies have not been conducted with EXUBERA. It is also not known whether EXUBERA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. EXUBERA should be given to a pregnant woman only if clearly needed."

The information obtained about human reproductive risk of Exubera® is not substantial enough at this time to conclude that Exubera® can cause fetal harm, and thus Pregnancy Categories D or X are not warranted. The clinical reviewer concurs with assignment of Pregnancy Category C for Exubera®.

7.1.15 Assessment of Effect on Growth

In Study 1009, conducted in children ages 6-11 years, height was not reported after baseline, and no datasets were provided. In Studies 106 and 107, which included adolescents ages 12-18, height was not reported after baseline, and datasets did not include height data. The applicant's Table 4.2.1.1.1.1 lists one case of growth retardation among Type 1 diabetics exposed to inhaled insulin in all Phase 2 and Phase 3 studies, but no patient identification number was included to permit review of this case. Data are insufficient for conclusions regarding the potential effect of Exubera® on growth.

7.1.16 Overdose Experience

One accidental overdose of inhaled insulin occurred during the drug development program, resulting in hypoglycemia, but no unexpected adverse effects.

7.1.17 Postmarketing Experience

Not applicable.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

An enormous volume of information was submitted for review with the Exubera® application. The original NDA, submitted 27 Dec 04, contained 17.9 GB of information, 17 of which were clinical. Between 28 Dec 04 and 20 Jun 05, the applicant submitted an additional 0.7 GB of information. One GB of electronic information is roughly equivalent to 100,000 pages of text information.

Safety data from all Phase 2 and Phase 3 studies were used in the safety evaluation. Information for comparison of rates of safety findings was obtained from the controlled Phase 2 and Phase 3 study data. The applicant provided, in electronic form, overall safety summary information, reports of all completed Phase 2 and Phase 3 studies, and partial reports of some ongoing studies. Datasets were provided for some, but not all, individual studies. An overall safety database was provided for the controlled Phase 2 and Phase 3 studies, including both inhaled insulin and comparator data. A separate database was provided for the population of inhaled insulin patients exposed in all Phase 2 and Phase 3 studies, both controlled and uncontrolled. This database did not include comparator patient data. Narratives or case report forms were provided only for deaths, serious adverse events that the applicant felt were study-drug-related, adverse events which led to discontinuation, and pulmonary adverse events.

7.2.1.1 Study type and design/patient enumeration

Please see Section 4.2 for a tabular summary of the type and design of clinical studies.

The cut-off date for routine safety data for the NDA was 25 Jun 04; the cut-off date for serious adverse event data was 1 Sep 04.

As of 25 Jun 04, a total of 3,603 patients had been exposed to inhaled insulin. Of these, 3,272 were adults, and 331 were <18 years old. For the 4-month safety update (cut-off 13 Dec 04), data for only two additional patients were submitted; both patients were exposed to inhaled insulin. The following table details overall exposure by patient number:

Table 7.2.1.1.1 Overall Exposure to Inhaled Insulin by Numbers of Patients, Data Cut-off 25 Jun 04

Study Type	Subject Type	Inh Ins	SQ	OA	Total
Clin Pharm	Nondiabetic	696	493	0	699
	Diabetic	125	123	0	127
	All Clin Pharm	821	616	0	826
Controlled Phase 2/3 Studies	Type 1 Diabetics	851	853	0	1,704
	Type 2 Diabetics	1,277	1,341	644	4,113
	All Contr Ph 2/3	2,128	1,365	644	4,133
All Phase 2/3 Studies	Type 1 Diabetics	1,209	869	0	1,714
	Type 2 Diabetics	1,578	496	645	2,419
	All Pts, Ph 2/3	2,787	1,365	648	4,133
All Studies	**All Subjects, All Studies**	**3,603**	**1,981**	**648**	**4,959**

Source: Applicant's Table 1.1.1, ISS Appendix

The following table presents pediatric exposure by numbers of patients. No Type 2 diabetic children were studied.

Table 7.2.1.1.2 Exposure for Patients <18 Years of Age, Data Cut-off 25 Jun 04

Study Type	Subject Type	Inh Ins	SQ	Total
Clin Pharm	Nondiabetic	20	20	20
	Type 1 Diabetic	25	26	27
	All Phase 1	45	46	47
Controlled Phase 2/3	Type 1 Diabetic	153	148	301
All Ph 2/3	Type 1 Diabetic	291	148	301
All Studies	**All Children, All Studies**	**331**	**194**	**348**

Source: Applicant's Table 1.1.2, Section 2.7.4

In the controlled Phase 2/3 studies in adults, a total of 214 Type 1 and 375 Type 2 diabetic patients were exposed to inhaled insulin for more than 12 months. The following table presents adult exposure in the controlled Phase 2/3 population.

Table 7.2.1.1.3 Exposure by Duration, Controlled Phase 2/3 Studies in Adults, Cut-off 25 Jun 04

	Type 1		Type 2		
Exposure (months)[1]	**Inh Ins n = 698 n (% of tx grp)**	**SQ n = 705 n (% of tx grp)**	**Inh Ins n = 1,277 n (% of tx grp)**	**SQ n = 488 n (% of tx grp)**	**OA n = 644 n (% of tx grp)**
>0-3	159 (22.8)	165 (23.4)	365 (28.6)	45 (9.2)	209 (32.5)
>3-6	264 (37.8)	249 (35.3)	288 (22.6)	141 (28.9)	137 (21.3)
>6-12	61 (8.7)	64 (9.1)	249 (19.5)	121 (24.8)	99 (15.4)
>12-18	158 (22.6)	169 (24.0)	183 (14.3)	148 (30.3)	48 (7.5)
>18-24	56 (8.0)	58 (8.2)	136 (10.6)	33 (6.8)	107 (16.6)
>24-30	0	0	56 (4.4)	0	44 (6.8)
Median Exposure (months)	5.59	5.65	5.88	9.71	5.60
Overall Exposure (patient-months)	**5,894**	**6,052**	**12,187**	**4,868**	**6,453**

1 Numbers not cumulative; patients counted only once in their final treatment duration category
Source: Applicant's ISS Appendix Tables 2.1.1.1, 2.1.1.2

Median exposure among inhaled insulin patients in all Phase 2 and Phase 3 trials was considerably longer than that seen in the controlled Phase 2/3 trial population (15.34 vs 5.59 for

Type 1, 17.49 vs 9.71 for Type 2). A total of 585 Type 1 and 996 Type 2 patients had exposure of at least 12 months, with some patients exposed for as long as 7 years.

The following table presents duration of exposure by ranges of exposure, and cumulative exposure for adult patients in all Phase 2 and Phase 3 studies.

