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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: No USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00359801

PROTOCOL NO.: A2171069

PROTOCOL TITLE: An International, Multicenter, Large Simple Trial to Evaluate the Long-Term Pulmonary and Cardiovascular Safety of Exubera in Patients with Diabetes Mellitus.

Study Centers: This study was performed at 44 centers in Germany, 4 centers in Sweden, 15 centers in the United Kingdom, and 140 centers in the United States.

Study Initiation Date and Primary Completion or Completion Dates: 22 July 2006 to 29 April 2009. The study was terminated early in accordance with a protocol amendment filed on April 16, 2008 specifying that all subjects randomized to Exubera had to be transitioned to usual diabetes care, and all study subjects followed for serious adverse events for 6 months. In accordance with this amendment, the study was terminated on April 29, 2009. Neither safety nor efficacy reasons were the cause of the study termination.

Phase of Development: Phase 4

Study Objectives: The primary objective of this study was to estimate the relative risk of a persistent decline in forced expiratory volume in 1 second (FEV_1) exceeding 20% from baseline among subjects with diabetes randomized to Exubera® as compared with those not randomized to Exubera. For both treatment groups, a persistent decline in FEV_1 exceeding 20% from baseline was defined as an observed decline in FEV_1 exceeding 20% from baseline, 3 months after a confirmed decline in FEV_1 exceeding 20% from baseline.[1]

[1] Per the summary of product characteristics (SmPC)/United States prescribing information (USPI), subjects treated with Exubera were to discontinue use of Exubera upon a confirmed decline in FEV_1 exceeding 20% from baseline. Thus, among those randomized to Exubera, the primary outcome assessment took place 3 months after the subject discontinued Exubera therapy.

The secondary objectives were to compare subjects randomized to Exubera to those not randomized to Exubera by estimating the relative: (1) risk of pulmonary serious adverse event (SAE) composite, including: SAEs of asthma, chronic obstructive pulmonary disease (COPD), pneumonia, or acute bronchitis, (2) risk of all-cause mortality, (3) risk of cardiovascular SAE composite, including: SAEs of cardiovascular mortality, non-fatal myocardial infarction (MI), or non-fatal stroke, (4) risk of allergic response SAE composite, including: SAEs of anaphylaxis, angioedema, generalized allergic reaction, and allergic bronchospasm, and (5) change in glycosylated hemoglobin (HbA_{1c}) from baseline at Month 6, and Years 1, 2, 3, 4, and 5 (efficacy evaluation).

Since the study was stopped earlier than anticipated and the number of subjects randomized (n = 1976) was well below the planned 5300 subjects, the study had insufficient power to address the primary endpoint in the absence of unanticipated large effects. However, the study data still provided important descriptive information. Assuming the primary and secondary endpoints had insufficient power, the risk of each endpoint was estimated via descriptive measures among subjects randomized to Exubera (inhaled insulin) and subjects not randomized to Exubera (comparator).

Study Design: This Large Simple Trial (LST) was a randomized, open-label, post-approval study, designed to evaluate long-term pulmonary and cardiovascular safety of Exubera in routine clinical practice. Subjects with diabetes mellitus eligible to take Exubera according to the approved local label were randomized to Exubera plus usual diabetes care or non-Exubera usual diabetes care and followed the regimen prescribed by his or her physician. Inhaled insulin-treated subjects were compared with comparator-treated subjects, under routine, actual practice diabetes care to assess the relative risk of persistent pulmonary function decline and pulmonary, cardiovascular, and allergic SAEs, as well as the effectiveness of glycemic control.

Subjects were seen for a baseline visit; for visits at Month 6, Year 1, and Year 2 (if prior to the index visit date) during the controlled follow-up period; for the index visit (occurring 2 to 4 months after the country-specific approval of the final study protocol amendment 2); and for an end-of-study visit at the end of the 6-month observational follow-up period.

Number of Subjects (Planned and Analyzed): Approximately 5300 subjects were planned to be recruited, but due to early termination of the study, a total of 1976 subjects were enrolled, 987 in the inhaled insulin group and 989 in the comparator group.

