Table 6.5.4.2.1 Percentage of Children Achieving HbA1c <8% and <7%, Study 1009, Per Protocol Population

		N	BL # pts (%)	12 Weeks # pts (%)	Odds Ratio (Inh Ins Grp vs SQ Grp)	95% CI Limits for Odds Ratio
<8%						
	Inh Ins	60	25 (41.7)	33 (55.0)	1.44	0.57, 3.63
	SQ	59	23 (39.0)	28 (47.5)		
<7%						
	Inh Ins	60	3 (5.0)	11 (18.3)	1.81	0.53, 6.12
	SQ	59	5 (8.5)	10 (16.9)		

Source: Applicant's Tables 5.3.1.2 and 5.3.2.2, Study 1009 report; baseline percentages from Section 11, Item 11, Table 2.2. Study 1009 report

6.5.4.2.2 Fasting and Postprandial Plasma Glucose

In Study 1009, mean fasting plasma glucoses remained undesirably high in both treatment groups, with no significant difference between groups. There was no significant difference between groups for change in postprandial glucose excursion, with small declines in both treatment groups.

Table 6.5.4.2.2 Mean Fasting Plasma Glucose and Mean 2-hr Postprandial Glucose Excursion on HBGM, Study 1009, Per Protocol Population

		n	BL (SD)	Wk 12 Change (SD)	Difference between Inh Ins Grp and SQ Grp	95% CI Limits for Difference between Grps
FPG						
	Inh Ins	58	200 (61)	3 (11)	-1.85	-33.25, 29.54
	SQ	58	193 (86)	5 (11)		
Two-hour Postprandial Glucose Change (from Preprandial Value)						
	Inh Ins	43	27.3 (51.3)	-18.9 (11.3)	-4.15	-31.13, 22.82
	SQ	46	22.9 (56.9)	-14.7 (10.1)		

Source: Applicant's Tables 5.6.1 and 5.5.4, Study 1009 report

6.5.5 Clinical Microbiology

Not applicable.

6.5.6 Efficacy Conclusions

Although children in the inhaled insulin and SQ treatment groups had similar values for change from baseline in HbA1c for Studies 106, 107 and 1009, the clinical reviewer is unable to conclude that inhaled insulin was noninferior to subcutaneous insulin, because there was little change from baseline in either group, and mean HbA1c at end of study did not fall into the desirable range for control of Type 1 diabetes. In Study 1009, a slightly higher percentage of children in the inhaled insulin group achieved HbA1cs <7% and <8% than did children in the

subcutaneous group. There was no significant difference between groups for changes in fasting plasma glucose and postprandial glucose excursion.

Studies performed in children and adolescents to date do not show that the desirable level of glucose control (i.e. that associated with decreased risk for later diabetic complications) can be achieved with inhaled insulin. Should Exubera® be approved for use in adults, further study in children is warranted.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

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%).

The following tables summarize deaths occurring in the inhaled insulin and comparator groups.

Table 7.1.1.1.1
Deaths Listing[1]
Treatment = Exubera®
Cutoff Date: 1 Sep 04

Trial	Center	Patient	Age (yrs)	Gender	Total Daily Dose[2] (mg)	Time (days)[3]	Source[4]	Description
102E	5007	0106	57	M	23	1073	N	Ischemic heart disease
102E	5011	0077	35	F	5	1460	N	Automobile accident (MVA)
103E	5006	0048	62	M	27	1016 (3)	N	Acute myocardial infarction (AMI)
104E	5016	0005	65	M	24	950 (3)	N	AMI
104E	5016	0007	63	M	13	1772	N	Cardiopulmonary arrest
108	5010	8003	75	M	9	121 (1)	N	Gastrointestinal (GI) bleed, esophageal cancer
108	5048	8119	48	M	24	65 (14)	N	Esophageal bleed
111	5044	8013	73	M	12	669 (6)	N	Multiorgan failure
111	5046	8336	76	M	22	907 (10)	N	AMI
111	5048	0412	64	M	6	592	N	Cerebral hemorrhage
111	5048	0414	73	M	6	240	N	AMI, possible fall from ladder
111	5049	6770	54	F	14	328 (8)	N	MI
1001	0004	0025	63	M	19	307 (23)	N	Ventricular tachycardia (V tach)
1001	0134	1373	66	M	4	13 (11)	N	Acute MI, ventricular fibrillation
1022	1016	0891	51	M	10	229	N	MI
1022	1039	NS01[5]	0 (2 days)	M	7	28 (194)	N	Congestive heart failure
1022	5152	3622	48	F	13	27 (25)	N	MI
1022	5154	3682	58	M	15	353	N	Found dead at home
1027	1016	0648	49	M	3	89 (1)	N	MI after hypoglycemic episode
1029	1026	0659	61	M	22	307 (6)	N	Metastatic colon cancer
1036	5005	1006	70	M	32	97	N	MI
1036	5011	1004	48	F	18	2367	N	MI

1 Includes all deaths that occurred during drug exposure; or within 30 days following discontinuation from drug; or later but resulting from adverse events that had onset during drug exposure or had onset within 30 days following drug exposure
2 Dose at time of death. If died after discontinuation, last dose prior to discontinuation
3 Days on drug at time of death. If death occurred after discontinuation, includes number of days on drug before discontinuation followed, in parentheses, by number of days off drug prior to death
4 N = NDA
5 Newborn infant of study subject who conceived while on inhaled insulin. Mother received inhaled insulin for appr 3-4 wks postconception. Last dose = 7 mg. Drug discontinued upon discovery of pregnancy; infant died 6 months later, 2 days postpartum

Table 7.1.1.1.2
Deaths Listing[1]
Treatment = Comparator
Cutoff Date: 1 Sep 04

Trial	Center	Patient	Age (years)	Gender	Comparator	Dose[2] (mg)	Time (Days)[3]	Source[4]	Description
1002	0005	5030	64	M	Glibenclamide	2.5	89	N	Automobile accident
					Metformin	2000	89		
1002	0047	6086	59	M	Glibenclamide	10	83	N	Acute myocardial infarction (AMI)
					Metformin	2000	110		
1002	0096	5203	62	M	Glibenclamide	5	64 (3)	N	MI
					Metformin	2500	64 (3)		
1030	1032	3085	64	M	Isophane insulin	49	84 (9)	N	MI
					Regular insulin	19	84 (9)		
					Metformin	1000	93		
					Glipizide	10	93		
1030	1055	5665	73	M	Isophane insulin	32	135	N	Sudden death at home
					Regular insulin	10	135		

1 Includes all deaths that occurred during drug exposure; or within 30 days following discontinuation from drug; or later but resulting from adverse events that had onset during drug exposure or had onset within 30 days following drug exposure
2 Dose at time of death. If died after discontinuation, last dose prior to discontinuation
3 Days on drug at time of death. If death occurred after discontinuation, includes number of days on drug before discontinuation followed, in parentheses, by number of days off drug prior to death
4 N = NDA

The following table details mortality by treatment group.

Table 7.1.1.2
Mortality by Treatment Group
Pool of Phase 2 and Phase 3 Studies with Inhaled Insulin
Cutoff Date 1 Sep 04

Treatment Group	Total Number of Patients	Total Number of Deaths	Crude Mortality	Patient Exposure Years (PEY)	Total Deaths with Person-Time	Mortality per PEY
Inhaled Insulin	2787	22	0.8 %	3938.2	22	0.6
SQ Insulin	1365	2	0.1 %	910.0	2	0.2
Oral Agents	648	3	0.5 %	537.7	3	0.5

Source: Applicant's Tables 3, 5 and 6, ISS pages 18-20

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.

Death Narratives

A brief summary of each death narrative for inhaled insulin group patients follows. Patients are identified by their study number, then their center number, then their patient ID number.

102E-5007-0106: 57 year old (yo) man with Type 1 DM, complicated by (c/b) retinopathy and neuropathy, who received inhaled insulin 5.1-26.8 mg/day for 1073 days. Also received extended zinc suspension insulin. On Study Day 1073, while on a boating outing, developed chest heaviness, vomited twice, and collapsed. CPR performed, but patient (pt) pronounced dead at scene by paramedics. Autopsy listed cause of death as ischemic heart disease.

102E-5011-0077: 35 yo woman with Type 1 DM who received inhaled insulin, 3-7.6 mg/day, for 1460 days. Also received extended zinc suspension insulin. On Study Day 1460, had a motor vehicle accident (MVA) while driving home after dinner with friends. Friends state she had no alcohol, but had blood alcohol level of 201 mg/dL. Blood glucose (BG) at scene 120 mg/dL. No skid marks at scene. Pronounced dead at scene; autopsy revealed multiple internal and external injuries.

103E-5006-0048: 62 yo man with Type 2 DM c/b hypertension (htn), neuropathy. Received inhaled insulin 17.7-32.1 mg/day for 1016 days. Also received extended zinc suspension insulin. Acute MI on Study Day 1016; died on Study Day 1019, 3 days after last dose of inhaled insulin.

104E-5016-0005: 65 yo man with Type 2 DM c/b retinopathy and htn. Received inhaled insulin 17.4-23.9 mg for 950 days. Also received glibenclamide. At 6 mo of study, had a 25% decline in forced expiratory volume in one second (FEV1) and a 21% decline in forced vital capacity (FVC). Had numerous hypoglycemic episodes, which the applicant describes as mild, and two episodes of moderate hypoglycemia. On Study Day 953, had acute MI while at racetrack; pronounced dead on arrival (DOA) at emergency room (ER).

104E-5016-0007: 63 yo man with Type 2 DM c/b hyperlipoproteinemia (HLP) and cardiomegaly. Received inhaled insulin, 8.1-13.3 mg/day, for 1858 days. Also received

glibenclamide. On Study Day 1858, collapsed at church after complaining of chest pain. In ventricular fibrillation (V fib) when paramedics arrived. Prolonged resuscitation attempt in ER failed. BG in ER 132 mg/dL. FEV1 had declined 16% from baseline by Study Day 817, and 19% by Study Day 1822.

108-5010-8003: 75 yo man with Type 2 DM, c/b nephropathy and neuropathy, received inhaled insulin at doses ranging from 11.3-25.2 mg, for 116 days. Also received zinc suspension insulin. On Study Day 116, developed melena, was hospitalized, and found to have esophageal cancer. Inhaled insulin stopped on admission. Died on Study Day 122 of gastrointestinal (GI) bleeding and progression of cancer.

108-5048-8119: 48 yo man with Type 2 DM, c/b neuropathy, received 17.2-19.5 mg inhaled insulin for 65 days. Also received extended zinc suspension insulin. On Study Day 65, hematemesis and hospitalization. Esophageal bleed diagnosed; underwent band ligation. Condition deteriorated and patient required mechanical ventilation. Died on Study Day 78 of esophageal bleed.

111-5044-8013: 73 yo man with Type 2 DM. Received inhaled insulin, 13-26.9 mg/day, for 669 days. Also received insulin glargine and extended zinc suspension insulin. On Study Day 637, investigator noted cardiac arrhythmia on subject's electrocardiogram (ECG) and referred pt to ER emergently (stat). Pt refused to go, stating he had to catch a plane to Arizona. On Study Day 670, presented to ER with acute renal failure, congestive heart failure, atrial fibrillation, elevated liver function tests (LFTs), and hyperammonemia. Inhaled insulin was discontinued. Developed progressive liver failure and was found to be positive for Hepatitis B and C. Developed esophageal bleeding and anuria. On Study Day 675, family chose to discontinue care due to multiorgan failure.

111-5046-8336: 76 yo man with Type 2 DM c/b retinopathy, neuropathy, htn, coronary heart disease (CHD), atherosclerotic peripheral vascular disease (ASPVD). Received inhaled insulin, 10.8-24.5 mg/day, for 907 days. Died in his sleep at home on Study Day 917. No autopsy done; death certificate listed cause of death as cardiac arrest, acute myocardial infarction and coronary artery disease. Pt had had decline in diffusion capacity for carbon monoxide (DLco).

111-5048-0412: 64 yo man with Type 2 DM c/b htn. Also had history of (hx) recurrent deep venous thrombosis (DVT) and was on warfarin. Received inhaled insulin, 7.1-12.2 mg/day for 592 days. Also received metformin. On Study Day 589, was punched in the face during an altercation. Later that day, complained of headache and went to hospital. Died on Study Day 592 of cerebral hemorrhage (autopsy done).

111-5048-0414: 73 yo man with Type 2 DM c/b HLP, htn, CHD, hx coronary artery bypass grafting (CABG). Received inhaled insulin, 1-2 mg/day, for 240 days. Also received glipizide and metformin. On Study Day 240, had been painting on a ladder at a neighbor's house. Was found dead on the ground by his wife. Autopsy revealed "massive" MI.

111-5049-6770: 54 yo woman with Type 1 DM. Received inhaled insulin, 8.2-14.4 mg/day, for 328 days. Also received extended zinc suspension insulin. On Study Day 329, found unresponsive and diagnosed with MI. Placed on mechanical ventilatory support; family decided to discontinue ventilator on Study Day 335 and pt died on Study Day 336.

1001-0004-0025: 63 yo man with Type 2 DM, c/b angina pectoris, who received inhaled insulin 6.5-22.4 mg/day for 306 days. Also received glibenclamide. On Study Day 307, admitted to hospital with chest pain. Inhaled insulin discontinued. Developed v fib and was resuscitated. Found to have extensive anterior wall MI. Developed pneumonia, sepsis, congestive heart failure (CHF), multiple episodes ventricular tachycardia (V tach). Died on Study Day 330, 24 days after last dose of inhaled insulin, of V tach.

1001-0134-1373: 66 yo man with Type 2 DM c/b htn and ischemic heart disease, who received inhaled insulin 4 mg/day for 13 days. On Study Day 13, experienced chest pain at rest. Admitted to hospital with acute MI. Inhaled insulin stopped. Underwent CABG on Study Day 22; deteriorated and died of ventricular fibrillation on Study Day 24, 11 days after last dose of inhaled insulin.

1022-1016-0891: 51 yo man with Type 1 DM, c/b retinopathy, received 10-11 mg inhaled insulin per day for 229 days. Also received insulin glargine (glargine). Died on study day 229 due to MI- no autopsy.

1022-1039-NS01: 2 day old neonate born of a study subject. Born preterm with macrosomia and cardiomegaly, and died of congestive heart failure and cardiogenic shock. Mother was a 22 yo woman with Type 1 DM who received inhaled insulin 7 mg/day for 110 days. Also received isophane insulin. Was taking oral contraceptive pills (OCP). On Study Day 72, had last menstrual period (LMP). Mother was unaware of pregnancy until Study Day 111, when she had a positive pregnancy test. Inhaled insulin stopped, and switched to isophane and regular insulins, and insulin lispro. On Study Day 261, 150 days after last dose of inhaled insulin, fetal ultrasound revealed macrosomia and polyhydramnios. On Study Day 292, 181 days after last dose of inhaled insulin, mother experienced preterm labor at 31 wks EGA. Treated with tocolytics. On Study Day 295, mother developed diabetic ketoacidosis (DKA). On Study Day 297, Caesarian section. Neonate macrosomic and had cardiomegaly. Neonate developed congestive heart failure and cardiogenic shock and died on Day 2 of life.

1022-5152-3622: 48 yo woman with 40 year history Type 1 DM c/b retinopathy, nephropathy, HLP and htn. Received average dose of inhaled insulin of 13 mg/day for 27 days; was withdrawn from study due to noncompliance. Also received extended zinc suspension insulin. Died of MI 25 days after last dose of inhaled insulin.

1022-5154-3682: 58 yo man with Type 1 DM c/b retinopathy, HLP and htn. Received inhaled insulin in doses ranging from 10-22.7 mg/day for 353 days. Also received isophane insulin. Patient was found dead at home; reported to have been dead for 24 hours.

1027-1016-0648: 49 yo man with Type 1 DM, c/b prior MI, received inhaled insulin, 4.4-6.0 mg for 89 days. Also received glargine. After three months of inhaled insulin, complained of headaches, which had been a rare occurrence for him in the past. Had acupuncture on Study Day 89. That evening, had a large meal, followed by a blood sugar of 350 mg/dL. Gave himself aspart insulin (dose unknown). Shortly before midnight, asked his wife for juice for a possible low blood sugar. Patient then had a seizure with incontinence of urine, and became unresponsive. EMS performed CPR en route to ER; patient died a few hours later. Autopsy revealed cause of death as MI. Old MI also noted on autopsy.

1029-1026-0659: 61 yo man with Type 2 DM c/b retinopathy, macular edema and history of foot ulcer. Received inhaled insulin, 30.4-41.1 mg/day for 307 days. Also received insulin glargine. On Study Day 226 was diagnosed with widely metastatic colon cancer. Died on Study Day 313, 6 days after last dose of inhaled insulin.

1036-5005-1006: 70 yo man with Type 2 DM c/b htn, CHD. Also had history of (hx) aortic valve replacement (AoVR). Received inhaled insulin, 9 mg/day, for 97 days. Also received isophane insulin and glibenclamide. On Study Day 97, collapsed at home after playing golf and swimming. Wife reported that patient had "massive" myocardial infarction. No autopsy.

1036-5011-1004: 48 yo woman with Type 2 DM c/b htn, HLP and retinopathy. Received inhaled insulin, for 2367 days (over 3 studies). Also received insulin glargine, rosiglitazone, metformin and glibenclamide. On inhaled insulin administration day 2367, began choking and coughing while riding as a passenger in a car. Was given epinephrine and atropine *en route* to hospital; arrived in full arrest. Resuscitation unsuccessful. Cause of death listed as MI; no autopsy performed.

Discussion of Deaths

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.

A total of 7/21 of these deaths occurred in Type 1 diabetics who were taking inhaled insulin. In a metaanalysis of randomized controlled trials (including the DCCT) of intensive management of Type 1 diabetes, 15/1028 (1.5%) of patients in intensive insulin treatment groups died (Egger 1997). In this development program, 7/1209 (0.6%) of Type 1 patients who were exposed to inhaled insulin in the entire development program died, and 4/851 (0.5%) of those in controlled Phase 2 and Phase 3 trials died. In the Eggers metaanalysis, 5/1028 (0.5%) of patients died of sudden death or macrovascular disease, compared to 6/1209 (0.5%) of Type 1 patients in this development program, and 4/851 (0.5%) in controlled Phase 2 and Phase 3 trials. 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. Mean age at death for Type 1 diabetics in this development program was 50.2 years. In the U.S. population of Type 1 diabetics born between 1939 and 1959, median age at death is 47 years for men and 52 years for

women (Becker 1995). Mean age of Type 1 diabetics at entry into study was 38 years for both inhaled and SQ groups. Patients who were older at entry were at greater risk for cardiovascular mortality. Patients with recent cardiovascular events were excluded from study, but those with established coronary artery disease without recent events were not excluded.

Mean age at death for Type 2 diabetics treated with inhaled insulin was 64.8 years; mean age at study entry for the overall Type 2 study population was 57.2 years. Patients who were older at entry were more likely to have atherosclerotic disease. Patients with recent cardiovascular events were excluded from study, but those with established coronary artery disease without recent events were not excluded.

In trials of intensive management of diabetes, severe hypoglycemic events with resultant injury or death have been a concern. The clinical reviewer searched for hypoglycemic event histories for those patients who died of injury, myocardial infarction or apparent sudden cardiac death (n = 14).

Table 7.1.1.3: Hypoglycemic Event and HbA1c Data for Patients who Died of MI or other Sudden Causes

Patient ID	Type DM	Baseline HbA1C	Last HbA1C	Total Number Severe Hypoglycemic Episodes[1]	Number Severe Hypoglycemic Episodes Recorded in Month Before Death
102E-5011-0077	1	no dataset[2] (8.4)	8.2	1	0
103E-5006-0048	2	no dataset (7.9)	9.6	0	0
104E-5016-0005	2	no dataset (10.6)	7.1	0	0
111-5046-8336	2	7.7	7.5	0	0
111-5048-0414	2	8.4	7.7	0	0
111-5049-6770	1	8.2	7.3	0	0
1001-0004-0025	2	9.1	8.3	0	0
1001-0134-1373	2	10.1	10.1	0	0
1022-1016-0891	1	no dataset (8.0)	7.6	0	0
1022-5152-3622	1	no dataset (8.6)	7.8	0	0
1022-5154-3682	1	no dataset (6.1)	6.8	0	0
1027-1016-0648	1	no dataset (7.6)	6.5	0	0
1036-5005-1006	2	no dataset (9.0)	7.7	1	0
1036-5011-1004	2	no dataset (8.4)	7.5	0	0

1 Severe = requiring the assistance of another person and/or BG ≤ 36 mg/dL
2 For patients for whom no dataset was found, the clinical reviewer requested data from the sponsor. This is contained in their submission of 10 Jun 05, Table 2

Those patients who died of acute causes do not appear to have 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. Patient 102E-5011-0077, a 35 year old woman who died in a motor vehicle accident, had a history of 147 nonserious hypoglycemic events over her 1463 days of inhaled insulin treatment. However, her blood sugar at the accident scene was recorded as 120 mg/dL. Patient 104E-5016-0005, a 65 year old man who died of an acute myocardial infarction, had 37 episodes of nonserious hypoglycemia over 1037 days of inhaled insulin treatment. Patient 1022-5154-3682, a 58 year old man who was found dead at home, had 116 nonserious hypoglycemic episodes over 352 days of inhaled insulin treatment. Patient 1027-1016-0648, a 49 year old man who died of a myocardial infarction, asked for juice for what he felt was a low blood sugar; he then suffered a seizure and died a few hours later of an MI. This patient had had 19 nonserious episodes of hypoglycemia over 89 days of inhaled insulin treatment.

Overall, the deaths which occurred in inhaled insulin group patients do not seem to have a stronger association with hypoglycemia than expected in diabetics treated with subcutaneous insulin. It is an unfortunate fact that tight glycemic control comes with a price of periodic episodes of severe hypoglycemia, which under certain circumstances can lead to death from accidents or acute cardiovascular events. As discussed in Sections 5.1 and 5.2, Exubera® has problems with dose proportionality and dose equivalence which are unique to this form of inhaled insulin administration, which do not occur with subcutaneous insulin, and which may increase the risk for hypoglycemia.

Three of the patients who died, all Type 2 diabetics, had significant declines in one or more pulmonary function tests prior to death. A significant decline was defined as a decrease of >15% in FEV1, FVC or TLC; or >20% in DLco. These 3 patients represent 21.4% (3/14) of the Type 2 diabetic patients who died. The incidence of significant declines in one or more pulmonary function tests in the controlled Phase 2/3 population of Type 2 diabetics was 13.1% (167/1277). All three of these patients died of apparent cardiac causes. The number of deaths is too small to permit meaningful statistical comparisons between the incidences of abnormal pulmonary function tests among Type 2 diabetics who died and the overall Type 2 diabetic population. However, a significant decline in pulmonary function could have more serious consequences for a patient with underlying cardiac disease and an already decreased ability to deliver oxygen to the myocardium, than for a patient without underlying cardiac disease.

