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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Exubera® / Insulin human (rDNA origin) inhalation powder

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00134147

PROTOCOL NO.: A2171018

PROTOCOL TITLE: A One Year, Open-Label Outpatient, Parallel Group Trial Assessing the Impact of the Availability of Inhaled Insulin (Exubera®) on Glycemic Control in Patients with Type 2 Diabetes Mellitus Who Are Poorly Controlled on a Minimum of Two Oral Anti Diabetic Agents

Study Center(s): One hundred eleven centers enrolled subjects; 10 centers in Canada, 9 centers in France, 31 centers in Germany, 13 centers in Italy, 15 centers in Spain, 19 centers in the United Kingdom and 14 centers in the United States

Study Initiation and Completion Dates: 01 April 2005 to 11 May 2007

Phase of Development: Phase 3b

Study Objective(s): The primary objective of the study was to demonstrate that mean reduction in HbA1c after 26 weeks (approximately 6 months) was greater in subjects to whom inhaled insulin was made available compared to subjects to whom it was not.

Secondary objectives of the study included durability of glycemic control, additional measurements of glycemic control (eg, fasting plasma glucose [FPG]), hypoglycemia, body weight and body mass index, patient reported outcomes (PRO) as well as the safety of both treatment groups.

The objective for the extended treatment period was to examine long term safety as well as the maintenance of glycemic control through a six month extended treatment.

METHODS

Study Design: This study was a 52 week, open, randomized, parallel, multi-center study with a two-week run-in period in subjects, ages ≥35 years and ≤80 years, with type 2 diabetes. The study period between Weeks 0 and 26 was considered the core study period, and from Week 26 to Week 52 the extended treatment period.

A total of approximately 648 male and female subjects with type 2 diabetes were to be randomized across approximately 125 study sites in seven countries (Germany, United Kingdom, France, Italy, Spain, Canada, USA). The goal was to have approximately 518 subjects completing 52 weeks of treatment.

Subjects were stratified into two groups according to previous diabetes treatment (ie, either two oral agents or three or more oral agents) and then randomized to one of two experimental groups as described below:

- Group 1 was given the choice of inhaled insulin and all other marketed anti-hyperglycemic drugs as treatment options, including SC insulin.
- Group 2 did **not** have the choice of inhaled insulin as an option, but had all marketed anti-hyperglycemic drugs as treatment options as in Group 1.

At study entry, all subjects in both groups, and in agreement with their study physician, could choose freely any of the marketed anti-hyperglycemic medications, or remained on their current anti-hyperglycemic regimens. Choices made at the beginning of the study could be revisited and changed as follows:

- At 3 months for lack of efficacy,
- At 6 months via study designed open selection and
- At any time for safety concerns.

In addition to changing treatments, all other marketed anti-hyperglycemic drugs could be appropriately titrated to optimize glycemic control.

Group 1 study subjects who had chosen options other than inhaled insulin at randomization could elect at Week 26 to initiate inhaled insulin. All subjects were required to take pulmonary function test (PFT) and device training prior to dosing.

Number of Subjects (Planned and Analyzed): Planned enrollment was 648 randomized subjects (259 subjects per group). A total of 739 subjects were randomized to study drug treatment and 730 were treated; 357 in Group 1 and 373 in Group 2.

Diagnosis and Main Criteria for Inclusion: Male and female subjects 35 to 80 years, inclusive, with a diagnosis of type 2 diabetes made $\geq$6 months prior to study entry, HbA1c $\geq$8.0%, body mass index (BMI) $\geq$23 kg/m^2 and $\leq$40 kg/m^2 at screening, and currently treated and on a stable dose of at least two oral hypoglycemic agents for at least 3 months prior to study entry with at least half maximum dose per country guidelines or half maximum tolerable dose.

Study Treatment: Subjects using inhaled insulin or SC insulin regimens were encouraged to perform home blood glucose monitoring as often as necessary to determine adequate dose changes. The total daily dose of inhaled insulin was based on body weight. The total daily dose should have been divided into three preprandial doses. If new oral agents were chosen

these agents were initiated and dosed per approved prescribing instructions. All subjects who used oral agents only, including those subjects who chose no change, were also encouraged to perform periodic glucose monitoring as deemed appropriate by the treating physician.