Diagnosis and Main Criteria for Inclusion: This study included subjects aged 18 years or older who were eligible to receive Exubera treatment based on the approved local label.

Study Treatment: Physicians were referred to the local package inserts for the inhaled insulin Exubera or usual diabetes care for use and administration information.

Safety Evaluations: Safety evaluations included pulmonary function tests (PFT; FEV_1) at the baseline, Month 6, Year 1, Year 2 (few subjects), and index visits (if during any follow-up PFT a FEV_1 decline from baseline exceeding 20% was observed, a confirmatory PFT had to be performed 3 to 4 weeks later); recording of SAEs, AEs associated with the

device component of Exubera, and exposure-in-utero during the whole study duration. In addition, a subject education and training survey was to be filled in by subjects in the United Kingdom and Germany at baseline.

Efficacy Evaluations: Efficacy evaluations included measurement of HbA_{1c} at the baseline, Month 6, Year 1, Year 2, and index visits.

Statistical Methods: The full analysis set, defined as all subjects randomized, was used for the primary and secondary endpoints. The safety analysis set included all enrolled subjects and was used for all follow-up safety information contributed by subjects.

No formal hypothesis testing was done; instead, the analyses provided an exploratory context. As detailed in an amended statistical analysis plan, continuous variables (FEV_1 and HbA_{1c}, etc) were summarized with various quantiles, means and standard deviation.

Two different analyses were performed for tabulation of the persistent declines in FEV_1: (1) an analysis based on the original protocol definition, where a confirmed decline was a second consecutive PFT showing a >20% decline in FEV_1, occurring within 14 to 42 days (inclusive) of the initial decline, and where a persistent decline was a third consecutive PFT showing a >20% decline in FEV_1, occurring within 60 to 120 days (inclusive) of the confirming (second) decline; and (2) an analysis using a supplemental definition where a confirmed decline was a second consecutive PFT showing a >20% decline in FEV_1 occurring ≥14 days after the initial decline, and where a persistent decline was a third consecutive PFT showing a >20% decline in FEV_1 occurring ≥60 days after the initial decline. The supplemental clinical definition for the primary endpoint was designed by the independent endpoint committee before data unblinding to capture more events.

In addition to the planned tabulation of persistent declines in FEV_1, the following were also tabulated by treatment group for both the original protocol definition and the supplemental clinical definition of the primary endpoint: a) the number of subjects experiencing an initial FEV_1 decline (≥20% change from baseline), b) the number of subjects in (a) above, but not experiencing a confirmed decline, and c) the number of subjects in (a) above, who also experienced a confirmed decline.

A sensitivity analysis was applied to the original protocol definition of the primary endpoint. Subjects not having FEV_1 measurements beyond an initial decline and/or beyond a confirming decline were included. Certain fractions of them (25, 50, 75, and 100%) were assumed to constitute further declines.

The secondary adjudicated endpoints for pulmonary SAE composite score, cardiovascular SAE composite score, and allergic response SAE composite score were tabulated by various categories such as definite, possible, non-event, other, or insufficient, and all cause mortalities were confirmed and reported. Additional tables were stratified according to when the event occurred (up to 31 October 2008 versus after 01 November 2008). Additional sensitivity analyses were performed where fractions (25, 50, 75, and 100%) of the insufficient counts (ie, those events deemed by the independent endpoint committee to have insufficient data for adjudication) were included with the definite and possible cases.

RESULTS

Subject Disposition and Demography: Subject disposition and subjects analyzed are summarized in Table 1.