Table 7.2.1.1.4 Duration of Exposure, All Phase 2 and Phase 3 Studies, Inhaled Insulin Patients, Data Cut-off 25 Jun 04

	Type 1 n = 918	Type 2 n = 1,578		Type 1 n = 918	Type 2 n = 1,578
Exposure (months)[1]	**n (%)**	**n (%)**	**Cumulative Exposure (months)[2]**	**n (%)**	**n (%)**
>0-3	144 (15.7)	114 (7.2)	>0	918 (100)	1,578 (100.0)
>3-6	90 (9.8)	171 (10.8)	>3	774 (84.3)	1,464 (92.8)
>6-12	99 (10.8)	297 (18.8)	>6	684 (74.5)	1,293 (81.9)
>12-18	195 (21.2)	250 (15.8)	>12	390 (42.5)	746 (47.3)
>18-24	144 (15.7)	244 (15.3)	>24	246 (26.8)	502 (31.8)
>24-30	115 (12.5)	241 (15.3)	>24	246 (26.8)	502 (31.8)
>30-36	83 (9.0)	156 (9.9)	>30	131 (14.3)	261 (6.7)
>36-42	17 (1.9)	45 (2.9)	>36	48 (5.2)	105 (6.7)
>42-48	1 (0.1)	5 (0.3)	>42	31 (3.4)	60 (3.8)
>48-54	1 (0.1)	4 (0.3)	>48	30 (3.3)	55 (3.5)
>54-60	3 (0.3)	3 (0.2)	>54	29 (3.2)	51 (3.2)
>60-66	2 (0.2)	5 (0.3)	>60	26 (2.8)	48 (3.0)
>66-72	0	16 (1.0)	>66	24 (2.6)	43 (2.7)
>72-78	1 (0.1)	14 (0.9)	>72	24 (2.6)	27 (1.7)
>78-84	15 (1.6)	8 (0.5)	>78	23 (2.5)	13 (0.8)
>84	8 (0.9)	5 (0.3)	>84	8 (0.9)	5 (0.3)
Median Exposure (months)	15.34	17.49		15.34	17.49
Overall Exposure (patient-months)	**16,571**	**30,688**		**16,571**	**30,688**

1 Numbers not cumulative; patients counted only once in their final treatment category
2 Includes all patients exposed for at least the stated duration
Source: Applicant's Table 6, ISS

For Type 1 patients <18 years of age, the following total subject-months of exposure occurred:

- inhaled insulin, controlled Phase 2/3 trials: 690 patient-months for 153 patients
- SQ insulin, controlled Phase 2/3 trials: 663 patient-months for 148 patients
- inhaled insulin, all Phase 2/3 trials: 6,242 patient-months for 291 patients

7.2.1.2 Demographics

The distribution of common baseline demographic characteristics does not suggest problems with randomization. Among Type 1 diabetics, few non-Caucasians participated. A larger percentage of the Type 2 population was either black or Hispanic, although the vast majority of patients were Caucasian. In the U.S. diabetic population, Type 1 diabetics are much more likely to be Caucasian than non-Caucasian. Type 2 diabetes, however, is increasing in incidence in all racial groups, but especially among African Americans and Hispanics. The underlying cause of this increasing incidence is less tied to race *per se* than it is to a more rapidly increasing incidence of obesity in these groups, although certain racial groups (e.g. Pima Indians) have a stronger genetic predisposition. Because the etiology of the increasing incidence of Type 2

diabetes in most racial and ethnic groups in the United States is related to obesity rather than to race, efficacy data obtained in this development program can likely be extrapolated to most obese Type 2 diabetics, despite the predominance of Caucasians in the clinical trials. However, Dr. Talmadge King of the Endocrine and Metabolic Drugs Advisory Committee pointed out that lung function in African Americans differs from other U.S. racial and ethnic groups. The clinical reviewer confirmed that African Americans have been described to have lower baseline lung function than Caucasian Americans and Mexican-Americans (Hankinson 1999). Therefore, pulmonary safety data obtained in the program for non-African-Americans may not be extrapolatable to African Americans.

Table 7.2.1.2 Demographic Characteristics, Adult Patients, Controlled Phase 2/3 Studies

	Number (%) of Subjects				
	Type 1		Type 2		
	INH	SC	INH	SC	OA
N	698	705	1,277	488	644
Gender [number (%) of subjects]:					
Male	390 (55.9)	385 (54.6)	795 (62.3)	307 (62.9)	361 (56.1)
Female	308 (44.1)	320 (45.4)	482 (37.7)	181 (37.1)	283 (43.9)
Age (yr):					
Mean	38.0	38.0	57.2	55.6	56.6
Range	18-65	18-65	28-80	23-78	29-80
Race [number (%) of subjects]:					
White	616 (88.3)	642 (91.1)	1,043 (81.7)	348 (71.3)	569 (88.4)
Hispanic	43 (6.2)	35 (5.0)	94 (7.4)	63 (12.9)	28 (4.3)
Black	24 (3.4)	11 (1.6)	85 (6.7)	46 (9.4)	23 (3.6)
Asian	7 (1.0)	6 (0.9)	21 (1.6)	11 (2.3)	12 (1.9)
Other	8 (1.1)	11 (1.6)	34 (2.7)	20 (4.1)	12 (1.9)
BMI* (kg/m^2):					
Mean	25.3	25.3	30.2	30.1	30.4
Range	18-36	17-35	18-51	20-40	18-57

*Body Mass Index
INH=inhaled insulin, SC=subcutaneous short-acting insulin, OA=oral antidiabetic agents, and N= number of subjects.
Source: Appendix Tables 3.1.1.1.2 and 3.1.1.2

For the most part, exclusion criteria used in Phase 2 and Phase 3 trials were unlikely to limit the general applicability of trial results. However, the following exclusion criteria could have excluded significant numbers of diabetics who might be encountered in clinical practice:

- BMI >35 kg/m^2 for Type 2 diabetics
- HbA1c >12%
- Renal impairment
- Requirement of >150 units per day of subcutaneous insulin
- Signs of autonomic neuropathy, such as gastroparesis or orthostatic hypotension
- Tobacco smoking within 6 months of study or during study
- Two or more serious hypoglycemic episodes within the year prior to study

- Hospitalization or emergency room visit within the six months prior to study for poor diabetes control

Information regarding the safety of large doses of inhaled insulin, such as that required for very obese patients, and those who have already demonstrated a high subcutaneous requirement, is lacking. Significant renal impairment and autonomic neuropathy are common complications of diabetes. Although the applicant proposes in its label to exclude smokers from use of inhaled insulin, it is likely that smokers will use the drug, either because the smoking exclusion is not noted by their physician, or because smokers may be unwilling to share their smoking history with their physician.

In controlled Phase 2/3 studies, mean duration of diabetes at diagnosis was similar for inhaled insulin and SQ patients for Type 1 patients (means 18.5 years for inhaled, 18.3 for SQ), but differed somewhat for Type 2 patients. Patients who were eligible for oral agent studies would be expected to have a shorter duration of diabetes than patients who had failed oral agents and required subcutaneous insulin. The overall Type 2 inhaled insulin population was a mix of patients who were and were not insulin-requiring at study entry; mean duration of diabetes for this group would be expected to be intermediate to the durations of diabetes for the SQ and OA groups. This was the case for Type 2 diabetics, with mean durations of diabetes of 10.6, 13.4 and 7.9 years respectively for inhaled, SQ and OA patients.

