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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Exubera® / Inhaled human insulin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: No USPI.

NCT NO.: NCT00282971

PROTOCOL NO.: A2171063

PROTOCOL TITLE: A Six Month, Open-Label Outpatient, Parallel Group Trial Assessing the Impact of Inhaled Insulin (Exubera®) on Glycemic Control in Patients with Type 2 Diabetes Mellitus Who Are Poorly Controlled on Two Oral Anti-Diabetic Agents - EXubera® as an Alternative to usual Care in patients failing Two oral Agents (EXACTA)

Study Centers: 6 centers in Portugal, 14 centers in Canada, 16 centers in France, 3 centers in Sweden, 17 centers in Spain, 5 centers in Greece, and 3 centers in Turkey

Study Initiation and Completion Dates: 6 March 2006 to 19 February 2008. This study was terminated prematurely.

Phase of Development: Phase 3b

Study Objectives: The primary objective was to compare the efficacy between subjects who were treated with the combination of oral hypoglycemic agents (OHAs) and EXUBERA® compared to subjects treated with usual diabetes care, by looking at the mean reduction in HbA_1c after 24 weeks in both groups.

The following secondary objectives were to be assessed at the end of study:

- Proportion of subjects who achieved target glycemic control ($HbA_1c \leq 6.5\%$ and $\leq 7.0\%$).
- Time to achieve glycemic control ($HbA_1c \leq 6.5\%$ and $HbA_1c \leq 7.0\%$).
- Change from baseline in fasting plasma glucose (FPG) level.
- Incidence and severity of hypoglycemia.
- Change from baseline in body weight (BW) and body mass index (BMI).

- Change from baseline in fasting lipid profile.
- Treatment categories: Inhaled insulin, subcutaneous (SC) insulin, changed oral anti-diabetic agents, no change in treatment choice.
- Number of subjects who required additional treatment 12 weeks after randomization.
- Number of subjects who discontinued due to insufficient clinical response.
- Change from baseline in pulmonary forced expiratory volume in 1 second (FEV_1).
- Incidence and severity of clinical adverse events (AEs).
- Subject reported treatment satisfaction and health status.

METHODS

Study Design: This was an international, multicenter, open-label, randomized (1:1), parallel group, outpatient study conducted in both male and female subjects with type 2 diabetes aged between 35 to 80 years, inclusive. Subjects were to be randomized to receive either dry powder inhaled insulin (EXUBERA) plus usual oral drugs (2 OHAs) or usual care therapy. Usual care may have consisted of short- or long-acting insulin preparations, and oral anti-diabetic drugs alone or in combination. A total of 432 subjects were to be randomized (216 subjects per arm) in order to obtain 388 subjects who complete the study. The duration of the study was planned to be 28 weeks, including a 4-week screening period followed by a 24-week active study treatment period.

This study was terminated early since the sponsor stopped marketing and manufacturing of EXUBERA and withdrew Market Authorization in Europe in September 2008. Despite persistent efforts to market EXUBERA and the large amount of efficacy and safety data supporting clinical utility, EXUBERA failed to gain wide acceptance among patients and physicians; hence, a decision was made to stop marketing EXUBERA. There was no efficacy, safety, or quality reason associated with the premature halt of this study.

Number of Subjects (Planned and Analyzed): A total of 432 subjects were planned to be randomized (216 subjects per arm). A total of 536 subjects were screened for the study, and 351 subjects were randomized to study treatment. One hundred eighty subjects were treated with inhaled human insulin and 171 subjects were treated with usual care.

Diagnosis and Main Criteria for Inclusion: Subjects were to be males and females between the ages of 35 and 80 years, inclusive, who had been diagnosed with type 2 DM as defined by the American Diabetes Association (ADA) at least 6 months prior to screening. Subjects were required to have an HbA_1c $\geq$8% and $\leq$11.0% at screening and a BMI $\geq$23 kg/m^2 and $\leq$40 kg/m^2. Subjects must have been on a stable dose of 2 OHAs for at least 3 months prior to study entry, have had documentation of a full ophthalmologic exam by an ophthalmologist within 6 months prior to randomization, and had to be willing and able to

perform specified home blood glucose monitoring (HBGM). Subjects currently treated with thiazolidinediones (TZDs) could enter the study after a 12-week washout period.

Study Treatment: Subjects were randomized (1:1) to dry powder inhaled insulin (EXUBERA) versus usual care therapy for the 24-week active study treatment period. Usual care could have consisted of short- or long-acting insulin preparations and oral anti-diabetic drugs alone or in combination. Subjects on Exubera were also allowed to continue on their usual oral anti-diabetic drugs.

For the EXUBERA-treated group, a dose of EXUBERA 1 mg and 3 mg was to be administered before major meals (eg, breakfast, lunch, and evening meal) using the EXUBERA Insulin Dry Powder Inhaler device and a blister package containing 1 or 3 mg of dry powder human insulin.

