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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Exubera® / Inhaled Human Insulin

PROTOCOL NO.: A2171035

PROTOCOL TITLE: A 52 Week Multicenter, Open-Label, Randomized, Parallel, Two-Arm Study Comparing Exubera (Inhaled Human Insulin) vs Humalog (Insulin Lispro), Both in Combination With Insulin Glargine in Subjects With Type 1 Diabetes Mellitus

Study Centers: A total of 23 centers took part in the study and enrolled subjects with 3 centers each in Belgium, France, and the United Kingdom (UK); 2 centers each in Austria, Sweden, Spain, and the United States (US); 1 center each in Denmark, Finland, Ireland, Netherland, Norway, and Portugal.

Study Initiation and Final Completion Dates: 20 March 2007 to 30 June 2008. This study was terminated prematurely.

Phase of Development: Phase 4

Study Objectives: The primary objective of the study was to demonstrate non-inferiority of an insulin regimen using insulin glargine as the basal insulin with Exubera as the mealtime insulin, compared to a regimen using insulin glargine as the basal insulin and insulin lispro as the mealtime insulin in terms of glycemic control (hemoglobin A1c [HbA1c]) after 52 weeks of treatment with each treatment regimen.

Secondary objectives of the study included durability of glycemic control, additional measurements of glycemic control (fasting plasma glucose [FPG], postprandial glucose), hypoglycemia, body weight, and body mass index [BMI] changes, subject reported outcomes as well as the safety of both treatment regimens, each after 52 weeks of treatment with each treatment regimen.

METHODS

Study Design: This was a randomized open-label, parallel-group outpatient, and inpatient study with a 4-week run-in period, and a 52-week treatment period. Subjects were randomized to either inhaled insulin (Exubera) or subcutaneous (SC) insulin (lispro) in 1:1 randomization schedule. All subjects received insulin glargine as a basal regimen.

Subjects were seen weekly during the 4-week run-in period. Throughout the first week after the randomization visit, subjects were contacted daily by telephone (a minimum of 5 times) to report the prior day's home glucose monitoring results, and as needed thereafter to ensure clinical safety. Weekly clinic visits were required for the first 4 weeks after randomization,

and mid-week telephone contact was recommended. The next visit occurred 2 weeks later, at Week 6. Thereafter, visits were to occur every 2 weeks until Week 12, and then every 4 to 6 weeks until Week 52. The Investigator or designee was to telephone the subject 7 to 10 days before planned visits to remind the subject to take the required 6- and 8-point glucose profiles over the next week and to bring their medication and completed study worksheets to the visit.

Several sub-studies were planned; however, due to the early termination of this study and low enrollment, only the 24-hour home monitored blood glucose (HMBG) sub-study was implemented. HMBG was conducted as soon as possible after randomization at Week 0 (within 2 days), prior to starting treatment, and again at Weeks 24 and 52 in a subset of subjects at selected sites.

At all visits, the Investigator reviewed HMBG results as well as the hypoglycemic event worksheet and, if warranted, adjusted insulin doses accordingly. Table 1 presents the schedule of activities in the study.

Table 1. Schedule of Activities

Visit Designator	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Study Week	**-4**	**-3**	**-2**	**-1**	**0**	**1**[a]	**2**[b]	**3**[b]	**4**[b]	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
		Baseline Run-In				**Treatment Period**																	
Informed consent, medical history, PE, vital signs	X																						
Height	X																						
Weight	X				X								X			X			X				X
Brief PE (HR, BP, throat, chest, vital signs)					X				X		X		X	X	X	X	X	X	X	X	X	X	X
ECG	X																						
CBC, U/A, chemistry	X															X							X
Urinary albumine-creatine ratio					X								X			X							
Pregnancy test[c]	X																						X
Fasting C-peptide[d]	X																						
HbA1c	X			X	X					X			X			X			X				X
Insulin antibodies					X											X							X
Fasting plasma glucose[e], [d]					X		X		X	X			X			X			X				X
Fasting lipid profile[d, f],					X											X							X
Dietician/dispense glucometer		X																					
Dispense/review HBGM /dosing worksheets		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense/review hypoglycemic event worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2 x 8-pt blood glucose profiles prior to visit																							
Dispense worksheet				X					X			X			X			X				X	
Review worksheet					X					X			X			X			X				X
1 x 6-pt blood glucose profile prior to visit																							
Dispense worksheet			X		X	X	X	X		X	X		X	X		X	X		X	X	X		
Review worksheet				X		X	X	X	X		X	X		X	X		X	X		X	X	X	
Spirometry		X[g]														X[h]							X[h]
Review concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Activities