Overall, results of Phase 2 and Phase 3 trials are applicable to patients with uncomplicated diabetes, but it is unclear if these results may be extrapolated to patients with common diabetic complications, to the severely obese, or to very insulin-resistant patients.

7.2.1.3 Extent of exposure (dose/duration)

Extent of exposure by duration is presented above in Section 7.2.1.1.

For both Type 1 and Type 2 diabetics, the mean dose of long-acting insulin for inhaled insulin group patients was somewhat lower for inhaled insulin patients than for subcutaneous insulin patients. The mean dose of inhaled insulin gradually increased over time, while the dose of subcutaneous short-acting insulin increased from baseline to Month 3, and then remained stable until Month 12. It is difficult to attach particular significance to either of these observations. The mean lower dose of long-acting insulin for inhaled insulin patients implies that, on average, glycemic control was not disproportionately "carried" by the long-acting component of inhaled insulin patients' regimens. The gradual increase in inhaled insulin dose without a corresponding increase in short-acting SQ dose could indicate developing resistance to the action of inhaled insulin, or neutralization of insulin action by insulin antibodies; or it could merely represent increasing familiarity and comfort with upward titration of a novel agent. In major diabetes trials, such as UKPDS and DCCT, insulin dose tended to increase gradually over time; however, it is not clear why this occurred in the inhaled insulin group here and not in the SQ group, in the Exubera® development program.

Table 7.2.1.3.1 Summary of Average Total Daily Insulin Dose and Dose per Kg of Body Weight, Adult Patients with Type 1 Diabetes

	INH				SC Insulin			
	Dose LA (Dose/kg)		Dose SA (Dose/kg)		Dose-LA (Dose/kg)		Dose SA (Dose/kg)	
	N	Mean	N	Mean	N	Mean	N	Mean
Study 1022								
Baseline	288	30.68 (0.42)	287	22.59 (0.30)	285	32.94 (0.45)	286	23.91 (0.32)
Month 3	280	30.48 (0.41)	280	10.46 (0.14)*	285	34.98 (0.48)	285	25.09 (0.33)
Month 6	271	30.58 (0.41)	271	11.51 (0.15)*	278	35.40 (0.48)	279	25.08 (0.33)
Month 9	254	31.02 (0.41)	256	12.00 (0.16)*	266	35.39 (0.48)	267	24.92 (0.33)
Month 12	243	30.66 (0.41)	243	12.68 (0.17)*	258	35.69 (0.47)	262	25.37 (0.33)
				INH				
	Phase 2 Extension: 48-month completers				Study 111: 24-month completers			
Month 3			31	11.04 (0.15)*			244	11.14 (0.14)*
Month 6			31	11.86(0.16)*			244	11.95 (0.15)*
Month 12			31	12.94 (0.17)*			244	13.64 (0.18)*
Month 18			31	14.51 (0.20)*			244	14.76 (0.19)*
Month 24			31	14.55 (0.19)*			244	15.20 (0.19)*
Month 30			31	14.48 ((0.19)*				
Month 36			31	14.47 (0.19)*				
Month 42			31	15.35 (0.20)*				
Month 48			31	15.14 (0.20)*				

*Dose in mg (mg/kg where body weight was available for subject)
LA=long-acting; N=number of subjects with dosing information (not all subjects may have had body weight measured at each timepoint); SA=short-acting.
Source Data: Module 2.7.3, Appendix Tables 5.4.2.1, 5.5.2.1, 1022 CSR; Tables 5.10.1.2, 5.10.2.2, 111 CSR; Section 11, Item 11 Tables 1.3.1.4, 1.3.3.4.

Table 7.2.1.3.2 Summary of Average Total Daily Dose and Dose per Kg of Body Weight, Type 2 Diabetics

	INH				SC Insulin			
	Long-acting Dose (Dose/kg)		Short-acting Dose (Dose/kg)		Long-acting Dose (Dose/kg)		Short-acting Dose (Dose/kg)	
	N	Mean	N	Mean	N	Mean	N	Mean
Study 1029								
Baseline	307	43.1(0.5)	308	27.4 (0.3)	302	43.8 (0.5)	301	26.7 (0.3)
Month 3	301	44.3 (0.5)	301	12.7 (0.1)*	298	47.8 (0.5)	300	31.5 (0.4)
Month 6	289	43.9 (0.5)	289	13.2 (0.1)*	290	47.1 (0.5)	292	32.0 (0.4)
Month 9	272	43.6 (0.5)	273	13.5 (0.2)*	280	47.8 (0.5)	282	31.6 (0.4)
Month 12	235	44.8 (0.5)	235	14.7 (0.2)*	239	47.9 (0.5)	242	33.0 (0.4)

	INH			
Study 1001 and 1002 – 2 Year				
Week 10		444	11.7 (0.14)*	
Week 18		431	12.5 (0.14)*	
Week 24		439	12.8 (0.15)*	
Week 36		329	13.8 (0.16)*	
Week 52		314	14.7 (0.17)*	
Week 65		168	15.4 (0.18)*	
Week 78		167	15.6 (0.18)*	
Week 91		161	15.9 (0.18)*	
Week 104		154	16.8 (0.19)*	
	Phase 2 Extension: 48-month completers		**Study 111: 24-month completers**	
Month 3		58	13.81 (0.15)*	397 16.33 (0.18)*
Month 6		58	14.34 (0.16)*	397 17.05 (0.18)*
Month 12		58	15.81 (0.17)*	397 18.11 (0.19)*
Month 18		58	15.47 (0.17)*	397 18.78 (0.20)*
Month 24		58	16.47 (0.17)*	397 19.46 (0.21)*
Month 30		58	15.98 (0.17)*	
Month 36		58	16.98 (0.18)*	
Month 42		58	17.00 (0.18)*	
Month 48		58	17.15 (0.18)*	

*Dose in mg (mg/kg where body weight was available for subject)
N=number of subjects with dosing information (not all subjects may have had body weight measured at each timepoint).
Source Data: Module 2.7.3, Appendix Tables 4.2.8, 5.4.2.2, 5.5.2.2, 1029 CSR: Tables 5.10.1.2, 5.10.2.2, 111 CSR: Section 11, Item 11 Tables 1.3.1.6, 1.3.3.6; Study 1001/1002 (2-year): Table 1.5.10.1

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Reports of all published clinical trials of Exubera® were included in the NDA.

7.2.2.2 Postmarketing experience

Not applicable.

7.2.2.3 Literature

The clinical reviewer conducted an extensive literature search to look for safety information. No additional adverse events related to Exubera® were found in the medical literature as of 20 Jun 05. Other articles are referenced in the appropriate sections of the review.