In summary, the percentage of deaths among inhaled insulin patients in the development program does not exceed that seen in comparator patients, and does not exceed that seen in major diabetes trials. The causes of deaths are in general what one expects for diabetics, i.e. predominantly cardiovascular causes. The age at death of inhaled insulin patients does not appear to be lower than expected among diabetics in general. Patients who died of acute causes do not appear to have had a significant number of severe hypoglycemic events over the course of their participation in the trials, although some had a large number of nonserious hypoglycemic events, and one patient died shortly after what appears to have been a hypoglycemic episode. No

clear difference was demonstrated between inhaled insulin and comparator patients for incidence or cause of death.

7.1.2 Other Serious Adverse Events

For purposes of this review, a serious adverse event is defined as an event that results in any one of the following outcomes:

- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity
- a congenital anomaly or defect

The applicant's definition of serious adverse events was essentially the same. Investigators for the clinical trials included in the application may also have considered other events serious, even if they did not strictly meet the above outcome criteria; these events are also included in the serious adverse event review.

Adverse event terms were coded using MedDRA and COSTART terminology.

7.1.2.1 Serious Adverse Events by Type of Event

7.1.2.1.1 Serious Adverse Events in Type 1 Adult Patients

In controlled Phase 2 and Phase 3 studies in Type 1 patients, serious adverse events occurred at a slightly higher frequency in SQ group patients than in inhaled insulin group patients, when comparing subject-months of exposure. The frequency of serious adverse events by exposure in inhaled insulin group patients was comparable in the controlled and overall Phase 2/3 populations.

Table 7.1.2.1.1.1 All-causality Serious Adverse Event Frequency in Type 1 Patients

	n	Subject-Months of Exposure (SME)	All-causality SAE Cases	All-Causality SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies, Inh Ins	698	5,894	52	8.8
Controlled Phase 2/3 Studies, SQ	705	6,052	73	12.1
All Phase 2/3 Studies, Inh Ins	1,209	16,571	129	7.8

Source: Applicant's Tables 1.1.1, 2.1.1.1, 2.1.1.2, 2.2.1.1, 2.2.1.2, 6.1.1.2, 6.1.2.2, 6.2.1.2, 6.2.2.2, ISS Appendix

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. The following table lists the types of SAEs that occurred in the controlled Phase 2/3 population.

Table 7.1.2.1.1.2 Serious Adverse Events Occurring in Adult Type 1 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total n = 698 # events (# events per 100 patients)	SQ total n = 705 # events (# events per 100 patients)
Cardiac Disorders		5 (0.7)	6 (0.9)
	Angina pectoris	1 (0.1)	0
	Angina unstable	0	1 (0.1)
	Coronary artery disease	0	2 (0.3)
	Myocardial infarction	3 (0.4)	2 (0.3)
	Sinus arrhythmia	0	1 (0.1)
	Sinus tachycardia	0	1 (0.1)
	Supraventricular tachycardia	1 (0.1)	0
Eye disorders		2 (0.3)	1 (0.1)
	Eye hemorrhage	1 (0.1)	0
	Macular degeneration	1 (0.1)	0
	Retinal detachment	0	1 (0.1)
Gastrointestinal disorders		2 (0.3)	4 (0.6)
	Abdominal hernia	1 (0.1)	0
	Colonic polyp	0	1 (0.1)
	Gastritis	1 (0.1)	0
	Gastrointestinal disorder	0	1 (0.1)
	Peptic ulcer	0	1 (0.1)
	Small intestinal obstruction	0	1 (0.1)
	Umbilical hernia	1 (0.1)	0
	Vomiting	0	1 (0.1)
General disorders and administration site conditions		3 (0.4)	1 (0.1)
	Chest pain	2 (0.3)	1 (0.1)
	Hypothermia	1 (0.1)	0
Hepatobiliary disorders		2 (0.3)	0
	Cholecystitis	1 (0.1)	0
	Cholelithiasis	1 (0.1)	0
Infections and infestations		5 (0.7)	7 (1.0)
	Appendicitis	0	2 (0.3)
	Cellulitis	0	1 (0.1)
	Gastroenteritis	1 (0.1)	1 (0.1)
	Influenza	0	1 (0.1)
	Kidney infection	1 (0.1)	0
	Localised infection	0	1 (0.1)
	Meningitis	0	1 (0.1)
	Postprocedural cellulitis	1 (0.1)	0
	Pyelonephritis	1 (0.1)	0
	Wound infection	1 (0.1)	0
Injury, poisoning and procedural complications		5 (0.7)	5 (0.7)
	Accidental overdose	1 (0.1)	0
	Ankle fracture	2 (0.3)	0
	Drug exposure during pregnancy	0	1 (0.1)
	Foot fracture	0	1 (0.1)
	Intentional overdose	0	1 (0.1)
	Joint sprain	0	1 (0.1)
	Laceration	1 (0.1)	1 (0.1)
	Patella fracture	0	1 (0.1)
	Road traffic accident	1 (0.1)	1 (0.1)
	Skin laceration	0	1 (0.1)
Metabolism and nutrition disorders		27 (3.9)	38 (5.4)
	Diabetic complication	0	1 (0.1)
	Diabetic foot	0	1 (0.1)
	Diabetic ketoacidosis	3 (0.4)	0

Table 7.1.2.1.1.2 Serious Adverse Events Occurring in Adult Type 1 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total n = 698 # events (# events per 100 patients)	SQ total n = 705 # events (# events per 100 patients)
	Hyperglycemia	1 (0.1)	1 (0.1)
	Hypoglycemia	23 (3.3)	35 (5.0)
	Ketoacidosis	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders		1 (0.1)	2 (0.3)
	Arthralgia	1 (0.1)	0
	Back pain	0	1 (0.1)
	Intervertebral disc protrusion	0	2 (0.3)
Neoplasms, benign, malignant and unspecified, including cysts and polyps		1 (0.1)	3 (0.4)
	Breast cancer	1 (0.1)	0
	Breast cancer female	0	1 (0.1)
	Pancreatic carcinoma	0	1 (0.1)
	Uterine leiomyoma	0	1 (0.1)
Nervous system disorders		10 (1.4)	23 (3.3)
	Amnesia	0	2 (0.3)
	Aphasia	0	1 (0.1)
	Coma	0	1 (0.1)
	Convulsion	2 (0.3)	7 (1.0)
	Disturbance in attention	0	1 (0.1)
	Hypoglycemic coma	1 (0.1)	0
	Loss of consciousness	7 (1.0)	12 (1.7)
	Syncope	0	2 (0.3)
Pregnancy, puerperium and perinatal conditions		2 (0.3)	2 (0.3)
	Abortion spontaneous	1 (0.1)	0
	Pregnancy	0	1 (0.1)
	Premature labor	1 (0.1)	1 (0.1)
Psychiatric disorders		0	9 (1.3)
	Confusional state	0	1 (0.1)
	Depression	0	5 (0.7)
	Major depression	0	1 (0.1)
	Mental status change	0	2 (0.3)
	Suicidal ideation	0	1 (0.1)
Renal and urinary disorders		2 (0.3)	0
	Renal colic	1 (0.1)	0
	Urinary incontinence	1 (0.1)	0
Skin and subcutaneous disorders		0	2 (0.3)
	Hyperhidrosis	0	2 (0.3)
Total preferred event terms		71 (10.2)	114 (16.2)
Total number of cases		52 (7.4 cases per 100 patients)	73 (10.4 cases per 100 patients)
Total number of patients with SAEs		46 (6.7 patients with SAEs per 100 patients in group)	57 (8.1 patients with SAEs per 100 patients in group)

Source: Applicant's Table 6.1.1.2, ISS

In Type 1 adult patients, no pattern emerged of a single type of serious adverse event, or grouping of serious 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.

The clinical reviewer did not find evidence of "splitting" of terms that could mask the true incidence of certain adverse events. The following table, constructed by the clinical reviewer, groups types of event terms (accidents, injuries, acute neurologic, acute cardiovascular) which may occur during or as a result of hypoglycemic episodes.

Table 7.1.2.1.1.3 Serious Adverse Event Terms Potentially Related to Hypoglycemia, Controlled Phase 2/3 Trials[1] in Type 1 Patients

Event	Inhaled Insulin Groups (total n = 851) # events (# events x 100/ total subjects in group)	SQ Insulin Groups (total n = 853) # events (# events x 100/ total subjects in group)
Angina pectoris	1 (0.1)	0
Angina unstable	0	1 (0.1)
Chest pain	2 (0.2)	1 (0.1)
Myocardial infarction	3 (0.4)	2 (0.2)
Sinus tachycardia	0	1 (0.1)
Supraventricular tachycardia	1 (0.1)	0
Vomiting	0	1 (0.1)
Hypothermia	1 (0.1)	0
Ankle fracture	2 (0.2)	0
Foot fracture	0	1 (0.1)
Joint sprain	0	1 (0.1)
Laceration	1 (0.1)	1 (0.1)
Patella fracture	0	1 (0.1)
Road traffic accident	1 (0.1)	1 (0.1)
Skin laceration	0	1 (0.1)
Hypoglycemia	23 (2.7)	35 (4.1)
Amnesia	0	2 (0.2)
Aphasia	0	1 (0.1)
Coma	0	1 (0.1)
Convulsion	2 (0.2)	7 (0.8)
Grand mal convulsion	1 (0.1)	0
Hypoglycemic coma	1 (0.1)	0
Loss of consciousness	7 (0.8)	12 (1.4)
Syncope	0	2 (0.2)
Confusional state	0	1 (0.1)
Mental status changes	0	2 (0.2)
Hyperhidrosis	0	2 (0.2)
Total event terms conceivably related to hypoglycemia	46 (5.4)	77 (9.0)

1 includes Studies 106, 107, 1022, 1026, 1027

Event terms potentially 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.

7.1.2.1.2 Serious Adverse Events in Type 2 Patients

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. In the group of all Phase 2 and Phase 3 studies SAEs occurred with approximately equal frequency

in inhaled insulin patients as among inhaled insulin patients in the controlled Phase 2/3 population.

Table 7.1.2.1.2.1 All-causality Serious Adverse Event Frequency in Type 2 Patients

	n	Subject-Months of Exposure (SME)	All-causality SAE Cases	All-Causality SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies, Inh Ins	1,277	12,186	140	11.5
Controlled Phase 2/3 Studies, SQ	488	4,868	63	12.9
Controlled Phase 2/3 Studies, OA	644	6,452	78	12.1
All Phase 2/3 Studies, Inh Ins	1,578	30,688	386	12.5

Source: Applicant's Tables 6.1.1.3, 6.1.2.3, 6.2.1.3, 6.2.2.3, 2.2.1.1, 2.2.1.2, ISS Appendix

Myocardial infarction, chest pain, angina and hypoglycemia were the most common SAE terms among Type 2 patients. The following table lists SAE terms occurring among Type 2 patients. Because study drug exposure duration was significantly greater among inhaled insulin patients than among comparator patients, event rates are compared using exposure duration.

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
Blood and lymphatic system disorders		1 (0.1)	1 (0.2)	0
	Anemia	1 (0.1)	1 (0.2)	0
Cardiac disorders		30 (2.5)	12 (2.5)	14 (2.2)
	Acute myocardial infarction	4 (0.3)	0	2 (0.3)
	Angina pectoris	2 (0.2)	1 (0.2)	4 (0.6)
	Angina unstable	4 (0.3)	1 (0.2)	1 (0.2)
	Arrhythmia	1 (0.1)	0	1 (0.2)
	Atrial fibrillation	0	3 (0.6)	0
	Atrial flutter	0	0	1 (0.2)
	Bradycardia	2 (0.2)	0	0
	Cardiac failure	1 (0.1)	0	0
	Cardiac failure acute	1 (0.1)	0	0
	Cardiac failure congestive	3 (0.2)	0	1 (0.2)
	Coronary artery disease	5 (0.4)	3 (0.6)	0
	Coronary artery occlusion	1 (0.1)	2 (0.4)	0
	Coronary artery stenosis	1 (0.1)	0	0
	Myocardial infarction	7 (0.6)	2 (0.4)	5 (0.8)
	Myocardial ischemia	1 (0.1)	1 (0.2)	0
	Palpitations	1 (0.1)	0	0
	Tachyarrhythmia	1 (0.1)	0	0
	Ventricular extrasystoles	1 (0.1)	0	0
	Ventricular fibrillation	1 (0.1)	0	0
	Ventricular tachycardia	1 (0.1)	0	0
Endocrine disorders		2 (0.2)	0	0
	Cushing's syndrome	1 (0.1)	0	0
	Hypothyroidism	1 (0.1)	0	0

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
Eye disorders		1 (0.1)	0	2 (0.3)
	Cataract	1 (0.1)	0	0
	Eye movement disorder	0	0	1 (0.2)
	Optic ischemic neuropathy	0	0	1 (0.2)
Gastrointestinal disorders		12 (1.0)	7 (1.4)	11 (1.7)
	Abdominal discomfort	0	0	1 (0.2)
	Abdominal hernia	0	0	1 (0.2)
	Abdominal pain	0	0	2 (0.3)
	Abdominal pain upper	1 (0.1)	1 (0.2)	1 (0.2)
	Abdominal strangulated hernia	0	1 (0.2)	0
	Ascites	0	0	1 (0.2)
	Duodenal ulcer	0	1 (0.2)	1 (0.2)
	Dyspnea	0	0	1 (0.2)
	Esophageal hemorrhage	1 (0.1)	0	0
	Esophageal spasm	1 (0.1)	0	1 (0.2)
	Esophagitis	0	1 (0.2)	0
	Esophagitis ulcerative	0	1 (0.2)	0
	Food poisoning	0	0	1 (0.2)
	Gastric ulcer	0	0	1 (0.2)
	Gastric volvulus	0	1 (0.2)	0
	Gastritis	0	1 (0.2)	0
	Gastrointestinal gangrene	1 (0.1)	0	0
	Gastrointestinal hemorrhage	2 (0.2)	0	0
	Inguinal hernia	3 (0.2)	1 (0.2)	0
	Inguinal hernia, obstructive	1 (0.1)	0	0
	Pancreatitis	2 (0.2)	1 (0.2)	0
	Pancreatitis acute	0	0	1 (0.2)
	Small intestinal obstruction	1 (0.1)	1 (0.2)	0
	Vomiting	0	2 (0.4)	1 (0.2)
General disorders and administration site conditions		8 (0.7)	5 (1.0)	6 (0.9)
	Asthenia	0	1 (0.2)	0
	Chest pain	6 (0.5)	2 (0.4)	4 (0.6)
	Ill-defined disorder	0	0	1 (0.2)
	Noncardiac chest pain	1 (0.1)	1 (0.2)	0
	Edema peripheral	1 (0.1)	0	0
	Pain exacerbated	0	1 (0.2)	0
Hepatobiliary disorders		3 (0.2)	1 (0.2)	4 (0.6)
	Bile duct obstruction	1 (0.1)	0	0
	Biliary colic	0	0	1 (0.2)
	Cholecystitis	0	0	1 (0.2)
	Cholecystitis acute	1 (0.1)	0	1 (0.2)
	Cholelithiasis	1 (0.1)	1 (0.2)	1 (0.2)
Immune system disorders		2 (0.2)	0	0
	Drug hypersensitivity	1 (0.1)	0	0
	Hypersensitivity	1 (0.1)	0	0
Infections and infestations		20 (1.6)	9 (1.8)	4 (0.6)
	Appendicitis	2 (0.2)	0	0
	Bronchitis	2 (0.2)	0	0
	Bronchitis acute	1 (0.1)	0	0

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
	Bronchopneumonia	1 (0.1)	0	0
	Cellulitis	4 (0.3)	3 (0.6)	0
	Diverticulitis	1 (0.1)	0	0
	Herpes zoster	1 (0.1)	0	0
	Infected insect bite	1 (0.1)	0	0
	Infected skin ulcer	0	1 (0.2)	0
	Osteomyelitis	2 (0.2)	1 (0.2)	0
	Peritonsillar abscess	1 (0.1)	0	0
	Pneumocystis carinii pneumonia	0	0	1 (0.2)
	Pneumonia	2 (0.2)	3 (0.6)	0
	Postoperative infection	0	1 (0.2)	0
	Sepsis	1 (0.1)	0	0
	Subcutaneous abscess	0	0	1 (0.2)
	Urinary tract infection	2 (0.2)	0	0
	Urosepsis	0	0	1 (0.2)
	Vulvar abscess	0	0	1 (0.2)
Injury, poisoning and procedural complications		8 (0.7)	4 (0.8)	4 (0.6)
	Accidental overdose	0	1 (0.2)	0
	Concussion	1 (0.1)	0	0
	Fall	1 (0.1)	0	0
	Foot fracture	1 (0.1)	0	0
	Hip fracture	1 (0.1)	1 (0.2)	0
	Multiple fractures	0	0	1 (0.2)
	Pelvic fracture	0	1 (0.2)	0
	Postoperative adhesion	2 (0.2)	0	0
	Rib fracture	0	2 (0.4)	1 (0.2)
	Road traffic accident	0	2 (0.4)	1 (0.2)
	Stitch abscess	0	0	1 (0.2)
	Tendon injury	1 (0.1)	0	0
	Upper limb fracture	1 (0.1)	0	0
	Wound	1 (0.1)	0	0
Investigations		7 (0.6)	14 (2.9)	4 (0.6)
	Blood glucose decreased	1 (0.1)	0	0
	Exercise electrocardiogram abnormal	1 (0.1)	0	0
	Gamma-glutamyl transferase increased	1 (0.1)	0	0
	Pulmonary function test decreased	0	0	1 (0.2)
Metabolism and nutrition disorders		7 (0.6)	14 (2.9)	4 (0.6)
	Diabetic foot	0	0	1 (0.2)
	Hyperglycemia	1 (0.1)	1 (0.2)	1 (0.2)
	Hyperkalemia	1 (0.1)	0	0
	Hypoglycemia	5 (0.4)	13 (2.7)	2 (0.3)
Musculoskeletal and connective tissue disorders		8 (0.7)	4 (0.8)	9 (1.4)
	Arthralgia	1 (0.1)	1 (0.2)	0
	Back pain	1 (0.1)	1 (0.2)	2 (0.3)
	Bunion	0	1 (0.2)	0
	Cataplexy	0	1 (0.2)	0
	Intervertebral disc	1 (0.1)	1 (0.2)	1 (0.2)

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
	protrusion			
	Localized osteoarthritis	1 (0.1)	0	1 (0.2)
	Musculoskeletal stiffness	1 (0.1)	0	0
	Myalgia	1 (0.1)	0	0
	Myositis	0	0	1 (0.2)
	Pain in extremity	1 (0.1)	0	0
	Periarthritis	1 (0.1)	0	0
	Polymyalgia rheumatica	0	0	2 (0.3)
	Rheumatoid arthritis	1 (0.1)	0	0
	Toe deformity	0	0	2 (0.3)
Neoplasms, benign, malignant and unspecified, including cysts and polyps		13 (1.1)	5 (1.0)	4 (0.6)
	Basal cell carcinoma	1 (0.1)	0	1 (0.2)
	Blast cell crisis	1 (0.1)	0	0
	Carcinoid tumor of the stomach	0	1 (0.2)	0
	Carcinoma	1 (0.1)	0	0
	Chronic myeloid leukemia	1 (0.1)	0	0
	Colon cancer	1 (0.1)	1 (0.2)	1 (0.2)
	Colon cancer metastatic	1 (0.1)	0	0
	Esophageal carcinoma	1 (0.1)	0	0
	Lung adenocarcinoma	1 (0.1)	0	0
	Lung neoplasm malignant	0	0	1 (0.2)
	Malignant neoplasm progression	1 (0.1)	0	0
	Metastases to kidney	1 (0.1)	0	0
	Metastases to liver	2 (0.2)	0	0
	Metastases to lung	1 (0.1)	0	0
	Metastases to pancreas	1 (0.1)	0	0
	Metastatic bronchial carcinoma	1 (0.1)	0	0
	Ovarian cancer	0	1 (0.2)	1 (0.2)
	Ovarian cancer metastatic	0	1 (0.2)	0
	Prostate cancer	2 (0.2)	1 (0.2)	0
	Renal neoplasm	1 (0.1)	0	0
	Small intestine carcinoma	1 (0.1)	0	0
Nervous system disorders		18 (1.5)	10 (2.1)	12 (1.9)
	Carotid artery stenosis	1 (0.1)	0	1 (0.2)
	Carpal tunnel syndrome	0	0	2 (0.3)
	Cerebrovascular accident	1 (0.1)	2 (0.4)	2 (0.3)
	Convulsion	1 (0.1)	1 (0.2)	0
	Facial palsy	2 (0.2)	0	0
	Facial paresis	0	0	1 (0.2)
	Global amnesia	1 (0.1)	0	0
	Hydrocephalus	0	0	2 (0.3)
	Ischemic stroke	1 (0.1)	0	0
	Loss of consciousness	3 (0.2)	6 (1.2)	1 (0.2)
	Lumbar radiculopathy	1 (0.1)	0	0
	Migraine	1 (0.1)	0	0
	Multiple sclerosis	0	1 (0.2)	0
	Nerve compression	1 (0.1)	0	0
	Neuritis	1 (0.1)	0	1 (0.2)
	Syncope	1 (0.1)	0	2 (0.3)

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
	Transient ischemic attack	3 (0.2)	1 (0.2)	0
Psychiatric disorders		2 (0.2)	7 (1.4)	1 (0.2)
	Anxiety	0	0	1 (0.2)
	Bipolar disorder	1 (0.1)	3 (0.6)	0
	Confusional state	0	1 (0.2)	0
	Depression	1 (0.1)	2 (0.4)	0
	Panic attack	0	1 (0.2)	0
Renal and urinary disorders		5 (0.4)	1 (0.2)	3
	Dysuria	1 (0.1)	0	0
	Nephrolithiasis	0	0	2 (0.3)
	Renal artery stenosis	0	0	1 (0.2)
	Renal colic	3 (0.2)	0	0
	Renal failure acute	1 (0.1)	1 (0.2)	0
Reproductive system and breast disorders		1 (0.1)	0	2 (0.3)
	Dysfunctional uterine bleeding	0	0	1 (0.2)
	Erectile dysfunction	1 (0.1)	0	0
	Uterine prolapse	0	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders		9 (0.7)	5 (1.0)	2 (0.3)
	Asthma	3 (0.2)	0	0
	Bronchospasm	1 (0.1)	0	0
	Cough	1 (0.1)	0	0
	Dyspnea	1 (0.1)	2 (0.4)	2 (0.3)
	Epistaxis	1 (0.1)	0	0
	Hypoxia	0	1 (0.2)	0
	Pneumothorax	1 (0.1)	1 (0.2)	0
	Respiratory distress	0	1 (0.2)	0
	Respiratory failure	1 (0.1)	0	0
	Vocal cord polyp	1 (0.1)	0	0
Skin and subcutaneous tissue disorders		3 (0.2)	1 (0.2)	0
	Diabetic bullosis	1 (0.1)	0	0
	Skin ulcer	2 (0.2)	1 (0.2)	0
Surgical and medical procedures		1 (0.1)	0	2 (0.3)
	Carpal tunnel decompression	0	0	1 (0.2)
	Removal of internal fixation	1 (0.1)	0	0
	Transurethral prostatectomy	0	0	1 (0.2)
Vascular disorders		6 (0.5)	1 (0.2)	3 (0.5)
	Arteriopathic disease	0	0	1 (0.2)
	Arteritis	0	0	1 (0.2)
	Deep vein thrombosis	0	1 (0.2)	0
	Hypertension	2 (0.2)	0	0
	Hypertensive crisis	1 (0.1)	0	0
	Intermittent claudication	0	0	1 (0.2)
	Orthostatic hypotension	1 (0.1)	0	0
Total preferred term events		184 (15.1)	96 (19.7)	92 (14.3)

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies				
MedDRA System Organ Class	**MedDRA Preferred Event Term**	**Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)**	**SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)**	**OA total subject-months = 6,452 # events (# events per 1,000 subject-months)**
Total number of patients with SAEs		128 (10.5 patients with SAEs per 1000 patient-months)	49 (10.1 patients with SAEs per 1000 patient-months)	62 (9.6 patients with SAEs per 1000 patient-months)
Source: Applicant's Table 6.1.1.3, ISS				

The clinical reviewer grouped certain adverse event terms of interest for a total incidence rate. Term groupings of interest included:

- terms related to coronary artery disease, as macrovascular disease is the major cause of mortality among Type 2 diabetics
- hypoglycemia-related terms
- terms related to loss of consciousness and seizure, which may accompany severe hypoglycemia
- terms related to accidents and injuries, which also may accompany severe hypoglycemia
- immune system disorders, because of concern regarding insulin antibody formation in patients exposed to inhaled insulin

Pulmonary terms are also of interest; these will be discussed in Dr. Seymour's pulmonary review.