The initial daily dose of EXUBERA was to be determined based on the subject's body weight and was to be calculated according to the following formulas:

body weight (kg) X 0.15 mg/kg = daily dose in (mg)

daily dose (mg)/3 = initial pre-meal dose (mg)

The premeal doses were to be modified based on meal size and preprandial blood glucose readings. Subjects were to combine 1 and 3 mg doses before each meal to control postprandial glycemia in addition to continuing on their usual oral anti-diabetic drugs. Sufficient amount of blisters of each strength (1 mg and 3 mg) were to be provided to last until next visit. Based on lack of bioequivalence, subjects were instructed not to substitute one 3 mg blister with three 1 mg blisters.

Subjects randomized to the inhaled insulin therapy group took the first study-dose of inhaled insulin under observation at the site and received training in use of the device, a breathing maneuver for inhalation of insulin, practice dosing with empty blisters change of insulin release unit, and maintenance of the inhaler. Written instructions for use and maintenance of the inhaler were to be given. Advice on titrating insulin doses with respect to self monitoring of blood glucose, meals and exercise was also to be given. Subjects were to be supervised when taking the first dose of inhaled insulin that was to be followed by breakfast/snack.

Recommended doses for pre-breakfast, pre-lunch and pre-supper inhaled insulin dosing were based on review of the mean results for the pre-lunch, pre-supper and bedtime glucose values, respectively. Target glucose values included plasma glucose of <90 mg/dL (<5.0 mmol/L) at pre-breakfast, pre-lunch, and pre-supper; <160 mg/dL (<8.9 mmol/L) post-meal; <135 mg/dL (<7.5 mmol/L) at bedtime; and a >60 mg/dL (>3.3 mmol/L) lower limit. If typical glucose values at any of the testing times fell out of the goal range, a new insulin dose was to be recommended for the preceding dosing period (eg, a high pre-supper mean glucose required an upward adjustment of the pre-lunch inhaled insulin dose). Postprandial blood glucose was to be tested 120 min after the start of a meal if HbA_{1c} did not improve despite pre-meal and bedtime values being in the target range. The frequency of post-prandial HBGM was to be at the discretion of the investigator.

In the control group, all marketed hypoglycemic agents could have been used in this study when their use was in accordance with their approved label (eg, short- or long-acting insulin preparations, oral anti-diabetic drugs in various combinations e.g., oral agents plus bedtime insulin, triple combination of oral anti-diabetic agents in subjects who fail on dual combinations, etc).

Subjects who were currently treated with TZDs were allowed to enter the study after a 12-week washout period. At Week 0, TZDs may have been reintroduced after the 12 week washout period in those subjects who had been randomized to the usual care arm and who were on OHAs only. TZDs were not to be added to those usual care regimens that included SC insulin. SC insulin could not be added at 12 weeks to any subject who had been taking TZDs in their usual care regimen since Week 0 as a 12 week washout of TZD's was required.

Decision on the best treatment for each individual was to be made either by: optimizing their current OHA's by increasing the daily dosage without changing OHA's and in accordance with dosing specifications in the proper use of the medication(s) and change in glucose self-monitoring schedule when appropriate; replacing 1 or both OHA's by another OHA; adding a third OHA; or starting SC insulin (short- or long-acting insulin preparations) combined or not with oral agents that were approved to be used in combination with insulin, etc.

Subjects had to be willing to perform blood glucose monitoring during the study. This was to be performed from capillary blood using home blood glucose monitoring kits provided by the Sponsor. Subjects were to be instructed in the use of this meter. Sufficient amount of lancets and glucose testing strips were to be provided for the duration of the study. Subjects were to be allowed to keep their blood glucose monitoring kit upon completion of their involvement in the study.

Once initiated, no change of anti-diabetic agent(s) was permitted during the study. However, in the usual care arm only, change of treatment regimen and introduction of a new hypoglycemic agent including SC insulin may have occurred after Week 12. This was only to be done if, in the investigator's opinion, diabetes remained poorly controlled despite following all available dose titration steps. These subjects were allowed to continue in the study.

EXUBERA was not to be provided after subject's participation in the study was completed. If, at the time of completion of the study, EXUBERA was not commercially available, then the subject together with the investigator were to decide which currently marketed diabetes treatments, in accordance with best medical practice, was to be appropriate for the subject. Guidance on how to make the conversion from EXUBERA to SC insulin was to be provided by the sponsor.

Efficacy Evaluations: The primary efficacy variable was the change from baseline in HbA_1c at Week 24. HbA_1c was to be measured at Weeks -4, -1, 0, 4, 12, and 24/end of treatment. Baseline was defined as the assessment taken at Week 0 (Visit 3).

