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

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** No USPI.

**NATIONAL CLINICAL TRIAL NO.:** NCT00391027

**PROTOCOL NO.**: A2171084

**PROTOCOL TITLE**: A Six Month, Open-Label Outpatient, Randomized Parallel Group Trial Assessing the Impact of Dry Powder Inhaled Insulin (Exubera®) on Glycemic Control Compared to Insulin Glargine (Lantus®) in Patients with Type 2 Diabetes Mellitus Who Are Poorly Controlled on a Combination of Two or More Oral Agents

**Study Centers**: This study was conducted at 61 sites in Belgium, Finland, France, Germany, the Netherlands, Norway, Poland, Spain, Sweden, and Switzerland.

**Study Initiation and Completion Dates:** 29 January 2007 to 12 August 2008. The enrollment period of this study was concluded earlier than planned.

**Phase of Development**: Phase 4

**Study Objectives:** The primary objective of this study was to demonstrate non-inferiority of dry powder inhaled insulin (Exubera) compared to insulin glargine (Lantus) in terms of glycemic control ($HbA_{1c}$) after 26 weeks of treatment in subjects with type 2 diabetes. Secondary objectives were to demonstrate superiority of Exubera over Lantus on the following endpoints: change of fasting glucose and postprandial glucose excursions from baseline to end of the treatment period, the percentage of subjects who have an $HbA_{1c}$ of less than 6.5%, 7.0%, or 8.0% at the end of the treatment period, rates of overall and nocturnal hypoglycemia, changes in body weight and body mass index (BMI), glucose excursions over 24 hours in a subset of subjects, and subject reported outcomes at Week 26 compared to baseline. Additional secondary objectives are changes in urinary free 8-iso-prostaglandin F2α in a subset of patients, high sensitivity C-reactive protein (hs CRP), interleukin 6 (IL-6), thrombin-antithrombin complexes (tat-complexes), and soluble tissue factor from baseline to end of the treatment period.

There was an early conclusion of the enrollment period for this study (last subject screened on 16 January 2008) due to the cancellation of the Exubera program. The final enrollment for this study was undersized to meet the requirements to adequately address its inferential objectives. Therefore, the planned analysis was revised to implement a statistical analysis

approach that was descriptive and graphical in nature, thereby removing any inferential analyses that were originally planned.

## METHODS

**Study Design:** This study was a multi-national, 6-month, open-label, outpatient, parallel group, randomized (1:1), multi-center study, designed to assess the impact of dry powder inhaled insulin (Exubera®) on glycemic control compared to insulin Glargine (Lantus®) in male and female subjects, age ≥30 years, diagnosed with Type 2 diabetes mellitus who were poorly controlled on a combination of 2 or more oral agents. Randomization was stratified by baseline $HbA_{1c}$ to ensure that subjects with a wide range of $HbA_{1c}$ were balanced in the study. There were 2 strata based on Week -2 $HbA_{1c}$ (ie, 7.0≤ $HbA_{1c}$ ≤9.0% and $HbA_{1c}$ >9.0%). The choice of the stratification cutoff (9.0%) was based on the median of baseline $HbA_{1c}$ in protocol 217-1017, a Phase 3 study with a similar study population and design.

For subjects randomized to Group A, a dose of Exubera was administered before major meals (eg, breakfast, lunch, supper) using the Exubera® Insulin Dry Powder Inhaler device and a blister package containing 1 or 3 mg dry powder human insulin. The initial daily dose of Exubera was determined based on the subject's body weight and divided into 3 doses administered prior to major meals. The pre-meal doses were modified based on meal size and pre-prandial blood glucose readings. Subjects combined 1 and 3 mg doses before each meal to control postprandial glycemia in addition to continuing on their usual oral drugs at the pre-study doses unless clinical need justified a dose modification.

For Group B (control group), subjects added 10 IU Lantus, initially, to their usual oral regimen to be continued at pre-study doses unless clinical need justified a dose modification. The daily dose of Lantus was modified based on glucose measurements at the discretion of the treating physician. Lantus was injected once daily at the same time of day for the duration of the study using a pen device where available. It was recommended that Lantus be dosed in the morning.