Table 7.1.2.1.2.3 Serious Adverse Event Terms of Special Interest in Type 2 Patients, Controlled Phase 2 and Phase 3 Studies			
Event Term Grouping	**Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)**	**SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)**	**OA total subject-months = 6,452 # events (# events per 1,000 subject-months)**
Coronary artery disease terms[1]	25 (2.1)	10 (2.0)	12 (1.9)
Immune system terms[2]	2 (0.2)	0	0
Accident and injury terms[3]	6 (0.5)	6 (1.2)	3 (0.5)
Hypoglycemia terms[4]	6 (0.5)	13 (2.7)	2 (0.3)
Loss of consciousness and seizure[5]	5 (0.4)	7 (1.4)	3 (0.5)
1 Includes acute myocardial infarction, angina pectoris, angina unstable, coronary artery disease, coronary artery occlusion, coronary artery stenosis, myocardial infarction, myocardial ischemia **2 Includes drug hypersensitivity, hypersensitivity** **3 Includes concussion, fall, foot fracture, hip fracture, multiple fractures, pelvic fracture, rib fracture, road traffic accident, tendon injury, upper limb fracture** **4 Includes hypoglycemia, blood glucose decreased** **5 Includes convulsion, loss of consciousness, syncope**			

None of these groups of terms occurred with significantly higher frequency among inhaled insulin patients than among comparator patients; hypoglycemia adverse event terms occurred

numerically more frequently among SQ patients than among inhaled insulin patients or OA patients.

Neoplastic events did not occur with greater frequency in inhaled insulin group patients than in comparator groups. Two lung cancer events occurred in the inhaled insulin groups, and one occurred in the oral agent groups.

7.1.2.1.3 Serious Adverse Events in Pediatric Patients

A total of 331 patients <18 years of age were exposed to inhaled insulin in the development program. Of these, 153 participated in controlled Phase 2 and Phase 3 trials in Type 1 diabetes; there were also 147 control children who received subcutaneous insulin. At the request of DMEDP, the applicant provided comparative serious adverse event information for pediatric patients for controlled Phase 2/3 trials; the applicant chose a cut-off date of 1 Aug 03. The overall incidence of SAEs was somewhat higher for pediatric inhaled insulin patients than for pediatric SQ patients.

Table 7.1.2.1.3.1 All-causality Serious Adverse Event Frequency in Pediatric Patients (Cut-off Date 1 Aug 03)

	n	Subject-Months of Exposure (SME)	All-causality SAE Cases	All-causality SAEs per 100 pts	All-causality SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies, Inh Ins	153	690	30	19.6	43.4
Controlled Phase 2/3 Studies, SQ	148	663	25	16.9	37.7

Source: Applicant's Table 4.1.1.1.1.1.2, p 2766, ISS

The following table summarizes the types of serious adverse events seen in children as of 1 Aug 03:

Table 7.1.2.1.3.2 Serious Adverse Events in Pediatric Patients, Controlled Phase 2/3 Trials, Cut-off Date 3 Aug 03

COSTART Organ System	COSTART Event Term	Inh Ins total n = 153 total SME = 690 # events (# events per 1,000 SME)	SQ total n = 148 total SME = 663 # events (# events per 1,000 SME)
Body as a whole		3 (4.3)	1 (1.5)
	Abdominal pain	1 (1.4)	0
	Accidental injury	0	1 (1.5)
	Flu syndrome	1 (1.4)	0
	Suicidal ideation	1 (1.4)	0
Digestive		1 (1.4)	2 (3.0)
	Gastritis	1 (1.4)	0
	Hematemesis	0	1 (1.5)
	Vomiting	0	1 (1.5)
Metabolic and nutritional		25 (36.2)	24 (36.2)
	Hypoglycemia	25 (36.2)	22 (33.2)
	Ketosis	1 (1.4)	2 (3.0)
Musculoskeletal		0	1 (1.5)
	Bone fracture accidental	0	1 (1.5)
Nervous		0	2 (3.0)

Table 7.1.2.1.3.2 Serious Adverse Events in Pediatric Patients, Controlled Phase 2/3 Trials, Cut-off Date 3 Aug 03

COSTART Organ System	COSTART Event Term	Inh Ins total n = 153 total SME = 690 # events (# events per 1,000 SME)	SQ total n = 148 total SME = 663 # events (# events per 1,000 SME)
	Convulsion	0	2 (3.0)
Respiratory		1 (1.4)	0
	Cough increased	1 (1.4)	0

Source: Applicant's Table 4.1.1.1.1.1.2, ISS

Hypoglycemia reported as a serious adverse event occurred somewhat more frequently among children taking inhaled insulin than among those 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. In the inhaled insulin groups, 20.3 severe hypoglycemic events were reported as severe events per 100 children, compared to 2.7 such events per 100 adult Type 1 patients. This also held true for the SQ groups, with 20.4 events/100 children and 4.1 events/100 adult Type 1 patients.

7.1.2.2 Serious Adverse Events by Patient

Due to the large size of the by-patient serious adverse event listings, the clinical reviewer placed them in Appendix 10.4. These listings include all serious adverse events by patient; separate tables are provided for Type 1, Type 2, and pediatric patients. Separate tables are also provided for comparator agents.

Hypoglycemic events warrant a few points. Because the applicant provided narratives only for serious adverse events that resulted in death or discontinuation, or were pulmonary in nature, or that were felt by the applicant to be treatment-related, many adverse events which are sometimes associated with hypoglycemia in clinical practice had no narrative or case report form to assist the clinical reviewer in determining whether these events (accidents, injuries, acute neurologic events and acute cardiac events) occurred in close proximity to a hypoglycemic event. The clinical reviewer asked Mr. Brian Green, Associate Director for Worldwide Regulatory Strategy for Pfizer, to clarify whether investigators routinely queried patients who had such events about whether the patient could have been hypoglycemic at the time of the event. On 19 Apr 05, Mr. Green replied that such events did not trigger an inquiry regarding possible hypoglycemia by the investigator at the study site. However, the applicant's Internal Safety and Risk Management Group (ISRMG) always sent a query regarding hypoglycemia (if the study site report did not include hypoglycemia information) back to the study site, for the following types of serious adverse events: loss of consciousness, syncope, seizure, accidents and injuries. For all other acute central nervous system and acute cardiac events, the ISRMG reviewed the study site's report of the event, and made a judgment about whether to query for possible hypoglycemia. It

clear difference was demonstrated between inhaled insulin and comparator patients for incidence or cause of death.

7.1.2 Other Serious Adverse Events

For purposes of this review, a serious adverse event is defined as an event that results in any one of the following outcomes:

- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity
- a congenital anomaly or defect

The applicant's definition of serious adverse events was essentially the same. Investigators for the clinical trials included in the application may also have considered other events serious, even if they did not strictly meet the above outcome criteria; these events are also included in the serious adverse event review.

Adverse event terms were coded using MedDRA and COSTART terminology.

7.1.2.1 Serious Adverse Events by Type of Event

7.1.2.1.1 Serious Adverse Events in Type 1 Adult Patients

In controlled Phase 2 and Phase 3 studies in Type 1 patients, serious adverse events occurred at a slightly higher frequency in SQ group patients than in inhaled insulin group patients, when comparing subject-months of exposure. The frequency of serious adverse events by exposure in inhaled insulin group patients was comparable in the controlled and overall Phase 2/3 populations.

Table 7.1.2.1.1.1 All-causality Serious Adverse Event Frequency in Type 1 Patients

	n	Subject-Months of Exposure (SME)	All-causality SAE Cases	All-Causality SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies, Inh Ins	698	5,894	52	8.8
Controlled Phase 2/3 Studies, SQ	705	6,052	73	12.1
All Phase 2/3 Studies, Inh Ins	1,209	16,571	129	7.8

Source: Applicant's Tables 1.1.1, 2.1.1.1, 2.1.1.2, 2.2.1.1, 2.2.1.2, 6.1.1.2, 6.1.2.2, 6.2.1.2, 6.2.2.2, ISS Appendix

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. The following table lists the types of SAEs that occurred in the controlled Phase 2/3 population.

Table 7.1.2.1.1.2 Serious Adverse Events Occurring in Adult Type 1 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total n = 698 # events (# events per 100 patients)	SQ total n = 705 # events (# events per 100 patients)
Cardiac Disorders		5 (0.7)	6 (0.9)
	Angina pectoris	1 (0.1)	0
	Angina unstable	0	1 (0.1)
	Coronary artery disease	0	2 (0.3)
	Myocardial infarction	3 (0.4)	2 (0.3)
	Sinus arrhythmia	0	1 (0.1)
	Sinus tachycardia	0	1 (0.1)
	Supraventricular tachycardia	1 (0.1)	0
Eye disorders		2 (0.3)	1 (0.1)
	Eye hemorrhage	1 (0.1)	0
	Macular degeneration	1 (0.1)	0
	Retinal detachment	0	1 (0.1)
Gastrointestinal disorders		2 (0.3)	4 (0.6)
	Abdominal hernia	1 (0.1)	0
	Colonic polyp	0	1 (0.1)
	Gastritis	1 (0.1)	0
	Gastrointestinal disorder	0	1 (0.1)
	Peptic ulcer	0	1 (0.1)
	Small intestinal obstruction	0	1 (0.1)
	Umbilical hernia	1 (0.1)	0
	Vomiting	0	1 (0.1)
General disorders and administration site conditions		3 (0.4)	1 (0.1)
	Chest pain	2 (0.3)	1 (0.1)
	Hypothermia	1 (0.1)	0
Hepatobiliary disorders		2 (0.3)	0
	Cholecystitis	1 (0.1)	0
	Cholelithiasis	1 (0.1)	0
Infections and infestations		5 (0.7)	7 (1.0)
	Appendicitis	0	2 (0.3)
	Cellulitis	0	1 (0.1)
	Gastroenteritis	1 (0.1)	1 (0.1)
	Influenza	0	1 (0.1)
	Kidney infection	1 (0.1)	0
	Localised infection	0	1 (0.1)
	Meningitis	0	1 (0.1)
	Postprocedural cellulitis	1 (0.1)	0
	Pyelonephritis	1 (0.1)	0
	Wound infection	1 (0.1)	0
Injury, poisoning and procedural complications		5 (0.7)	5 (0.7)
	Accidental overdose	1 (0.1)	0
	Ankle fracture	2 (0.3)	0
	Drug exposure during pregnancy	0	1 (0.1)
	Foot fracture	0	1 (0.1)
	Intentional overdose	0	1 (0.1)
	Joint sprain	0	1 (0.1)
	Laceration	1 (0.1)	1 (0.1)
	Patella fracture	0	1 (0.1)
	Road traffic accident	1 (0.1)	1 (0.1)
	Skin laceration	0	1 (0.1)
Metabolism and nutrition disorders		27 (3.9)	38 (5.4)
	Diabetic complication	0	1 (0.1)
	Diabetic foot	0	1 (0.1)
	Diabetic ketoacidosis	3 (0.4)	0

Table 7.1.2.1.1.2 Serious Adverse Events Occurring in Adult Type 1 Patients, Controlled Phase 2/3 Studies			
MedDRA System Organ Class	**MedDRA Preferred Event Term**	**Inh Ins total n = 698 # events (# events per 100 patients)**	**SQ total n = 705 # events (# events per 100 patients)**
	Hyperglycemia	1 (0.1)	1 (0.1)
	Hypoglycemia	23 (3.3)	35 (5.0)
	Ketoacidosis	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders		1 (0.1)	2 (0.3)
	Arthralgia	1 (0.1)	0
	Back pain	0	1 (0.1)
	Intervertebral disc protrusion	0	2 (0.3)
Neoplasms, benign, malignant and unspecified, including cysts and polyps		1 (0.1)	3 (0.4)
	Breast cancer	1 (0.1)	0
	Breast cancer female	0	1 (0.1)
	Pancreatic carcinoma	0	1 (0.1)
	Uterine leiomyoma	0	1 (0.1)
Nervous system disorders		10 (1.4)	23 (3.3)
	Amnesia	0	2 (0.3)
	Aphasia	0	1 (0.1)
	Coma	0	1 (0.1)
	Convulsion	2 (0.3)	7 (1.0)
	Disturbance in attention	0	1 (0.1)
	Hypoglycemic coma	1 (0.1)	0
	Loss of consciousness	7 (1.0)	12 (1.7)
	Syncope	0	2 (0.3)
Pregnancy, puerperium and perinatal conditions		2 (0.3)	2 (0.3)
	Abortion spontaneous	1 (0.1)	0
	Pregnancy	0	1 (0.1)
	Premature labor	1 (0.1)	1 (0.1)
Psychiatric disorders		0	9 (1.3)
	Confusional state	0	1 (0.1)
	Depression	0	5 (0.7)
	Major depression	0	1 (0.1)
	Mental status change	0	2 (0.3)
	Suicidal ideation	0	1 (0.1)
Renal and urinary disorders		2 (0.3)	0
	Renal colic	1 (0.1)	0
	Urinary incontinence	1 (0.1)	0
Skin and subcutaneous disorders		0	2 (0.3)
	Hyperhidrosis	0	2 (0.3)
Total preferred event terms		71 (10.2)	114 (16.2)
Total number of cases		52 (7.4 cases per 100 patients)	73 (10.4 cases per 100 patients)
Total number of patients with SAEs		46 (6.7 patients with SAEs per 100 patients in group)	57 (8.1 patients with SAEs per 100 patients in group)
Source: Applicant's Table 6.1.1.2, ISS			

In Type 1 adult patients, no pattern emerged of a single type of serious adverse event, or grouping of serious 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.

The clinical reviewer did not find evidence of "splitting" of terms that could mask the true incidence of certain adverse events. The following table, constructed by the clinical reviewer, groups types of event terms (accidents, injuries, acute neurologic, acute cardiovascular) which may occur during or as a result of hypoglycemic episodes.

Table 7.1.2.1.1.3 Serious Adverse Event Terms Potentially Related to Hypoglycemia, Controlled Phase 2/3 Trials[1] in Type 1 Patients

Event	Inhaled Insulin Groups (total n = 851) # events (# events x 100/ total subjects in group)	SQ Insulin Groups (total n = 853) # events (# events x 100/ total subjects in group)
Angina pectoris	1 (0.1)	0
Angina unstable	0	1 (0.1)
Chest pain	2 (0.2)	1 (0.1)
Myocardial infarction	3 (0.4)	2 (0.2)
Sinus tachycardia	0	1 (0.1)
Supraventricular tachycardia	1 (0.1)	0
Vomiting	0	1 (0.1)
Hypothermia	1 (0.1)	0
Ankle fracture	2 (0.2)	0
Foot fracture	0	1 (0.1)
Joint sprain	0	1 (0.1)
Laceration	1 (0.1)	1 (0.1)
Patella fracture	0	1 (0.1)
Road traffic accident	1 (0.1)	1 (0.1)
Skin laceration	0	1 (0.1)
Hypoglycemia	23 (2.7)	35 (4.1)
Amnesia	0	2 (0.2)
Aphasia	0	1 (0.1)
Coma	0	1 (0.1)
Convulsion	2 (0.2)	7 (0.8)
Grand mal convulsion	1 (0.1)	0
Hypoglycemic coma	1 (0.1)	0
Loss of consciousness	7 (0.8)	12 (1.4)
Syncope	0	2 (0.2)
Confusional state	0	1 (0.1)
Mental status changes	0	2 (0.2)
Hyperhidrosis	0	2 (0.2)
Total event terms conceivably related to hypoglycemia	46 (5.4)	77 (9.0)

1 includes Studies 106, 107, 1022, 1026, 1027

Event terms potentially 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.

7.1.2.1.2 Serious Adverse Events in Type 2 Patients

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. In the group of all Phase 2 and Phase 3 studies SAEs occurred with approximately equal frequency

in inhaled insulin patients as among inhaled insulin patients in the controlled Phase 2/3 population.

Table 7.1.2.1.2.1 All-causality Serious Adverse Event Frequency in Type 2 Patients

	n	Subject-Months of Exposure (SME)	All-causality SAE Cases	All-Causality SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies, Inh Ins	1,277	12,186	140	11.5
Controlled Phase 2/3 Studies, SQ	488	4,868	63	12.9
Controlled Phase 2/3 Studies, OA	644	6,452	78	12.1
All Phase 2/3 Studies, Inh Ins	1,578	30,688	386	12.5

Source: Applicant's Tables 6.1.1.3, 6.1.2.3, 6.2.1.3, 6.2.2.3, 2.2.1.1, 2.2.1.2, ISS Appendix

Myocardial infarction, chest pain, angina and hypoglycemia were the most common SAE terms among Type 2 patients. The following table lists SAE terms occurring among Type 2 patients. Because study drug exposure duration was significantly greater among inhaled insulin patients than among comparator patients, event rates are compared using exposure duration.

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
Blood and lymphatic system disorders		1 (0.1)	1 (0.2)	0
	Anemia	1 (0.1)	1 (0.2)	0
Cardiac disorders		30 (2.5)	12 (2.5)	14 (2.2)
	Acute myocardial infarction	4 (0.3)	0	2 (0.3)
	Angina pectoris	2 (0.2)	1 (0.2)	4 (0.6)
	Angina unstable	4 (0.3)	1 (0.2)	1 (0.2)
	Arrhythmia	1 (0.1)	0	1 (0.2)
	Atrial fibrillation	0	3 (0.6)	0
	Atrial flutter	0	0	1 (0.2)
	Bradycardia	2 (0.2)	0	0
	Cardiac failure	1 (0.1)	0	0
	Cardiac failure acute	1 (0.1)	0	0
	Cardiac failure congestive	3 (0.2)	0	1 (0.2)
	Coronary artery disease	5 (0.4)	3 (0.6)	0
	Coronary artery occlusion	1 (0.1)	2 (0.4)	0
	Coronary artery stenosis	1 (0.1)	0	0
	Myocardial infarction	7 (0.6)	2 (0.4)	5 (0.8)
	Myocardial ischemia	1 (0.1)	1 (0.2)	0
	Palpitations	1 (0.1)	0	0
	Tachyarrhythmia	1 (0.1)	0	0
	Ventricular extrasystoles	1 (0.1)	0	0
	Ventricular fibrillation	1 (0.1)	0	0
	Ventricular tachycardia	1 (0.1)	0	0
Endocrine disorders		2 (0.2)	0	0
	Cushing's syndrome	1 (0.1)	0	0
	Hypothyroidism	1 (0.1)	0	0

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
Eye disorders		1 (0.1)	0	2 (0.3)
	Cataract	1 (0.1)	0	0
	Eye movement disorder	0	0	1 (0.2)
	Optic ischemic neuropathy	0	0	1 (0.2)
Gastrointestinal disorders		12 (1.0)	7 (1.4)	11 (1.7)
	Abdominal discomfort	0	0	1 (0.2)
	Abdominal hernia	0	0	1 (0.2)
	Abdominal pain	0	0	2 (0.3)
	Abdominal pain upper	1 (0.1)	1 (0.2)	1 (0.2)
	Abdominal strangulated hernia	0	1 (0.2)	0
	Ascites	0	0	1 (0.2)
	Duodenal ulcer	0	1 (0.2)	1 (0.2)
	Dyspnea	0	0	1 (0.2)
	Esophageal hemorrhage	1 (0.1)	0	0
	Esophageal spasm	1 (0.1)	0	1 (0.2)
	Esophagitis	0	1 (0.2)	0
	Esophagitis ulcerative	0	1 (0.2)	0
	Food poisoning	0	0	1 (0.2)
	Gastric ulcer	0	0	1 (0.2)
	Gastric volvulus	0	1 (0.2)	0
	Gastritis	0	1 (0.2)	0
	Gastrointestinal gangrene	1 (0.1)	0	0
	Gastrointestinal hemorrhage	2 (0.2)	0	0
	Inguinal hernia	3 (0.2)	1 (0.2)	0
	Inguinal hernia, obstructive	1 (0.1)	0	0
	Pancreatitis	2 (0.2)	1 (0.2)	0
	Pancreatitis acute	0	0	1 (0.2)
	Small intestinal obstruction	1 (0.1)	1 (0.2)	0
	Vomiting	0	2 (0.4)	1 (0.2)
General disorders and administration site conditions		8 (0.7)	5 (1.0)	6 (0.9)
	Asthenia	0	1 (0.2)	0
	Chest pain	6 (0.5)	2 (0.4)	4 (0.6)
	Ill-defined disorder	0	0	1 (0.2)
	Noncardiac chest pain	1 (0.1)	1 (0.2)	0
	Edema peripheral	1 (0.1)	0	0
	Pain exacerbated	0	1 (0.2)	0
Hepatobiliary disorders		3 (0.2)	1 (0.2)	4 (0.6)
	Bile duct obstruction	1 (0.1)	0	0
	Biliary colic	0	0	1 (0.2)
	Cholecystitis	0	0	1 (0.2)
	Cholecystitis acute	1 (0.1)	0	1 (0.2)
	Cholelithiasis	1 (0.1)	1 (0.2)	1 (0.2)
Immune system disorders		2 (0.2)	0	0
	Drug hypersensitivity	1 (0.1)	0	0
	Hypersensitivity	1 (0.1)	0	0
Infections and infestations		20 (1.6)	9 (1.8)	4 (0.6)
	Appendicitis	2 (0.2)	0	0
	Bronchitis	2 (0.2)	0	0
	Bronchitis acute	1 (0.1)	0	0