Visit Designator	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Study Week	**-4**	**-3**	**-2**	**-1**	**0**	**1[a]**	**2[b]**	**3[b]**	**4[b]**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
		Baseline Run-In				**Treatment Period**																	
Review/demonstrate inhaler device					X																		
Commence insulin glargine[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study drug					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug accountability						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D			X		X					X						X							X
Phase V outcome system			X		X					X						X							X

AEs = adverse events; BP = blood pressure; CBC = complete blood count; ECG = electrocardiogram; EC = Ethics Committee; HbA1c = Glycated Hemoglobin A1c; HBGM = Home Blood Glucose Monitoring; HCG = human chorionic gonadotropin; HDL = high density lipoprotein; HR = heart rate; IRB = Institutional Review Board; LDL = low density lipoprotein; PE = physical examination; U/A = urine analysis.

a. Subjects were to be contacted daily by telephone (a minimum of 5 times) to report prior day's home glucose monitoring results, and as needed thereafter to ensure clinical safety.

b. Mid-week telephone contact was recommended.

c. Pregnancy test (beta-HCG) in women of childbearing potential only. Pregnancy tests could also be repeated during the study as per request of EC/IRBs or if required by local regulations.

d. Obtained in the morning after a minimum 8 hour overnight fast.

e. Oxalate (gray-stoppered) tube to be used.

f. Oxalate (gray-stoppered) tube to be used.

g. Baseline spirometry results had to be known before proceeding to further run-in procedures/visits or commencement of insulin glargine.

h. In subjects randomized to Exubera only.

Number of Subjects (Planned and Analyzed): A total of 340 subjects were planned to be randomized (170 per treatment arm) in the study.

A total of 87 subjects were screened and 58 were assigned to study treatment (38 subjects in the Exubera group and 20 subjects in the lispro group): 11 in Belgium; 10 in France; 9 in Spain; 6 in Denmark; 5 in Sweden; 4 in Austria; 3 each in Norway and Portugal; 2 each in the UK and the US; 1 each in Finland, Ireland, Netherlands.

Diagnosis and Main Criteria for Inclusion: The subject population consisted of male and female subjects ≥18 years of age with a diagnosis of type 1 diabetes mellitus for more than 1 year, on a stable insulin regimen that involved at least 3 injections daily of insulin or an insulin analogue (ie, no change in the type[s] of insulin or in the schedule of injections; dose changes were acceptable) for the 2 months prior to Screening, with 5.5% ≤ HbA1c ≤9.0%, BMI ≤30 kg/m^2, and fasting plasma C peptide <0.20 nmol/L at Screening.

Study Treatment: The control regimen was a SC insulin regimen of pre-prandial insulin lispro and administration of insulin glargine given once daily (QD) at the same time each day in the morning. The experimental regimen was pre-prandial inhaled insulin plus QD administration of insulin glargine given at the same time each day in the morning. The time of injection of insulin glargine could only be changed once during the course of the study and only if there was a clinical need. Titration of all insulins was to be based on prospective and retrospective study insulin titration algorithms provided to the Investigator and subject. Achievement of fasting blood glucose (pre-breakfast) targets based on titration of insulin glargine was a priority ahead of adjusting prandial insulin to meet mealtime targets.

Modifications in the insulin doses were considered at the discretion of the Investigator according to meal size, nutrient composition, illness, and recent or anticipated exercise.

Efficacy Endpoints:

The primary efficacy endpoint was the change in percent HbA1c from baseline (average of Week 1 and Week 0 HbA1c values) to Week 52. Change from baseline in HbA1c between the 2 arms was to be compared following adjustment according to baseline HbA1c values.

