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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: NCT00437489

PROTOCOL NO.: A2171086

PROTOCOL TITLE: A 16 Week Open-Label Outpatient, Randomized Parallel Study Assessing the Impact of Two Different Initial Dose Prescriptions for Dry Powder Inhaled Insulin (Exubera®) on Glycemic Control in Patients with Type 2 Diabetes Mellitus Who are Poorly Controlled on a Combination of Two or More Oral Agents

Study Centers: Five centers in the Philippines, 2 centers in Singapore, 1 center in Hong Kong, and 1 center in Pakistan enrolled subjects.

Study Initiation and Completion Dates: 25 June 2007 to 23 November 2007. The study was terminated prematurely.

Phase of Development: Phase 4

Study Objectives: The primary objective of this study was to assess whether a simple initial dose prescription of inhaled insulin (Exubera) achieved glycemic control (HbA_{1c}) after 16 weeks that was non-inferior compared to the standard weight-based formula.

The secondary objectives of this study were to assess the speed of achieving a stable prescribed dose, the glucose control at 16 weeks, the incidence of hypoglycemia during the first 4 weeks and over 16 weeks, and to assess the safety and tolerability of Exubera.

METHODS

Study Design: This was designed as a multinational, open-label, outpatient, parallel, randomized, multi-center study comparing 2 different initial dose prescriptions of Exubera® in approximately 424 male and female subjects. Subjects were randomized in a 1:1 ratio into 2 treatment groups. Subjects in Group A self-administered 1 mg Exubera TID before each meal (breakfast, lunch, and dinner), and subjects in Group B self-administered a dose of Exubera that was determined by the body weight-based formula (body weight [kg] x 0.05 [mg/kg]) TID before each meal (breakfast, lunch, and dinner). Throughout the study, the dose of Exubera could be adjusted to achieve glucose control targets.

Subjects were to attend 8 visits over a 18-week period. Screening assessments were performed over 2 visits within 14 days before Visit 2 (Week 0). Subjects were randomized at Visit 2 and received the first dose of study drug under medical supervision. Subjects returned to the study site for Visits 3 to 8 (at Weeks 1, 2, 4, 8, 12, and 16). Subjects were given worksheets at Visits 1 to 5, and 7 (at Weeks -2, 0, 1, 2, 4, and 12) for recording their blood glucose concentrations and concomitant medications. A telephone visit occurred between Visits 2 and 3 (between Week 0 and Week 1). Telephone visits then occurred every 3 days (eg, Monday and Thursday) during the remaining 3 of the first 4 weeks (up to Visit 5) after initiation of Exubera to report and review the previous 3 days' home glucose monitoring results. Recommendations for insulin titration were communicated accordingly. Thereafter, until Visit 8 (Week 16), subjects were contacted once a week to assure clinical efficacy and safety (a mid-week telephone contact was recommended to review blood glucose values).

In addition to scheduled telephone visits, subjects were to immediately report any symptom, side effect, or injury experienced during the study to the study physician or a member of the study staff. Contact information for the study physician and the research nurse were provided and a 24-hour contact number was also available to each subject.

Follow-up procedures were performed for all subjects at Visit 8 (Week 16 or early termination).

Number of Subjects (Planned and Analyzed): It was planned that approximately 424 subjects would be enrolled in this study. However, because the study was terminated early, a total of 82 subjects were screened and 49 subjects were assigned to treatment: 25 subjects in Group A and 24 subjects in Group B.

Diagnosis and Main Criteria for Inclusion: The study enrolled male and female subjects aged ≥18 years old, who had been diagnosed with type 2 diabetes according to the American Diabetes Association criteria (Diabetes Care 25: S5-S20, 2002) at least 6 months before entry into the study, and who had HbA_{1c} ≥7.0% at screening.