All inhaled insulin was provided in 1 mg and 3 mg distinctly labeled blister packs. These milligram strength designations referred to the mass of insulin in the blister pack. Because of losses in the device and airways, approximately 10% of the insulin in the blister pack was actually absorbed into the circulation, relative to subcutaneous insulin. As an approximation, one inhalation of the 1 mg delivered the equivalent of 2-3 units of SC injected insulin. Each inhalation used one blister. Typically, one or two inhalations were administered per dosing session. Doses were administered immediately prior to meals (within 10 minutes).

Efficacy Evaluations: Efficacy evaluations consisted of assessment of HbA1c at Weeks –2, 4, 12, 26, 34, 42, 52 or end of study, fasting plasma glucose at Weeks -2, 12, 26, 52 or end of study, weight (BMI) at Weeks –2, 12, 26, 34, 52 or end of study, and fasting lipids (HDL, LDL and triglycerides) at Weeks -2, 12, 26, 52 or end of study.

Outcomes Research: The Diabetes Treatment Satisfaction Questionnaire - Status (DTSQs), and the EQ-5D Health Questionnaire were completed at Weeks –1, 26, 52 or end of study, and the Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc) was completed at Weeks 26, 52 or end of study.

Safety Evaluations: Safety evaluations included monitoring of adverse events (AEs) and serious adverse events (SAEs), laboratory evaluations, pulmonary function testing, hypoglycemia, vital signs and physical examination.

Statistical Methods: The Full Analysis Set (FAS) included all randomized subjects with baseline (pre-randomization) and post-baseline HbA1c measurements. Subjects with errors in treatment allocation were included in the FAS set based on their randomized treatment group, but excluded from the Per Protocol set.

The Per-Protocol (PP) set included all randomized subjects with HbA1c measurements at baseline and 12 weeks, at least 12 weeks of study medication, and no major protocol violations. Specifically, a subject receiving inhaled insulin but randomized to Group 2 (Standard group) was excluded from the Per-Protocol set.

The Safety Analysis set consisted of all subjects known to have taken at least one dose of study medication (any oral agent, SC insulin or inhaled insulin). Further, each subject was classified according to their randomized group.

There were additional safety summaries based on subject classifications arising from the Therapeutic Categories as defined below. As this study compares treatment choice, not treatment itself, it was beneficial to have safety illustrated via multiple vantage points. Each subject made a treatment choice at randomization (Visit 3). At three months (Visit 5), there was the potential (due to adverse event or lack of efficacy) to change this treatment choice. Therapeutic Category was assessed over the time interval from Visit 3 (randomization) to Visit 9 (6-month visit); this being considered to be “during the study.”

Each subject was assigned to exactly one of the following four therapeutic categories. These four therapeutic categories were mutually exclusive and exhaustive. For clarity, a change in oral agents implied that there was a change with respect to drug class.

- **Inhaled Insulin** - Subjects who used inhaled insulin (at least one dose of inhaled insulin, irrespective of SC insulin status) during the study;
- **SC Insulin** - Subjects who used SC insulin during the study without inhaled insulin;
- **Changed Oral Agents** - Subjects who did not use insulin (either SC or inhaled) but changed oral agents (OA) (versus OA regimen at screening) during the study;
- **No Change** - Subjects who did not change OA therapy (as stated at screening) during the study.

The primary endpoint was the change in HbA1c from baseline at Week 26.

Secondary efficacy endpoints related to Week 26 and were the following:

- Proportion of subjects achieving HbA1c ≤6.5%
- Proportion of subjects achieving HbA1c ≤7.0%
- The time it takes to get to "be treated with" insulin (inhaled or SC)
- Change from baseline in fasting plasma glucose (FPG) level
- Incidence and severity of hypoglycemia
- Change from baseline in body weight
- Change from baseline in body mass index
- Change from baseline in fasting total cholesterol
- Change from baseline in fasting HDL cholesterol
- Change from baseline in fasting LDL cholesterol
- Change from baseline in fasting triglycerides
- Number of subjects who discontinued due to insufficient clinical response

Endpoints based on HbA1c and FPG are direct measures of glycemic control, while those based on discontinuation for insufficient response and use of insulin are indirect measures. Endpoints based on weight and lipids are associated with changes generally seen in the treatment of diabetes.