Secondary endpoints (reported at all post-baseline visits up to and including Week 52 where relevant data was captured) included:

- Hypoglycemic event rates during the entire study;
- Non-severe hypoglycemic event rates;
- Total and severe hypoglycemic event rates in subjects who attained HbA1c levels <6.5%, <7%, <8% and those who fail with HbA1c levels ≥8% at the end of the study;
- Percentage of subjects with an HbA1c <8%, <7%, <6.5%, and ≥8% at 24 weeks and at the end of study/early termination;

- Percentage of subjects with ≥0.5%, ≥0.7% and ≥1.0% absolute reduction in HbA1c levels at the end of the study from baseline levels;
- Percentage of subjects who attain target FPG values 4.0-6.5 mmol/L (72-117 mg/dL) at each evaluation;
- Change in FPG from baseline to endpoint and change in fasting and postprandial blood glucose from baseline to endpoint based on glucometer data and in-hospital assessments;
- Change from baseline to Week 52 in fasting lipids;
- Change from baseline to Week 52 in body weight and BMI;
- Change in insulin antibody levels and body weight from baseline to endpoint;
- Change in basal and prandial insulin doses from baseline to endpoint;
- Blood glucose values determined by home blood glucose monitoring;
- Change from baseline in subject reported health state, quality of life, preference and diabetes treatment satisfaction;
- Change from baseline to Week 24 in glucose uptake into thigh muscle as assessed by 18 Flurodeoxyglucose Positron Emission Tomography in a subset of subjects;
- Change from baseline to Week 24 in postprandial and fasting glucose metabolism as assessed by infusion of stable isotopes in a subset of subjects;
- Variability in a 24-hour glucose profile assessed at baseline, at Week 24 and at Week 52 in a subset of subjects

Safety Evaluations: Safety evaluations included clinical monitoring, electrocardiogram, physical examination (vital signs [heart rate, blood pressure], throat, and chest), spirometry, hypoglycemia monitoring, insulin antibodies, adverse events (AEs), and safety laboratory tests.

Statistical Methods: As the study was underpowered due to early termination, the inferential analysis of the original study objectives were no longer attainable. Therefore, no inferential comparisons were made. Descriptive statistics were provided for safety endpoints. The safety population included all randomized subjects who received at least 1 dose of study medication.

For hypoglycemic events, all events occurring between randomization (first day of active treatment) and the last day of active treatment +1 day lag were included. Crude event rates were used to summarize all hypoglycemic events, severe hypoglycemic events, as well as hypoglycemic events that occurred after 1 month of the start of treatment.

Hypoglycemia was defined as 1 of the following:

- Characteristic symptoms of hypoglycemia with no blood glucose check. Clinical picture must have included prompt resolution with food intake, SC glucagon, or intravenous (IV) glucose.

- Characteristic symptoms of hypoglycemia with blood glucose check showing glucose <3.27 mmol/L (59 mg/dL). Symptoms associated with blood glucose ≥3.33 mmol/L (60 mg/dL) could not be reported as hypoglycemia.

- Any glucose measurement ≤2.72 mmol/L (49 mg/dL) with or without symptoms.

Severe hypoglycemia was defined as an event that met all 3 of the following criteria:

- The subject was unable to treat himself or herself.

- The subject exhibited at least 1 of the following neurological symptoms: memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, suspected seizure, seizure, and loss of consciousness.

- The subject exhibited either: blood glucose ≤2.72 mmol/L (49 mg/dL), or if the blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, SC glucagon, or IV glucose.

RESULTS

Subject Disposition and Demography: A total of 87 subjects were screened for the study, and 58 subjects were randomized to study treatment prior to study termination. Table 2 summarizes subject disposition, subject discontinuations, and the number of subjects included in the safety analyses. Many subjects discontinued due to early termination of the study and not for reasons attributed to study treatment.

One subject in the Exubera group, had no post-baseline laboratory tests. Therefore, 37/38 Exubera treated subjects were included in safety laboratory test analysis.