Study Treatment: In both groups, a dose of CP 464-005 (dry powder inhaled insulin [Exubera], also referred to as 'inhaled insulin') consisting of combinations of 1 mg and/or 3 mg blisters was administered before major meals (breakfast, lunch, and dinner) for a 16-week period. In subjects randomized to the fixed initial dose arm (Group A), the total initial dose prescribed was 3 mg daily, divided into three 1 mg doses. In subjects randomized to body weight-based dose initiation (Group B), the initial total daily dose of Exubera was determined based on the subject's body weight (defined as a multiple of body weight by factor 0.15 [mg/kg]) and divided equally into 3 doses (body weight [kg] x 0.05 [mg/kg] = pre-meal dose). Calculated doses were rounded to the nearest whole integer, (eg, 3.8 mg was rounded to 4 mg). Pre-meal doses were modified based on meal size prescribed per individual dietary plan at Visit 2 (Week 0) and pre-prandial blood glucose readings. Subjects combined 1 mg and 3 mg doses as necessary before each meal to control postprandial glycemia in addition to continuing on their usual oral drugs.

Efficacy Evaluations: Because this study was terminated early, the primary and secondary efficacy endpoints defined in the final statistical analysis plan (SAP) were amended to the following in the amended SAP (dated 09 January 2008):

- Change in HbA_{1c} from baseline, by visit.
- Change from baseline in fasting plasma glucose, by visit.
- Change from baseline in mean average blood glucose based on a 7-point blood glucose profile, by visit.
- Incidence of overall and severe hypoglycemia collected at baseline (Week 0), and by visit.
- Incidence of nocturnal hypoglycemia collected at baseline (Week 0), and by visit. Nocturnal hypoglycemia was defined as any hypoglycemia occurring after the subject had commenced his/her usual night-time sleeping period and before the subject had gotten up at his/her usual time next morning.

Safety Evaluations:

- Adverse events (AEs).
- Pulmonary function (FEV_1).
- Clinical chemistry (creatinine, AST, ALT).
- Hematology (hemoglobin, hematocrit, erythrocytes, leukocytes).
- Vital signs (blood pressure and heart rate).
- Body weight.
- Body mass index (BMI).

Statistical Methods: No inferential statistical analyses were planned in the amended SAP. For continuous efficacy endpoints, descriptive statistics (N, mean, standard deviations [SD], range, and median) were presented by randomized group. For categorical efficacy endpoints, frequency distributions (counts and percentages) were presented by randomized group.

Descriptive statistics were used to present safety data.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table S1.

Table S1. Subject Disposition

	Group A	Group B
Treated	25	24
Safety population	25	24
FAS population	25	24
Completed	2	2
Discontinued:		
Study terminated by sponsor	23	21
Lost to follow-up	0	1

FAS = full analysis set.

All subjects were included in both the safety and FAS populations.

All subjects were Asian, and the distribution of demographic and other baseline characteristics was comparable between randomized groups.

The number of subjects receiving any 2-drug, 3-drug, or 4-drug combinations of oral diabetes medication before entry into the study was similar in Group A and Group B. Combinations of 2 diabetes drugs were most commonly taken prior to the start of the study, and metformin plus gliclazide was the most common drug combination overall.

Efficacy Results: As a result of Pfizer's decision on 18 October 2007 to return the worldwide rights for Exubera (insulin human [rDNA origin]) Inhalation Powder) to Nektar, the company from which Pfizer licensed the inhaled insulin technology, it was decided to terminate Protocol A2171086 before the study had recruited the target number of subjects and followed them for the per protocol specified period.

Descriptive statistics for HbA_{1c}, fasting plasma glucose, and overall absolute, pre-meal, and post-meal blood glucose are summarized in Table S2.