For all analyses, baseline was defined as the last assessment prior to randomization. The LOCF (last post-baseline observation carried forward) rule was applied to impute missing data for the efficacy endpoint analyses at Week 26 (and secondarily at Week 52 or End of study). Imputation was not performed at any of the other visits. For safety endpoints with efficacy aspects (such as insulin antibodies, PFT parameters, or hypoglycemic events), imputation was not used in the analyses. Within the text of this clinical study report, the "Week 26" label will refer to a summary that utilizes the LOCF rule when appropriate while the "Week 26 Completers" label will indicate a summary that forgoes any LOCF imputation. Likewise for Week 52 or end of study labels it will be presumed that LOCF was used, whenever appropriate, unless the Completer term is indicated.

The primary endpoint was the change in HbA1c in the FAS at Week 26. For the primary endpoint analysis, ANCOVA (analysis of covariance) with a model consisting of treatment group, number of oral agents at baseline ("2" or "3 or more"), pooled center and covariate baseline HbA1c value was utilized to compare between treatment groups. To support the interpretation of the primary analysis, an identical analysis was performed based upon the PP set rather than the FAS. An additional supportive analysis using the FAS was also provided where, in this case, site was viewed as a random effect.

With respect to secondary endpoints, change from baseline for continuous variables (HbA1c, fasting plasma glucose, lipids, weight, BMI, etc.) was analyzed via ANCOVA with a model consisting of pooled center, number of oral agents at baseline ("2" or "3 or more"), baseline endpoint value (covariate), and treatment group. Mean values at baseline and other timepoints were compared using the same model but without the baseline covariate.

A Cox proportional hazards model, with covariates for number of oral agents at baseline, pooled center and baseline HbA1c, was used to test for a treatment group effect with respect to survival data endpoints. The proportionality assumption was tested (evaluated significance of coefficient for interaction term between treatment group and log time). In the event of significant non-proportionality an appropriate time-varying covariate (eg, the treatment group and log time interaction term) was incorporated in a sensitivity analysis of the original endpoint. To deal with the potential of a multitude of ties within the data, the "exact" method (as available in SAS® via Proc PhReg) was employed.

For continuous endpoints, the following descriptive statistics were presented by treatment groups: n, mean, standard deviation, median, minimum and maximum. Descriptive summary by therapeutic category (by treatment group as well as for overall) was also presented.

For ordered categorical endpoints, frequency distributions (counts and percentages) were presented by treatment groups. The Cochran-Mantel-Haenszel test stratified by the number of oral agents at baseline and pooled center was used for treatment group comparison purposes.

For binary efficacy endpoints, frequency distributions (counts and percentages) were presented by treatment groups. Logistic regression was used with factors for pooled center and number of oral agents at baseline, with baseline endpoint value included as a covariate. Fisher's exact test could have been used if logistic regression was deemed not appropriate.

RESULTS

Subject Disposition and Demography: A total of 1137 subjects were screened and 739 subjects were randomized to study drug treatment. Of the 739 randomized subjects, 9 subjects did not receive treatment; 7 subjects randomized to Group 1 and 2 subjects randomized to Group 2. Of the 730 treated subjects, 357 were in Group 1 (had the choice of inhaled insulin and all other marketed anti-hyperglycemic drugs as treatment options) and 373 were in Group 2 (did not have the choice of inhaled insulin as an option but had all marketed anti-hyperglycemic drugs as treatment options).

Subject disposition by randomized group and therapeutic category are summarized through 26 weeks and through 52 weeks in Tables S1 and S2, respectively.

Table S1. Subject Disposition by Randomized Group and Therapeutic Category, 26 Weeks