Table 2. Subject Disposition and Subjects Analyzed

	Exubera	Lispro
Number (%) of subjects		
Screened, N=87		
Assigned to study treatment, N=58	38	20
Treated	38	20
Completed	6	3
Discontinued	32	17
Related to study drug:	18	12
Lack of efficacy	3	0
Other	15	12
Not Related to study drug:	14	5
Other	5	3
Subject no longer willing to participate in study	9	2
Analyzed for safety:		
Adverse events	38	20
Laboratory data	37	20

N = number of subjects.
Discontinuations that occurred outside the lag period were attributed to the last study treatment received.

Demographic characteristics are summarized in Table 3. The mean age of the subjects was 41.6 years in the Exubera treatment group and 39.1 years in the lispro treatment group. The majority of subjects were between 18 to 44 years of age. All subjects were White and there were more males than females in both treatment groups.

Table 3. Subject Demographics

	Exubera			Lispro		
	Male	Female	Total	Male	Female	Total
Number (%) of subjects	21	17	38	14	6	20
Age (years):						
Mean (SD)	42.2 (14.1)	40.8 (12.8)	41.6 (13.3)	42.9 (14.8)	30.0 (10.2)	39.1 (14.6)
Range	20-72	22-69	20-72	21-66	18-42	18-66

SD = standard deviation.

Efficacy Results: Due to early termination, this study was underpowered to attain the inferential orientation of the original study objectives. Therefore, no inferential comparisons were made. A total of 6 subjects on Exubera and 3 subjects on lispro completed the study. Due to the low number of subjects that completed, no descriptive statistics for the efficacy endpoints were provided.

Safety Results: Of the 38 subjects treated with Exubera, 35 subjects experienced a total of 129 treatment-emergent AEs. All 20 subjects who were treated with lispro experienced AEs (total of 58 treatment-emergent AEs). A summary of all causality and treatment-related AEs is presented in Table 4.

Table 4. Summary of Treatment-Emergent Adverse Events (All Causality and Treatment-Related)

	Exubera		Lispro	
	All Causality	**Treatment-Related**	**All Causality**	**Treatment-Related**
Number (%) of subjects:				
Subjects evaluable for AEs	38	38	20	20
Number of AEs	129	52	58	13
Subjects with AEs	35	26	20	11
Subjects with SAEs	2	0	1	0
Subjects with severe AEs	4	0	4	0
Subjects discontinued due to AEs	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	5	3	2	1

Includes data up to 1 day after last dose of study drug.
Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs were according to the Investigator's assessment.
MedDRA (v11.0) coding dictionary was applied.
AEs and SAEs are not separated out in the table.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

The most frequently reported AEs (all causality) for the Exubera and lispro groups, by system organ class (SOC), were metabolism and nutrition disorders; infections and infestations and respiratory, thoracic, and mediastinal disorders. No lung neoplasms were reported at any time during the study. The majority of AEs (all causality) in the Exubera and lispro groups were considered to be mild (88/129 and 36/58, respectively) or moderate (29/129 and 18/58, respectively) in severity. There were 12/129 severe AEs in the Exubera group and 4/58 severe AEs in the lispro group. The only severe AE reported in more than 1 subject in either treatment group was hypoglycemia (3 severe events in the Exubera group and 2 severe events in the lispro group). None of the severe AEs of hypoglycemia were considered to be related to the study drug in either the Exubera or lispro treatment groups. The most frequently reported treatment related AEs were hypoglycemia (25 [Exubera] and 11 [lispro]) and cough (5 [Exubera] and 0 [lispro]). All causality and treatment related AEs are presented in the Table 5.

Hypoglycemia was reported by 33 subjects in the Exubera group and 18 subjects in the lispro group. In the Exubera and Lispro treatment groups, 25 and 11 subjects, respectively, had hypoglycemic events that were considered by the Investigator to be related to the study drug. All of the treatment-related events of hypoglycemia were mild or moderate in severity.