Secondary endpoints included the following:

- Diabetes related secondary endpoints including the following: the proportion of subjects who achieved good glycemic control (2 definitions of good glycemic control were used: an HbA_1c result of ≤6.5% or ≤7.0%); the time taken to achieve glycemic control (HbA_1c ≤6.5% and ≤7.0%); and the incidence and severity of hypoglycemia.

- The incidence and severity of AEs.

- The change from baseline to end of treatment in fasting FPG level. Fasting plasma glucose levels were evaluated at baseline and then every subsequent visit.

- The change from baseline to end of treatment in BW and BMI. Body weight was to be measured at Weeks –4, 0, 12, and 24 (end of treatment).

- The change from baseline to end of treatment in fasting lipid profile. Fasting lipids were to be measured at Weeks 0, 12, and 24 (end of treatment).

- The number of subjects who required additional treatment 12 weeks after randomization.

- The number of subjects who discontinued due to insufficient clinical response; where insufficient clinical response was defined as having an HbA_1c result of >8.0% at end of study.

- The FEV_1 at baseline, end of treatment, and change from baseline to end of treatment. FEV_1 was to be collected on all study subjects at Weeks -4 and 24, or at the 'Early Discontinuation Visit' in the case of premature termination from the study.

- Subject reported endpoints including treatment satisfaction using a 8-item Diabetes Treatment Satisfaction Questionnaire (DTSQs), a 8-item Diabetes Treatment Satisfaction Questionnaire Change (DTSQc), and health status using the 6-item EQ-5D. DTSQs and EQ-5D assessments were to be recorded at Weeks -4, 0, 12, and 24 (or end of study). DTSQc assessments were recorded at Week 24 (or end of study). Baseline was defined as the Week 0 assessment. The DTSQs, DTSQc, and the EQ-5D were self-administered and each took about 5 minutes to complete.

Safety Evaluations: Safety evaluations included the incidence and severity of AEs, including hypoglycemia, and the change from baseline to end of treatment in FEV_1. The following safety evaluations were also performed: clinical chemistry, hematology, and urinalysis laboratory assessments (Weeks -4, 12, and 24 [end of treatment]); vital signs (Weeks -4 to 24 [end of treatment]); brief physical examination (Weeks -1 to 24 [end of treatment]); and electrocardiogram (Week 0). A screening chest X-ray (Week -1; or a chest X-ray or chest CT and MRT obtained within 6 months prior to screening was acceptable) was obtained according to the protocol to exclude subjects with clinically significant abnormalities on screening chest X-ray (or chest MRI).

Statistical Methods: Due to early termination of this study, only summary statistics were produced for the primary endpoint, 2 key secondary endpoints, and for safety data. The planned non-inferiority analysis was not carried out.

Primary Analysis: The primary endpoint was the change from baseline in HbA1c at Week 24. HbA1c and the change in HbA1c were summarized using summary statistics, including the number of observations, arithmetic mean, standard deviation, 95% 2-sided CI for the arithmetic mean, median, minimum, and maximum values, at each time point using the Full Analysis Set (FAS) population. The FAS was defined as the set of subjects that were randomized, who received at least 1 dose of medication and have at least 1 post-randomization efficacy evaluation (ie, HbA_1c, FEV_1, FPG, or fasting lipid profile assessment). Observed data were to be reported at each time point, except at the end of treatment visit where a last observation carried forward (LOCF) approach was used.

Secondary Analyses: Due to early termination of this study, only 2 secondary endpoints were summarized. The proportion of subjects who achieved good glycemic control, were summarized at each time point, using the FAS population and an LOCF approach to handling missing data. FEV_1 was summarized at baseline and end of treatment. The change from baseline to end of treatment was also summarized. Summaries were provided using the FAS population and an LOCF approach to handling missing data. All other secondary endpoints were listed.

Safety Analyses: Standard safety endpoints were presented based on the safety population, and according to the Sponsor's data standards. The safety population was defined as those subjects who received at least 1 dose of assigned treatment. The following non-standard safety tables were also summarized: discontinuations by respiratory, thoracic, and mediastinal disorders; and hypoglycemic AEs.

RESULTS

Subject Disposition and Demography: A total of 536 subjects were screened for the study, and 351 subjects were randomized to study treatment. One hundred eighty subjects were treated with inhaled human insulin (146 subjects [81.1%] completed the study), and 171 subjects were treated with usual care (149 subjects [87.1%] completed the study). In both treatment groups, the mean age was 59.5 years and the majority of subjects were between 45 and 64 years of age. The majority of subjects were white (83.9% and 83.6% in the inhaled human insulin and the usual care groups, respectively). There were more males than females in both treatment groups. In general, the 2 treatment groups were similar in terms of age, race, weight, and height. Table S1 summarizes subject disposition, subject discontinuations, and the number of subjects included in the efficacy and safety analyses.