Screening for this study consisted of 3 clinic visits approximately 1 week apart. The treatment period of this study consisted of 6 visits occurring at Weeks 0, 2, 4, 8, 12, 18, and 26 (or early termination).

**Number of Subjects (Planned and Analyzed):** A total of 478 subjects were planned to be randomized in order to have a total of 191 per treatment arm complete the study. A total of 424 subjects were screened and 257 were randomized and treated (135 subjects in the Exubera group and 122 subjects in the Lantus group).

**Diagnosis and Main Criteria for Inclusion:** To be eligible for inclusion into the study, subjects had to be ≥30 years old with a diagnosis of type 2 diabetes mellitus ≥6 months prior to study start, as defined by the American Diabetes Association. Subjects also had to be on a stable dose of at least 2 oral hypoglycemic agents, which had to include combinations of sulfonylureas and metformin for at least 3 months prior to study entry, and have a screening $HbA_{1c}$ of ≥7%.

**Study Treatment:** Subjects were randomized to receive either Exubera or Lantus for 26 weeks.

For subjects randomized to receive Exubera, a dose was administered before major meals (eg, breakfast, lunch, supper) using the Exubera Insulin Dry Powder Inhaler device and a blister package containing 1 or 3 mg dry powder human insulin. The initial daily dose of Exubera was determined based on the subject's body weight and divided into 3 doses administered prior to major meals. The pre-meal doses were modified based on meal size and pre-prandial blood glucose readings. Subjects combined 1 and 3 mg doses before each meal to control postprandial glycemia in addition to continuing on their usual oral drugs at the pre-study doses unless clinical need justified a dose modification.

For subjects randomized to receive subcutaneous insulin, 10 IU Lantus was added initially to their usual oral regimen and was to be continued at pre-study doses unless clinical need justified a dose modification. The daily dose of Lantus was modified based on glucose measurements at the discretion of the treating physician. Lantus was injected once daily at the same time of day for the duration of the study using a pen device where available. It was recommended that Lantus be dosed in the morning.

**Efficacy Evaluations:** The primary evaluation was the comparison of $HbA_{1c}$ after 26 weeks of treatment with Exubera or Lantus. Secondary evaluations included $HbA_{1c}$, fasting plasma glucose, body mass index (BMI), Home Blood Glucose Monitoring (HBGM), hypoglycemia, Continuous Glucose Monitoring Substudy (CGMS), Urinary 8-iso Prostanes substudy, and biomarkers (high sensitive C-reactive protein [hs-CRP], interleukin 6 [IL-6], thrombin-antithrombin complexes [tat-complexes], and soluble tissue factor).

Fasting plasma glucose and $HbA_{1c}$ were evaluated at Weeks -2, 0, 2, 4, 8, 12, 18, 26, or early termination. Change in fasting plasma glucose (FPG) and subjects achieving glycemic control (HbA1c <6.5%, <7.0%, and <8.0%) at the end of treatment was evaluated.

Height was assessed at Week -2. Weight was assessed at Weeks -2, 12, 26, or early termination. BMI was assessed at Weeks -2, 26, or early termination. Changes in body weight and BMI were evaluated.

Blood glucose was self-monitored by the use of HBGM. At Visit 2, subjects received their blood glucose monitors/supplies and were instructed how to perform HBGM. Between Visits 2 and 3, subjects were encouraged to measure their blood glucose before each meal. Subjects who were randomized to Exubera at Visit 3 were instructed to perform a HBGM prior to administration of Exubera and at bedtime from that visit forward. Subjects who were randomized to Lantus at Visit 3 were instructed to perform HBGM on a daily basis at the discretion of the treating physician or at least once daily in the morning prior to breakfast when Lantus was administered from that visit forward. Monitoring frequency with Lantus was to be increased in case of hypoglycemic episodes or suspected lack of efficacy. All subjects were requested to do an 8-point blood glucose profile (fasting, 2-hours after breakfast, pre-lunch, 2 hours after lunch, pre-dinner, 2 hours after dinner, bedtime, 02:00 AM) at least once between Visits 2 and 3 and between Visits 8 and 9. Subjects were also required to do a 7-point blood glucose profile (fasting, 2 hours after breakfast, pre-lunch,

2 hours after lunch, pre-dinner, 2 hours after dinner, and bedtime) between each visit from Visit 3 to Visit 8. Results were captured on worksheets provided to the subject.