7.2.3 Adequacy of Overall Clinical Experience

Data submitted from the Exubera® development program were in general adequate to assess the efficacy of the product in adult diabetics, but not for pediatric patients. Nonpulmonary safety data were in general adequate to assess the relative frequencies of common nonpulmonary adverse events that might be expected to occur over the period of observation of the included studies. However, obese patients, patients with high subcutaneous insulin requirements, and patients with common complications of diabetes were excluded from study. While duration of exposure was substantial for some patients, longterm risk of malignancy cannot be assessed with these data. In order to assess human carcinogenic potential, longterm data collection in large numbers of patients would be needed. DPADP has concerns regarding the lack of data regarding the safety of the product in patients with underlying lung disease.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please see Dr. Alavi's Pharmacologic Toxicology review. The lack of an animal carcinogenicity study is of potential concern, because insulin is a growth factor, and the single-cell lining of the lung is receiving a large dose of a protein powder when inhaled insulin is administered. The higher frequency of adverse events of cough, and the brisk antibody response seen with this inhaled insulin product suggest that it has a chronic irritant effect. Certain other inhaled chronic irritants are carcinogenic to the lung. The mean duration of study for inhaled insulin patients may have been too short to assess the human carcinogenic potential of inhaled insulin. However, Dr. Alavi, the animal toxicology reviewer, states that it is unlikely that animal carcinogenicity studies would have resolved questions regarding human carcinogenic potential, due to problems administering the drug chronically via inhalation to rodents, and due to a potential nonrelevant tumorigenic response in rodents, which have insulin receptors in the lung.

7.2.5 Adequacy of Routine Clinical Testing

In general, routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The biopharmaceutics review is ongoing as of 15 Sep 05. The clinical reviewer has concerns regarding the lack of dose proportionality and dose equivalence seen with Exubera®, and feels that these could lead to an increased risk for hypoglycemia, and to problems with titration. Recommendations for a method of titration are needed for labeling; if the applicant is unable to construct a useful algorithm based on available PK/PD data, a study to determine the optimal titration method might be useful.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

In general, the data provided by the applicant appear adequate to allow characterization of adverse events associated with Exubera®. However, the extent of pulmonary safety data contained in the NDA falls far short of the amount that was repeatedly requested by the Division of Pulmonary and Allergy Drug Products. Concerns regarding lack of data due to certain exclusion criteria, and lack of data in African Americans, have already been discussed.

7.2.8 Assessment of Quality and Completeness of Data

An enormous volume of data was submitted by the applicant in this NDA. Some important summary and database information was missing, however. During review, the clinical reviewer noted errors in certain of the applicant's tables and figures that limited the interpretability of these data sources. In general, the applicant has been responsive in submitting missing and corrected data, but submissions related to several requests took weeks or months to arrive. Applications are expected to be complete at the time of initial NDA submission; piecemeal and delayed submission of new and corrected data complicated the review of this application.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted a safety update on 27 Apr 05.

Two additional patients had died between the original safety data cut-off date of 1 Sep 04 and the safety update cut-off of 13 Dec 04; both patients were in subcutaneous insulin treatment groups.

The reported types of adverse events, and the frequency of these adverse events, appeared to be similar to those noted in the original NDA submission. However, the applicant provided only summary tables, and did not provide updated datasets to permit complete review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

A total of 22 deaths occurred among 3,603 subjects (0.6%) exposed to inhaled insulin in the clinical development program, as of the safety cut-off date of 1 Sep 04. Of these, 21 patients were participants in the clinical development program and one was a neonate born of a mother exposed to inhaled insulin. Ten deaths, including that of the neonate, occurred during controlled Phase 2/3 trials, which included 1,975 adult patients (0.5%). Twelve deaths occurred during extension studies, which included 1,449 patients (0.8%). Five patients who received comparator drugs died, out of 1,938 comparator patients (0.3%). When taking into account the longer duration of exposure for inhaled insulin groups, there is little difference in mortality rates between inhaled insulin and comparator treatments.

experienced a severe hypoglycemic event. However, when one considers duration of exposure, patients with high insulin binding activity did not experience severe hypoglycemia more frequently than did the population of Type 1 patients in all Phase 2/3 trials.

- The applicant made extensive attempts to [redacted] but was unable to do so. Development of neutralizing insulin antibodies might be associated with increasing insulin requirements or worsening indices of glycemic control. However, there was no association between degree of insulin binding activity and HbA1c, postprandial glucose, fasting glucose or insulin requirement.
- The actual drug substance used [redacted] insulin, Aventis) did not exhibit inherent immunogenicity in Aventis Study 3002, in which 476 insulin-naïve Type 2 patients were randomized to receive either [redacted] or SQ Huminsulin® (Eli Lilly human insulin) for one year. Rates of insulin binding activity did not differ between groups.
- Discontinuation of inhaled insulin resulted in a decline in insulin binding activity, although levels did not return to baseline by 12 weeks of followup.

Overall, it appears that although inhaled insulin patients demonstrate a brisk increase in insulin antibody levels, studies to date do not demonstrate a clinical correlate of this finding, over the period of observation in these studies.

Observations of note regarding reasons for discontinuation among Type 1 diabetics include:

- In controlled trials, discontinuations due to adverse events were more common among inhaled insulin patients than among SQ patients.
- A large number of inhaled insulin patients withdrew consent during uncontrolled portions of Phase 2 and Phase 3 trials

Observations of note regarding reasons for discontinuation among Type 2 diabetics include:

- Discontinuations due to adverse events occurred slightly numerically more frequently among inhaled insulin patients than among SQ patients, but occurred with equal frequency between inhaled insulin patients and patients in oral agent groups.
- As noted with Type 1 patients, a large number of patients were discontinued from study for "withdrawn consent" in the uncontrolled portions of Phase 2 and Phase 3 trials.

In controlled Phase 2 and Phase 3 studies in Type 1 diabetics, the most common category of events leading to discontinuation was respiratory, and all discontinuations due to respiratory adverse events occurred in inhaled insulin group patients. When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common category of adverse events leading to discontinuation, with a total of 21 (2.3%) of inhaled insulin group patients discontinuing due to respiratory AEs. Cough was the most common AE leading to discontinuation, accounting for 10 discontinuations (1.1% of all Ph 2/3 Type 1 patients).

In controlled Phase 2 and Phase 3 studies in Type 2 diabetics, the most common category of events leading to discontinuation was respiratory, and 26/28 discontinuations due to respiratory adverse events occurred in inhaled insulin group patients. When considering all Phase 2 and Phase 3 trials, both controlled and uncontrolled, respiratory events were again the most common

Of the adult patients who died during the clinical development program, 15/21 appear to have died of cardiac causes. Most diabetics die of cardiovascular disease, and the percentage of deaths which were due to cardiovascular disease during the study of this product is consistent with the usual incidence of cardiovascular death among diabetics. Those patients who died of acute causes do not appear to have had an unusually high incidence of severe hypoglycemic events (those requiring the assistance of another person, or events with a blood sugar <36 mg/dL). However, four of these patients had histories of a large number of nonserious hypoglycemic events prior to death, and one death occurred shortly after what appears to have been a hypoglycemic episode. Overall, the deaths which occurred in inhaled insulin group patients do not seem to have a stronger association with hypoglycemia than that expected in diabetics treated with subcutaneous insulin. A total of 7/21 total deaths occurred in Type 1 diabetics who were taking inhaled insulin. The rate of death among Type 1 inhaled insulin patients does not exceed that found in the intensive treatment groups of large randomized trials in Type 1 diabetics. No clear difference was demonstrated between inhaled insulin and comparator patients for incidence or cause of death.