Table S1. Subject Disposition and Subjects Analyzed

	Inhaled Human Insulin	Usual Care
Number (%) of Subjects		
Screened, N = 536		
Assigned to Study Treatment, N = 351		
Treated	180	171
Completed	146 (81.1)	149 (87.1)
Discontinued:	34 (18.9)	22 (12.9)
Related to Study Drug:	23 (12.8)	17 (9.9)
Adverse Event	4 (2.2)	0
Lack of Efficacy	1 (0.6)	0
Other	18 (10.0)	17 (9.9)
Not Related to Study Drug:	11 (6.1)	5 (2.9)
Adverse Event	3 (1.7)	2 (1.2)
Other	4 (2.2)	2 (1.2)
Subject no longer willing to participate in study	4 (2.2)	1 (0.6)
Analyzed for Efficacy:		
Full Analysis Set	179 (99.4)	170 (99.4)
Analyzed for Safety:		
Adverse Events	180 (100.0)	171 (100.0)
Laboratory Data	177 (98.3)	170 (99.4)

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

The median duration of treatment was 168.0 and 169.0 days for the inhaled human insulin and usual care groups, respectively. The majority of subjects in both treatment groups had a duration of treatment greater than or equal to 91 days (163/180 subjects in the inhaled human insulin group and 159/171 subjects in the usual care group).

The proportion of subjects with at least 1 disease or syndrome in their present medical history was comparable in the 2 treatment groups (93.9% of subjects in the inhaled human insulin group and 95.3% of subjects in the usual care group). The current diseases or syndromes that were reported by greater than or equal to 5% of subjects in any treatment group (greater than or equal to 9 subjects in any treatment group) were hypothyroidism, dyslipidemia, hypercholesterolemia, hyperlipidemia, obesity, osteoarthritis, depression, insomnia, benign prostatic hyperplasia, erectile dysfunction, and hypertension. At least 1 concomitant drug treatment was taken by all subjects in both the inhaled human insulin and usual care groups.

Efficacy Results: Primary Objective: Subjects treated with a combination of OHAs and inhaled human insulin had a greater mean reduction in HbA_1c after 24 weeks of treatment compared to subjects treated with usual diabetes care (mean decrease from baseline in HbA_1c at Week 24 [LOCF] of -1.94 [1.09 standard deviation (SD)] and -1.42 [1.09 SD], respectively). HbA_1c baseline values and changes from baseline at Weeks 4, 12, 24, and at Week 24 (LOCF) are summarized in Table S2. No formal statistical analysis was performed on the primary endpoint as the study was stopped early and therefore was under powered.

Table S2. Summary of HbA_1c Baseline and Changes from Baseline

	Inhaled Human Insulin N = 179	Usual Care N = 170
Baseline:		
n	176	170
Mean (SD)	9.39 (0.98)	9.32 (0.88)
95% CI for the mean	9.25, 9.54	9.19, 9.45
Median (Minimum, Maximum)	9.40 (6.70, 13.10)	9.20 (7.20, 12.00)
Change from Baseline to Week 4:		
n	164	158
Mean (SD)	-1.08 (0.61)	-0.62 (0.55)
95% CI for the mean	-1.17, -0.98	-0.71, -0.53
Median (Minimum, Maximum)	-1.10 (-3.20, 0.40)	-0.60 (-2.10, 1.00)
Change from Baseline to Week 12:		
n	159	150
Mean (SD)	-2.03 (0.97)	-1.37 (0.92)
95% CI for the mean	-2.18, -1.88	-1.52, -1.23
Median (Minimum, Maximum)	-2.10 (-4.10, 0.90)	-1.40 (-3.60, 0.80)
Change from Baseline to Week 24:		
n	142	150
Mean (SD)	-2.02 (1.10)	-1.44 (1.10)
95% CI for the mean	-2.21, -1.84	-1.62, -1.26
Median (Minimum, Maximum)	-2.10 (-5.30, 1.40)	-1.40 (-3.90, 2.50)
Change from Baseline to Week 24 (LOCF):		
n	175	170
Mean (SD)	-1.94 (1.09)	-1.42 (1.09)
95% CI for the mean	-2.10, -1.78	-1.59, -1.25
Median (Minimum, Maximum)	-2.00 (-5.30, 1.40)	-1.40 (-3.90, 2.50)

N = number of subjects in the indicated treatment population, n = number of subjects evaluated, SD = standard deviation, LOCF = last observation carried forward.