Table 1. Subject Disposition and Subjects Analyzed - Full Analysis Set

Number (%) of Subjects	Inhaled Insulin	Comparator	Total
Enrolled	987	989	1976
Received treatment	987 (100.0)	989 (100.0)	1976 (100.0)
Completed study [a]	682 (69.1)	769 (77.8)	1451 (73.4)
Discontinued from study	298 (30.2)	216 (21.8)	514 (26.0)
Withdrawn during study period			
Lost to follow up	72 (7.3)	58 (5.9)	130 (6.6)
Subject no longer willing to participate in study	143 (14.5)	96 (9.7)	239 (12.1)
Other	83 (8.4)	62 (6.3)	145 (7.3)
Analysis sets			
Full analysis set [b]	987 (100.0)	989 (100.0)	1976 (100.0)

Note: Eleven subjects had no subject summary page and therefore were not accounted for in the completed study row or the discontinued from study row.
[a] The completed study row included subjects who had baseline, index, and final visits.
[b] The full analysis set included any subject who was randomized.

The majority of subjects were white, and demographic and other baseline characteristics, eg primary diagnoses and durations, cardiovascular baseline characteristics, and baseline HbA_{1c} and FEV_1, were generally comparable between the treatment groups.

Safety Results:

Primary endpoint: Small, non-progressive median reductions from baseline in FEV_1 occurred in both treatment groups with similar magnitude at all visits except the Week 104 visit, where the subject number was very low. There were no clinically meaningful differences between the treatment groups. Stratification of the index visit according to the time in the study revealed small, slightly progressive median reductions from baseline in both treatment groups. The median reductions from baseline were smaller in the inhaled insulin group compared with the comparator group for index visits that occurred at 12 months and later in the study. The treatment group differences observed in these values are unlikely to be clinically meaningful given the magnitude of the differences and the variability in the FEV_1 data.

The number of subjects experiencing an FEV_1 decline is provided in Table 2 using the original protocol definition of the primary endpoint. Fewer subjects experienced an initial decline from baseline in FEV_1 in the inhaled insulin group compared with the comparator group, but more subjects in the inhaled insulin group experienced a confirmed decline and a persistent decline from baseline in FEV_1 compared with subjects in the comparator group. A sensitivity analysis, where certain fractions of subjects not having FEV_1 measurements beyond an initial decline and/or beyond a confirming decline were assumed to constitute further declines, supported these results.

Table 2. Summary of Subjects Experiencing an FEV_1 Decline - Full Analysis Set

	Inhaled Insulin N = 987	Comparator N = 989
Number (%) of subjects experiencing an initial FEV_1 decline	100 (10.1)	112 (11.3)
Number (%) of subjects experiencing an initial FEV_1 decline but not a confirmed decline	81 (8.2)	105 (10.6)
Number (%) of subjects experiencing a confirmed FEV_1 decline[a]	19 (1.9)	7 (0.7)
Number (%) of subjects experiencing confirmed FEV_1 decline but not a persistent decline	11 (1.1)	7 (0.7)
Number (%) of subjects experiencing a persistent FEV_1 decline[a]	8 (0.8)	0 (0.0)
Median time (days) from baseline to persistent FEV_1 decline (IQR)[a]	444.5 (312.5)	-

[a] 1) The second PFT that confirmed the decline was to occur within 14 to 42 days (inclusive) of the decline.
2) The PFT that established persistence was to occur within 60 to 120 days (inclusive) of the confirming (second) decline.

FEV_1 = forced expiratory volume in 1 second, IQR = interquartile range (75^{th} – 25^{th} percentile), N = number of subjects in the treatment group, PFT = pulmonary function test.

The number of subjects experiencing an FEV_1 decline is provided in Table 3 using the supplemental definition of the primary endpoint (defined post-hoc but before the data were unblinded). The supplemental definition of the primary endpoint utilized broader windows for the timing of the PFT measurements in an attempt to capture FEV_1 declines that may be potentially clinically meaningful, but were conducted outside the windows in the original definition. As a result of these broader windows for PFT measurements, more events were captured using the supplemental definition. In contrast with results obtained using the original protocol definition of the primary endpoint, the number of subjects experiencing a confirmed decline and a persistent decline from baseline in FEV_1 were similar between the treatment groups.