In controlled Phase 2 and Phase 3 studies in adult Type 1 patients, serious adverse events occurred at a slightly higher frequency in SQ group patients than in inhaled insulin group patients. The most common serious adverse events among Type 1 patients were hypoglycemia and loss of consciousness. In the controlled Phase 2/3 population, these occurred with slightly greater frequency in SQ patients than in inhaled insulin patients. However, the hypoglycemia analysis model used by the applicant was somewhat flawed; actual rates of hypoglycemia probably did not differ between groups when a more appropriate model was used, as discussed in Ms. Mele's statistical analysis. In Type 1 adult patients, no pattern emerged of a single type of serious nonpulmonary adverse event, or grouping of serious nonpulmonary adverse events, that occurred with significantly greater frequency among inhaled insulin group patients than among SQ patients. Pulmonary serious adverse events will be discussed separately in Dr. Seymour's review. Event terms such as accidents and injuries that could potentially be related to hypoglycemia did not occur more frequently in Type 1 adult patients receiving inhaled insulin, and appear to have occurred less frequently numerically among inhaled insulin patients than among patients receiving SQ insulin.

In controlled Phase 2 and Phase 3 studies in Type 2 patients, serious adverse events occurred with approximately equal frequency among inhaled insulin patients and comparator patients. Myocardial infarction, chest pain, angina and hypoglycemia were the most common SAE terms among Type 2 patients. Inhaled insulin group patients did not have a significantly higher frequency of serious nonpulmonary adverse event term groupings of interest, such as terms related to coronary artery disease, hypoglycemia, loss of consciousness, seizure, accidents, injuries, neoplastic events, or immune system disorders. Hypoglycemia adverse event terms occurred numerically more frequently among SQ patients than among inhaled insulin patients or OA patients. As discussed above, the applicant's hypoglycemia event analysis model was somewhat flawed, and actual rates of hypoglycemia probably did not differ between subcutaneous groups and inhaled insulin groups when a more appropriate model is used. Pulmonary adverse event term groupings will be addressed in Dr. Seymour's pulmonary review.

Hypoglycemia reported as a serious adverse event occurred somewhat more frequently among children taking inhaled insulin than among children taking SQ insulin. Otherwise, no single type of serious adverse event or grouping of adverse events occurred more frequently among pediatric patients taking inhaled insulin than among pediatric patients taking SQ only. Almost all serious adverse events among pediatric patients were related to hypoglycemia. Severe hypoglycemia was reported as a serious adverse event term more frequently among pediatric patients than among either adult Type 1 or Type 2 patients.

When evaluating serious hypoglycemic adverse events, the clinical reviewer also considered whether the nature of serious hypoglycemic adverse events differed between inhaled insulin and comparator patients. The clinical reviewer examined all adverse event narratives provided by the applicant, and identified those hypoglycemia events which had serious accompanying events, e.g. loss of consciousness, syncope, accidents and injuries. Adult inhaled insulin group patients do not appear to have had a higher incidence of potentially dangerous accompanying events to serious hypoglycemic episodes than did comparator patients.

For further evaluation of serious adverse events, the clinical reviewer compared the event terms used by the applicant in its serious adverse event listings to the terms used by the investigators. This was done in order to ascertain whether the nature of serious adverse events could have been downplayed in the inhaled insulin groups, or embellished in the comparator groups. Upon review of all serious hypoglycemic event narratives, the clinical reviewer noted some cases in which the event was reported only as hypoglycemia, and an accompanying accident or injury was not mentioned in the listing. Although the serious adverse event listings for hypoglycemic events sometimes did not include mention of an accompanying accident or injury, this reconciliation difference did not occur more frequently among inhaled insulin patients than among comparator patients. Terms used for other types of serious adverse events in the applicant's serious adverse event listings almost always reconciled closely with those found in provided event narratives.

Because diabetic ketoacidosis is the leading cause of mortality among pediatric Type 1 diabetics, it was an event of significant interest. No deaths from diabetic ketoacidosis occurred in children in this development program, and no cases of cerebral edema accompanying DKA were reported. Pediatric serious adverse events of diabetic ketoacidosis did not occur more frequently among inhaled insulin patients than among SQ patients in controlled Phase 2/3 trials (one case among inhaled insulin patients, two cases among SQ patients). In the extension Study 111, a total of 21 serious adverse events of ketoacidosis occurred among 17 patients. This study had a large total duration of exposure for pediatric patients, with a total of 5,801 subject-months of exposure. Comparative incidence rates for DKA were 0.04 cases of diabetic ketoacidosis per child-year for inhaled insulin patients in all Phase 2/3 trials and 0.04 cases of DKA per child-year for SQ patients in controlled Phase 2/3 trials. In the medical literature, the reported incidence of DKA (after initial diagnosis) ranges from 1-10% per year (Dunger 2003).

When considering all adverse events (serious and nonserious), in controlled Phase 2/3 studies in Type 1 diabetics, the overall incidence of adverse events was similar between inhaled insulin patients and SQ patients, with 99.4% and 98.7% of patients, respectively, experiencing some type of adverse event. In controlled Phase 2/3 studies in Type 2 patients, adverse events

occurred with nearly equal frequency between inhaled insulin patients [93.7% with event(s)] and SQ patients [96.7% with event(s)]. Among Type 2 patients treated with oral agents, 81.7% experienced an adverse event. This lower rate among oral-agent treated patients is due to a lower rate of hypoglycemia among these patients than among inhaled insulin or SQ patients.

Hypoglycemia was the most common adverse event among Type 1 patients, and occurred with equal frequency in inhaled insulin and SQ group patients. Cough was a common adverse event, and occurred with significantly greater frequency among inhaled insulin patients (196/698, 28.1%) than among SQ patients (59/705, 8.4%). Other respiratory adverse events (dyspnea, respiratory disorder) also occurred with greater frequency among inhaled insulin patients. Nasopharyngeal adverse events (epistaxis, pharyngitis, rhinitis, sinusitis) occurred at a higher frequency in inhaled insulin groups (310/698, 44.4%) than in SQ groups (220/705, 31.2%). Adverse event terms related to accidents occurred with equal frequency between groups. The event term "allergic reaction" occurred with slightly greater numeric frequency in inhaled insulin patients (31/698, 4.4%) than among SQ patients (23/705, 3.3%).