Table S2. Descriptive Statistics for HbA_{1c}, Fasting Plasma Glucose, and Overall Absolute, Pre-meal, and Post-meal Blood Glucose Change from Baseline to Week 16 (LOCF) - FAS Population

	Group A (N=25)			Group B (N=24)		
	Mean (SD)			Mean (SD)		
Endpoint Measurement	**Baseline**	**Week 16**	**Change**	**Baseline**	**Week 16**	**Change**
HbA_{1c} (%)	9.4 (1.57)	7.6 (1.04)	-1.9 (1.56)	9.7 (1.86)	7.7 (1.11)	-2.0 (1.17)
Fasting plasma glucose (mmol/l)	8.7 (2.40)	7.0 (1.53)	-1.8 (2.36)	10.8 (5.40)	7.9 (2.42)	-2.9 (5.62)
Overall absolute blood glucose (mmol/l)[a]	11.1 (3.20)	8.5 (2.04)	-2.5 (3.62)	12.4 (3.93)	8.0 (1.51)	-4.3 (4.20)
Pre-meal blood glucose (mmol/l)[b]	10.0 (2.90)	8.4 (2.26)	-1.7 (3.58)	11.5 (3.75)	8.2 (1.86)	-3.3 (4.05)
Post-meal blood glucose (mmol/l)[b]	12.5 (3.68)	8.6 (2.38)	-4.1 (3.78)	13.5 (4.37)	8.3 (1.86)	-5.5 (4.28)
Change from pre-meal to post-meal blood glucose (mmol/l)[c]	2.5 (1.92)	0.3 (2.15)	-2.5 (2.14)	1.9 (2.65)	0.0 (2.06)	-2.1 (2.96)

SD = standard deviation.
Note: Descriptive statistics were produced using LOCF for Week 16, therefore all subjects are included in the Week 16 data.
[a] Based on the mean of 7-point home blood glucose monitoring (HGM) values.
[b] Based on the mean of pre-meal or post-meal HGM values.
[c] Based on the mean of difference of pre-meal HGM values from post-meal HGM values.

Mean HbA_{1c}, fasting plasma glucose, and overall absolute, pre-meal, post-meal blood glucose levels, and change from pre-meal to post-meal blood glucose levels decreased from baseline in both randomized groups. No statistical inference can be drawn because of the small sample size.

The number of subjects who experienced hypoglycemia and nocturnal hypoglycemia is summarized in Table S3, and the hypoglycemia event rate per month is summarized in Table S4.

Table S3. Cumulative Number of Subjects Who Experienced Hypoglycemia and Nocturnal Hypoglycemia at Week 16 - FAS Population

	Group A (N=25)	Group B (N=24)
Cumulative number of subjects who experienced hypoglycemia by Week 16 (n [%])	12 (48.0)	5 (20.8)
Cumulative number of subjects who experienced nocturnal hypoglycemia by Week 16 (n [%])	2 (8.0)	2 (8.3)

Note: Descriptive statistics were produced using LOCF for Week 16, therefore all subjects are included in the Week 16 data.

Table S4. Hypoglycemia Event Rate Per Month- FAS Population

	Group A		Group B	
	n	Mean (SD)	n	Mean (SD)
Hypoglycemia event rate per month up to Week 4[a]	8	3.3 (3.3)	4	8.3 (9.1)
Hypoglycemia event rate per month up to Week 16[a]	12	2.4 (2.4)	5	2.5 (1.3)

SD = standard deviation.
[a] Monthly event rate was calculated as the daily event rate multiplied by 30, and the daily event rate was calculated as the total number of events divided by the days in study up to the specified timepoint (*ie,* Week 4 or Week 16).

There was an approximate 2.3-fold increase in the incidence of hypoglycemia by Week 16 in Group A compared with Group B. Nocturnal hypoglycemia was experienced by 2 subjects in Group A and 2 subjects in Group B during the study. The mean hypoglycemia event rate per month decreased from up to Week 4 compared with up to Week 16, in both randomized groups. No subject experienced severe hypoglycemia during the study. No statistical inference can be drawn because of the small sample size.