Secondary Objectives: A larger proportion of subjects in the inhaled human insulin group achieved $HbA_1c \leq 7\%$ at Week 24 (LOCF) compared to subjects in the usual care group (32.0% and 12.9%, respectively). A larger proportion of subjects in the inhaled human insulin group also achieved $HbA_1c \leq 6.5\%$ at Week 24 (LOCF) compared to subjects in the usual care group (15.2% and 5.9%, respectively). The inhaled human insulin and usual care treatment groups had mean baseline FEV_1 values of 4.44 (12.82 SD) and 3.92 (11.00 SD), respectively; and had mean changes from baseline in FEV_1 at Week 24 LOCF of -0.27 (9.85 SD) and -0.08 (0.61 SD), respectively. Data from the DTSQs, DTSQc, and EQ-5D were collected, but were not statistically analyzed. No formal statistical analysis was performed on the secondary endpoints as the study was stopped early.

Safety Results: There were no deaths that occurred during the study. A total of 13 SAEs were experienced by 9 subjects treated with inhaled human insulin, and 4 of these events were considered by the investigator to be related to the study treatment (inhaled human insulin) (Table S3). Six subjects in the usual care group experienced a total of 7 SAEs, and 1 of these events was considered by the investigator to be related to study treatment (usual care). The only SAEs that were reported by more than 1 subject were myocardial infarction (2 subjects with acute myocardial infarction in the inhaled human insulin group and 1 subject with myocardial infarction in the usual care group) and colon cancer (1 subject each in the inhaled human insulin and usual care groups).

Table S3. Summary of Serious Adverse Events

Treatment	MedDRA Preferred Term	Causality per Investigator	Outcome
Inhaled human insulin	Blood glucose increased	Study Drug	Recovered
	Device malfunction	Study Drug	Recovered
	Ketoacidosis[a]	Other	Recovered
	Acute myocardial infarction[a]	Other	Recovered
	Atrial fibrillation[a]	Other	Not recovered
	Incision site infection	Other illness	Recovering
	Cholecystitis [b]	Disease under study	Recovered
	Cardiac failure [c]	Other illness	Recovered
	Colon cancer [c]	Other illness	Not recovered
	Acute myocardial infarction [c]	Other illness	Recovered
	Vertebrobasilar insufficiency [b]	Other illness	Recovered
	Edema peripheral[c]	Study Drug	Recovered
	Dyspnea [c]	Study Drug	Recovered
Usual Care	Prostate cancer [c]	Other	Recovered
	Diabetes mellitus inadequate control	Disease under study	Recovered
	Transient ischemic attack	Other illness	Recovered
	Pancreatitis acute [b,d]	Study drug	Recovered
	Myocardial infarction	Other illness	Recovered with sequelae
	Coronary artery disease	Other illness	Recovered with sequelae
	Colon cancer[e]	Other	Recovered

[a] = AEs of ketoacidosis, acute myocardial infarction, and atrial fibrillation occurred post-treatment.
[b] = Subject had study drug stopped temporarily.
[c] = Subject was permanently discontinued.
[d] = This subject reported a SAE of pancreatitis acute which was attributed to a concomitant medication (acarbose), which is used to treat type 2 diabetes.
[e] = This subject also had a post-treatment SAE of abdominal pain on Day 155.

Seven subjects in the inhaled human insulin group and 2 subjects in the usual care group withdrew from the study due to AEs (Table S4). In the inhaled human insulin group, the AEs of stomach discomfort, dyspnea exertional, bronchitis, edema peripheral, and dyspnea which led to discontinuation were considered by the investigator to be treatment-related. None of the discontinuations due to AEs were considered by the investigator to be device related. None of the discontinuations due to AEs in the usual care arm were considered to be treatment-related.

Table S4. Discontinuations Due to Adverse Events

	Adverse events leading to study discontinuation			
Treatment	**MedDRA Preferred Term**	**SAE**	**Severity**	**Outcome**
Inhaled Human Insulin	Stomach discomfort[a]	No	Moderate	Resolved
	Dyspnea exertional[a]	No	Mild	Still Present
	Cardiac failure	Yes	Severe	Resolved
	Bronchitis[a]	No	Severe	Resolved
	Colon cancer	Yes	Severe	Still Present
	Acute myocardial infarction	Yes	Severe	Resolved
	Edema peripheral[a]/Dyspnea[a]	Yes	Moderate/Severe	Resolved/Resolved
Usual Care	Prostate cancer	Yes	Severe	Resolved
	Abdominal pain, Colon cancer	Yes	Severe	Still Present/Resolved

SAE = serious adverse event according to investigators assessment.
MedDRA (v11.0) coding dictionary was applied.
[a] Adverse event was considered to be treatment-related by the investigator.

Three subjects had pulmonary-related AEs that led to subject discontinuation. One subject (inhaled human insulin) had an AE of dyspnea exertional on Day 53 that was considered by the investigator to be of mild severity. This event was still present at the end of study (>Day 156). One subject (inhaled human insulin) had an AE of bronchitis on Day 108 that was considered by the investigator to be of severe intensity. This event stopped on Day 115. One subject had SAEs of peripheral edema and dyspnea on Day 8 (events ended on the same day) that were considered by the investigator to of moderate and severe severity, respectively. All of these events were considered by the investigator to be related to the study drug.