Among Type 2 patients, hypoglycemia was the most common adverse event term, and occurred most commonly in SQ patients (360/488, 73.8%). Inhaled insulin patients had a lower rate of hypoglycemic events than SQ patients, but had a higher rate than OA patients [inh ins = 794/1277 (62.2%), OA = 185/644 (28.7%)]. Cough was also very common, and occurred with significantly higher frequency among inhaled insulin patients than among comparator patients (inh ins 21.0%, SQ 7.4%, OA 3.7%). Accident and injury terms occurred numerically more frequently among SQ patients than among other groups. Several respiratory events (e.g. asthma, bronchitis, dyspnea) had a somewhat higher frequency among inhaled insulin patients than among comparator patients; please see Dr. Seymour's pulmonary review for discussion. Headache and paresthesia occurred at a slightly higher numeric rate in inhaled insulin groups than in comparator groups.

Hypoglycemic event rates did not differ between pediatric inhaled insulin and SQ patients. Among pediatric patients, the adverse event term seen with the greatest excess frequency for inhaled over SQ was cough. Nausea, headache and dizziness also occurred numerically more frequently in inhaled insulin patients than in SQ patients. When combining ear terms, adverse events related to the ear occurred more frequently in children in inhaled insulin groups than in SQ groups. The terms ear pain, ear disorder and otitis media had a combined event rate of 18/153 (11.8%) in the inhaled insulin patients vs 7/148 (4.7%) in SQ patients. This difference could be due to chance; however, the Eustachian tube in children provides an anatomically more direct route to the middle ear than does the Eustachian tube of the adult. Data were insufficient to determine a mechanism for the finding of increased ear events in children, but inflammation or the inhalation maneuver may have contributed to the entry of inhaled insulin or oral secretions into the Eustachean tube and middle ear.

Common adverse events which seem likely to be related to inhaled insulin use include cough; nasopharyngeal adverse events such as pharyngitis, rhinitis and sinusitis; and certain respiratory adverse events such as dyspnea. Adverse events related to the ear seem to be related to inhaled insulin use in children.

There is no clear relationship between age and incidence of rhinitis or sinusitis in patients exposed to inhaled insulin, and dose-dependency was not demonstrated. Inhaled insulin patients who developed rhinitis did so sooner than SQ patients who developed rhinitis.

Regarding serious but rare adverse events, the events "retinal hemorrhage" and "allergic reaction" occurred more frequently per unit of patient-time over all Phase 2/3 trials than these events occurred per unit of patient time in comparator groups in the controlled Phase 2/3 trials. Concern exists for the development of undesirable immune responses to inhaled insulin. Malignant neoplasms did not occur with greater frequency in inhaled insulin patients per unit of patient-time than in comparator patients.

Hypoglycemia reported as a serious adverse event was discussed above with other serious adverse events. Hypoglycemia was also evaluated by two specified definitions. Hypoglycemia was a secondary outcome measure in the major trials, with a study-specific definition. There was also a definition of severe hypoglycemic events for the overall safety evaluation, in which severe hypoglycemia was defined as a hypoglycemic event in which the subject had a measured blood glucose of ≤ 36 mg/dL and/or required assistance.

For adult Type 1 patients overall, inhaled insulin was not associated with a higher rate of severe hypoglycemia was SQ insulin. However, in Study 107, the "intensive control" study in Type 1 diabetics, the applicant reported that severe hypoglycemic events did occur more frequently in the inhaled insulin group than in the SQ only group. This is a potentially important finding, because intensive control is now the standard of care for Type 1 diabetics, and severe hypoglycemia tends to be the limiting factor in achieving tight control. Severe hypoglycemia is associated with higher rates of accidents, injuries and other acute serious adverse events. If a new treatment for Type 1 diabetes is noninferior, but not superior, in efficacy to the standard of care of intensive subcutaneous insulin management, the new treatment's rate of severe hypoglycemia should not be significantly higher than that seen with the standard of care. That, however, did not appear to be the case in Study 107, where inhaled insulin was noninferior (but not superior) to subcutaneous insulin in efficacy, but was associated with a higher rate of severe hypoglycemic events by the applicant's analysis. It should be noted that the FDA Biostatistics reviewer calls into question the statistical model used by Pfizer for comparison of hypoglycemic event rates. Reanalysis by the FDA Biostatistics reviewer is ongoing, but it appears that a more appropriate model may show that severe hypoglycemia event rates did not actually differ between treatment groups.

Among Type 1 diabetics overall, in both the inhaled insulin and SQ groups, overall hypoglycemia (severe and nonsevere) event rates declined over time, with similar rates of decline between groups. This could indicate an initial period of adjustment to the study regimen, with declining incidence of severe hypoglycemic events as the study progressed, or a decline in reporting of clinical events. Although there was an apparent decline over time in controlled Phase 2/3 studies, severe hypoglycemic adverse events continued to occur in extension studies; the occurrence of severe hypoglycemic adverse events cannot be entirely attributed to an initial learning period for inhaled insulin.

Among Type 1 diabetics, inhaled insulin group patients tended to have higher hypoglycemic event rates in the early morning than did SQ group patients, while the converse was true for midday. This pattern was noted for the overall pattern in Phase 2 and Phase 3 trials, and held true across most studies. The reason for this consistent pattern of prebreakfast hypoglycemia in inhaled insulin group patients is unclear. One would expect prebreakfast hypoglycemia to be related to evening dosing of longacting insulin, rather than to the patient's shortacting insulin. However, in Study 107, the intensive control study in Type 1 diabetics, mean dose of longacting insulin was actually somewhat lower for inhaled insulin group patients, both for the evening dose and for the total daily dose. Study 1026 was the only study in which 0200 blood sugars were routinely measured. In this study, hypoglycemia was more common at 0200 for inhaled insulin group patients than for SQ patients. For the overall population of Type 1 diabetics in all Phase 2/3 studies, the majority of hypoglycemic episodes reported as serious adverse events among inhaled insulin patients occurred in the early morning hours (for those patients for whom serious adverse event narratives were provided).

Overall, severe hypoglycemic events were less common among patients with Type 2 diabetes compared to patients with Type 1 diabetes. Inhaled insulin group patients were not more likely to experience severe hypoglycemic events than were SQ group patients, in studies of Type 2 patients who were using insulin at baseline. However, inhaled insulin group patients were more likely to experience severe hypoglycemia than were patients in oral agent comparator groups in studies of patients who were not insulin-using at baseline. Control of glycemia was in general better with inhaled insulin than with oral agents, and thus a higher rate of hypoglycemia would be expected. In Studies 104, 109 and 110, all severe hypoglycemic events occurred in inhaled insulin group patients.

In studies of Type 2 diabetics where SQ was used as a comparator, rates of hypoglycemia declined over time for both SQ and inhaled insulin patients. In studies of Type 2 diabetics where oral agents were used as a comparator, event rates were too low to distinguish a time trend. The applicant provided data regarding time of day of hypoglycemic events for Type 2 patients, but the number of events was too low to discern a trend for any particular time of day.