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
	Bronchopneumonia	1 (0.1)	0	0
	Cellulitis	4 (0.3)	3 (0.6)	0
	Diverticulitis	1 (0.1)	0	0
	Herpes zoster	1 (0.1)	0	0
	Infected insect bite	1 (0.1)	0	0
	Infected skin ulcer	0	1 (0.2)	0
	Osteomyelitis	2 (0.2)	1 (0.2)	0
	Peritonsillar abscess	1 (0.1)	0	0
	Pneumocystis carinii pneumonia	0	0	1 (0.2)
	Pneumonia	2 (0.2)	3 (0.6)	0
	Postoperative infection	0	1 (0.2)	0
	Sepsis	1 (0.1)	0	0
	Subcutaneous abscess	0	0	1 (0.2)
	Urinary tract infection	2 (0.2)	0	0
	Urosepsis	0	0	1 (0.2)
	Vulvar abscess	0	0	1 (0.2)
Injury, poisoning and procedural complications		8 (0.7)	4 (0.8)	4 (0.6)
	Accidental overdose	0	1 (0.2)	0
	Concussion	1 (0.1)	0	0
	Fall	1 (0.1)	0	0
	Foot fracture	1 (0.1)	0	0
	Hip fracture	1 (0.1)	1 (0.2)	0
	Multiple fractures	0	0	1 (0.2)
	Pelvic fracture	0	1 (0.2)	0
	Postoperative adhesion	2 (0.2)	0	0
	Rib fracture	0	2 (0.4)	1 (0.2)
	Road traffic accident	0	2 (0.4)	1 (0.2)
	Stitch abscess	0	0	1 (0.2)
	Tendon injury	1 (0.1)	0	0
	Upper limb fracture	1 (0.1)	0	0
	Wound	1 (0.1)	0	0
Investigations		7 (0.6)	14 (2.9)	4 (0.6)
	Blood glucose decreased	1 (0.1)	0	0
	Exercise electrocardiogram abnormal	1 (0.1)	0	0
	Gamma-glutamyl transferase increased	1 (0.1)	0	0
	Pulmonary function test decreased	0	0	1 (0.2)
Metabolism and nutrition disorders		7 (0.6)	14 (2.9)	4 (0.6)
	Diabetic foot	0	0	1 (0.2)
	Hyperglycemia	1 (0.1)	1 (0.2)	1 (0.2)
	Hyperkalemia	1 (0.1)	0	0
	Hypoglycemia	5 (0.4)	13 (2.7)	2 (0.3)
Musculoskeletal and connective tissue disorders		8 (0.7)	4 (0.8)	9 (1.4)
	Arthralgia	1 (0.1)	1 (0.2)	0
	Back pain	1 (0.1)	1 (0.2)	2 (0.3)
	Bunion	0	1 (0.2)	0
	Cataplexy	0	1 (0.2)	0
	Intervertebral disc	1 (0.1)	1 (0.2)	1 (0.2)

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
	protrusion			
	Localized osteoarthritis	1 (0.1)	0	1 (0.2)
	Musculoskeletal stiffness	1 (0.1)	0	0
	Myalgia	1 (0.1)	0	0
	Myositis	0	0	1 (0.2)
	Pain in extremity	1 (0.1)	0	0
	Periarthritis	1 (0.1)	0	0
	Polymyalgia rheumatica	0	0	2 (0.3)
	Rheumatoid arthritis	1 (0.1)	0	0
	Toe deformity	0	0	2 (0.3)
Neoplasms, benign, malignant and unspecified, including cysts and polyps		13 (1.1)	5 (1.0)	4 (0.6)
	Basal cell carcinoma	1 (0.1)	0	1 (0.2)
	Blast cell crisis	1 (0.1)	0	0
	Carcinoid tumor of the stomach	0	1 (0.2)	0
	Carcinoma	1 (0.1)	0	0
	Chronic myeloid leukemia	1 (0.1)	0	0
	Colon cancer	1 (0.1)	1 (0.2)	1 (0.2)
	Colon cancer metastatic	1 (0.1)	0	0
	Esophageal carcinoma	1 (0.1)	0	0
	Lung adenocarcinoma	1 (0.1)	0	0
	Lung neoplasm malignant	0	0	1 (0.2)
	Malignant neoplasm progression	1 (0.1)	0	0
	Metastases to kidney	1 (0.1)	0	0
	Metastases to liver	2 (0.2)	0	0
	Metastases to lung	1 (0.1)	0	0
	Metastases to pancreas	1 (0.1)	0	0
	Metastatic bronchial carcinoma	1 (0.1)	0	0
	Ovarian cancer	0	1 (0.2)	1 (0.2)
	Ovarian cancer metastatic	0	1 (0.2)	0
	Prostate cancer	2 (0.2)	1 (0.2)	0
	Renal neoplasm	1 (0.1)	0	0
	Small intestine carcinoma	1 (0.1)	0	0
Nervous system disorders		18 (1.5)	10 (2.1)	12 (1.9)
	Carotid artery stenosis	1 (0.1)	0	1 (0.2)
	Carpal tunnel syndrome	0	0	2 (0.3)
	Cerebrovascular accident	1 (0.1)	2 (0.4)	2 (0.3)
	Convulsion	1 (0.1)	1 (0.2)	0
	Facial palsy	2 (0.2)	0	0
	Facial paresis	0	0	1 (0.2)
	Global amnesia	1 (0.1)	0	0
	Hydrocephalus	0	0	2 (0.3)
	Ischemic stroke	1 (0.1)	0	0
	Loss of consciousness	3 (0.2)	6 (1.2)	1 (0.2)
	Lumbar radiculopathy	1 (0.1)	0	0
	Migraine	1 (0.1)	0	0
	Multiple sclerosis	0	1 (0.2)	0
	Nerve compression	1 (0.1)	0	0
	Neuritis	1 (0.1)	0	1 (0.2)
	Syncope	1 (0.1)	0	2 (0.3)

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
	Transient ischemic attack	3 (0.2)	1 (0.2)	0
Psychiatric disorders		2 (0.2)	7 (1.4)	1 (0.2)
	Anxiety	0	0	1 (0.2)
	Bipolar disorder	1 (0.1)	3 (0.6)	0
	Confusional state	0	1 (0.2)	0
	Depression	1 (0.1)	2 (0.4)	0
	Panic attack	0	1 (0.2)	0
Renal and urinary disorders		5 (0.4)	1 (0.2)	3
	Dysuria	1 (0.1)	0	0
	Nephrolithiasis	0	0	2 (0.3)
	Renal artery stenosis	0	0	1 (0.2)
	Renal colic	3 (0.2)	0	0
	Renal failure acute	1 (0.1)	1 (0.2)	0
Reproductive system and breast disorders		1 (0.1)	0	2 (0.3)
	Dysfunctional uterine bleeding	0	0	1 (0.2)
	Erectile dysfunction	1 (0.1)	0	0
	Uterine prolapse	0	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders		9 (0.7)	5 (1.0)	2 (0.3)
	Asthma	3 (0.2)	0	0
	Bronchospasm	1 (0.1)	0	0
	Cough	1 (0.1)	0	0
	Dyspnea	1 (0.1)	2 (0.4)	2 (0.3)
	Epistaxis	1 (0.1)	0	0
	Hypoxia	0	1 (0.2)	0
	Pneumothorax	1 (0.1)	1 (0.2)	0
	Respiratory distress	0	1 (0.2)	0
	Respiratory failure	1 (0.1)	0	0
	Vocal cord polyp	1 (0.1)	0	0
Skin and subcutaneous tissue disorders		3 (0.2)	1 (0.2)	0
	Diabetic bullosis	1 (0.1)	0	0
	Skin ulcer	2 (0.2)	1 (0.2)	0
Surgical and medical procedures		1 (0.1)	0	2 (0.3)
	Carpal tunnel decompression	0	0	1 (0.2)
	Removal of internal fixation	1 (0.1)	0	0
	Transurethral prostatectomy	0	0	1 (0.2)
Vascular disorders		6 (0.5)	1 (0.2)	3 (0.5)
	Arteriopathic disease	0	0	1 (0.2)
	Arteritis	0	0	1 (0.2)
	Deep vein thrombosis	0	1 (0.2)	0
	Hypertension	2 (0.2)	0	0
	Hypertensive crisis	1 (0.1)	0	0
	Intermittent claudication	0	0	1 (0.2)
	Orthostatic hypotension	1 (0.1)	0	0
Total preferred term events		184 (15.1)	96 (19.7)	92 (14.3)

Table 7.1.2.1.2.2 Serious Adverse Events Occurring in Type 2 Patients, Controlled Phase 2/3 Studies

MedDRA System Organ Class	MedDRA Preferred Event Term	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
Total number of patients with SAEs		128 (10.5 patients with SAEs per 1000 patient-months)	49 (10.1 patients with SAEs per 1000 patient-months)	62 (9.6 patients with SAEs per 1000 patient-months)

Source: Applicant's Table 6.1.1.3, ISS

The clinical reviewer grouped certain adverse event terms of interest for a total incidence rate. Term groupings of interest included:

- terms related to coronary artery disease, as macrovascular disease is the major cause of mortality among Type 2 diabetics
- hypoglycemia-related terms
- terms related to loss of consciousness and seizure, which may accompany severe hypoglycemia
- terms related to accidents and injuries, which also may accompany severe hypoglycemia
- immune system disorders, because of concern regarding insulin antibody formation in patients exposed to inhaled insulin

Pulmonary terms are also of interest; these will be discussed in Dr. Seymour's pulmonary review.

Table 7.1.2.1.2.3 Serious Adverse Event Terms of Special Interest in Type 2 Patients, Controlled Phase 2 and Phase 3 Studies

Event Term Grouping	Inh Ins total subject-months = 12,186 # events (# events per 1,000 subject-months)	SQ total subject-months = 4,868 # events (# events per 1,000 subject-months)	OA total subject-months = 6,452 # events (# events per 1,000 subject-months)
Coronary artery disease terms[1]	25 (2.1)	10 (2.0)	12 (1.9)
Immune system terms[2]	2 (0.2)	0	0
Accident and injury terms[3]	6 (0.5)	6 (1.2)	3 (0.5)
Hypoglycemia terms[4]	6 (0.5)	13 (2.7)	2 (0.3)
Loss of consciousness and seizure[5]	5 (0.4)	7 (1.4)	3 (0.5)

1 Includes acute myocardial infarction, angina pectoris, angina unstable, coronary artery disease, coronary artery occlusion, coronary artery stenosis, myocardial infarction, myocardial ischemia
2 Includes drug hypersensitivity, hypersensitivity
3 Includes concussion, fall, foot fracture, hip fracture, multiple fractures, pelvic fracture, rib fracture, road traffic accident, tendon injury, upper limb fracture
4 Includes hypoglycemia, blood glucose decreased
5 Includes convulsion, loss of consciousness, syncope

None of these groups of terms occurred with significantly higher frequency among inhaled insulin patients than among comparator patients; hypoglycemia adverse event terms occurred

numerically more frequently among SQ patients than among inhaled insulin patients or OA patients.

Neoplastic events did not occur with greater frequency in inhaled insulin group patients than in comparator groups. Two lung cancer events occurred in the inhaled insulin groups, and one occurred in the oral agent groups.

7.1.2.1.3 Serious Adverse Events in Pediatric Patients

A total of 331 patients <18 years of age were exposed to inhaled insulin in the development program. Of these, 153 participated in controlled Phase 2 and Phase 3 trials in Type 1 diabetes; there were also 147 control children who received subcutaneous insulin. At the request of DMEDP, the applicant provided comparative serious adverse event information for pediatric patients for controlled Phase 2/3 trials; the applicant chose a cut-off date of 1 Aug 03. The overall incidence of SAEs was somewhat higher for pediatric inhaled insulin patients than for pediatric SQ patients.

Table 7.1.2.1.3.1 All-causality Serious Adverse Event Frequency in Pediatric Patients (Cut-off Date 1 Aug 03)

	n	Subject-Months of Exposure (SME)	All-causality SAE Cases	All-causality SAEs per 100 pts	All-causality SAE Cases per 1,000 SME
Controlled Phase 2/3 Studies, Inh Ins	153	690	30	19.6	43.4
Controlled Phase 2/3 Studies, SQ	148	663	25	16.9	37.7

Source: Applicant's Table 4.1.1.1.1.1.2, p 2766, ISS

The following table summarizes the types of serious adverse events seen in children as of 1 Aug 03:

Table 7.1.2.1.3.2 Serious Adverse Events in Pediatric Patients, Controlled Phase 2/3 Trials, Cut-off Date 3 Aug 03

COSTART Organ System	COSTART Event Term	Inh Ins total n = 153 total SME = 690 # events (# events per 1,000 SME)	SQ total n = 148 total SME = 663 # events (# events per 1,000 SME)
Body as a whole		3 (4.3)	1 (1.5)
	Abdominal pain	1 (1.4)	0
	Accidental injury	0	1 (1.5)
	Flu syndrome	1 (1.4)	0
	Suicidal ideation	1 (1.4)	0
Digestive		1 (1.4)	2 (3.0)
	Gastritis	1 (1.4)	0
	Hematemesis	0	1 (1.5)
	Vomiting	0	1 (1.5)
Metabolic and nutritional		25 (36.2)	24 (36.2)
	Hypoglycemia	25 (36.2)	22 (33.2)
	Ketosis	1 (1.4)	2 (3.0)
Musculoskeletal		0	1 (1.5)
	Bone fracture accidental	0	1 (1.5)
Nervous		0	2 (3.0)

Table 7.1.2.1.3.2 Serious Adverse Events in Pediatric Patients, Controlled Phase 2/3 Trials, Cut-off Date 3 Aug 03

COSTART Organ System	COSTART Event Term	Inh Ins total n = 153 total SME = 690 # events (# events per 1,000 SME)	SQ total n = 148 total SME = 663 # events (# events per 1,000 SME)
	Convulsion	0	2 (3.0)
Respiratory		1 (1.4)	0
	Cough increased	1 (1.4)	0

Source: Applicant's Table 4.1.1.1.1.1.2, ISS

Hypoglycemia reported as a serious adverse event occurred somewhat more frequently among children taking inhaled insulin than among those 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. In the inhaled insulin groups, 20.3 severe hypoglycemic events were reported as severe events per 100 children, compared to 2.7 such events per 100 adult Type 1 patients. This also held true for the SQ groups, with 20.4 events/100 children and 4.1 events/100 adult Type 1 patients.

7.1.2.2 Serious Adverse Events by Patient

Due to the large size of the by-patient serious adverse event listings, the clinical reviewer placed them in Appendix 10.4. These listings include all serious adverse events by patient; separate tables are provided for Type 1, Type 2, and pediatric patients. Separate tables are also provided for comparator agents.

Hypoglycemic events warrant a few points. Because the applicant provided narratives only for serious adverse events that resulted in death or discontinuation, or were pulmonary in nature, or that were felt by the applicant to be treatment-related, many adverse events which are sometimes associated with hypoglycemia in clinical practice had no narrative or case report form to assist the clinical reviewer in determining whether these events (accidents, injuries, acute neurologic events and acute cardiac events) occurred in close proximity to a hypoglycemic event. The clinical reviewer asked Mr. Brian Green, Associate Director for Worldwide Regulatory Strategy for Pfizer, to clarify whether investigators routinely queried patients who had such events about whether the patient could have been hypoglycemic at the time of the event. On 19 Apr 05, Mr. Green replied that such events did not trigger an inquiry regarding possible hypoglycemia by the investigator at the study site. However, the applicant's Internal Safety and Risk Management Group (ISRMG) always sent a query regarding hypoglycemia (if the study site report did not include hypoglycemia information) back to the study site, for the following types of serious adverse events: loss of consciousness, syncope, seizure, accidents and injuries. For all other acute central nervous system and acute cardiac events, the ISRMG reviewed the study site's report of the event, and made a judgment about whether to query for possible hypoglycemia. It

appears that the applicant made specific attempts to identify all cases of accidents, injuries, acute neurologic events and acute cardiac events that could be related to hypoglycemia; however, event narratives were not always submitted for review in order for the clinical reviewer to confirm the absence of hypoglycemia as a contributing factor in these types of acute events. Further discussion of severe hypoglycemic events occurs later in the review, in Section 7.1.2.3.

The clinical reviewer examined all (>750) adverse event narratives that were provided. Adverse event terms used in the narratives were compared to adverse event terms used in the applicant's adverse event listings and datasets, in order to evaluate whether the applicant substituted a different name for the event, or whether the nature of the adverse event was worse than that implied by the term the applicant used. In general, the applicant's terms matched those of the narrative and those used by investigators in individual study reports very well. However, the clinical reviewer identified some serious hypoglycemic events that were accompanied by an accident or injury, in which the applicant did not include the accident or injury term in the adverse event listing. These are further discussed in Section 7.1.2.3. The by-patient serious adverse event listings in Appendix 10.4 note those SAEs for which narratives were provided, and whether the applicant's adverse event term was accurate and matched the term used by the investigator.

Dr. Seymour, DPADP clinical reviewer, will discuss pulmonary SAEs in her review. The clinical reviewer prepared a brief summary of each nonpulmonary SAE for which a narrative was provided. Because of the large number of these narratives, they appear in Appendix 10.5.

7.1.2.3 Summary of Findings from Review of Narratives

For those patients for whom serious adverse event narratives were available, the applicant's assigned event term generally matched that given by the investigator, and generally correctly indicated the nature of the event.

Information from these narratives was useful in further characterizing serious hypoglycemic adverse events.

Serious hypoglycemia is always a concern in the management of diabetes, and may be of particular concern with Exubera® given the marked variability in delivered dose with the device, the lack of dose proportionality, and the lack of dose equivalence. Each of these aspects of this drug-device combination could increase the risk of unpredictable and serious hypoglycemia; and in brittle patients, or patients of low body weight, could also increase the risk for diabetic ketoacidosis. Therefore, the clinical reviewer paid particular attention to both the number and the nature of serious hypoglycemic events. Numbers of serious hypoglycemic events overall have been discussed above in Section 7.1.2.1. Regarding the nature of serious hypoglycemic events, the clinical reviewer identified those events which had serious accompanying events, e.g. loss of consciousness, syncope, accidents and injuries. The incidence of these events is presented in the following table.

Table 7.1.2.3.1 Incidence of Serious Hypoglycemic Events Accompanied by Loss of Consciousness, Syncope, Accident or Injury, All Phase 2/3 Trials

Diabetes Type	Inh Ins # events (# events per 1,000 patient-months)	SQ # events (# events per 1,000 patient-months)	OA # events (# events per 1,000 patient-months)
Type 1 Adult (SME[1] inh = 16,571, SQ = 6,052)	29 (1.8)	19 (3.1)	n/a
Type 2 Adult (SME inh = 30,688, SQ = 4,868, OA = 6,453)	7 (0.2)	8 (1.6)	2 (0.3)
Type 1 Pediatric (SME inh = 6,242, SQ = 663)	12 (1.9)	2 (3.0)	n/a

1 Total subject-months of exposure

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.

Upon review of all serious hypoglycemic events narratives, the clinical reviewer noted some cases in which the event was reported only as hypoglycemia, and an accompanying accident or injury that appeared in the narrative was not mentioned in the listing. These cases are counted in the above table. The clinical reviewer was concerned that the serious adverse event listings provided by the applicant might not accurately reflect the nature of serious hypoglycemic events that occurred among inhaled insulin patients. Therefore, the clinical reviewer also reviewed all narratives provided by the applicant for serious hypoglycemic events for patients in comparator groups as well as inhaled insulin groups. The clinical reviewer then compared the hypoglycemic events noted in the applicant's serious adverse event listing (Table 6.3.1.1, Section 2.7.4) to the accompanying narratives. The following table includes patients whose narrative reported that an accident or injury accompanied their hypoglycemic event, but whose adverse event listing did not note the injury.

Table 7.1.2.3.2 Patients with Accidents or Injuries Accompanying a Serious Hypoglycemic Event, for Whom the Accident or Injury was Reported in a Narrative but not in the Applicant's Serious Adverse Event Listing[1]

Patient ID	Diabetes Type	Tx	Event Term in SAE Listing	Event from Narrative
1022-1006-0302	1	Inh Ins	Hypoglycemia	Also had accompanying motorcycle accident, clavicular rhegma
1022-1026-1489	1	Inh Ins	Hypoglycemia	Also had accompanying motor vehicle accident
1029-1093-3857	2	Inh Ins	Hypoglycemia, loss of consciousness	Also had accompanying fall and front teeth injury
106-5065-6947	1	SQ	Hypoglycemia, seizure, intentional overdose of study drug	Also had accompanying tongue biting and airway obstruction
1022-1037-2135	1	SQ	Hypoglycemia	Also had accompanying fall
1027-1016-0643	2	SQ	Hypoglycemia, loss of consciousness	Also had accompanying car accident
1029-1065-2794	2	SQ	Hypoglycemia, unconsciousness, seizure	Also had accompanying tongue laceration

1 Table 6.3.1.1, Section 2.7.4

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. It is possible that investigators did not consider the accident or injury as a serious event itself, and therefore did not include it. It is also possible that investigators considered the accident or injury as part of the hypoglycemic event, and therefore did not mention it separately.

Diabetic ketoacidosis is the leading cause of mortality among pediatric Type 1 diabetics (Dunger 2003, Edge 1999), and therefore is 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; cerebral edema accounts for 57-87% of DKA deaths in children (Edge 2001, Glaser 2001). 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). However, 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; 3.6 cases of DKA occurred per 1,000 SME. The total number of subject-months of pediatric exposure for both treatment groups in the total safety database was 6,242 patient-months (520.2 patient-years) for inhaled insulin and 663 patient-months (55.3 patient-years) for SQ. This gives comparative incidence rates of 0.04 cases of diabetic ketoacidosis per child-year for inhaled insulin patients, and 0.04 cases of DKA per child-year for SQ patients. The incidence of DKA in the overall pediatric development program does not appear to be higher for children receiving inhaled insulin than for children receiving SQ insulin. The reported incidence of DKA (after initial diagnosis) in the medical literature ranges from 1-10% per year (Dunger 2003). In Study 111, there were 483.4 child-years of exposure, and 17 patients had DKA, for an incidence of .04 cases per child-year. Although no concurrent control exists for this comparison to the medical literature, the incidence of DKA among children treated with inhaled insulin does not appear to exceed the expected incidence in the general pediatric Type 1 diabetic population.