Dose reduction or temporary discontinuation due to AEs occurred in 37 subjects (20.6%) in the inhaled human insulin group and 5 subjects (2.9%) in the usual care group (Table S5). The majority of these dose reductions or temporary discontinuations were due to AEs of hypoglycemia. Three of the temporary discontinuations of study drug were due to events considered by the investigator to be SAEs (see Table S3).

Of the 180 subjects treated with inhaled human insulin, 149 subjects (82.8%) experienced a total of 313 treatment-emergent AEs. In the usual care group, 104 subjects (60.8%) experienced a total of 270 treatment-emergent AEs. A summary of all causality and treatment-related AEs is presented in Table S5.

Table S5. Summary of Treatment-Emergent Adverse Events (All Causality and Treatment-Related)

	Inhaled Human Insulin		Usual Care	
	All Causality	Treatment-Related	All Causality	Treatment-Related
Number (%) of subjects:				
Subjects evaluable for AEs	180	180	171	171
Number of AEs	313	170	270	86
Subjects with AEs	149 (82.8)	112 (62.2)	104 (60.8)	75 (43.9)
Subjects with SAEs	8 (4.4)[a]	2 (1.1)	6 (3.5)	0[b]
Subjects with severe AEs	20 (11.1)	18 (10.0)	58 (33.9)	55 (32.2)
Subjects discontinued due to AEs	7 (3.9)	4 (2.2)	3 (1.8)[c]	1 (0.6)[c]
Subjects with dose reduced or temporary discontinuation due to AEs	37 (20.6)	27 (15.0)	5 (2.9)	2 (1.2)

AE = adverse event, SAE = serious adverse event.
Included 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.
Serious adverse events (SAEs) were according to the investigator's assessment.
MedDRA (v11.0) coding dictionary was applied.
[a] = One subject reported SAEs of ketoacidosis, acute myocardial infarction, and atrial fibrillation post-treatment (see Table S3) and these events are not reflected in this summary table.
[b] = One subject reported a SAE of pancreatitis acute which was attributed to a concomitant medication (acarbose), which is used to treat type 2 diabetes. Therefore this SAE should have been considered treatment-related.
[c] = One subject discontinued 1 usual care treatment due to a treatment-emergent, treatment-related AE, but remained in the study on other usual care medications. This table reflects the inclusion of this subject, although this subject actually completed; and therefore there were only 2 subjects in the usual care group who discontinued the study due to AEs and no subjects in the usual care group discontinued the study due to a treatment-related AE.

Adverse events (all causality) reported by greater than 5% of subjects in the inhaled human insulin and/or the usual care group, ranked by frequency of reporting, populated the

following System Organ Classes (SOCs): metabolism and nutrition disorders (66.1% and 57.3%, respectively), infections and infestations (21.7% and 19.3%, respectively), nervous system disorders (10.6% and 11.1%, respectively), gastrointestinal disorders (10.0% and 11.1%, respectively), general disorders and administration site conditions (9.4% and 11.1%, respectively), respiratory, thoracic, and mediastinal disorders (11.1% and 4.1%, respectively), and musculoskeletal and connective tissue disorders (5.0% and 7.6%, respectively).

Adverse events (all causality and treatment-related) reported by ≥2% of subjects in any treatment group during the study are presented in Table S6.

Table S6. Incidence of Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in Any Treatment Group

	Inhaled Human Insulin N = 180		Usual Care N = 171	
System Order Class Preferred Term	**All Causality n (%)**	**Treatment-related n (%)**	**All Causality n (%)**	**Treatment-related n (%)**
Gastrointestinal disorders	**18 (10.0)**	**8 (4.4)**	**19 (11.1)**	**2 (1.2)**
Abdominal pain	2 (1.1)	1 (0.6)	4 (2.3)	1 (0.6)
Diarrhea	4 (2.2)	1 (0.6)	3 (1.8)	1 (0.6)
General disorders and administration site conditions	**17 (9.4)**	**11 (6.1)**	**19 (11.1)**	**5 (2.9)**
Asthenia	5 (2.8)	5 (2.8)	6 (3.5)	2 (1.2)
Fatigue	4 (2.2)	4 (2.2)	3 (1.8)	1 (0.6)
Pyrexia	4 (2.2)	0	1 (0.6)	0
Infections and infestations	**39 (21.7)**	**3 (1.7)**	**33 (19.3)**	**0**
Bronchitis	5 (2.8)	1 (0.6)	2 (1.2)	0
Influenza	6 (3.3)	0	7 (4.1)	0
Nasopharyngitis	8 (4.4)	1 (0.6)	4 (2.3)	0
Upper respiratory tract infection	5 (2.8)	0	5 (2.9)	0
Urinary tract infection	7 (3.9)	0	6 (3.5)	0
Metabolism and nutrition disorders	**119 (66.1)**	**105 (58.3)**	**98 (57.3)**	**73 (42.7)**
Hypoglycemia	118 (65.6)	105 (58.3)	98 (57.3)	73 (42.7)
Nervous system disorders	**19 (10.6)**	**13 (7.2)**	**19 (11.1)**	**4 (2.3)**
Dizziness	6 (3.3)	5 (2.8)	3 (1.8)	1 (0.6)
Headache	2 (1.1)	1 (0.6)	6 (3.5)	2 (1.2)
Tremor	8 (4.4)	7 (3.9)	5 (2.9)	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	**20 (11.1)**	**13 (7.2)**	**7 (4.1)**	**1 (0.6)**
Cough	10 (5.6)	8 (4.4)	2 (1.2)	1 (0.6)
Vascular disorders	**5 (2.8)**	**1 (0.6)**	**6 (3.5)**	**0**
Hypertension	2 (1.1)	1 (0.6)	4 (2.3)	0