In Studies 106 and 1009, children and adolescents who were treated with inhaled insulin were somewhat less likely to experience protocol-defined hypoglycemia (severe or nonsevere) than patients who were taking SQ insulin. In Study 107, there was no demonstrated difference between groups. Protocol-defined severe hypoglycemic events did not occur more frequently among pediatric inhaled insulin patients in Studies 106 and 1009. In Study 107, there were 16 events of severe hypoglycemia in the inhaled insulin group, and 10 events in the SQ group. Although the risk ratio was 1.62 for occurrence of severe hypoglycemia for inhaled insulin-treated adolescents vs SQ-treated adolescents, the limits of the confidence interval fell on either side of 1, and therefore the difference between groups was not statistically significant. Overall, protocol-defined hypoglycemia, and protocol-defined severe hypoglycemia, did not occur statistically significantly more frequently in pediatric patients treated with inhaled insulin compared to those treated with SQ alone.

Dose dependency of adverse events was explored. Among Type 1 diabetics treated with inhaled insulin, increased sputum production may be dose-related. When one examines the overall incidence of accidents and fractures, these events occurred at a higher numerical rate in patients on higher doses of inhaled insulin than in patients on lower doses of inhaled insulin. There is no clear explanation for this observation.

Among Type 2 diabetics, the incidence of dyspnea among inhaled insulin patients appeared to be dose-related. Several respiratory events occurred with lower frequency in patients who were taking <10 mg/day of inhaled insulin than in those taking ≥ 10 mg/day, but with roughly equal frequency between patients taking 10-20 mg/day and those taking >20 mg/day. These events included total respiratory events, bronchitis, respiratory tract infection, and rhinitis. The overall incidence of cardiovascular events appeared to be dose-related, although no one type of event predominated. Accidental injury and fracture also appear to be dose-related. Retinal disorders appear to be dose-related. The overall incidence of malignant neoplasms does not appear to be dose-related, nor does the incidence of any single malignancy. While the possible dose-relatedness of these events is concerning, these findings must be interpreted with caution. As Type 2 diabetes progresses, beta cell failure occurs with progressive loss of endogenous insulin secretion and increasing requirement for drug therapy, and eventually for increasing insulin requirement. A higher insulin requirement may be a reflection of duration of disease, which is in turn associated with aging; either duration of disease or aging could be associated with an increased incidence of many adverse events.

Time dependency of adverse events was also explored. Among Type 1 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, rhinitis, sputum increased, epistaxis), the time interval in which these adverse events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Decreased reporting of these events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again. For Type 1 patients, accidental injury, motor vehicle accidents, and accidental fractures were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period. Among Type 1 patients, hyperglycemia and hypoglycemia were more likely to be reported as adverse events (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. As with respiratory adverse events, decreased reporting of these metabolic events in subsequent treatment time intervals could either be due to a true decrease in the occurrence of the event, to dropout due to the event, or to nonreporting by patients who felt they had already brought the event to the attention of investigators, and therefore did not report it again. For Type 1 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months. This could be due to a true increase in the incidence of the events, or to longer per-patient exposure during this time period.

Among Type 2 patients, for respiratory events in general, and for some specific respiratory events (cough, respiratory tract infection, epistaxis), the time interval in which these adverse

events were more likely to be reported (per patient) was during the first 6 months of inhaled insulin treatment. Accidental injuries and fractures were more likely to be reported (per patient) during the time interval beyond 24 months. Hypoglycemia was more likely to be reported as an adverse event (per patient) in the time interval of 0-6 months of inhaled insulin treatment. This may be due to the learning process involved in instituting a novel treatment. No clear temporal pattern emerged among Type 2 patients for malignant neoplasms in general or for any particular neoplasm. For Type 2 patients, retinal disorders were more likely to be reported (per patient) during the time interval beyond 24 months.

Demographic interactions for adverse events were also explored. A summary of the observations for demographic differences for adverse events includes:

- Numbers of non-Caucasian patients were too small to permit meaningful comparisons between treatment groups.
- For Type 1 patients, the event "sputum increased" had a higher incidence in older patients and in males in inhaled insulin patients, than was seen in SQ patients.
- For Type 1 patients in the SQ group, overall respiratory events occurred with decreasing frequency by age group, but in inhaled insulin patients, overall respiratory events occurred with approximately equal frequency between age groups. For patients age 18 and older, overall respiratory events occurred more frequently among inhaled insulin group patients than among SQ patients.
- For Type 1 diabetic children, otitis media occurred more frequently in inhaled insulin group children than in SQ group children. Otitis media occurred with low and approximately equal frequency in adult Type 1 patients in both treatment groups.
- For Type 1 patients, the events "allergic reaction" and "diarrhea" occurred with higher frequency among males than among females in the inhaled insulin group. This gender difference was not apparent in comparator groups.
- For Type 2 patients, the event "dry mouth" appeared to decrease in incidence with age in inhaled and oral agent groups, but not in the SQ group.
- For Type 2 patients, for all treatment groups, women were more likely to experience cough than men; for both genders, cough occurred much more frequently in inhaled insulin group patients than in comparator patients.
- For Type 2 patients, the incidence of bronchitis increased by age group for inhaled insulin patients, but not for comparator patients.
- For Type 2 patients, accidental injury, hypoglycemia, and respiratory tract infection occurred more frequently in men than in women in the inhaled insulin group. This gender difference was not observed in the comparator groups.
- For Type 2 patients, paresthesia occurred more frequently in women than in men in the inhaled insulin group. This gender difference was not observed in the comparator groups.

Among these observations, those most likely to have clinical significance include:

- Otitis media in children appears related to inhaled insulin treatment.
- The incidence of bronchitis appears to increase by age group for inhaled insulin patients, but not for comparator patients.

- For Type 2 patients, accidental injury and hypoglycemia appear to occur more frequently in men than in women taking inhaled insulin. This gender difference was not observed in the comparator groups.

Across the development program, greater increases occurred in insulin antibody levels, as reflected by insulin binding activity, for patients taking inhaled insulin than for patients taking either subcutaneous insulin alone or oral agents alone. This observation led to concerns about potential clinical consequences of this antibody formation. The following points can be synthesized from extensive data regarding insulin antibodies associated with inhaled insulin use, and the potential clinical consequences of these antibodies:

- Seroconversion rates were higher among inhaled insulin patients than among comparator patients. In studies in which a quantitative insulin binding activity assay was used, 75% of all inhaled insulin patients who had undetectable insulin binding activity at baseline had measurable insulin binding activity at end of study or last measurement, while only 10% of comparator patients seroconverted. Seroconversion rates for inhaled insulin patients were higher among Type 1 patients than among Type 2 patients, and were higher among children than among adults.
- For both Type 1 and Type 2 patients, inhaled insulin was associated with higher end-of-study insulin binding activity, and with greater change from baseline, than was SQ insulin.
- Among Type 1 inhaled insulin patients, pediatric patients had higher end-of-study insulin binding activity and greater changes from baseline than did patients ≥ age 18 years. Among Type 1 inhaled insulin patients, female patients had higher end-of-study insulin binding activity and greater changes from baseline than did male patients.
- Among Type 2 patients, patients who had been using injected insulin prior to study enrollment had higher insulin binding activity at end of study, and greater changes from baseline, than did patients who had not been using injected insulin prior to study. Among Type 2 patients using inhaled insulin, insulin binding activity appeared to correlate with age.
- Insulin antibodies were predominantly IgG for both inhaled insulin patients and comparator patients. Binding profile was consistent with low affinity, high binding capacity antibodies.
- In general, adverse events of an allergic nature tended to occur with similar frequency between inhaled insulin and SQ group patients. For Type 1 patients, the event terms "allergic reaction" and "rhinitis" occurred somewhat more frequently among inhaled insulin patients than among SQ patients.
- There were no apparent associations between degree of insulin binding activity and incidence of hypoglycemic events. Patients who had severe hypoglycemic events (by specific hypoglycemia event definition) did not tend to have higher insulin binding activity than patients who did not have severe hypoglycemic events.
- When examining those patients who had the highest insulin binding activity (>2,000 μU/mL), 33/37 were Type 1 diabetics, and 11 were children. Three of these patients experienced adverse events of a potentially allergic nature (allergic bronchiolitis, dermatitis of face and arms, bilateral eyelid swelling). Among the Type 1 patients with high insulin binding activity, 9 patients experienced a total of 67 severe hypoglycemic events. These 9 patients represent 27% of the total Type 1 study population with high insulin binding activity; in the overall controlled Phase 2/3 population, 17% of inhaled insulin patients