7.1.2.4 Summary of Serious Adverse Event Findings

Among all patients in the study population, serious hypoglycemia was the most commonly reported serious adverse event. Among adult patients in general, serious hypoglycemia reported as a serious adverse event did not occur more frequently among inhaled insulin patients than among comparator patients. Hypoglycemia reported as a serious adverse event occurred somewhat more frequently among children taking inhaled insulin than among children taking SQ insulin. 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.

Pulmonary serious adverse events will be discussed in Dr. Seymour's pulmonary review. No other type of serious adverse event occurred with significantly greater frequency among inhaled insulin patients than among comparator patients. Explorations for event groupings of special interest also did not reveal an increased incidence among inhaled insulin patients.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The following tables summarize dropouts among Type 1, Type 2 and pediatric subjects:

Table 7.1.3.1.1: Summary of Dropouts among Adult Type 1 Patients, Controlled Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (n = 698) n (%)	SQ (n = 705) n (%)
Total Discontinuations	96 (13.8)	83 (11.8)
Adverse Event	22 (3.2)	6 (0.9)
Insufficient Clinical Response	10 (1.4)	3 (0.4)
Laboratory Abnormality	3 (0.4)	0
Patient Died	3 (0.4)	0
Did not Meet Entrance Criteria	0	2 (0.3)
Lost to Followup	8 (1.1)	15 (2.1)
Protocol Violation	5 (0.7)	5 (0.7)
Subject no Longer Willing to Participate in Study	29 (4.2)	30 (4.3)
Withdrawn Consent	8 (1.1)	13 (1.8)
Other	3 (0.4)	7 (1.0)
Source: Applicant's Table 7.1.1.1.2, Safety Summary pg 2365		

Table 7.1.3.1.2: Summary of Dropouts among Adult Type 1 Patients Receiving Inhaled Insulin in all Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (total n = 918) n (%)
Total Discontinuations	292 (31.8)
Adverse Event	35 (3.8)
Insufficient Clinical Response	32 (3.5)
Laboratory Abnormality	3 (0.3)
Patient Died	6 (0.7)
Lost to Followup	19 (2.1)
Protocol Violation	21 (2.3)
Subject No Longer Willing to Participate in Study	30 (3.3)
Withdrawn Consent	118 (12.9)
Withdrawn Due to Pregnancy	5 (0.5)
Source: Applicant's Table 7.2.1.1.2, Safety Summary pg 2521	

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

Specific adverse events leading to discontinuation are discussed in Section 7.1.3.2.

Table 7.1.3.1.3: Summary of Dropouts among Adult Type 2 Patients, Controlled Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (n = 1,277) n (%)	SQ (n = 488) n (%)	OA (n = 644) n (%)
Total Discontinuations	163 (12.8)	64 (13.1)	93 (14.4)
Adverse Event	46 (3.6)	9 (1.8)	21 (3.3)
Insufficient Clinical Response	8 (0.6)	3 (0.6)	10 (1.6)
Laboratory Abnormality	1 (0.1)	0	0
Patient Died	4 (0.3)	0	3 (0.5)
Did not Meet Entrance Criteria	1 (0.1)	0	4 (0.6)
Lost to Followup	8 (0.6)	11 (2.3)	7 (1.1)
Protocol Violation	14 (1.1)	10 (2.0)	9 (1.4)
Subject no Longer Willing to Participate in Study	23 (1.8)	24 (4.9)	0
Withdrawn Consent	35 (2.7)	4 (0.8)	25 (3.9)
Other	23 (1.8)	6 (1.2)	14 (2.2)

Source: Applicant's Table 7.1.1.2.0, Safety Summary pg 2366

Table 7.1.3.1.4: Summary of Dropouts among Adult Type 2 Patients Receiving Inhaled Insulin in all Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (total n = 1578) n (%)
Total Discontinuations	452 (28.6)
Adverse Event	109 (6.9)
Insufficient Clinical Response	15 (1.0)
Laboratory Abnormality	1 (0.1)
Patient Died	12 (0.8)
Lost to Followup	41 (2.6)
Protocol Violation	46 (2.9)
Subject No Longer Willing to Participate in Study	25 (1.6)
Withdrawn Consent	134 (8.5)

Source: Applicant's Table 7.2.1.2, Safety Summary pg 2522

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 agents 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.

Specific adverse events leading to discontinuation are discussed in Section 7.1.3.2.

Table 7.1.3.1.5: Summary of Dropouts among Pediatric Type 1 Patients, Controlled Phase 2 and Phase 3 Studies

Reason for Discontinuation	Inh Ins (n = 153) n (%)	SQ (n = 148) n (%)
Total Discontinuations	5 (3.3)	5 (3.4)
Adverse Event	0	0
Insufficient Clinical Response	1 (0.7)	1 (0.7)
Laboratory Abnormality	0	0
Patient Died	0	0
Did not Meet Entrance Criteria	0	0
Lost to Followup	0	1 (0.7)
Protocol Violation	1 (0.7)	1 (0.7)
Subject no Longer Willing to Participate in Study	0	0
Withdrawn Consent	3 (2.0)	2 (1.4)
Other	0	0

Source: Applicant's Table 7.1.2.1.0, Safety Summary pg 2368

The clinical reviewer was unable to locate the applicant's definition for "withdrawn consent" in the submitted NDA materials. The large number of patients for whom consent was withdrawn is of concern, because it raises the question of whether some of these patients actually dropped out for adverse events, tolerability issues, device use problems, or other noteworthy reasons. On 4 May 05, the clinical reviewer called Mr. Brian Green, Pfizer Regulatory Affairs, and asked him the following questions:

- What was the definition of "withdrawn consent"?
- What was the difference between the reasons "subject no longer willing to participate in study" and "withdrawn consent"?
- What were the reasons given by patients for withdrawal of consent?

On 10 Jun 05, Pfizer submitted responses to the above questions.

"'Withdrawn consent' was used to document a voluntary withdrawal on the part of the patient with no medical issue contributing to the discontinuation. Use of this reason would have required that the patient had expressed a desire to withdraw from the study as opposed to 'having' to withdraw from the study for other reasons (i.e. the subject moved, the subject had a scheduling conflict, etc).

The definitions of 'withdrawn consent' and 'patient no longer willing to participate in study' are the same. In early 2001, Pfizer decided to change the case report form (CRF) terminology of 'withdrawn consent' to 'subject no longer willing to participate in study'."

Pfizer stated that, for Studies 102, 103, 104, 106, 107, 108, 109, 110, 1001 and 1002, the CRF used the term "withdrawn consent", but had "no allowance for specification of reason". Pfizer provided reasons for "withdrawn consent" and "patient no longer willing to participate in study" for Studies 111, 1022, 1027, 1028, 1029 and 1030. Most of these reasons do not relate to adverse events, tolerability issues, or device problems. Some patients, however, had noteworthy reasons for withdrawal, i.e. it appears that they may actually have withdrawn for adverse events, lack of efficacy, or device concerns.

Table 7.1.3.1.6 Discontinuations for "Withdrew Consent", "No Longer Willing to Participate" and "Other" that May Actually Have Been Due to Adverse Events, Lack of Efficacy, or Device Concerns

Patient ID	Study	Tx Grp	Original Listed Category of Discontinuation	Reason for Withdrawal Given in Applicant's 10 Jun 05 Submission
106-5002-6848	111	Inh ins	Withdrew consent	patient felt blood sugars were erratic and hard to control
106-5021-6166	111	Inh ins	Withdrew consent	"pt wanted more consistent control preferred previous insulin regimen"
106-5040-6575	111	Inh ins	Withdrew consent	"felt he could get better glucose control on SQ regimen"
106-5044-6270	111	Inh ins	Withdrew consent	"didn't have enough control of diabetes on Exubera"
106-5044-6276	111	Inh ins	Withdrew consent	lack of efficacy
106-5047-6553	111	Inh ins	Withdrew consent	insufficient clinical response
106-5055-6133	111	Inh ins	Withdrew consent	"pt wants definitive tx"
106-5055-6621	111	Inh ins	Withdrew consent	"pt wanted definitive tx"
106-5059-6679	111	Inh ins	Withdrew consent	poor blood glucose control
106-5062-6209	111	Inh ins	Withdrew consent	"poor glycemic control and future protocol changes"
106-5064-6104	111	Inh ins	Withdrew consent	suboptimal blood glucose control
107-5005-7687	111	Inh ins	Withdrew consent	subject unhappy with HbA1c results
107-5007-7985	111	Inh ins	Withdrew consent	subject unhappy with efficacy of inhaled insulin
107-5010-7610	111	Inh ins	Withdrew consent	pt believed she had better glucose control on pump
107-5010-7615	111	Inh ins	Withdrew consent	pt feels she has inadequate control of dosing of inhaled insulin
107-5066-7742	111	Inh ins	Withdrew consent	insufficient clinical response
107-5066-7744	111	Inh ins	Withdrew consent	insufficient clinical response
107-5066-7745	111	Inh ins	Withdrew consent	poor blood sugar control
107-5088-7030	111	Inh ins	Withdrew consent	no longer interested, unhappy with diabetes control
107-5095-7485	111	Inh ins	Withdrew consent	poor control of blood sugars
107-5095-7487	111	Inh ins	Withdrew consent	poor glucose control
108-5055-8539	111	Inh ins	Withdrew consent	pt wants definitive tx
109-5020-0245	111	Inh ins	Withdrew consent	"did not feel receiving any benefit from study drug"
1022-1022-1255	1022	Inh ins	No longer willing to participate	subject's blood sugar control declined after randomization
1022-1037-2140	1022	Inh ins	No longer willing to participate	subject felt "it was just not working"
1022-1042-2437	1022	Inh ins	No longer willing to participate	pt feels she was under better blood sugar control prior to inhaled insulin treatment
1022-1046-2670	1022	Inh ins	No longer willing to participate	subject felt that Exubera inadequately controlled his sugars
1022-5155-3738	1022	Inh ins	No longer willing to participate	pt feels blood glucose levels were better on SQ insulin
1028-1001-0395	1028	Inh ins	No longer willing to participate	pt's blood sugar control was not acceptable, pt unhappy with the results
1028-1050-	1028	Inh ins	No longer willing to participate	subject felt glucose not controlled well enough

Table 7.1.3.1.6 Discontinuations for "Withdrew Consent", "No Longer Willing to Participate" and "Other" that May Actually Have Been Due to Adverse Events, Lack of Efficacy, or Device Concerns

Patient ID	Study	Tx Grp	Original Listed Category of Discontinuation	Reason for Withdrawal Given in Applicant's 10 Jun 05 Submission
4769				
1029-1029-0780	1029	Inh ins	No longer willing to participate	insufficient clinical response
1029-1079-3262	1029	Inh ins	No longer willing to participate	pt was not satisfied with blood glucose control
1029-1100-3320	1029	SQ	No longer willing to participate	"pt started himself back on oral antihyperglycemic agents due to elevated BGs"
1029-1115-5395	1029	SQ	No longer willing to participate	"Pt too stressed out over slightly elevated BG levels."
107-5010-7614	111	Inh ins	Withdrew consent	device large, cumbersome
107-5063-7419	111	Inh ins	Withdrew consent	device clumsy and conspicuous
107-5067-7759	111	Inh ins	Withdrew consent	inhaler too bulky to carry around while traveling
107-5098-7514	111	Inh ins	Withdrew consent	"device too big, blister mg's do not allow for fine adjustment"
107-5127-7219	111	Inh ins	Other	"patient finds inhaler an inconvenient size"
107-5127-7774	111	Inh ins	Other	"inconvenience of inhaler"
108-5060-8437	111	Inh ins	Withdrew consent	subject finds device too big
107-5083-7499	111	Inh ins	Withdrew consent	frequent hypoglycemic episodes
107-5102-7144	111	Inh ins	Withdrew consent	frequent hypoglycemic episodes and concern about elevated insulin antibodies
107-5127-7221	111	Inh ins	Other	"too many serious hypoglycemias (sic) caused by the study drug"
1001-0133-3332	1001	Inh ins	Other	hs and early a.m. low blood sugars
1022-1031-1789	1022	Inh ins	No longer willing to participate	"Subject was not 'comfortable' with inhaled insulin. He felt he was having more hypoglycemic events. In reality he was not, but he was just really uncomfortable so he withdrew."
1022-1038-2194	1022	Inh ins	No longer willing to participate	subject with middle of the night lows despite lowering Lantus
1022-1038-2195	1022	Inh ins	No longer willing to participate	"subject felt Exubera did not adequately bring down his high BG and having too many hypos"
1028-1048-4574	1028	Inh ins	No longer willing to participate	experienced hypoglycemic events and was unable to self-treat
1029-1047-2431	1029	Inh ins	No longer willing to participate	"hypoglycemic events- numbness to mouth, tongue and lips"
1029-1065-2791	1029	Inh ins	No longer willing to participate	recurrent hypoglycemic reactions
107-5066-7741	111	Inh ins	Other	PFT abnormalities
109-5052-0408	111	Inh ins	Other	worsening of PFTs
1002-0069-5134	1002	Inh Ins	Other	decrease in PFT results
1002-0127-5251	1002	OA	Other	DLco <75% predicted
1029-1048-2491	1029	Inh ins	Other	PFTs >15% decrease from baseline
1029-1111-4859	1029	Inh ins	Other	decline in FEV1
107-5102-7639	111	Inh ins	Withdrew consent	pt concerned about elevated insulin antibodies

Table 7.1.3.1.6 Discontinuations for "Withdrew Consent", "No Longer Willing to Participate" and "Other" that May Actually Have Been Due to Adverse Events, Lack of Efficacy, or Device Concerns

Patient ID	Study	Tx Grp	Original Listed Category of Discontinuation	Reason for Withdrawal Given in Applicant's 10 Jun 05 Submission
1026-1001-0034	1026	Inh ins	No longer willing to participate	psychological problems
1027-1028-1628	1027	Inh ins	No longer willing to participate	depression
1028-1024-2193	1028	Inh ins	No longer willing to participate	diarrhea
1028-1056-5367	1028	Inh ins	No longer willing to participate	not able to return for clinic visit due to broken leg
1029-1010-0366	1029	Inh ins	No longer willing to participate	"pt feels that he needs to recuperate after the Herpes infection and concentrate on getting better"
1029-1074-3141	1029	Inh ins	No longer willing to participate	"pt feels lousy and dizzy all the time"
1029-1059-2615	1029	SQ	No longer willing to participate	"pt no longer wants the obligation of continuing in the study and wants to focus on his last SAE"

These revised reasons for withdrawal have some impact on the profile of reasons for discontinuation from study.

Study 111 was an uncontrolled extension study, and thus had no control group for comparisons of rates. However, review of these revised reasons changes the following data for reasons for discontinuation for inhaled insulin patients in all Phase 2/3 trials:

Table 7.1.3.1.7 Comparison of Original and Revised Reasons for Discontinuation, All Phase 2/3 Studies, Inhaled Insulin Patients

Diabetes Type	Reason for Discontinuation	Original n (%)	Revised n (%)
1 (total n = 918)	Adverse Event	35 (3.8)	44 (4.8)
	Insufficient Clinical Response	32 (3.5)	58 (6.3)
	Device Concerns	n/a	6 (0.7)
2 (total n = 1578)	Adverse Event	109 (6.9)	119 (7.5)
	Insufficient Clinical Response	15 (1.0)	20 (1.3)
	Device Concerns	n/a	1 (0.1)

This revision appears to increase the percentage of Type 1 diabetics who withdrew for insufficient clinical response in the population of all Phase 2/3 trials. However, one cannot conclude on the basis of uncontrolled data that misrepresentation of reasons for discontinuation occurred.

The following table details the effect of the revisions on the reasons for discontinuation for controlled studies. Revised data for Study 1028 were not included, because diabetes type was not listed in the study report for the affected patients.

Table 7.1.3.1.8 Comparison of Original and Revised Reasons for Discontinuation, Controlled Phase 2/3 Studies

		Inh Ins Type 1 n = 698 Type 2 n = 1277		SQ Type 1 n = 705 Type 2 n = 488		OA Type 1 n = 0 Type 2 n = 644	
Diabetes Type	**Reason for Discontinuation**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**
1	Adverse Event	22 (3.2)	26 (3.7)	6 (0.9)	same	n/a	n/a
	Insufficient Clinical Response	10 (1.4)	15 (2.1)	3 (0.4)	same	n/a	n/a
2	Adverse Event	46 (3.6)	55 (4.3)	9 (1.8)	10 (2.0)	21 (3.3)	22 (3.4)
	Insufficient Clinical Response	8 (0.6)	10 (0.8)	3 (0.6)	5 (1.0)	10 (1.6)	same

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. Because revised discontinuation data were available for only a few of the controlled trials, the overall effect might be diluted. The following table compares the original and revised reasons for discontinuation for those trials for which revised data were available.

Table 7.1.3.1.9 Comparison of Original and Revised Reasons for Discontinuation, Controlled Phase 2/3 Studies for Which Revised Discontinuation Data Were Available[1]

		Inh Ins Type 1 n = 425 Type 2 n = 538		SQ Type 1 n = 430 Type 2 n = 314		OA Type 1 n = 0 Type 2 n = 201	
Diabetes Type	**Reason for Discontinuation**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**	**Original n (%)**	**Revised n (%)**
1	Adverse Event	9 (2.1)	13 (3.1)	3 (0.7)	same	n/a	n/a
	Insufficient Clinical Response	7 (1.6)	12 (2.8)	0	same	n/a	n/a
2	Adverse Event	24 (4.5)	33 (6.1)	4 (1.3)	5 (1.6)	7 (3.5)	8 (4.0)
	Insufficient Clinical Response	4 (0.7)	6 (1.1)	3 (1.0)	5 (1.6)	2 (1.0)	same

1 Includes Studies 1001, 1022, 1026, 1027 and 1029

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)

This disparity in rates of apparent misclassification of reasons for discontinuation cannot be completely explained, but raises a question of investigator reporting bias for these studies. These trials included about 60% of the Type 1 patients in the controlled Phase 2/3 population, and about 40% of Type 2 patients in controlled Phase 2/3 trials. Inability to obtain revised data for the remaining clinical trials leaves unanswered the question of whether this was a pervasive

problem. However, because many of the study centers participated in multiple trials, it is possible that misclassification also occurred in trials other than those for which revised reasons for discontinuation were available.

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.

Analysis of demographic data (age, gender and race) for permanent discontinuations revealed few differences by demography. Among Type 1 patients, older patients (ages 45-64 years) in inhaled insulin groups were more likely to discontinue study than younger patients (ages 18-44) in inhaled insulin groups. Older inhaled insulin group patients (ages 45-64) were more likely to discontinue study than SQ group patients in the same age range [37/190 (19.5%) vs 19/196 (9.7%)]. Among older Type 2 diabetics (ages 65-74), inhaled insulin group patients were somewhat more likely to discontinue study than comparator patients [inh ins 46/264 (17.4%), SQ 14/102 (13.7%), OA 15/122 (12.3%)]. Little difference existed between groups by gender. Few non-Caucasian subjects participated in the development program, and no clear differences emerged among discontinuation rates or reasons. Sources for demographic data for discontinuations included the applicant's Tables 7.1.2.1.0, 7.1.3.1, 7.1.4.1, 7.1.2.2.0, 7.1.3.2, and 7.1.4.2 in the safety summary.

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.

Specific information regarding temporary discontinuations among pediatric patients across the entire development program was not included in the NDA. In Study A2171009, a pediatric study involving 121 patients, 61 of whom were exposed to inhaled insulin, a single temporary

discontinuation occurred. This occurred in an inhaled insulin group child, and was due to an upper respiratory tract infection.

7.1.3.2 Adverse events associated with dropouts

The following tables summarize adverse events leading to dropout:

Table 7.1.3.2.1 Adverse Events Resulting in Discontinuation of Type 1 Diabetics in Controlled Phase 2 and Phase 3 Studies

		Inh Ins	SQ
Total n each tx grp		698	705
Total subject-months		5894	6052
Total n d/c due to AEs		20 (2.9%)	6 (0.9%)
Body System	**COSTART AE Term**	**Inh Ins n (%)**	**Inh Ins n (%)**
Body as a Whole		3 (0.4)	1 (0.1)
	Abdominal pain	1 (0.1)	0
	Accidental injury	0	1 (0.1)
	Asthenia	1 (0.1)	0
	Lab test abnormal	1 (0.1)	0
Cardiovascular		1 (0.1)	0
	Angina pectoris	1 (0.1)	0
Digestive		0	1 (0.1)
	Gastrointestinal carcinoma	0	1 (0.1)
Metabolic and Nutritional		2 (0.3)	1 (0.1)
	Diabetic coma	1 (0.1)	0
	Hypoglycemia	2 (0.3)	1 (0.1)
Musculoskeletal		0	2 (0.3)
	Bone fracture accidental	0	1 (0.1)
	Myalgia	0	1 (0.1)
Nervous		2 (0.3)	0
	Anxiety	1 (0.1)	0
	Neuropathy	1 (0.1)	0
Respiratory		11 (1.6)	0
	Asthma	1 (0.1)	0
	Cough increased	7 (1.0)	0
	Dyspnea	3 (0.4)	0
	Laryngitis	1 (0.1)	0
	Pharyngitis	2 (0.3)	0
	Respiratory disorder	2 (0.3)	0
	Respiratory tract infection	1 (0.1)	0
	Sinusitis	1 (0.1)	0
	Sputum increased	1 (0.1)	0
Special Senses		1 (0.1)	0
	Eye hemorrhage	1 (0.1)	0
Urogenital		1 (0.1)	0
	Breast carcinoma	1 (0.1)	0

Source: Applicant's Table 7.1.5.1, Safety Summary pg 2379

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).

When data are added from the revisions to the reasons for discontinuations submitted by the applicant on 10 Jun 05, information regarding adverse events leading to discontinuations among Type 1 patients in controlled Phase 2/3 trials changes somewhat. Three additional discontinuations due to hypoglycemia appear to have occurred in inhaled insulin patients, for a total of 5 cases (0.7 discontinuations due to hypoglycemia per 100 inhaled insulin patients). No additional cases of discontinuation due to hypoglycemia were found in SQ patients; one case had originally been reported (0.1 discontinuations due to hypoglycemia per 100 SQ patients).