Table 5. Incidence of Treatment-Emergent Adverse Events

	Exubera N=38		Lispro N=20	
System Order Class Preferred Term	All Causality n	Treatment-Related n	All Causality n	Treatment-Related n
Blood and lymphatic system disorders	0	0	1	0
Lymphadenitis	0	0	1	0
Ear and labyrinth disorders	1	0	0	0
Vertigo	1	0	0	0
Gastrointestinal disorders	5	1	3	0
Abdominal pain	0	0	1	0
Aphthous stomatitis	1	1	0	0
Dyspepsia	1	0	0	0
Hemorrhoids	0	0	1	0
Nausea	2	0	1	0
Vomiting	3	0	2	0
General disorders and administration site conditions	4	2	3	0
Asthenia	1	1	0	0
Chest pain	0	0	1	0
Drug intolerance	1	0	0	0
Fatigue	0	0	1	0
Hunger	2	2	0	0
Malaise	2	0	0	0
Pyrexia	0	0	1	0
Infections and infestations	16	0	13	1
Balanitis candida	0	0	1	0
Ear infection	1	0	0	0
Gastroenteritis	3	0	1	0
Gastrointestinal infection	1	0	0	0
Influenza	2	0	1	0
Localized infection	2	0	0	0
Nasopharyngitis	9	0	7	1
Onychomycosis	1	0	0	0
Pharyngitis	0	0	2	0
Respiratory tract infection	0	0	2	0
Respiratory tract infection viral	1	0	0	0
Sinusitis	2	0	0	0
Tooth abscess	0	0	1	0
Tracheitis	1	0	0	0
Upper respiratory tract infection	0	0	1	0
Vaginal candidiasis	1	0	0	0
Viral pharyngitis	1	0	0	0
Vulvovaginitis	1	0	0	0
Injury, poisoning, and procedural complications	4	0	1	0
Eye injury	1	0	0	0
Fall	1	0	0	0
Joint sprain	0	0	1	0
Thermal burn	1	0	0	0
Wound	1	0	0	0
Investigations	3	1	0	0
Alanine aminotransferase increased	1	1	0	0
Blood creatinine increased	1	0	0	0
Weight decreased	1	0	0	0
Weight increased	1	0	0	0
Metabolism and nutrition disorders	33	25	18	11
Anorexia	1	0	0	0
Hyperglycemia	2	2	1	1
Hypoglycemia	33	25	18	11
Ketoacidosis	1	0	1	0

Table 5. Incidence of Treatment-Emergent Adverse Events

	Exubera N=38		Lispro N=20	
System Order Class Preferred Term	All Causality n	Treatment-Related n	All Causality n	Treatment-Related n
Polydipsia	1	0	0	0
Musculoskeletal and connective tissue disorders	7	1	2	0
Arthralgia	2	1	0	0
Back pain	2	0	1	0
Bone pain	1	0	0	0
Joint swelling	1	0	0	0
Musculoskeletal pain	0	0	1	0
Myalgia	1	0	0	0
Myositis	1	0	0	0
Neck pain	1	0	0	0
Tendonitis	1	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	0	1	0
Thyroid neoplasm	0	0	1	0
Nervous system disorders	7	5	1	0
Disturbance in attention	1	1	0	0
Dizziness	2	2	0	0
Headache	4	2	1	0
Somnolence	1	0	0	0
Tremor	1	0	0	0
Psychiatric disorders	3	1	0	0
Depression	1	0	0	0
Disorientation	1	1	0	0
Mental disorder	1	0	0	0
Renal and urinary disorders	1	0	1	0
Ketonuria	0	0	1	0
Polyuria	1	0	0	0
Reproductive system and breast disorders	1	0	0	0
Endometriosis	1	0	0	0
Respiratory, thoracic, and mediastinal disorders	11	7	5	0
Cough	5	5	0	0
Dyspnea	1	0	0	0
Hyperventilation	0	0	1	0
Laryngeal edema	1	0	0	0
Pharyngolaryngeal discomfort	0	0	1	0
Pharyngolaryngeal pain	2	0	2	0
Rhinitis allergic	0	0	1	0
Rhinorrhea	2	2	0	0
Throat irritation	4	3	0	0
Skin and subcutaneous tissue disorders	1	1	1	0
Pruritus	1	1	0	0
Rash macular	0	0	1	0
Vascular disorders	3	2	1	0
Hematoma	1	1	1	0
Hot flush	1	1	0	0
Hypertensive crisis	1	0	0	0

Adverse events and serious adverse events are not separated out in the table.
If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken.
Includes data up to 1 day after last dose of study drug.
MedDRA (v11.0) coding dictionary was applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subject.