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.
Included data up to 1 day after last dose of study drug.
MedDRA (v11.0) coding dictionary was applied.

The most frequently reported AEs of all-causality were reported by a larger percentage of subjects in the inhaled human insulin group compared to the usual care group, including hypoglycemia (65.6% and 57.3%), cough (5.6% and 1.2%, respectively); tremor (4.4% and 2.9%, respectively); and dizziness (3.3% and 1.8%) (Table S6). The most frequently reported treatment-related AEs were also reported by a larger percentage of subjects in the inhaled human insulin group compared to the usual care group, including hypoglycemia (58.3% and 42.7%), cough (4.4% and 0.6%, respectively); tremor (3.9% and 0.6%,

respectively); dizziness (2.8% and 0.6%), fatigue (2.2% and 0.6%, respectively), and asthenia (2.8% and 1.2%, respectively) (Table S6).

A total of 20 subjects (11.1%) and 7 subjects (4.1%) in the inhaled human insulin and usual care groups, respectively, had AEs belonging to the SOC of respiratory, thoracic, and mediastinal disorders. In the inhaled human insulin group: 10 subjects had AEs of cough; 3 subjects had AEs of dyspnea; 2 subjects each had AEs of dyspnea exertional (1 of these events led to subject withdrawal [Table S4]) and pharyngolaryngeal pain; and 1 subject each had AEs of bronchospasm, dry throat, lung disorder, pharyngeal erythema, and snoring. In the usual care group: 2 subjects had AEs of cough; and 1 subject each had AEs of dyspnea, nasal congestion, nocturnal dyspnea, pharyngolaryngeal pain, productive cough, and throat irritation. Also, an AE of aspiration tracheal (system order class: investigations) was reported by 1 subject in the usual care group during the study. All of these AEs were of mild or moderate severity, except for 1 severe AE of dyspnea that led to subject discontinuation (see Table S4).

The majority of AEs (all causality) in the inhaled human insulin and usual care groups were considered by the investigator to be mild (189/313 and 151/270, respectively) or moderate (101/313 and 58/270, respectively) in severity. There were 23/313 severe AEs in the inhaled human insulin group and 61/270 severe AEs in the usual care group. The only severe AE that occurred in greater than 1 subject in either the inhaled human insulin or usual care group was hypoglycemia (17 [9.4%] and 55 [32.2%] subjects, respectively); and all of these events were considered by the investigator to be treatment-related.

For the purpose of this study, the following definition was used to categorize severe hypoglycemia. In order to categorize a hypoglycemic event as severe, all 3 of the following criteria had to be met:

1. The subject was unable to treat him/herself. Neurologic impairment should have been the reason why the subject could not treat him/herself and required assistance. Age or pre-existing disability was not acceptable as a reason to classify the episode of hypoglycemia as severe.

2. 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, or loss of consciousness.

3. Either blood glucose was measured and was 49 mg/dL (2.7 mmol/L) or less or if blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, SC glucagon, or IV glucose.

Events that did not meet all 3 criteria for severe hypoglycemia were characterized as “mild to moderate.”

A total of 118 subjects (65.6%) in the inhaled human insulin group and 98 subjects (57.3%) in the usual care group experienced hypoglycemic AEs during the study. None of these events were considered by the investigator to be SAEs and none of these events led to subject discontinuation. Seventeen subjects (9.4%) in the inhaled human insulin group and

55 subjects (32.2%) in the usual care group had hypoglycemic AEs that were considered by the investigator to be of severe intensity. Thirty subjects (16.7%) in the inhaled human insulin group and 3 subjects (1.8%) in the usual care group had dose reduced or temporary discontinuation due to an AE of hypoglycemia.