Table 7.1.3.2.2 Adverse Events Resulting in Discontinuation of Type 2 Diabetics in Controlled Phase 2 and Phase 3 Studies

		Inh Ins	SQ	OA
Total n each tx grp		**1277**	**488**	**644**
Total subject-months		**12186**	**4868**	**6452**
Total n d/c due to AEs		**15**	**3**	**11**
Body System	**COSTART AE Term**	**Inh Ins n (%)**	**SQ n (%)**	**OA n (%)**
Body as a whole		8 (0.6)	1 (0.2)	5 (0.8)
	Abdominal pain	1 (0.1)	0	2 (0.3)
	Accidental injury	1 (0.1)	0	0
	Ascites	0	0	1 (0.2)
	Back pain	1 (0.1)	0	1 (0.2)
	Chest pain	1 (0.1)	0	1 (0.2)
	Flu syndrome	1 (0.1)	0	0
	Headache	3 (0.2)	0	1 (0.2)
	Motor vehicle accident	0	1 (0.2)	0
	Neoplasm	1 (0.1)	0	0
Cardiovascular		2 (0.2)	1 (0.2)	6 (0.9)
	Bradycardia	1 (0.1)	0	0
	Cerebrovascular accident	1 (0.1)	0	1 (0.2)
	Congestive heart failure	0	0	1 (0.2)
	Heart failure	1 (0.1)	0	0
	Myocardial infarct	1 (0.1)	0	3 (0.5)
	Myocardial ischemia	1 (0.1)	1 (0.2)	1 (0.2)
	Tachycardia	0	0	1 (0.2)
	Ventricular arrhythmia	1 (0.1)	0	0
Gastrointestinal		5 (0.4)	1 (0.2)	5 (0.8)
	Diarrhea	0	0	4 (0.6)
	Duodenal ulcer	0	0	1 (0.2)
	Dyspepsia	0	0	1 (0.2)
	Gastroenteritis	1 (0.1)	0	0
	Gastrointestinal carcinoma	0	1 (0.2)	0
	Gingivitis	1 (0.1)	0	0
	Glossitis	1 (0.1)	0	0
	Nausea	2 (0.2)	0	1 (0.2)
	Pancreatitis	1 (0.1)	0	0
	Stomach ulcer	0	0	1 (0.2)
Hemic and lymphatic		1 (0.1)	0	0
	Chronic myelocytic leukemia	1 (0.1)	0	0
Metabolic and nutritional		2 (0.2)	0	2 (0.3)

Table 7.1.3.2.2 Adverse Events Resulting in Discontinuation of Type 2 Diabetics in Controlled Phase 2 and Phase 3 Studies

		Inh Ins	SQ	OA
Total n each tx grp		**1277**	**488**	**644**
Total subject-months		**12186**	**4868**	**6452**
Total n d/c due to AEs		**15**	**3**	**11**
Body System	**COSTART AE Term**	**Inh Ins n (%)**	**SQ n (%)**	**OA n (%)**
	Hyperglycemia	1 (0.1)	0	0
	Peripheral edema	0	0	1 (0.2)
	SGPT increased	0	0	1 (0.2)
	Wt gain	1 (0.1)	0	0
Musculoskeletal		0	1 (0.2)	1 (0.2)
	Leg cramps	0	1 (0.2)	0
	Myalgia	0	0	1 (0.2)
Nervous		3 (0.2)	0	0
	Amnesia	1 (0.1)	0	0
	Anxiety	1 (0.1)	0	0
	Dizziness	1 (0.1)	0	0
Respiratory		28 (2.2)	0	2 (0.3)
	Asthma	7 (0.5)	0	0
	Bronchitis	3 (0.2)	0	0
	Carcinoma of lung	1 (0.1)	0	1 (0.2)
	Cough increased	13 (1.0)	0	0
	Dyspnea	5 (0.4)	0	1 (0.2)
	Pharyngitis	1 (0.1)	0	0
	Respiratory disorder	2 (0.2)	0	0
	Respiratory tract infection	3 (0.2)	0	0
	Sputum increased	1 (0.1)	0	0
Skin and appendages		1 (0.1)	0	1 (0.2)
	Sweating	1 (0.1)	0	1 (0.2)
Special senses		1 (0.1)	0	1 (0.2)
	Abnormal vision	0	0	1 (0.2)
	Retinal disorder	1 (0.1)	0	0
Urogenital		2 (0.2)	1 (0.2)	2 (0.3)
	Acute kidney failure	1 (0.1)	0	0
	Kidney function abnormal	0	0	2 (0.3)
	Prostatic carcinoma	1 (0.1)	1 (0.3)	0

Source: Applicant's Table 7.1.5.2, Safety Summary pg 2381

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 category of adverse events leading to discontinuation, with a total of 42 (3.9%) of inhaled insulin group patients discontinuing due to respiratory AEs (Source Applicant's Table 7.2.2.2, safety summary pg 2527). 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.

When data are added from the revisions to the reasons for discontinuations submitted by the applicant on 10 Jun 05, information regarding adverse events leading to discontinuations among Type 2 patients in controlled Phase 2/3 trials changes somewhat. Three discontinuations due to hypoglycemia, and three discontinuations due to abnormal PFTs, appear to have occurred in inhaled insulin patients, compared to zero in each of the comparator groups.

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. 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, as illustrated in the following table:

Table 7.1.3.2.3 Neoplastic Adverse Events Leading to Discontinuation, All Phase 2 and Phase 3 Trials in Type 2 Diabetics

	Inh Ins	SQ	OA
Total Subject-years	**1016**	**406**	**538**
COSTART Event Term	**# events (# events/ 100 subject-yrs)**	**# events (# events/ 100 subject-yrs)**	**# events (# events/ 100 subject-yrs)**
Carcinoma	1 (0.1)	0	0
Lymphoma malignant	1 (0.1)	0	0
Neoplasm	1 (0.1)	0	0
Gastrointestinal carcinoma	1 (0.1)	1 (0.2)	0
Chronic myelogenous leukemia	1 (0.1)	0	0
Carcinoma lung	3 (0.3)	0	1 (0.2)
Prostate carcinoma	1 (0.1)	1 (0.1)	0
Renal carcinoma	1 (0.1)	0	0
Total neoplastic events leading to discontinuation	10 (1.0)	2 (0.5)	1 (0.2)

Source: Applicant's Tables 7.2.2.2 and 7.1.5.2, safety summary

Insulin is a growth factor, and concern has been expressed regarding the potential for promotion of tumor formation or growth. However, this is a small difference in discontinuations due to neoplastic events, and neoplastic events (whether reported as leading to discontinuation or not) did not occur with greater frequency among inhaled insulin group patients.

In summary, permanent discontinuations from controlled Phase 2 and Phase 3 studies were slightly more common for adult Type 1 patients in inhaled insulin groups than among Type 1 patients in SQ groups. Permanent discontinuation rates were comparable for Type 2 patients between inhaled insulin, SQ insulin, and oral agent groups. Large numbers of patients withdrew consent during the uncontrolled portions of Phase 2 and Phase 3 trials for both Type 1 and Type 2 diabetics. Reasons for withdrawal of consent were not included in the original NDA submission. Upon request, the applicant provided a separate submission containing the actual wording for the reasons for discontinuation for trials which included about 60% of Type 1 patients and 40% of Type 2 patients in the Phase 2/3 controlled trial population. Review of these revised reasons for discontinuation revealed that some of those patients that were listed as having

discontinued study due to "withdrawn consent", "patient no longer willing to participate", or "other", actually withdrew due to adverse events, lack of efficacy, or device concerns. This apparent misclassification of reasons for discontinuation was more common among inhaled insulin group patients than among comparator group patients. The reason for this difference between groups is unclear, but it raises a question of investigator reporting bias favoring inhaled insulin.

The most common category of adverse event leading to discontinuation among inhaled insulin group patients (both Type 1 and Type 2) was respiratory; withdrawals due to respiratory adverse events were rare among comparator group patients. The most common single adverse event leading to permanent discontinuation was cough; this reason for discontinuation occurred exclusively among inhaled insulin group patients. Permanent discontinuations due to neoplastic adverse events occurred slightly (not statistically significantly) more frequently on a person-time basis among Type 2 inhaled insulin group patients than among comparator group patients in the set of all Phase 2 and Phase 3 studies. Addition of adverse event data from the applicant's 10 Jun 05 submission regarding revised reasons for discontinuation led to a higher percentage of discontinuations for hypoglycemia among inhaled insulin patients compared to SQ patients (both Type 1 and Type 2). Temporary discontinuations for adverse events were more common among inhaled insulin patients than among SQ group patients for both Type 1 and Type 2 patients, and the most common category of adverse events leading to temporary discontinuation was respiratory.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Hypoglycemic Events Identified by Specified Definitions

The review includes three general types of severe hypoglycemic events; those that were reported by investigators as serious adverse events per se, and those that were identified by either of two specific definitions.

Within most *individual studies*, there was a protocol definition of severe hypoglycemia; in order for the event to be classified as severe, the event had to meet all three of the following criteria:

- patient unable to treat themself
- patient exhibited at least one of the following- memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness
- measured BG $\leq$ 49 mg/dL; or if no BG measured, clinical manifestations reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose

Severe hypoglycemia defined in this way was evaluated as a secondary outcome variable in the major trials.

For purposes of the *overall safety review*, severe hypoglycemic events were defined as those in which the subject had a measured blood glucose of $\leq$ 36 mg/dL and/or required assistance. The specified blood glucose level was requested by FDA.

The frequency of these specifically defined events may differ from the frequency of hypoglycemic events that were reported as serious adverse events; investigators may not have always followed the same definition for adverse event reporting as was used for the secondary outcome variable hypoglycemia definition. This section deals with specifically defined hypoglycemia. Hypoglycemic events that were reported as adverse events or serious adverse events are discussed in Sections 7.1.2 and 7.1.5.

7.1.3.3.1.1 Specifically-defined Hypoglycemic Events among Adult Type 1 Patients

Among all severe hypoglycemic events (using the overall safety definition of hypoglycemia) in Type 1 patients, 94% met the criterion of blood glucose ≤ 36 mg/dL. The occurrence of these events is summarized in the following tables.

Table 7.1.3.3.1.1.1 Severe[1] Hypoglycemic Event Rates, Adult Type 1 Patients, Phase 2 and Phase 3 Trials[2]

	Inhaled Insulin Groups	SQ Groups
Total number patients in group	691	686
Total number subject-months for group	4931.1	5102.3
Number and percent of patients with at least one severe hypoglycemic event	547 (79.2%)	533 (77.7%)
Total number of severe hypoglycemic events in group	5134	5515
Event rate (number of events per subject-month)	1.041	1.081
Risk ratio (95% CI)	0.95 (0.91-0.98)	

1 includes Studies 102, 106, 107, 1022IA, 1026, 1027
2 defined as blood glucose ≤ 36 mg/dL or requiring assistance
Source: Applicant's Table 17, Section 2.7.3.3.2.1.6, pg 35

For adult Type 1 patients overall, inhaled insulin was not associated with a higher rate of severe hypoglycemia (using the overall safety definition) than the rate seen with SQ insulin. However, in Study 107, the "intensive control" study in Type 1 diabetics, the applicant reported that severe hypoglycemic events (using the individual study definition) 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 can be 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 had a higher rate of severe hypoglycemic events.

Table 7.1.3.3.1.1.2 Severe[1] Hypoglycemic Event Rates, ITT[2] Population, Study 107

	Inh Ins	SQ Only
Total number of patients	162	162
Total number (and percentage) of patients with any severe hypoglycemic event	26 (16.0)	22 (13.6)
Total number of severe hypoglycemic events	59	29
Total patient-months	905.4	895.5
Event rate (# events/100 patient-months)	6.5	3.2

Treatment comparison, inhaled/subcutaneous: Risk Ratio 2.02 (95% CI limits 1.30, 3.15)

1 In order to be classified as severe, event had to meet all three of the following criteria:
- **patient unable to treat themselves**
- **patient exhibited at least one of the following- memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness**
- **measured BG ≤ 49 mg/dL; or if no BG measured, clinical manifestations reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose**

2 ITT population included both adult and adolescent patients
Source: Applicant's Table 5.4.2.1, Study 107 report

It should also be noted that Study 107 excluded patients who had had two or more severe hypoglycemic episodes within the six months prior to study entry. Thus, the study did not include patients with a known predisposition to frequent severe hypoglycemia.

However, it should also be noted that the FDA Biostatistics reviewer has called into question the statistical model used by Pfizer for comparison of hypoglycemic event rates. Reanalysis is ongoing as of 15 Sep 05, but it appears that a more appropriate model may show that severe hypoglycemic event rates did not actually differ between treatment groups in Study 107.

The following table breaks down severe hypoglycemic event data by which criterion was met, for the overall controlled Phase 2/3 adult Type 1 patient population. This table uses the overall safety review definition of hypoglycemia.

Table 7.1.3.3.1.1.3 Breakdown of Severe Hypoglycemic Event Data for Type 1 Adult Patients by Which Criterion for Severe Hypoglycemia was Met

	Inhaled Insulin Groups		SQ Groups	
Definition of Hypoglycemic Event	**n (total # events = 5134)**	**% of Events Meeting this Criterion**	**n (total # events = 5515)**	**% of Events Meeting this Criterion**
Blood glucose ≤ 36 mg/dL	4836	94.2	5185	94.0
Required assistance	206	4.0	192	3.5
Blood glucose ≤ 36 mg/dL and required assistance	92	1.8	138	2.5

Source: Applicant's Table 2.5.15, Section 2.7.3, pg 261
Includes Studies 102, 106, 107, 1022, 1026, 1027

For the overall controlled Phase 2/3 Type 1 adult patient population, there was little difference between groups for the percentage of patients who met one or the other criterion for severe hypoglycemia.

The frequency distribution of severe hypoglycemic events (overall safety review definition) among adult Type 1 diabetics was also similar between groups overall. Because there was some variability among trials for the frequency distributions, each trial's data are listed separately.

Table 7.1.3.3.1.1.4 Frequency Distribution of Severe[1] Hypoglycemic Events Per Patient, Adult Type 1 Patients

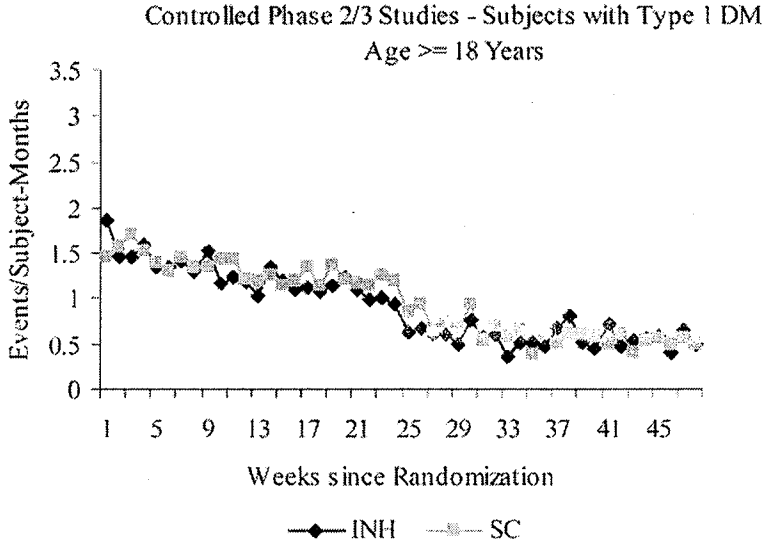
			% of Patients with Specified Number of Events				
Study	**n**	**Range of Number of Severe Hypoglycemic Events**	**0**	**≤ 5**	**≤ 10**	**≤ 20**	**≤ 30**
All adult Type 1 patients							
Overall Inh ins	691	0-75	20.8	59.8	76.8	90.5	95.9
Overall SQ	686	0-78	22.3	60.4	74.1	87.5	93.9
Study 102							
Inh ins	35	0-11	68.6	97.2	97.2	100.0	100.0
SQ	36	0-17	69.4	94.5	94.5	100.0	100.0
Study 106							
Inh ins	136	0-69	13.2	49.3	68.4	85.3	91.8
SQ	132	0-53	12.1	47.6	68.7	83.9	92.3
Study 107							
Inh ins	103	0-49	11.7	45.7	67.0	87.4	95.1
SQ	103	0-78	8.7	39.8	55.4	77.7	88.4
Study 1022IA							
Inh ins	288	0-75	18.8	58.0	76.8	89.6	95.7
SQ	286	0-69	18.9	61.5	73.6	87.0	94.1
Study 1026							
Inh ins	23	0-37	13.0	34.6	56.2	86.5	95.1
SQ	21	0-51	14.3	47.7	62.0	85.9	90.7
Study 1027							
Inh ins	106	0-17	31.1	84.8	94.3	100.0	100.0
SQ	108	0-32	42.6	83.3	94.5	98.2	99.1

1 Defined as blood glucose ≤ 36 mg/dL, or requiring assistance
Source: Applicant's Table 18, Section 2.7.3.3.2.1.6, pg 36

The number of patients who had either high numbers of severe hypoglycemic events or low numbers of severe hypoglycemic events did not differ between groups.

In both the inhaled insulin and SQ groups, overall hypoglycemia 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 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; please see the serious hypoglycemic adverse event summaries in Appendix 10.5. The occurrence of severe hypoglycemic adverse events cannot be entirely attributed to an initial learning period for inhaled insulin.

Figure 7.1.3.3.1.1.1 Hypoglycemia[1] Event Rates over Time, Adult Type 1 Subjects



Source: Applicant's Figure 2, Section 2.7.3.3.2.1.6, pg 38
1 Defined as BG ≤ 36 mg/dL, or pt required assistance

The applicant summarized time of onset of hypoglycemia events by hour of the day (e.g. 1-2 am, 5-6 pm). Because blood glucose measurements were done before meals (ac) and at bedtime (hs), one would expect higher numbers of events at these times. Inhaled insulin group patients tended to have higher hypoglycemic event rates than SQ group patients in the early morning, while the converse was true for midday. This pattern was true for the overall pattern in Phase 2 and Phase 3 trials, and held true across most studies, as illustrated in the following figures:

APPEARS THIS WAY ON ORIGINAL

Figure 7.1.3.3.1.1.2 Hypoglycemic Event[1] Rates, Onset by Time of Day, Adult Type 1 Patients, Phase 2 and Phase 3 Studies

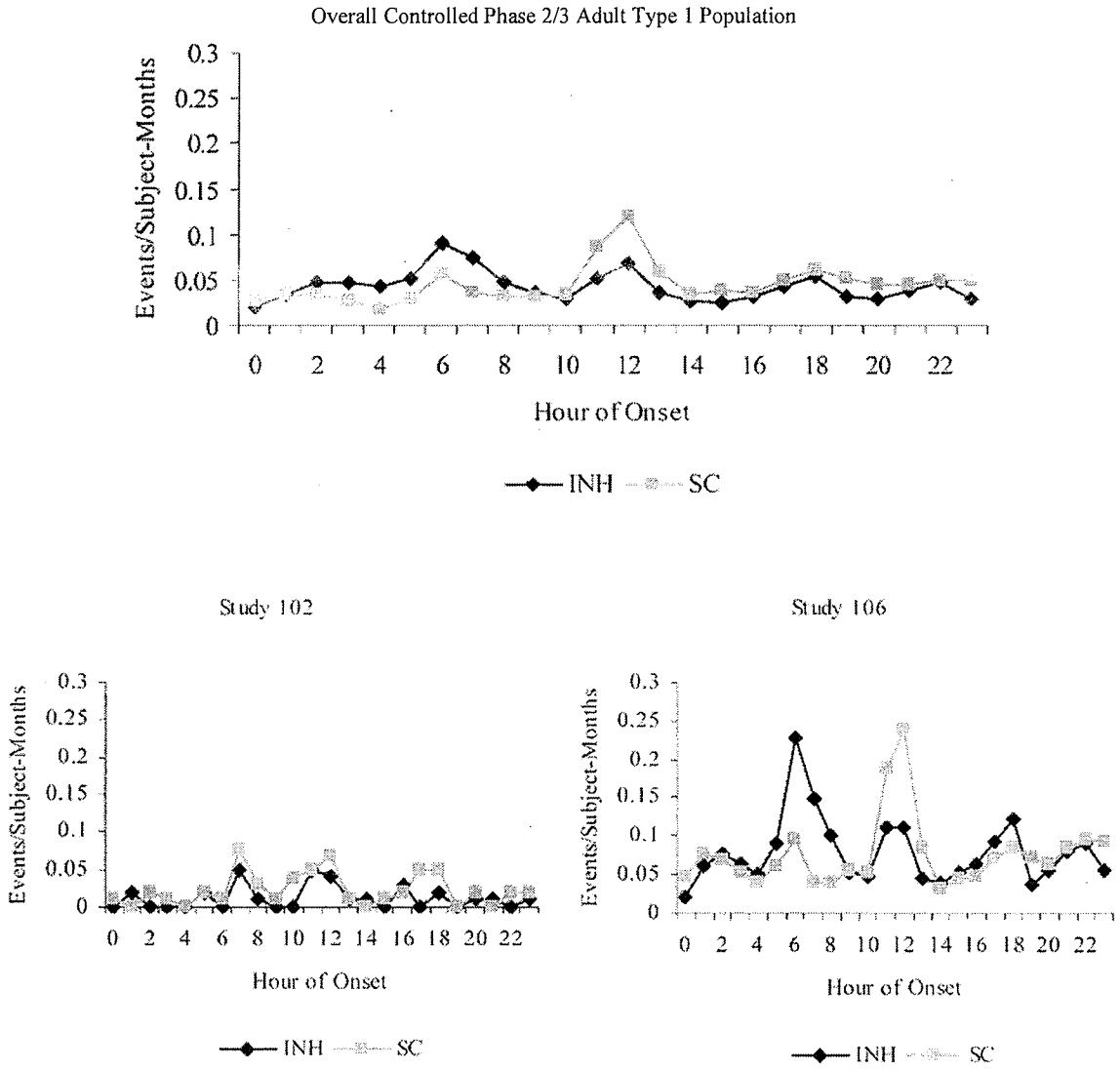
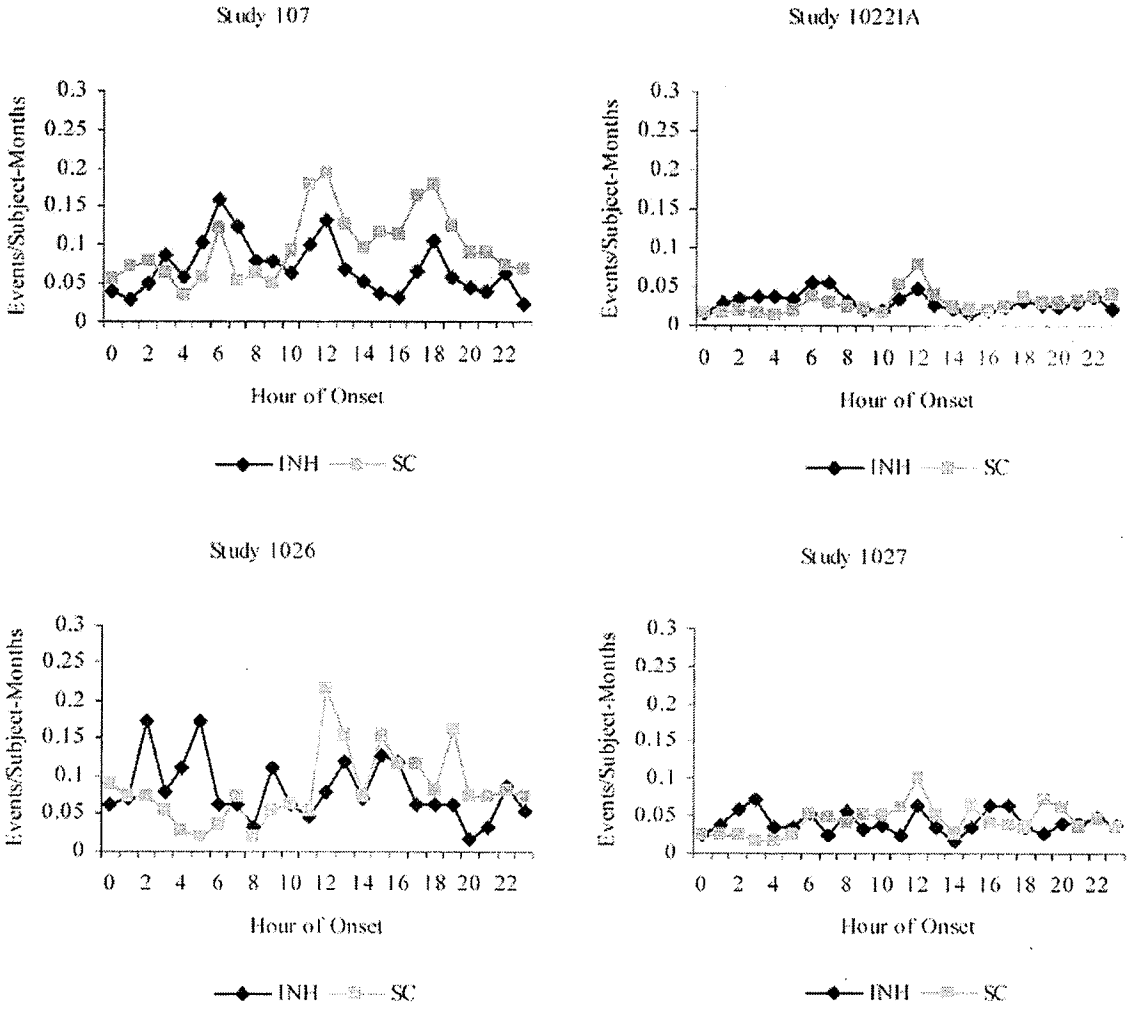


Figure 7.1.3.3.1.1.2 (cont.)