Table 3. Summary of Subjects Experiencing an FEV_1 Decline (Supplemental Definition with Broader PFT Windows) - Full Analysis Set

	Inhaled Insulin N = 987	Comparator N = 989
Number (%) of subjects experiencing an initial FEV_1 decline	100 (10.1)	112 (11.3)
Number (%) of subjects experiencing an initial FEV_1 decline but not a confirmed decline	62 (6.3)	74 (7.5)
Number (%) of subjects experiencing a confirmed FEV_1 decline[a]	38 (3.9)	38 (3.8)
Number (%) of subjects experiencing confirmed FEV_1 decline but not a persistent decline	11 (1.1)	14 (1.4)
Number (%) of subjects experiencing a persistent FEV_1 decline[a]	27 (2.7)	24 (2.4)
Median time (days) from baseline to persistent FEV_1 decline (IQR)[a]	468.0 (159.0)	496.5 (183.0)

[a] 1) Any 2 consecutive declines that were ≥14 days apart.
2) The PFT that established persistence was to occur ≥60 days after the initial decline.

FEV_1 = forced expiratory volume in 1 second, IQR = interquartile range (75^{th} – 25^{th} percentile), N = number of subjects in the treatment group, PFT = pulmonary function test.

Secondary endpoints: A summary of subjects meeting the secondary study endpoints after masked adjudication by the endpoint committee is provided in Table 4. Although overall numbers of relevant events were small, numerically more events were adjudicated as meeting the pulmonary and allergic response SAE composite endpoints and the non-MI, non-stroke cardiovascular endpoint in the inhaled insulin group compared with the comparator group.

There were no consistent treatment group differences in events adjudicated to meet the MI, stroke cardiovascular SAE composite endpoint, death from cardiovascular or cerebrovascular causes, or all cause mortality, but the low number of events precluded drawing firm conclusions.

Table 4. Summary of Subjects Meeting the Secondary Study Endpoints After Adjudication by the Endpoint Committee – Full Analysis Set

	Inhaled Insulin N = 987	Comparator N = 989
Pulmonary SAE Composite		
Total number of events adjudicated	16	10
Classification of adjudicated events (%)[a]		
Definite	4 (25.0)	1 (10.0)
Possible	3 (18.8)	2 (20.0)
Definite or possible	7 (43.8)	3 (30.0)
Insufficient	4 (25.0)	2 (20.0)
Cardiovascular SAE Composite		
Total number of events adjudicated	46	40
Classification of adjudicated events (%)[b]		
Definite	5 (10.9)	3 (7.5)
Possible	5 (10.9)	6 (15.0)
Other (non-MI, non-stroke)	15 (32.6)	9 (22.5)
Definite or possible	10 (21.7)	9 (22.5)
Insufficient	9 (19.6)	7 (17.5)
Death from cardiovascular or cerebrovascular	2 (4.3)	4 (10.0)
Definite or possible or death from cardiovascular or cerebrovascular	12 (26.1)	11 (27.5)
Allergic Response SAE Composite		
Total number of events adjudicated	6	1
Classification of adjudicated events (%)[c]		
Definite or possible	2 (33.3)	0 (0.0)
Insufficient	3 (50.0)	0 (0.0)
All Cause Mortality		
Classification of adjudicated events [d]		
Confirmed Deaths	12 [e]	9 [e]

Note: Percentages are based on total adjudicated events and not subjects.
[a] Definite: Definite pneumonia, definite COPD, or definite asthma; possible: possible pneumonia, possible COPD, possible asthma, probable obstructive lung disease not otherwise specified or probable acute bronchitis; definite or possible: either definite or possible; insufficient: insufficient data.
[b] Definite: definite MI or definite stroke; possible: possible MI or possible stroke; other (non-MI, non-stroke): other cardiovascular event (non-MI, non-stroke); definite or possible: either definite or possible; insufficient: insufficient data; death from cardiovascular or cerebrovascular: cardiovascular or cerebrovascular event; definite or possible or death from cardiovascular or cerebrovascular event: either definite or possible or cardiovascular or cerebrovascular event.
[c] Definite or possible: anaphylaxis, angioedema/urticaria, bronchospasm or possible allergic reaction NOS; insufficient: insufficient data.
[d] Confirmed death by medical records or death certificate.
[e] There were minor discrepancies between this death tabulation and deaths listed in the safety database. Twelve deaths occurred in the inhaled insulin group and 10 deaths in the comparator group.
COPD = chronic obstructive pulmonary disease, MI = myocardial infarction, N = number of subjects in the treatment group, SAE = serious adverse event.