	Randomized Groups[a]				Group 1 Therapeutic Categories[b]						Group 2 Therapeutic Categories[b]					
	Group 1		Group 2		INH-1		SC-1		COA-1		NCOA-1		SC-2		COA-2		NCOA-2	
Treated	357		373		279		37		21		20		221		109		43	
Completed	334	(93.6)	354	(94.9)	264	(94.6)	34	(91.9)	19	(90.5)	17	(85.0)	214	(96.8)	103	(94.5)	37	(86.0)
Discontinued	23	(6.4)	19	(5.1)	15	(5.4)	3	(8.1)	2	(9.5)	3	(15.0)	7	(3.2)	6	(5.5)	6	(14.0)
Analyzed for efficacy																		
Full analysis set	347	(97.2)	363	(97.3)	273	(97.8)	37	(100.0)	20	(95.2)	17	(85.0)	218	(98.6)	107	(98.2)	38	(88.4)
Per-protocol set	332	(93.0)	347	(93.0)	263	(94.3)	34	(91.9)	18	(85.7)	17	(85.0)	207	(93.7)	103	(94.5)	37	(86.0)
Analyzed for safety																		
Adverse events	357	(100.0)	373	(100.0)	279	(100.0)	37	(100.0)	21	(100.0)	20	(100.0)	221	(100.0)	109	(100.0)	43	(100.0)
Laboratory data	347	(97.2)	365	(97.9)	273	(97.8)	37	(100.0)	20	(95.2)	17	(85.0)	219	(99.1)	108	(99.1)	38	(88.4)

[a]Group 1 had Inhaled Insulin available, Group 2 did not have Inhaled Insulin available
bTherapeutic categories are not randomized
Nine subjects were randomized but did not receive treatment

Table S2. Subject Disposition by Randomized Group and Therapeutic Category, 52 Weeks

	Randomized Groups[a]				Group 1 Therapeutic Categories[b]						Group 2 Therapeutic Categories[b]					
	Group 1		Group 2		INH-1		SC-1		COA-1		NCOA-1		SC-2		COA-2		NCOA-2	
Treated	357		373		280		37		20		20		232		101		40	
Completed	313	(87.7)	336	(90.1)	250	(89.3)	33	(89.2)	16	(80.0)	14	(70.0)	213	(91.8)	92	(91.1)	31	(77.5)
Discontinued	44	(12.3)	37	(9.9)	30	(10.7)	4	(10.8)	4	(20.0)	6	(30.0)	19	(8.2)	9	(8.9)	9	(22.5)
Analyzed for efficacy																		
Full analysis set	347	(97.2)	363	(97.3)	274	(97.9)	37	(100.0)	19	(95.0)	17	(85.0)	229	(98.7)	99	(98.0)	35	(87.5)
Per-protocol set	335	(93.8)	349	(93.6)	266	(95.0)	35	(94.6)	17	(85.0)	17	(85.0)	220	(94.8)	95	(94.1)	34	(85.0)
Analyzed for safety																		
Adverse events	357	(100.0)	373	(100.0)	280	(100.0)	37	(100.0)	20	(100.0)	20	(100.0)	232	(100.0)	101	(100.0)	40	(100.0)
Laboratory data	347	(97.2)	365	(97.9)	274	(97.9)	37	(100.0)	19	(95.0)	17	(85.0)	230	(99.1)	100	(99.1)	35	(87.5)

[a]Group 1 had Inhaled Insulin available, Group 2 did not have Inhaled Insulin available
[b]Therapeutic categories are not randomized
Nine subjects were randomized but did not receive treatment

In Group 1 and Group 2, 6.4% and 5.1% of subjects discontinued from the study by Week 26. Reasons for discontinuation through Week 26 in Group 1 included adverse events (2.0%), subject defaulted (2.0%), and other (2.5% each). Reasons for discontinuation through Week 26 in Group 2 included adverse events (0.3%), subject defaulted (2.7%), and other (2.1%).

In Group 1 and Group 2, 12.3% and 9.9% of subjects discontinued from the study by Week 52. Reasons for discontinuation through Week 52 in Group 1 included subject died (0.3%), adverse events (3.4%), subject defaulted (5.0%), and other (3.6%). Reasons for discontinuation through Week 52 in Group 2 included adverse events (1.1%), subject defaulted (4.8%), and other (4.0%). Subject defaulted included lost to follow-up and subject no longer willing to participate in study. Other included protocol violation and subject withdrew consent.

Demographic characteristics were comparable between Group 1 and Group 2. In Groups 1 and 2, slightly more subjects were male (56.9% and 56.0%, respectively) than female (43.1% and 44.0%, respectively). In both Groups 1 and 2, the mean age was 58.7 years and the mean duration since diagnosis of diabetes was 11.1 years. The majority of subjects were white.

Efficacy Results: All efficacy results presented are through 26 weeks, unless noted otherwise.