Source: Applicant's Figure 10, pg 82, Efficacy Summary
1 Defined as BG ≤ 36 mg/dL, or pt required assistance

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 short-acting 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 (email from Mr. Brian Green of Pfizer, 16 Jun 05). In this study, hypoglycemia was more common at 0200 for inhaled insulin group patients than for SQ patients. This could be an inhaled insulin effect for those patients who received inhaled insulin with a bedtime snack, or a peaking effect of an evening longacting insulin. 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; see Table 8.1.3).

In summary, rates of serious hypoglycemic events did not differ between inhaled insulin and SQ insulin groups for the controlled Phase 2/3 adult Type 1 diabetic population. However, in Study 107, the intensive control study, inhaled insulin group patients were more likely (by the applicant's analysis) to have protocol-defined severe hypoglycemia than were SQ group patients. The FDA Biostatistics reviewer questions the applicant's model used in this analysis, however, and it is possible that no difference existed between groups. In the overall controlled Phase 2/3 adult Type 1 population, hypoglycemia was more likely to occur prebreakfast for inhaled insulin patients than for SQ patients; the converse was true for prelunch hypoglycemia, which was more likely to occur in SQ patients. In Study 1026, the only study with routine measurement of 0200 blood sugars, hypoglycemia at 0200 was more likely to occur among inhaled insulin group patients than among SQ group patients. Hypoglycemia reported as a serious adverse event (for inhaled insulin patients) was more likely to occur in the early morning hours than at other times of the day.

7.1.3.3.1.2 Specifically-defined Hypoglycemic Events Among Adult Type 2 Patients

Severe hypoglycemic events were less common among patients with Type 2 diabetes compared to patients with Type 1 diabetes. The same overall safety criteria for severe hypoglycemic events were used, namely a blood glucose of ≤ 36 mg/dL or an event requiring assistance. As with Type 1 diabetes, the majority of hypoglycemic events met the former criterion. However, comparator patients who were not using insulin at baseline (Studies 104, 109, 110, 1001, 1002) were less likely to meet the blood glucose criterion than comparator patients who were using insulin at baseline (Studies 103, 108, 1029) (93% vs 69%).

The following table presents data for severe hypoglycemic (overall safety definition) event rates for adult Type 2 patients. Because several different comparators were used, individual study data for event rates are also presented.

Table 7.1.3.3.1.2.1 Severe Hypoglycemic Events (Defined as Blood Glucose ≤ 36 mg/dL, or Patient Requiring Assistance), Adult Type 2 Patients, Full ITT Population[1]

Study	Treatment Group	Total # Patients in Treatment Group	N (% with Severe Hypoglycemic Event)	Total Events	Total Subject-months	Events per Subject-month	Risk Ratio (95% CI)
All Patients who Were Using Insulin at Study Entry	Inh ins	487	132 (27.1%)	353	4139.0	0.085	0.62 (0.55-0.71)
	SQ	480	123 (25.6)	576	4265.1	0.135	
Study 103[2]	Inh ins	28	3 (10.7)	5	76.1	0.066	1.61 (0.38-6.72)
	SQ	27	2 (7.4)	3	76.9	0.039	
Study 108[2]	Inh ins	146	34 (23.3)	80	793	0.101	0.80 (0.60-1.07)
	SQ	149	28 (18.8)	104	824	0.126	
Study 1029[2]	Inh ins	313	95 (30.4)	268	3569.9	0.082	0.58 (0.50-0.67)
	SQ	304	93 (30.6)	469	3364.2	0.139	

Table 7.1.3.3.1.2.1 Severe Hypoglycemic Events (Defined as Blood Glucose ≤ 36 mg/dL, or Patient Requiring Assistance), Adult Type 2 Patients, Full ITT Population[1]

Study	Treatment Group	Total # Patients in Treatment Group	N (% with Severe Hypoglycemic Event)	Total Events	Total Subject-months	Events per Subject-month	Risk Ratio (95% CI)
All Patients who Were not Using Insulin at Study Entry	Inh ins	757	77 (10.2)	135	3320.1	0.041	3.48 (2.37-5.12)
	Comparator	617	19 (3.1)	32	2803.8	0.011	
Study 104[3]	Inh ins	32	2 (6.3)	2	88.5	0.023	NE[4]
	OA[5]	36	0	0	99.4	0	
Study 109[3]	Inh ins	102	17 (16.7)	23	283.3	0.081	NE
	Inh ins + OA	100	21 (21.0)	48	284.3	0.169	
	OA	96	0	0	266.3	0	
Study 110[3]	Inh ins	75	9 (12.0)	15	214.6	0.07	NE
	Rosi[6]	67	0	0	186.9	0	
Study 1001-L[7]	Inh ins + SU	101	4 (4.0)	6	555.5	0.011	1.83 (0.46-7.32)
	Met[8] + SU	93	1 (1.1)	3	505.6	0.006	
Study 1001-H[7]	Inh ins + SU	113	11 (9.7)	14	630.7	0.022	2.09 (0.80-5.44)
	Met + SU	103	6 (5.8)	6	554.5	0.011	
Study 1002-L[7]	Inh ins + Met	125	7 (5.6)	16	683.7	0.023	1.01 (0.50-2.05)
	Gli[9] + Met	119	9 (7.6)	15	634	0.024	
Study 1002-H[7]	Inh ins + Met	109	6 (5.5)	11	579.7	0.019	1.33 (0.53-3.30)
	Gli + Met	103	3 (2.9)	8	557.3	0.014	

1 Includes Studies 103, 104, 108, 109, 110, 1001, 1002, 1029
2 Patients were insulin-using at Study Entry
3 Patients were not using insulin at Study Entry
4 Not estimable
5 Oral agent
6 Rosiglitazone
7 In Studies 1001 and 1002, patients were stratified on the basis of baseline HbA1c; L = 8-9.5; H ≥ 9.5-12. Data are for first 6 months of study for both studies.
8 Metformin
9 Glibenclamide
Source: Applicant's Table 27, Section 2.7.3.3.3.1.6, pg 53

Inhaled insulin group patients were not more likely to experience severe hypoglycemic events than 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. However, 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.

As with Type 1 diabetes, the vast majority of severe hypoglycemic events among Type 2 diabetics met the criterion of blood glucose ≤ 36 mg/dL, with relatively few patients requiring assistance during a hypoglycemic episode. There was little difference between treatment groups.

Table 7.1.3.3.1.2.2 Breakdown of Severe Hypoglycemic Event Data for Type 2 Diabetic Patients by Which Criterion for Severe Hypoglycemia was Met

	Inh Ins		SQ	
Definition of Hypoglycemic Event	**n (total # events = 353)**	**% of Events Meeting this Criterion**	**n (total # events = 576)**	
Blood glucose ≤ 36 mg/dL	322	91.2	534	92.7
Required assistance	22	6.2	25	4.3
Glucose ≤ 36 mg/dL and required assistance	9	2.5	17	3.0

Source: Applicant's Table 2.5.16, Section 2.7.1
Includes Studies 103, 108 and 1029

Table 7.1.3.3.1.2.3 Frequency Distribution of Severe[1] Hypoglycemic Events per Patient, Type 2 Patients

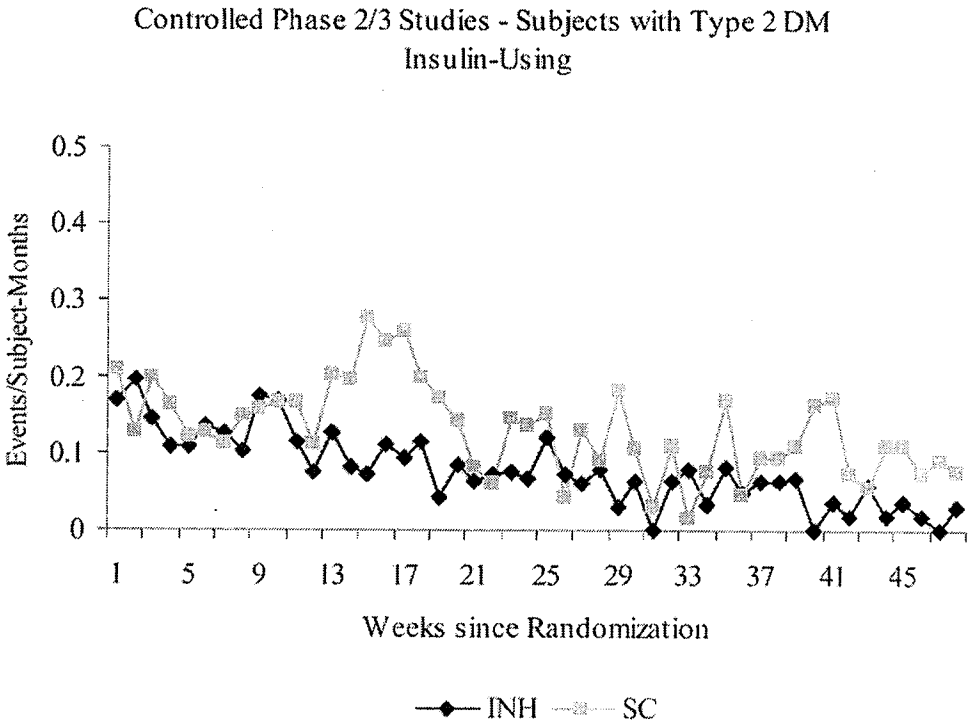
				% of Patients with Specified Number of Events			
Study	**Treatment Group**	**Total # Patients in Treatment Group**	**Range of Number of Severe Hypoglycemic Events**	**0**	**≤5**	**≤10**	**≤20**
All Patients who Were Using Insulin at Study Entry	**Inh ins**	487	0-17	72.9	96.2	99.0	99.8
	SQ	480	0-47	74.4	93.8	96.2	99.4
Study 103[2]	**Inh ins**	28	0-3	89.3	100.0	n/a	n/a
	SQ	27	0-2	92.6	100.0	n/a	n/a
Study 108[2]	**Inh ins**	146	0-10	76.7	97.3	100.0	n/a
	SQ	149	0-15	81.2	96.1	97.5	100.0
Study 1029[2]	**Inh ins**	313	0-17	69.6	95.5	98.6	100.0
	SQ	304	0-47	69.4	91.9	95.2	99.3
All Patients who Were not Using Insulin at Study Entry	**Inh ins**	757	0-15	89.8	99.6	99.7	100.0
	Comparator	617	0-6	96.9	99.8	100.0	n/a
Study 104[3]	**Inh ins**	32	0-1	93.8	100.0	n/a	n/a
	OA[5]	36	0	100.0	n/a	n/a	n/a
Study 109[3]	**Inh ins**	102	0-3	83.3	100.0	n/a	n/a
	Inh ins + OA	100	0-15	79.0	98.0	99.0	100.0
	OA	96	0	100.0	n/a	n/a	n/a
Study 110[3]	**Inh ins**	75	0-3	88.0	100.0	n/a	n/a
	Rosi[6]	67	0	100.0	n/a	n/a	n/a
Study 1001-L[7]	**Inh ins + SU**	101	0-3	96.0	100.0	n/a	n/a
	Met[8] + SU	93	0-3	98.9	100.0	n/a	n/a
Study 1001-H[7]	**Inh ins + SU**	113	0-3	90.3	100.0	n/a	n/a
	Met + SU	103	0-1	94.2	100.0	n/a	n/a
Study 1002-L[7]	**Inh ins + Met**	125	0-5	94.4	100.0	n/a	n/a
	Gli[9] + Met	119	0-3	92.4	100.0	n/a	n/a
Study 1002-H[7]	**Inh ins + Met**	109	0-4	94.5	100.0	n/a	n/a
	Gli + Met	103	0-6	97.1	99.0	100.0	n/a

1 Severe hypoglycemia defined as BG ≤ 36 mg/dL, or pt required assistance
2 Pts were insulin-using at study entry
3 Patients were not using insulin at study entry
5 Oral agent
6 Rosiglitazone
7 In Studies 1001 and 1002, patients were stratified on the basis of baseline HbA1c; L = 8-9.5, H ≥ 9.5-12. Data are for the first six months of study
8 Metformin
9 Glibenclamide

For studies in which SQ insulin was the comparator, there was little difference between inhaled insulin and SQ groups for the numbers of patients who had higher numbers of hypoglycemic events; the vast majority of patients had 5 or fewer events. For oral agent comparator studies, one oral agent patient had 6 events, and all other oral agent patients had fewer events. Even among inhaled insulin patients, only a small percentage of patients had >5 events; one patient in Study 109 had a total of 15 hypoglycemic events; that patient was in the combined inhaled insulin + sulfonylurea group.

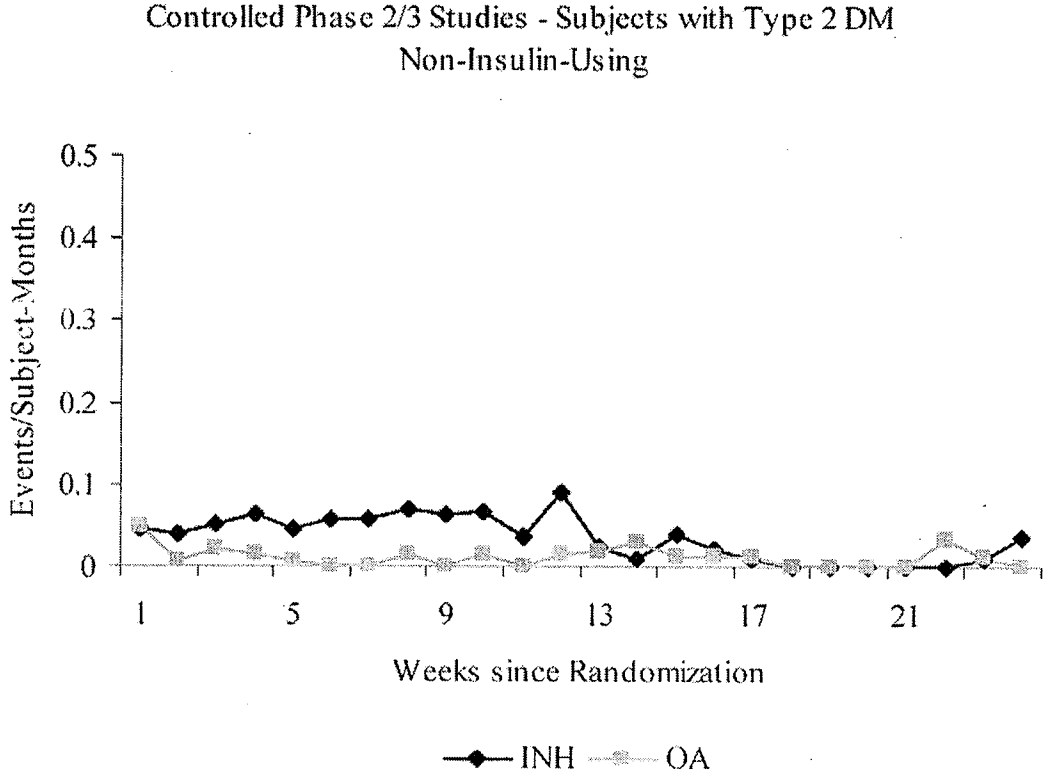
In studies of Type 2 diabetics where SQ was used as a comparator, rates of hypoglycemia declined over time for both SQ and inhaled insulin patients. In studies of Type 2 diabetics where oral agents were used as a comparator, event rates were too low to distinguish a time trend.

Figure 7.1.3.3.1.2.1 Hypoglycemic Events[1] in Type 2 Patients, over Time Since Randomization, Comparator = SQ Insulin



Source: Applicant's Figure 5, ISE
1 Defined as BG ≤ 36 mg/dL, or pt required assistance

Figure 7.1.3.3.1.2.2 Hypoglycemic Events[1] in Type 2 Patients, over Time Since Randomization, Comparator = Oral Agent(s)



Source: Applicant's Figure 5, ISE
1 Defined as BG ≤ 36 mg/dL, or pt required assistance

The applicant provided data regarding time of day of hypoglycemic events, but the number of events was too low to discern a trend for any particular time of day.

Overall, patients with Type 2 diabetes who were insulin using at study entry showed no differences in severe hypoglycemia rates when comparing inhaled insulin to SQ. In trials in which oral agents were the comparators, inhaled insulin patients were more likely to experience hypoglycemia than were oral agent group patients. However, inhaled insulin patients in these oral agent comparator studies also tended to achieve better glycemic control, which carries with it a price of increased hypoglycemic events.

7.1.3.3.1.3 Specifically-defined Hypoglycemia in Pediatric Patients

On 26 May 04, the applicant provided information to DMEDP regarding their pediatric clinical development program. Included in that submission (IND 43313-0263) was some information regarding hypoglycemia in children.

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.

Table 7.1.3.3.1.3.1 Total Protocol-defined Hypoglycemic Event Rates among Pediatric Type 1 Diabetics in Controlled Phase 2/3 Studies

Study	Tx Grp	N	n (%) with Event	Total Events	Total Patient-months	Event Rate (Events/ Pt-Mo)	Risk Ratio (95% CI)
106	Inh Ins	32	32 (100.0)	1427	181.9	7.8	0.89 (0.83, 0.96)
	SQ	29	29 (100.0)	1426	162.5	8.8	
107	Inh Ins	59	59 (100.0)	3063	335.4	9.1	1.04 (0.99, 1.10)
	SQ	59	58 (98.3)	2923	333.4	8.8	
1009	Inh Ins	60	60 (100.0)	1407	175.9	8.0	0.88 (0.82, 0.95)
	SQ	59	58 (98.3)	1548	170.7	9.1	

Source: Applicant's IND 43313, Submission 0263, Table A10

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.

Table 7.1.3.3.1.3.2 Severe[1] Protocol-defined Hypoglycemic Event Rates among Pediatric Type 1 Diabetics in Controlled Phase 2/3 Studies

Study	Tx Grp	N	n (%) with Event	Total Events	Total Patient-months	Event Rate (Events/ Pt-Mo)	Risk Ratio (95% CI)
106	Inh Ins	32	7 (21.9)	9	181.9	4.9	0.80 (0.33, 1.98)
	SQ	29	4 (13.8)	10	162.5	6.2	
107	Inh Ins	59	8 (13.6)	16	335.4	4.8	1.62 (0.73, 3.56)
	SQ	59	9 (15.3)	10	333.4	3.0	
1009	Inh Ins	60	9 (15.0)	15	175.9	8.5	0.81 (0.41, 1.61)
	SQ	59	9 (15.3)	18	170.7	10.5	

1 In order to be classified as severe in these studies, event had the meet all three of the following criteria:

- patient unable to treat themselves
- patient exhibited at least one of the following- memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, loss of consciousness
- measured BG $\leq$ 49 mg/dL; or if no BG measured, clinical manifestations reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose

Source: Applicant's IND 43313, Submission 0263, Table A11

The table below categorizes hypoglycemic events by other definitions.

Table 7.1.3.3.1.3.3 Hypoglycemic Event Rates Categorized by Definition of Hypoglycemia, Pediatric Type 1 Diabetics, Controlled Phase 2/3 Studies

Study	Tx Grp	N	Total Events	Sx of Hypogly, No BG n (%)	Sx of Hypogly, BG ≤ 59 mg/dL n (%)	No Sx of Hypogly, BG ≤49 mg/dL n (%)	BG ≤ 36 mg/dL or Required Assistance n (%)
106	Inh Ins	32	1427	71 (5.0)	1232 (86.3)	124 (8.7)	221 (15.5)
	SQ	29	1426	29 (2.0)	1193 (83.7)	203 (14.2)	242 (17.0)
107	Inh Ins	59	3063	34 (1.1)	2502 (81.7)	522 (17.0)	543 (17.7)
	SQ	59	2923	31 (1.1)	2483 (84.9)	409 (14.0)	528 (18.1)
1009	Inh Ins	60	1407	23 (1.6)	1047 (74.4)	337 (24.0)	240 (17.1)
	SQ	59	1548	26 (1.6)	1176 (76.0)	346 (22.4)	200 (12.9)

Source: Applicant's IND submission 43313-0263, Table A13
Sum of percentages in some groups may exceed 100% because some patients met multiple criteria.

For most categories, rates in the inhaled insulin group did not exceed rates in the SQ group. In Study 1009, more patients in the inhaled insulin group had hypoglycemic events characterized by a blood sugar ≤ 36 mg/dL or a requirement for the assistance of another person than did patients in the SQ group.