Sensitivity analyses for the pulmonary SAE composite, the cardiovascular SAE composite, and the allergic response SAE composite, where fractions (25, 50, 75, and 100%) of the

insufficient counts were included with the definite and possible cases, generally supported these results.

General safety results: In both treatment groups a similar number of subjects experienced SAEs (124 subjects in the inhaled insulin group and 109 subjects in the comparator group; Table 5).[2] SAEs by system organ class are listed in Table 5. In both treatment groups, the number of subjects experiencing SAEs was greatest in the cardiac disorders, nervous system disorders, and metabolism and nutrition disorders system organ classes; followed by the general disorders and administration site conditions system organ class in subjects in the inhaled insulin group. On the preferred term level, in both treatment groups, the number of subjects experiencing SAEs was greatest for hypoglycaemia (8 subjects in the inhaled insulin group and 6 subjects in the comparator group) and chest pain (7 subjects in the inhaled insulin group and 9 subjects in the comparator group).

[2] In the safety database not all subjects were listed under a treatment group and some subjects were listed under the wrong treatment group. These discrepancies were corrected in a separate table, where all but 2 subjects were listed under the correct treatment group.

Table 5. Serious Adverse Events by System Organ Class – Full Analysis Set

MedDRA system organ class	Number of Subjects	
	Inhaled Insulin N = 987	Comparator N = 989
Blood and lymphatic system disorders	3	2
Cardiac disorders	24	19
Congenital, familial and genetic disorders	1	0
Endocrine disorders	1	0
Eye disorders	2	4
Gastrointestinal disorders	7	10
General disorders and administration site conditions	16	14
Hepatobiliary disorders	1	3
Immune system disorders	1	0
Infections and infestations	13	16
Injury, poisoning, and procedural complications [a]	13	10
Investigations	5	1
Metabolism and nutrition disorders	16	17
Musculoskeletal and connective system disorders [a]	13	6
Neoplasms benign, malignant and unspecified (including cysts and polyps)	14	11
Nervous system disorders	17	17
Psychiatric disorders	3	1
Renal and urinary disorders	5	4
Respiratory, thoracic and mediastinal disorders	9	5
Skin and subcutaneous tissue disorders	4	2
Surgical and medical procedures	2	2
Vascular disorders	5	7
Total number of subjects with SAEs	124	109
Total preferred term events	208	163

Note: A case coded to several system organ classes could be counted as separate events and could include both serious and non-serious AEs. Subjects were only counted once per treatment for each row.
[a] Two additional subjects experienced SAEs in these system organ classes, but were not listed under a treatment group.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects in the treatment group, SAE = serious adverse event.

Any exposure-in-utero AEs and AEs associated with the device component of Exubera were to be forwarded to the Sponsor in this study. In total, there were 3 subjects (4 cases) with exposure-in-utero AEs. One female subject in the inhaled insulin group became pregnant and was permanently withdrawn. The event was recorded as the non-serious AE 'drug exposure during pregnancy'. The subject was lost to follow-up and no additional information was available. For another female subject who received inhaled insulin and comparator drug the non-serious AE 'drug exposure during pregnancy' was recorded. The outcome of the pregnancy was not described in the narrative. For 1 male subject in the comparator group, the non-serious AE 'paternal drugs affecting foetus' was recorded twice (2 cases). In 1 case, the subject's partner became pregnant and had a live, 3-weeks premature birth. In another case, the subject's partner became pregnant and had an induced/elective abortion.