The primary endpoint, mean change in HbA1c between Group 1 and Group 2 from baseline to Week 26, was statistically significant, favoring Group 1. At 26 weeks, mean changes in HbA1c from baseline were –2.0% and –1.7% in Groups 1 and 2, respectively, with an adjusted treatment difference of –0.2% (95% CI: –0.36% to –0.07%; p=0.0039). For both Groups 1 and 2, the within treatment comparison to baseline was statistically significant, and there was a statistically significant difference in the change in HbA1c between Group 1 and Group 2 at Week 4, Week 12, and Week 26. Glycemic control was maintained through Week 52.

A larger percentage of subjects achieved a HbA1c ≤7% in Group 1 than Group 2 at Weeks 4 (9.1% and 4.0%, respectively), 12 (40.2% and 29.6%, respectively), 26 completers (47.5% and 41.5%, respectively), and 26 (45.0% and 38.8%, respectively); the treatment difference was statistically significant at all timepoints. The percentage of subjects that achieved a HbA1c ≤7% in Group 1 when inhaled insulin was used was 47.3%, in Group 1 and Group 2 when SC insulin was used was 37.8% and 40.8%, respectively, when oral medication was changed was 45.0% and 38.3%, respectively, and when there was no treatment change was 23.5% and 28.9%, respectively.

A larger percentage of subjects achieved a HbA1c ≤6.5% in Group 1 than Group 2 at Weeks 4 (2.1% and 1.7%, respectively), 12 (16.9% and 11.4%, respectively), 26 completers (21.3% and 20.1%, respectively) and 26 (20.2% and 17.9%, respectively); however, the treatment difference was statistically significant only at Week 12.

In the full analysis set, the percentage of subjects with hypoglycemia was larger in Group 1 than Group 2 (43.5% and 28.1%, respectively), whether mild or moderate (43.5% and 27.8%,

respectively) or severe (1.4% and 0.6%, respectively). Overall, the total number of hypoglycemic events was larger in Group 1 than Group 2 (730 vs 366 events). The crude event rate per subject month was 0.3 for Group 1 and 0.2 for Group 2. The percentage of subjects with hypoglycemia was higher with inhaled insulin (48.4%) than for any other therapeutic category (range, 13.2% to 35.0%).

The mean decrease in fasting plasma glucose from baseline to Week 26 was similar for Groups 1 and 2 (-57.63 and -59.99 mg/dL, respectively); the within treatment comparisons to baseline were statistically significant.

There was a decrease in total cholesterol, LDL-C and triglycerides and an increase in HDL-C from baseline to Week 26 in both Group 1 and Group 2; for both Group 1 and Group 2 the comparison to baseline for these parameters was statistically significant, with the exception of LDL-C in Group 2. The treatment difference for Group 1 vs Group 2 in the change from baseline to Week 26 for total cholesterol, LDL-C, HDL-C and triglycerides was not statistically significant.

The mean increase in weight from baseline to Week 26 was larger in Group 1 than Group 2 (1.60 and 1.03 kg, respectively); the within treatment comparisons to baseline were statistically significant for both Groups. The treatment group comparison of Group 1 vs Group 2 was not statistically significant.

For Group 1 and Group 2, the within treatment comparison to baseline was statistically significant for the mean change in total score for DTSQc questionnaire and Questions 2 (blood sugar unacceptably high) and 3 (blood sugar unacceptably low). None of the treatment group comparisons were statistically significant.

Outcomes Research: There was a statistically significant correlation between the total DTSQs score and change in HbA1c for both Group 1 and Group 2, and a statistically significant correlation between the total DTSQs change score and change in HbA1c for Group 2 only.

Safety Results: An overview of all causality AEs is presented in Table S3. The percentage of subjects reporting all causality AEs was slightly larger in Group 1 than Group 2 both at 26 weeks (77.9% and 70.0%, respectively) and 52 weeks (86.6% and 80.2%, respectively), as were discontinuations due to AEs at 26 weeks (3.6% and 0.8%, respectively) and 52 weeks (5.6% and 0.8%, respectively).