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.

7.1.3.3.2 Development of Insulin Antibodies

Across the development program, greater increases occurred in insulin antibody levels (as reflected by percentage of radiolabeled insulin bound) 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 clinical review of insulin antibody data attempted to answer several questions:

- What were the rates of insulin antibody seroconversion among study populations?
- How did insulin antibody levels (as reflected by insulin binding activity) compare among different populations, and how did these levels correlate with demographic data?
- Did the qualitative nature of insulin antibodies differ between treatment groups?
- Did patients who increased their insulin binding activity have more adverse events of any given kind?
- Specifically, did such patients have more pulmonary, allergic, or other immunologic events?
- Was there evidence that these antibodies could neutralize the action of insulin?
- Was there evidence that these antibodies could have other effects on insulin pharmacodynamics or overall glycemic control?
- What happened to insulin binding activity after discontinuation of inhaled insulin?

7.1.3.3.2.1 What were the rates of insulin antibody seroconversion among study populations?

Two different types of insulin antibody measurement methods were used. In earlier studies (106, 107, 108, 109, 110, 111, 1009, 1036), a semi-quantitative radioligand binding assay was used (Mayo Medical Laboratories, Rochester, MN). In this assay, results were expressed as "% binding", and the lower limit of quantitation was 3% insulin binding. Because the Mayo assay was not useful for quantifying the highest levels of antibodies (or insulin binding activity), a quantitative radioligand binding assay was developed and validated by Esoterix®, Inc (Calabasas Hills, CA; Moxness M 2002). In this assay, results were expressed as μU/mL, with a lower limit of quantitation of 2.1 μU of insulin bound/mL. This assay was used in Studies 1001, 1002, 1022, 1026, 1027 and 1029.

In studies in which the Esoterix® assay was used, 75% (608/811) of all inhaled insulin patients (combined Type 1 and Type 2) who had an undetectable level of insulin binding activity at beginning of study had measurable insulin binding activity at end of study (or last insulin binding activity measurement). This compares to a 9.9% (77/778) seroconversion rate among comparator patients. The following tables illustrate seroconversion rates in Type 1 adults, Type 1 children, and Type 2 adults. Because of the differences in assays, separate tables are provided by assay type for each patient category.

Table 7.1.3.3.2.1.1. Seroconversion[1] Rates Among Type 1 Diabetics in Studies[3] Using Semiquantitative Mayo Assay

	Inhaled Insulin # Pts Converting (% Pts Converting)[2]	SQ # Pts Converting (% Pts Converting)[2]
Study 106, all ages	70 (87.5)	15 (20.5)
Study 107, all ages	73 (89.0)	9 (12.3)
Study 1009, all ages	10 (90.9)	4 (36.4)
Combined Studies, pts age ≥ 18 yrs	118 (86.8)	20 (17.4)
Combined Studies, pts age <18 yrs	35 (94.6)	8 (19.0)
Combined Studies, pts age 12-18 yrs	25 (96.2)	4 (13.3)
Combined Studies, all ages	153 (88.4)	28 (17.8)

1 Seroconversion defined as having nonmeasurable insulin binding activity at baseline and measurable insulin binding activity at end of study
2 % of patients who had nonmeasurable insulin binding activity at baseline who then seroconverted to measurable insulin binding activity at end of study
3 6 mo data for Studies 106 and 107; 3 mo data for Study 1009
Source: Applicant's Table 1.1.1, submission N-000-BZ, 6 May 05

Table 7.1.3.3.2.1.2 Seroconversion[1] Rates Among Type 1 Adult[3] Diabetics in Studies Using Quantitative Esoterix® Assay

	Inhaled Insulin # Pts Converting (% Pts Converting)[2]	SQ # Pts Converting (% Pts Converting)[2]
Study 1022	111 (91.7)	29 (25.0)
Study 1026	11 (91.7)	6 (35.3)
Study 1027	39 (78.0)	8 (15.7)
Combined Studies	161 (88.0)	43 (23.4)

1 Seroconversion defined as having nonmeasurable insulin binding activity at baseline and measurable insulin binding activity at end of study
2 % of patients who had nonmeasurable insulin binding activity at baseline who then seroconverted to measurable insulin binding activity at end of study
3 Studies 1022, 1026 and 1027 included only adult patients. 2 yr data for Study 1022, 6 mo data for Study 1026, 3 mo data for Study 1027
Source: Applicant's Table 1.2.1, Submission N-000-BZ, 6 May 05

Among Type 1 diabetics, rates of seroconversion were significantly higher among patients in inhaled insulin groups than among those in SQ only groups. Rates of seroconversion were higher among pediatric patients than among adult patients.

Table 7.1.3.3.2.1.3 Seroconversion[1] Rates Among Type 2 Adult[3] Diabetics in Studies Using Semiquantitative Mayo Assay

	Inhaled Insulin # Pts Converting (% Pts Converting)[2]	Comparator # Pts Converting (% Pts Converting)[2]
Study 104	5 (17.9)	no data
Study 108	65 (56.0)	8 (7.2)
Study 109	83 (43.5)	no data
Study 110	28 (41.8)	no data
Type 2 non-insulin-using at baseline	116 (40.6)	no data
Combined Studies, all Type 2s	181 (45.0)	not calculable

1 Seroconversion defined as having nonmeasurable insulin binding activity at baseline and measurable insulin binding activity at end of study
2 % of patients who had nonmeasurable binding activity at baseline who then seroconverted to measurable insulin binding activity at end of study
3 All Type 2 studies involved adults only. 3 mo data for Studies 104, 109, and 110; 6 mo data for Study 108
Source: Applicant's Table 1.1.1, submission N-000-BZ, 6 May 05

Table 7.1.3.3.2.1.4 Seroconversion[1] Rates Among Type 2 Adult[3] Diabetics in Studies Using Quantitative Esoterix® Assay

	Inhaled Insulin # Pts Converting (% Pts Converting)[2]	Comparator # Pts Converting (% Pts Converting)[2]
Study 1001	158 (74.9)	29 (25.0)
Study 1002	141 (65.0)	2 (1.0)
Study 1029	148 (74.0)	31 (14.9)
Type 2 non-insulin-using at baseline	299 (69.9)	3 (0.8)
Combined Studies, all Type 2s	447 (71.2)	34 (5.7)

1 Seroconversion defined as having nonmeasurable insulin antibodies at baseline and measurable insulin antibodies at end of study
2 % of patients who had nonmeasurable antibodies at baseline who then seroconverted to measurable insulin antibodies at end of study
3 All Type 2 studies involved adults only. 2 yr data for Studies 1001 and 1002; 1 yr data for Study 1029
Source: Applicant's Table 1.2.1, Submission N-000-BZ, 6 May 05

Seroconversion rates were significantly higher among Type 2 patients in inhaled insulin groups than among Type 2 patients in comparator groups. Seroconversion rates were lower among Type 2 patients than among Type 1 patients.

7.1.3.3.2.2 How did insulin binding activity compare among different populations, and how did degree of binding activity correlate with demographic data?

For Type 1 diabetic patients, inhaled insulin was associated with higher end-of-study insulin binding activity, and with greater change from baseline in insulin binding activity, than was SQ insulin.

The following tables illustrate the differences in insulin binding activity for Type 1 adult patients.

Table 7.1.3.3.2.2.1 Mean and Median Insulin Binding Activity at Baseline and End of Study, Adult Type 1 Patients, Studies 106 and 107, Mayo Assay (Semiquantitative, Expressed as % Binding[2])

	Inh Ins			SQ		
	n[1]	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	215	5.7 (9.8)	1.5	203	6.1 (10.3)	1.5
End of Study (6 months)	215	27.7 (20.7)	25.0	203	7.1(11.8)	1.5
Change from Baseline	215	22.0 (17.9)	20.5	203	1.0 (5.3)	0.0

1 n = number of patients evaluated for insulin binding activity at each time point
2 Applicant imputed values at lower limit of binding (3%) as 1.5%
Source: Applicant's Tables 3, 1.1.1, 1.1.4.1, and 1.1.4.2, Section 5.3.5.3.2

Table 7.1.3.3.2.2.2 Mean and Median Insulin Binding Activity at Baseline and End of Study, Adult Type 1 Patients, Studies 1022, 1026 and 1027, Esoterix® Assay (Quantitative, Expressed as µU/mL[2])

	Inh Ins			SQ		
	n[1]	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	415	28.3 (187.7)	3.6	420	20.9 (80.5)	3.5
3 Months	393	121.7 (300.1)	31.0	397	21.3 (71.6)	3.6
Change from Baseline to 3 Months	386	102.1 (285.4)	25.0	389	-0.19 (28.7)	0.0
6 Months	283	179.9 (239.1)	83.0	290	24.5 (91.9)	4.4
Change from Baseline to 6 Months	278	160.6 (224.3)	72.5	286	1.18 (20.78)	0.0

1 n = number of patients evaluated for insulin binding activity at each time point
2 Applicant imputed values at the lower limit of quantitation (2.1 µU /mL) as 1.05 µU /mL
Source: Applicant's Tables 3, 1.1.1, 1.1.4.1, and 1.1.4.2, Section 5.3.5.3.2

End-of-study and change from baseline in insulin binding activity were higher for pediatric patients than for patients ages 18 or older, as illustrated in the following table. For those patients ages 18 and over taking inhaled insulin, there was little difference between adult age groups for mean insulin binding activity at end-of-study, and little difference between adult age groups for change in insulin binding activity from baseline.

Table 7.1.3.3.2.2.3 Age Differences for End-of-Study Insulin Binding Activity and Change from Baseline in Insulin Binding Activity, Type 1 Patients, Controlled Phase 3 Studies which Included Children[2] (Mayo Assay, % Binding)

Age Range	Measurement	Inh Ins		SQ	
		n	% Binding[1] Mean (SD)	n	% Binding Mean (SD)
< 18 yrs	Baseline	138	10.37 (11.60)	138	8.71 (9.34)
	End-of-Study	138	36.12 (19.00)	138	10.08 (11.29)
	Change from Baseline	138	25.76 (15.89)	138	1.37 (4.53)
18-44 yrs	Baseline	155	5.15 (8.93)	149	5.73 (10.85)
	End-of-Study	155	26.92 (20.72)	149	7.10 (12.69)
	Change from Baseline	155	21.77 (18.11)	149	1.37 (5.12)
45-64 yrs	Baseline	59	7.11 (11.89)	53	6.88 (8.63)
	End-of-Study	59	29.75 (20.94)	53	6.92 (8.87)
	Change from Baseline	59	22.64 (17.47)	53	0.05 (5.66)
65-74 yrs	Baseline	1	5.00 (n/a)	1	13.00 (n/a)
	End-of-Study	1	24.00 (n/a)	1	15.00 (n/a)
	Change from Baseline	1	19.00 (n/a)	1	2.00 (n/a)

1 Applicant imputed values at lower limit of binding (3%) as 1.5%
2 Studies 106, 107, 1009
Source: Applicant's Table 3.1.1, Section 5.3.5.3.2, p 91

Female patients had higher mean end-of-study insulin binding activity, and had greater changes from baseline insulin binding activity than did male patients, as illustrated in the following tables:

Table 7.1.3.3.2.2.4 Gender Differences in Mean End-of-Study and Change-from-Baseline in Insulin Binding Activity, Type 1 Patients, Controlled Phase 3 Studies 106 and 107 (Mayo Assay % Binding)

	Inh Ins		SQ	
	Male (n = 90) Mean[1] % Binding (SD)	Female (n = 44) Mean % Binding (SD)	Male (n = 90) Mean % Binding (SD)	Female (n = 43) Mean % Binding (SD)
Baseline	5.17 (9.39)	6.24 (10.28)	6.96 (12.57)	4.99 (6.48)
End-of-Study (6 months)	23.04 (17.83)	32.64 (22.46)	8.20 (14.27)	5.77 (7.63)
Change from Baseline	17.86 (15.47)	26.40 (19.20)	1.24 (6.49)	0.78 (3.28)

1 Lower limit of quantitation = 3%, imputed by applicant as 1.5%; upper limit of quantitation = 90%, imputed by applicant as 91%
Source: Applicant's Table 3.2.1, Section 5.3.5.3.2

Table 7.1.3.3.2.2.5 Gender Differences in Mean End-of-Study and Change-from-Baseline in Insulin Binding Activity, Type 1 Patients, Controlled Phase 3 Study 1022 (Esoterix® Assay, µU /mL)

	Inh Ins		SQ	
	Male (n = 164) Mean[1] (SD)	Female (n = 121) Mean (SD)	Male (n = 158) Mean (SD)	Female (n = 126) Mean (SD)
Baseline	16.14 (39.94)	58.47 (340.47)	16.06 (47.64)	32.45 (127.00)
End-of-Study (12 months)	234.20 (467.59)	434.97 (1194.20)	15.67 (40.51)	38.05 (197.79)
Change from Baseline	218.06 (446.16)	376.50 (910.19)	-0.38 (26.50)	5.60 (82.48)

1 Lower limit of quantitation = <2.1 µU/mL, imputed by applicant as 1.05
Source: Applicant's Table 3.2.4, Section 5.3.5.3.2

The numbers of non-Caucasian Type 1 patients in the controlled studies for which antibody data were available were too small for meaningful comment on differences in antibody changes by race.

Patients with Type 2 diabetes who were exposed to inhaled insulin had higher mean insulin binding activity at end of study, and greater changes from baseline, than did patients in comparator groups. This difference was more marked among patients who had been using injected insulin prior to study than it was for patients who had not been using injected insulin prior to study.

Table 7.1.3.3.2.2.6 Mean and Median Insulin Binding Activity at Baseline and End of Study, Type 2 Patients, Controlled Phase 2/3 Studies[3] Using Mayo Assay (Semiquantitative, Expressed as % Binding[2])

	Inh Ins			Comparator		
	n[1]	Mean (SD)	Median	n	Mean (SD)	Median
Insulin-using at Study Entry	134			133		
Baseline		2.7 (4.3)	1.5		4.1 (9.3)	1.5
End of Study (6 months)		12.8 (18.2)	5.0		4.0 (8.0)	1.5
Change from Baseline		10.2 (16.1)	3.5		-0.1 (3.3)	0.0
Non-insulin-using at Study Entry	290			181		
Baseline		1.8 (4.6)	1.5		1.5 (0.3)	1.5
End of Study (6 months)		6.0 (8.0)	1.5		1.5 (0.0)	1.5
Change from Baseline		4.3 (9.2)	0.0		0.0 (0.3)	0.0

1 n = number of patients evaluated for insulin binding activity at each time point
2 Applicant imputed values at lower limit of binding (3%) as 1.5%
3 Studies 104, 108, 109, 110
Source: Applicant's Table 11, Section 5.3.5.3.2

Table 7.1.3.3.2.2.7 Mean and Median Insulin Binding Activity at Baseline and End of Study, Type 2 Patients, Controlled Phase 2/3 Studies[3] Using Esoterix® Assay (Quantitative, Expressed as µU/mL[2])

	Inh Ins			Comparator		
	n[1]	Mean (SD)	Median	n	Mean (SD)	Median
Insulin-using at Study Entry						
Baseline	307	12.2 (36.9)	1.1	307	14.9 (86.5)	1.1
End of Study (6 months)	203	78.2 (187.0)	17.0	212	14.6 (102.9)	1.1
Change from Baseline	202	68.5 (178.7)	13.5	208	3.5 (59.7)	0.0
Non-insulin-using at Study Entry						
Baseline	452	1.1 (2.2)	1.0	415	1.0 (0.2)	1.0
End of Study (12 months)	321	16.7 (48.4)	5.4	280	1.0 (0.1)	1.0
Change from Baseline	316	15.6 (48.9)	4.4	276	0.0 (0.2)	0.0

1 n = number of patients evaluated for insulin binding activity at each time point
2 Applicant imputed values at lower limit of quantitation (2.1 µU/mL) as 1.05
3 Studies 1001, 1002, 1029
Source: Applicant's Table 11, Section 5.3.5.3.2

For Type 2 patients, there was little difference by age in 3-month studies (Studies 104, 109, 110) in mean insulin binding activity at end of study and in change from baseline in insulin binding activity. Patients who were age 65 years or older did tend to have higher values in longer studies, and in studies using the Esoterix® assay, mean insulin binding activity appeared to correlate with age group up to age 74. These changes are illustrated in the following tables.

Table 7.1.3.3.2.2.8 Age Differences in Insulin Binding Activity Changes at 6 Months of Study, Type 2 Diabetics in Inhaled Insulin Group, Study 108 (Mayo Semiquantitative Assay, % Binding)

	Age 18-44 Yrs n = 10 Mean[1] % Binding (SD)	Age 45-64 Yrs n = 86 Mean % Binding (SD)	Age 65-74 Yrs n = 31 Mean % Binding (SD)	Age ≥ 75 Yrs n = 7 Mean % Binding (SD)
Baseline	2.55 (3.32)	1.99 (2.29)	4.85 (7.66)	1.50 (0.00)
End of Study	9.50 (12.12)	8.98 (13.15)	24.47 (26.72)	13.29 (13.04)
Change from Baseline	6.95 (11.03)	6.98 (11.96)	19.61 (23.47)	11.79 (13.04)

1 Applicant imputed lower limit of quantification (3%) as 1.5%, and upper limit of quantification (90%) as 91%
Source: Applicant's Table 3.1.2, Section 5.3.5.3.2

Table 7.1.3.3.2.2.9 Age Differences in Insulin Binding Activity Changes at 12 Months of Study, Type 2 Diabetics in Inhaled Insulin Group, Study 1029 (Esoterix® Quantitative Assay, µU/mL)

	Age 18-44 Yrs n = 34 Mean[1] (SD)	Age 45-64 Yrs n = 202 Mean (SD)	Age 65-74 Yrs n = 67 Mean (SD)	Age ≥ 75 Yrs n = 4 Mean (SD)
Baseline	9.81 (23.78)	10.68 (36.11)	18.49 (44.81)	2.80 (2.23)
End of Study	73.10 (140.18)	88.68 (202.15)	114.03 (254.36)	90.48 (141.68)
Change from Baseline	63.29 (126.04)	78.00 (193.88)	95.54 (250.32)	87.68 (141.33)

1 Applicant imputed lower limit of quantification (2.1 µU/mL) as 1.05 µU/mL
Source: Applicant's Table 3.1.5, Section 5.3.5.3.2

Table 7.1.3.3.2.2.10 Age Differences in Insulin Binding Activity Changes at 24 Months of Study, Type 2 Diabetics in Inhaled Insulin Group, Studies 1001 and 1002 (Esoterix® Quantitative Assay, µU/mL)

	Age 18-44 Yrs n = 35 Mean[1] (SD)	Age 45-64 Yrs n = 293 Mean (SD)	Age 65-74 Yrs n = 92 Mean (SD)	Age ≥ 75 Yrs n = 13 Mean (SD)
Baseline	1.00 (0.00)	1.03 (0.41)	1.56 (4.92)	1.00 (0.00)
End of Study	4.13 (4.87)	12.29 (37.18)	19.45 (50.04)	34.70 (66.86)
Change from Baseline	3.13 (4.87)	11.25 (37.16)	17.89 (50.43)	33.70 (66.86)

1 Applicant imputed lower limit of quantification (2.1 µU/mL) as 1.05 µU/mL
Source: Applicant's Table 3.1.6, Section 5.3.5.3.2

For Type 2 patients, no relationship was demonstrated between gender and insulin binding activity changes, and no consistent relationship was demonstrated between race and insulin binding activity changes.

7.1.3.3.2.3 Did the qualitative nature of insulin antibodies differ between treatment groups?

Anti-insulin antibodies appeared to be predominantly IgG for both inhaled and SQ patients, and antibodies of other immunoglobulin classes did not appear to occur with detectable frequency. The applicant analyzed residual samples from 88 patients from Studies 107 and 106, and found that serum IgG anti-insulin antibodies predominated in both inhaled and SQ patients, and the degree of IgG-specific insulin binding activity correlated directly with total insulin binding activity. For both inhaled and SQ group patients, IgA-, IgE- and IgM-specific insulin binding activities levels were below the limit of quantitation.

The applicant also examined the insulin binding capacity profile, using a range of insulin concentrations, for patients in Study 1026 at end of study. For inhaled insulin group patients, the profile was consistent with predominantly low affinity antibodies with high binding capacity. This insulin binding capacity pattern for the inhaled insulin group is similar to the pattern described in studies for subcutaneous insulin in the medical literature. High affinity antibodies have been associated with clinical concerns more often than low affinity antibodies (the type seen with inhaled insulin), and characteristically slow the early increase in plasma free insulin after subcutaneous insulin injection, with impairment of postprandial glucose control (van Haeften 1987). Low affinity insulin antibodies have been associated in rare circumstances with spontaneous autoimmune hypoglycemia (Basu 2005). Please see the discussion below regarding the evaluation for an association between severe hypoglycemia and insulin antibodies.

7.1.3.3.2.4 Did patients who had an increase in their insulin binding activity have more adverse events of any given kind? Specifically, did such patients have more pulmonary, allergic, or other immunologic events?

7.1.3.3.2.4.1 Allergic Events

In the overall Phase 2/3 controlled populations, overall events of an allergic nature occurred with similar frequency between inhaled insulin patients and SQ group patients. For Type 1 patients, the event term "allergic reaction" occurred in 31/698 (4.4%) of inhaled insulin patients vs 23/705 (3.3%) of SQ patients, and the term "rhinitis" occurred in 96/698 (13.8%) of inhaled insulin patients vs 67/705 (9.5%) of SQ patients. Narratives were not provided for these patients, and antibody data were not available for analyses for possible relationships. Numerous other event terms were examined with no difference between groups for Type 1 patients. For Type 2 patients, no significant difference was observed between inhaled insulin patients and comparator patients for any given type of allergic adverse event.

Please see Table 7.1.3.3.2.5 below for adverse events occurring among patients who had the highest degrees of insulin binding activity (>2,000 μU/mL by Esoterix® assay). Among Type 1 patients with insulin binding activity above this range, 3/33 experienced events of a potentially allergic nature (one case each of allergic bronchiolitis, dermatitis of the face and arms, and bilateral eyelid swelling).

7.1.3.3.2.4.2 Hypoglycemia

The applicant addressed the question of hypoglycemia by creating scatter plots in which end-of-study insulin binding activity was plotted against the monthly incidence of hypoglycemic events. The applicant found no association between these variables (applicant's Figures 2.20.1, pgs 233-240, Section 5.3.5.3.2). Separate plots were created for Type 1 and Type 2 patients, and Type 2 patients were evaluated separately by insulin-using status at study entry.

The applicant also addressed the issue of hypoglycemia in relation to antibody binding affinity and capacity by creating scatter plots of the range of affinities from Study 1026 (described above) against the monthly incidence of hypoglycemic events. No association was noted.