There were no deaths reported during the study. A total of 4 serious adverse events (SAEs) were experienced by 2 subjects treated with Exubera during the study, 1 of which was considered by the Investigator to be related to the study treatment (hypoglycemic seizure).

One subject in the lispro group experienced an SAE of ketoacidosis during the study, which was not considered by the Investigator to be related to the study drug. The SAEs that were reported by more than 1 subject were hypoglycemia (2 subjects in the Exubera treatment group) and ketoacidosis (1 subject each in the Exubera and lispro treatment groups). Summary of SAEs is presented in the Table 6.

Table 6 Summary of Serious Adverse Events

Treatment	MedDRA Preferred Term	Causality	Outcome
Exubera	Hypoglycemic seizure	Study drug	Recovered
	Blood creatinine increased[a]	Concomitant treatment	Recovered
	Hypoglycemia[a]	Other	Recovered
	Ketoacidosis[a]	Other	Recovered
Lispro	Ketoacidosis	Other	Recovered

MedDRA = Medical Dictionary for Regulatory Activities.
a. These adverse events were reported by the same subject.

No subjects in either treatment group withdrew from the study due to an AE. Dose reduction or temporary discontinuation due to AEs occurred for 5 subjects in the Exubera group and 2 subjects in the lispro group. Four of these (3 in Exubera and 1 in lispro group) were due to hypoglycemia, none of which were considered to be SAEs. Two events of ketoacidosis causing temporary discontinuation of the study drug were considered to be SAEs by the Investigator (1 event each in the Exubera and lispro groups).

No AEs related to forced expiratory volume in 1 second (FEV_1) were reported for any subject during the study. Two subjects in the Exubera group had laboratory test results that were reported as AEs during the study (alanine aminotransferase increased in 1 subject and blood creatinine increased in another subject). One subject each in the Exubera group had AEs of weight increased and weight decreased.

A total of 2 subjects in the Exubera group had significant changes in brief physical examination findings at the final visit from the baseline visit. One subject had cough at the final visit. This subject had an AE of cough. The event was considered to be of moderate severity and related to the study drug. One subject experienced erythema in throat, cough, and glairy mucus. This subject had AEs of rhinorrhea and throat irritation. These AEs were considered to be of mild severity and related to the study drug.

Table 7 presents the distribution of change from baseline in insulin antibodies at Week 0, Week 24, and Week 52.

Table 7 Distribution of Change From Baseline in Insulin Antibodies (Units/mL)

Time Point	Exubera N=38	Lispro N=20
Week 0:		
n	36	18
<3	19 (52.8)	9 (50.0)
3-10	8 (22.2)	5 (27.8)
11-20	2 (5.6)	2 (11.1)
21-30	5 (13.9)	1 (5.6)
>40	2 (5.6)	1 (5.6)
Week 24:		
n	17	10
<3	2 (11.8)	9 (90.0)
3-10	2 (11.8)	1 (10.0)
21-30	1 (5.9)	0
>40	12 (70.6)	0
Week 52:		
n	5	1
3-10	1 (20.0)	1 (100.0)
11-20	1 (20.0)	0
>40	3 (60.0)	0

One subject in the Exubera group had a missing baseline measurement.
N = number of subjects in the indicated treatment population; n = number of subjects evaluated.

CONCLUSIONS: This study was terminated early due to commercial reasons (Sponsor stopped marketing and manufacturing of Exubera). As the study was underpowered due to limited enrollment and early termination, the inferential orientation of the original study objectives was no longer attainable. A total of 6 Exubera subjects and 3 lispro subjects completed the study. Due to the low number of subjects that completed, no descriptive statistics for the efficacy endpoints are provided. No inferential analysis comparisons have been made.

Overall, 35 subjects in the Exubera group experienced 129 AEs and 20 subjects in the lispro group experienced 58 AEs. The majority of these AEs were considered by the Investigator to be mild or moderate in severity. There were no deaths reported during the study and no subjects discontinued due to AEs. The majority of dose reductions or temporary discontinuations were due to AEs of hypoglycemia. These safety findings are consistent with the product labeling.