Table S3. Overview of All Causality Adverse Events, 26 Weeks and 52 Weeks, Safety Population

	26 Weeks				52 Weeks			
	Group 1		Group 2		Group 1		Group 2	
Subjects evaluable for AEs	357		373		357		373	
Number of AEs	793		704		1108		1027	
Subjects with AEs	278	(77.9)	261	(70.0)	309	(86.6)	299	(80.2)
Subjects with severe AEs	19	(5.3)	17	(4.6)	37	(10.4)	32	(8.6)
Subjects discontinued due to AEs [a]	13	(3.6)	3	(0.8)	20	(5.6)	3	(0.8)
Subjects with dose reduced or temporary D/C due to AEs [a]	36	(10.1)	6	(1.6)	38	(10.6)	7	(1.9)

Includes data up to one day after last dose of study drug

The 5 most frequently reported AEs in Group 1 through 26 weeks or 52 weeks were hypoglycemia, cough increased, tremor, sweating, and pharyngitis. The 5 most frequently reported AEs in Group 2 through 26 weeks were hypoglycemia, tremor, sweating, respiratory tract infection and nausea, and through 52 weeks were hypoglycemia, tremor, pharyngitis, sweating, and respiratory tract infection (Table S4).

Table S4. Adverse Events Reported by ≥ 5% of Subjects in Either Group 1 or Group 2 through 26 Weeks or 52 Weeks, Safety Population

	26 Weeks				52 Weeks			
	Group 1 N=357		Group 2 N=373		Group 1 N=357		Group 2 N=373	
	n	(%)	n	(%)	n	(%)	n	(%)
Hypoglycemia	154	(43.1)	103	(27.6)	179	(50.1)	133	(35.7)
Cough increased	41	(11.5)	13	(3.5)	51	(14.3)	18	(4.8)
Tremor	37	(10.4)	34	(9.1)	43	(12.0)	39	(10.5)
Sweating	35	(9.8)	24	(6.4)	41	(11.5)	30	(8.0)
Pharyngitis	30	(8.4)	18	(4.8)	47	(13.2)	36	(9.7)
Asthenia	28	(7.8)	14	(3.8)	32	(9.0)	16	(4.3)
Respiratory tract infection	27	(7.6)	19	(5.1)	34	(9.5)	26	(7.0)
Dizziness	24	(6.7)	16	(4.3)	33	(9.2)	22	(5.9)
Headache	21	(5.9)	16	(4.3)	23	(6.4)	19	(5.1)
Nausea	15	(4.2)	19	(5.1)	23	(6.4)	22	(5.9)
Diarrhea	13	(3.6)	13	(3.5)	19	(5.3)	19	(5.1)
Back pain	13	(3.6)	8	(2.1)	22	(6.2)	19	(5.1)
Flu syndrome	9	(2.5)	12	(3.2)	12	(3.4)	20	(5.4)
Arthralgia	9	(2.5)	14	(3.8)	19	(5.3)	20	(5.4)
Accidental injury	6	(1.7)	17	(4.6)	11	(3.1)	25	(6.7)
Pain	6	(1.7)	16	(4.3)	9	(2.5)	25	(6.7)
Hypertension	5	(1.4)	14	(3.8)	10	(2.8)	21	(5.6)

Includes data up to one day after last dose of study drug.

There was a larger percentage of respiratory AEs in Group 1 than Group 2 (29.4% and 16.9%, respectively), however, the number of severe AEs was small and similar between the two groups (2 and 3 subjects with severe respiratory AEs, respectively). The most common respiratory AEs in Group 1 and Group 2 through 26 and 52 weeks were cough increased (26

weeks: 11.5% and 3.5%, respectively; 52 weeks: 14.3% and 4.8%, respectively), pharyngitis (26 weeks: 8.4% and 4.8%, respectively; 52 weeks: 13.2% and 9.7%, respectively) and respiratory tract infection (26 weeks: 7.6% and 5.1%, respectively; 52 weeks: 9.5% and 7.0%, respectively).

The percentage of subjects who discontinued for AEs was larger in Group 1 than Group 2 at 26 weeks (3.6% and 0.8%, respectively) and 52 weeks (5.6% and 0.8%, respectively) Permanent discontinuations for AEs are listed in Table S5.