One AE of decreased forced expiratory volume occurred during the study. One subject in the inhaled human insulin group had an AE of decreased forced expiratory volume (decrease of 15% on pulmonary capacity test [FEV_1]) on Day 36 that stopped on Day 137. This event was considered by the investigator to be of mild severity and related to the study drug, but not the device; and the event resolved.

A total of 143 subjects (81%) in the inhaled human insulin group and 148 subjects (87%) in the usual care group had laboratory test abnormalities (without regard to baseline abnormality) during the study. Five subjects had safety laboratory test results that were reported by the investigator as AEs during the study. Safety laboratory test AEs included: increased blood alkaline phosphatase and increased gamma-glutamyltransferase (1 subject in the inhaled human insulin group); decreased blood glucose (2 subjects in the inhaled human insulin group); increased blood glucose (1 subject in the usual care group); and increased blood triglycerides (1 subject in the usual care group). All of these events were considered to be related to study drug, except for the events of increased blood alkaline phosphatase, increased gamma-glutamyltransferase, and increased blood triglycerides.

A total of 3 subjects had vital signs results that were reported by the investigator as AEs during the study; including 1 subject in the usual care group who had an AE of increased heart rate, 1 subject in the usual care group who had AEs of pulse absent and pulse abnormal, and 1 subject in the inhaled human insulin group who had an AE of decreased pedal pulse. None of these events were considered by the investigator to be related to the study drug.

Two subjects had AEs of increased weight that began during study treatment. One subject (inhaled human insulin group) had an AE of increased weight that was considered by the investigator to be related to the study drug, and 1 subject (usual care group) had an AE of increased weight that was considered by the investigator to be not related to the study drug. Prior to receiving study treatment, 1 subject (inhaled human insulin group) had an AE of increased weight that was also considered by the investigator to be related to the study drug.

There were no ECG results reported by the investigator as AEs during the study.

Screening chest X-ray assessment results were also collected to exclude patients with clinically significant abnormalities on screening chest X-ray (or chest MRI).

CONCLUSIONS:

- Subjects treated with a combination of OHAs and inhaled human insulin had a greater mean reduction in HbA_1c after 24 weeks of treatment compared to subjects treated with usual diabetes care (mean decrease from baseline in HbA_1c at Week 24 [LOCF] of -1.94 [1.09 SD] and -1.42 [1.09 SD], respectively).

- At Week 24 (LOCF), a larger proportion of subjects treated with inhaled human insulin achieved good glycemic control compared to subjects treated with usual care (defined as $HbA_1c \leq 7.0\%$ (32.0% and 12.9%, respectively and $HbA_1c \leq 6.5\%$ (15.2% and 5.9%, respectively).

- The inhaled human insulin and usual care treatment groups had similar mean baseline FEV_1 values of 4.44 (12.82 SD) and 3.92 (11.00 SD), respectively; and had mean changes from baseline in FEV1 at Week 24 LOCF of -0.27 (9.85 SD) and -0.08 (0.61 SD), respectively.

- Overall, 82.8% of subjects treated with inhaled human insulin and 60.8% of subjects treated with usual care had treatment-emergent AEs (all causality); and the majority of these events were considered by the investigator to be mild or moderate in severity. The most frequently reported AEs of all-causality were reported by a larger percentage of subjects in the inhaled human insulin group compared to the usual care group, including hypoglycemia, cough, tremor, and dizziness.

- A total of 118 subjects (65.6%) in the inhaled human insulin group and 98 subjects (57.3%) in the usual care group experienced hypoglycemic AEs during the study. The increased incidence of hypoglycemic events seen in the inhaled human insulin group is most probably due to the initiation of inhaled insulin therapy and appropriate dose titration. None of these events were considered by the investigator to be SAEs and none of these events led to subject discontinuation.

- One AE of decreased forced expiratory volume occurred during the study in a patient receiving inhaled human insulin. During study treatment, 5 subjects had safety laboratory test results that were reported by the investigator as AEs, 3 subjects had vital signs AEs, and 2 subjects had AEs of increased weight. There were no ECG results reported by the investigator as AEs during the study. Serious adverse events occurred in 9 and 6 subjects in the inhaled human insulin and usual care groups, respectively. The only SAEs that were reported by more than 1 subject were myocardial infarction and colon cancer. Seven subjects in the inhaled human insulin group and 2 subjects in the usual care group withdrew from the study due to AEs; including 3 subjects in the inhaled human insulin group who had pulmonary-related AEs of dyspnea exertional (mild), bronchitis (severe), and dyspnea (severe) that led to subject discontinuation (all of these events were considered to be related to the study drug). Dose reduction or temporary discontinuation due to AEs occurred for 20.6% of the subjects in the inhaled human insulin group and 2.9% of the subjects in the usual care group. The majority of these dose reductions or temporary discontinuations were due to AEs of hypoglycemia. There were no deaths that occurred during the study.