category of adverse events leading to discontinuation, with a total of 42 (3.9%) of inhaled insulin group patients discontinuing due to respiratory AEs. Cough was the most common AE leading to discontinuation, accounting for 26 discontinuations (1.6% of all Ph 2/3 Type 2 patients). Three events of oropharyngeal irritation (glossitis, gingivitis, pharyngitis) resulted in discontinuation in controlled Phase 2/3 trials in inhaled insulin patients, with one additional discontinuation due to pharyngitis in extension trials. No discontinuations due to oropharyngeal irritation occurred in SQ or oral agent control patients. In controlled Phase 2 and Phase 3 trials in Type 2 diabetics, discontinuations due to neoplasia did not occur more frequently among inhaled insulin group patients than among control patients.

The large number of patients for whom consent was withdrawn was of concern to the clinical reviewer, because it raised the question of whether some of these patients actually dropped out for adverse events, tolerability issues, device use problems, or other noteworthy reasons. Upon request, the applicant submitted further information regarding the actual wording that the patient or investigator gave as the reason for those discontinuations that were listed as due to "withdrawn consent", "patient no longer willing to participate in study" or "other". This information was not available for all patients. Most of these stated reasons did not relate to adverse events, tolerability issues, or device problems, but some did. When considering the group of those studies for which revised data for reasons for discontinuation were available, the apparently more frequent misclassification of discontinuation reasons among inhaled insulin patients led to greater differences between groups in the rates of discontinuation for:

- adverse events (greater difference in frequency for both Type 1 and Type 2)
- insufficient clinical response (greater difference in frequency for Type 1)

If investigators were unclear on how reasons for discontinuation should have been classified, one would expect that they would have misclassified reasons with approximately equal frequency in inhaled insulin and control groups. However, discontinuations due to adverse events and insufficient clinical response appear to have been misclassified more frequently for inhaled insulin patients than for comparator patients in the controlled Phase 2/3 population. This disparity in rates of apparent misclassification of reasons for discontinuation is unexplained, but raises a question of investigator reporting bias.

On 23 Aug 05, in an email from Mr. Brian Green of Pfizer to Dr. Elekwachi Oluchi, DMEDP Project Manager, Pfizer provided details of continuing efforts they have made to improve the accuracy of reporting of reasons for discontinuation.

Temporary discontinuations due to adverse events were more common among Type 1 inhaled insulin patients than among Type 1 patients in SQ groups. For adult Type 1 patients in controlled Phase 2 and Phase 3 trials, 4.7% of inhaled insulin patients had temporary discontinuations due to adverse events, compared to 1.3% of SQ patients. The most common category of adverse events leading to temporary discontinuation among Type 1 diabetic inhaled insulin patients was respiratory, with 16 such events among inhaled insulin patients vs 1 such event in the SQ groups.

Temporary discontinuations due to adverse events were more common among Type 2 inhaled insulin patients (5.6% of patients) compared to Type 2 SQ group patients (1.6% of patients), but occurred with comparable frequency in patients in oral agent groups (6.8%). Again, the most common category of event leading to temporary discontinuation was respiratory, with 24 Type 2 subjects (1.9%) temporarily discontinuing inhaled insulin for respiratory reasons, vs 1 respiratory temporary discontinuation among SQ patients, and zero among oral agent patients. Temporary discontinuations due to hypoglycemia were also more common among Type 2 inhaled insulin patients, with 14 patients (1.1%) temporarily discontinuing due to hypoglycemia, vs 3 (0.6%) and 3 (0.5%) of SQ and oral agent patients, respectively. Temporary discontinuations due to digestive events, particularly diarrhea, occurred more frequently among Type 2 oral agent group patients.

The incidences of new or worsening laboratory abnormalities did not appear to differ between inhaled insulin group patients and comparator patients.

An intensive QTc study was not performed. From routine electrocardiograms from those studies for which postbaseline ECGs were obtained, mean changes in QTc were not significantly different between inhaled insulin and comparator patients in controlled Phase 2 and Phase 3 studies. From routine electrocardiograms, outlier abnormalities of the QTc interval did not occur more frequently among inhaled insulin patients than among comparator patients in controlled Phase 2 and Phase 3 studies. Among adult Type 1 and Type 2 diabetics, there was little difference between groups for mean ECG changes in heart rate, PR interval or QRS width.

Mean pulse and blood pressure did not change substantially from baseline to last observation for adult patients, and there were no significant differences between treatment groups.

Type 2 patients who were insulin-using at study entry did not gain more weight with inhaled insulin than with comparator; in Study 108, SQ patients actually gained statistically significantly more weight (1.28 kg, 95% CI 0.6-1.96). However, inhaled insulin patients who were not using insulin at study entry did have statistically significantly greater weight gain than comparator patients in several studies. The difference in weight gain was most evident in Study 1001, in which add-on inhaled insulin was compared to add-on metformin.

Study 1007 was a clinical pharmacokinetic and pharmacodynamic study conducted in 10 gestational and 3 pregestational diabetic women. It was an open-label, randomized, two-period, two-treatment, crossover study. Each subject received a single morning fasting dose of either 9 U regular SQ insulin or 1 puff of 3 mg inhaled insulin, then no study insulin for 14 days (with continued usual management of their diabetes), then a single dose of cross-over study medication. Insulin Tmax was earlier with inhaled insulin administration than with regular SQ insulin. Cmax was 83% higher with inhaled insulin than with regular SQ. AUC_{0-360} was similar for both treatments. Insulin Tmax in this study was similar to that seen in nonpregnant diabetics in other studies, where Tmax ranged from 38-78 minutes. Fasting insulin Cmax in these women was also similar to fasting insulin Cmax seen in nonpregnant diabetics. Bioavailability of inhaled insulin relative to SQ was 10% based on geometric mean; this relative bioavailability is similar to that seen in nonpregnant women. Time to maximum decline in glucose was somewhat