Table S5. Permanent Discontinuations for AEs by Group and Subject

Reason for Discontinuation by Group and Subject
Group 1 (up to 26 weeks)
Respiratory disorder[a]
Gingivitis[a]
Urticaria[a]
Chest pain
Fever[a], tachycardia[a]
Nausea[a]
Hyperglycemia, dyspnea[a]
Anxiety[b]
Bone disorder[b]
Cough increased[a]
Pneumonia[a, b]
Dyspnea[a]
Respiratory disorder[a]
Group 1 (26 to 52 weeks)
Cough increased[a], dyspnea[a]
Extrapyramidal syndrome[b]
Maculopapular rash[a, b]
Pulmonary embolus/subject died
Hypoglycemia[a]
Cough increased[a]
Dyspnea[a]
Group 2
Lymphoma malignant[b]
Breast carcinoma
Gastrointestinal carcinoma[b]

[a]Considered treatment related by the investigator
[b]Considered an SAE

Two subjects died during the study. One subject in Group 1 died from a pulmonary embolism, considered unrelated to study drug. One subject in Group 2 died because of pancreatic carcinoma, considered unrelated to study drug. The percentage of subjects reporting SAEs was 10.1% in Group 1 and 9.4% in Group 2. SAEs reported by ≥2 subjects in Group 1 were fall and hypoglycemia (2 subjects each), and in Group 2 were pneumonia and sciatica (3 subjects each) and coronary artery disease, gait disturbance, fall, breast cancer and pneumonia aspiration (2 subjects each) (Table S6).

Table S6. Serious Adverse Events Reported by ≥2 Subjects in Either Treatment Group

	Group 1 (N=357) n (%)	Group 2 (N=373) n (%)
Total subjects (%) with SAEs	36 (10.1)	35 (9.4)
No. of subjects with SAEs by preferred term		
Coronary artery disease	1	2
Gait disturbance	0	2
Pneumonia	1	3
Fall	2	2
Hypoglycemia	2	1
Breast cancer	0	2
Sciatica	1	3
Pneumonia aspiration	0	2

The mean FEV1 at baseline was 2.75 L in Group 1 and 2.73 L in Group 2. At the end of the study, the mean FEV1 was 2.71 L in Group 1 and 2.70 L in Group 2, with a mean percent change from baseline in FEV1 of -1.3 in Group 1 and -1.8 in Group 2. Six subjects (1.8%) in Group 1 and 4 subjects (1.2%) in Group 2 had a percentage change from baseline in FEV1 of <-20%. The mean FVC at baseline was 3.41 L in Group 1 and 3.35 L in Group 2. At the end of the study, the mean FVC was 3.38 L in Group 1 and 3.35 L in Group 2, with a mean percent change from baseline in FVC of -0.9 in Group 1 and -0.5 in Group 2. Six subjects (1.8%) in Group 1 and 5 subjects (1.5%) in Group 2 had a percentage change from baseline in FVC of <-20%.

The mean DLco at baseline was 23.85 mL/min/mmHg in Group 1 and 23.72 mL/min/mmHg in Group 2. At the end of the study, the mean DLco was 23.68 mL/min/mmHg in Group 1 and 23.57 mL/min/mmHg in Group 2, with a mean percent change from baseline in DLco of 0.6 in Group 1 and 0.1 in Group 2. The mean TLC at baseline was 5.63 L in Group 1 and 5.56 L in Group 2. At the end of the study, the mean TLC was 5.53 L in Group 1 and 5.48 L in Group 2, with a mean percent change from baseline in TLC of -1.4 in Group 1 and -1.2 in Group 2.

CONCLUSION(S): This study had a unique study design in which subjects were randomized to two treatment settings: Group 1 (usual care with the option of inhaled insulin) or Group 2 (usual care only), to assess whether inhaled insulin would increase insulin acceptance and improve glycemic control. The results of this study supported the following conclusions:

- Mean reduction of HbA1c at Week 26 was greater in Group 1 when compared to that in Group 2. This was the primary endpoint and this result supported the primary objective of the study, demonstrating that the availability of inhaled insulin improved glycemic control.

- A larger percentage of subjects used insulin earlier and throughout the study in Group 1 than Group 2.

- The overall safety profile is consistent with that seen in other Exubera studies. In this study it was observed that the percentage of subjects reporting all causality AEs was higher at 26 weeks and 52 weeks in Group 1 than Group 2. The difference in the AE rates between groups can be accounted for by the reported higher rates for hypoglycemia and upper respiratory tract events in Group 1. With respect to pulmonary function testing, both groups had a negative percent change comparable in magnitude from baseline with respect to both FEV_1 and FVC.