Safety Results: No deaths were reported during this study and no subject permanently discontinued the study due to AEs or laboratory abnormalities. A total of 3 treatment-emergent serious adverse events (SAEs) were reported for 2 subjects up to 1 day after the last dose of study drug in Group A:

- Subject 10041003 had 1 SAE of inadequately controlled blood pressure.
- Subject 10041013 had 2 SAEs, one of joint instability and one of diabetic neuropathy.

In addition, 1 SAE was reported for 1 subject in Group B more than 1 day after the last dose of study drug:

- Subject 10011002 had 1 SAE of groin abscess.

Each SAE was assessed as severe, not related to treatment, and resolved.

One subject in Group A and 5 subjects in Group B had a dose reduction or were temporarily discontinued due to AEs. None of the SAEs recorded met reporting criteria, therefore no narratives were produced.

Treatment-emergent AEs (TEAEs) that were reported for 2 or more subjects during the study are presented in Table S5.

Table S5. Incidence of TEAEs Observed in 2 or More Subjects - Safety Population

System organ class Medra (v10.1) preferred term	Group A (N=25) n	Group B (N=24) n
Eye disorders	**2**	**1**
Vision blurred	1	1
Gastrointestinal disorders	**4**	**2**
Abdominal pain upper	2	0
Vomiting	1	1
General disorders and administration site conditions	**5**	**6**
Asthenia	5	3
Hunger	2	0
Infections and infestations	**3**	**1**
Upper respiratory tract infection	2	1
Injury, poisoning and procedural complications	**0**	**2**
Drug administration error	0	2
Metabolism and nutrition disorders	**12**	**5**
Hypoglycaemia	12	5
Nervous system disorders	**10**	**6**
Dizziness	2	2
Headache	3	0
Hypoaesthesia	1	2
Tremor	5	4
Respiratory, thoracic and mediastinal disorders	**3**	**3**
Cough	1	3
Skin and subcutaneous tissue disorders	**4**	**3**
Hyperhidrosis	4	2
Rash	1	1

In Group A, 55 TEAEs were reported for 17 of the 25 subjects; 45 of these TEAEs, which were reported for 16 subjects, were considered treatment-related. All TEAEs were assessed as mild or moderate in severity, with the exception of 3 TEAEs (joint instability, diabetic neuropathy, and inadequately controlled blood pressure) in 2 subjects, which were assessed as severe. The most frequently reported treatment-related TEAEs were hypoglycemia (12 subjects), tremor (5 subjects), asthenia (4 subjects), and hyperhidrosis (4 subjects). All other treatment-related TEAEs were reported for a maximum of 2 subjects.

In Group B, 35 TEAEs were reported for 15 of the 24 subjects; 28 of these TEAEs, which were reported for 15 subjects, were considered treatment-related. All TEAEs were assessed as mild or moderate in severity. The most frequently reported treatment-related TEAEs were hypoglycemia (5 subjects), tremor (4 subjects), and asthenia (3 subjects). All other treatment-related TEAEs were reported for a maximum of 2 subjects.

A higher number of AEs of hypoglycemia were reported for subjects in Group A (12 subjects) compared to Group B (5 subjects). Each AE was considered treatment-related and was of mild or moderate severity. The number of subjects who experienced hypoglycemia and nocturnal hypoglycemia is summarized in Table S3, and the hypoglycemia event rate per month is summarized in Table S4.

CONCLUSIONS: As a result of Pfizer's decision on 18 October 2007 to return of the worldwide rights for Exubera (insulin human [rDNA origin]) Inhalation Powder) to Nektar, the company from which Pfizer licensed the inhaled insulin technology, it was decided to terminate Protocol A2171086 before the study had recruited the target number of subjects and followed them for the per protocol specified period. Consequently:

- No conclusions can be drawn from efficacy data because of the small sample size and short exposure of subjects to Exubera.

- Although there were small differences in safety data between Group A (1 mg Exubera, TID) and Group B (body weight-based formula of Exubera, TID), their clinical relevance cannot be determined.