For 1 subject in the inhaled insulin group, the AE 'device malfunction' was recorded. The physician reported that he did not consider the events hyperglycemia and hypoglycemia as serious. The patient had used various doses of Exubera, but not managed to find a dosage that fitted him. Exubera was discontinued and the events had not resolved. The physician

considered the events related to Exubera treatment. No more information was provided. The subject returned the device and it was tested, but no malfunction was found. By reason of this information, Pfizer did not consider this AE related to the device component of Exubera.

In this study, AEs that were not serious, not associated with the device component of Exubera, and not exposure-in-utero were not systematically collected, as agreed with the Committee for Medicinal Products for Human Use and the Food and Drug Administration at the time of study protocol finalization. However, investigators were able to report AEs deemed noteworthy for submission. In total, non-serious AEs were reported for 26 subjects in the inhaled insulin group and 11 subjects in the comparator group.

There were 22 deaths from any cause in this study; 12 deaths in the inhaled insulin group and 10 deaths in the comparator group.[3] In the inhaled insulin group, death was listed as the event with a fatal clinical outcome for 2 subjects (verbatim terms 'died in hospital' and 'unknown cause of death'), and the following fatal clinical outcomes (preferred terms) each occurred in 1 subject: acute myeloid leukemia; myocardial infarction; intentional self-injury; metastasis to liver and metastatic neoplasm; Non-Hodgkin's lymphoma, pneumonia, and sepsis; glioblastoma; B-cell lymphoma; cerebrovascular accident; cardio-respiratory arrest; and sudden death. In the comparator group, for 2 subjects, myocardial infarction (preferred term) was listed as the event with a fatal clinical outcome, and the following fatal clinical outcomes by preferred term each occurred in 1 subject: death; sudden death; pancreatic carcinoma; coronary artery disease; sepsis; arrhythmia, hypotension, and organ failure; cardiac arrest; and cardiac death.

Efficacy Results: Since this study was terminated early, only descriptive statistics were performed. Glycemic control, as defined by HbA_{1c} (%), was maintained similarly in both treatment groups at all visits except the Week 104 visit, where the number of subjects was very low. Glycemic control was minimally influenced by the time in the study at the index visit. Fewer subjects in the inhaled insulin group compared with the comparator group had severe hypoglycemic events, thus the event rate was slightly lower in the inhaled insulin group compared with the comparator group.

CONCLUSIONS: Since this study was terminated early in accordance with protocol amendment 2, the study had insufficient power to address the primary endpoint in the absence of any unanticipated large effects and no formal hypothesis testing could be performed. Instead, the risk of each endpoint was estimated for subjects randomized to inhaled insulin and subjects randomized to comparator treatment, using descriptive measures.

- The treatment group differences in change from baseline in FEV_1 are unlikely to be clinically meaningful given the magnitude of the differences and the variability in the FEV_1 data. The number of subjects who experienced a persistent decline in FEV_1 exceeding 20% from baseline was higher in the inhaled insulin group compared with

[3] The safety database lists 11 deaths under inhaled insulin and 11 deaths under comparative drug. One subject was incorrectly listed under comparative drug. After correctly accounting for this 1 subject, there were 12 deaths in the inhaled insulin group and 10 deaths in the comparator group (as of 22 June 2009).

subjects in the comparator group using the original protocol definition of the primary endpoint, and similar for subjects in both treatment groups using the prespecified supplemental definition of the primary endpoint.

- Although overall numbers of relevant events were small, numerically more events were adjudicated as meeting the pulmonary and allergic response SAE composite endpoints and the non-MI, non-stroke cardiovascular endpoint in the inhaled insulin group compared with the comparator group. There were no consistent treatment group differences in events adjudicated to meet the MI, stroke cardiovascular SAE composite endpoint, death from cardiovascular or cerebrovascular causes, or all cause mortality, but the low number of events precluded drawing firm conclusions.

- In both treatment groups a similar number of subjects experienced SAEs and deaths.

- Glycemic control (change in HbA_{1c}[%]) was maintained similarly in both treatment groups. Fewer subjects in the inhaled insulin group compared with the comparator group had severe hypoglycemic events.