Hypoglycemia was assessed throughout the study and was defined as one of the following:

- Characteristic symptoms of hypoglycemia with no blood glucose check. Clinical picture must have included prompt resolution with food intake, subcutaneous (SC) glucagon, or intravenous glucose.
- Characteristic symptoms of hypoglycemia with blood glucose check showing glucose <3.27 mmol/L (59 mg/dL). Symptoms associated with blood glucose ≥3.33 mmol/L (60 mg/dL) could not be reported as hypoglycemia.
- Any glucose measurement ≤2.72 mmol/L (49 mg/dL), with or without symptoms.

Nocturnal hypoglycemia was defined as any hypoglycemic event occurring after the subject had commenced his/her usual night-time sleeping period and before the subject got up at his/her usual time next morning.

Every hypoglycemic event was characterized with respect to its severity. In order to characterize the event as severe, all 3 of the following criteria must have been met**:**

1. The subject was unable to treat him or herself.
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, if blood glucose was measured and was ≤2.72 mmol/L (49 mg/dl) or, if the blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, SC glucagon, or intravenous glucose.

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

CGMS inpatient evaluation was done in a subset of subjects at selected centers and consisted of a continuous glucose monitoring study performed at baseline (before Week 0 on prestudy oral hypoglycemic medications) and at Week 26 / End of Study during a 3-day visit.

The urinary 8-iso-prostanes substudy was done in a subset of patients to compare glucose fluctuations and activation of oxidative stress as assessed by urinary 8-iso-$PGF_{2\alpha}$ (urinary isoprostanes) in subjects randomized to either mealtime Exubera or SC basal Lantus.

Changes in hs-CRP, IL-6, tat-complexes, and soluble tissue factor from baseline to end of the treatment period were evaluated.

**Other Evaluations:** Other evaluations for this study included the Diabetes Treatment Satisfaction Questionnaire-Status (DTSQs), Diabetes Treatment Satisfaction Questionnaire-

Status-Change (DTSQc), Patient Satisfaction with Insulin Therapy – 16 item (PSIT-16), Mental Health Inventory – 17 item (MHI-17), and the EQ-5D.

**Safety Evaluations:** Safety evaluations in this study included adverse events (AEs), clinical laboratory evaluations, physical examinations, vital signs (blood pressure and heart rate), electrocardiograms (ECGs), and spirometry.

**Statistical Methods:** Due to the early termination of the enrollment period for this study resulting from the cancellation of the Exubera® program, the final enrollment for this study was undersized to meet the requirements to adequately address its inferential objectives. Therefore, the statistical analyses provide descriptive and/or graphical summaries for: $HbA_{1c}$, percent of subjects reaching $HbA_{1c}$ goals, 8-point self-monitored blood glucose (SMBG) profiles, change in post-prandial blood glucose, change in fasting plasma glucose, change in weight, incidence and severity of hypoglycemia, and continuous glucose monitoring system (CGMS) at a participating substudy site(s).

For continuous efficacy endpoints, descriptive statistics were presented by treatment groups. The summary statistics included were: N, mean, standard error of the mean, median, standard deviation, minimum, and maximum. Graphical summaries were presented in the form of a scatter plot of response over time by treatment group, with error bars representing ±1.0 standard error (typically, response was either mean endpoint or mean change from baseline in endpoint).

For categorical efficacy endpoints, frequency distributions (counts and percentages) were presented by treatment groups.

For binary efficacy endpoints, frequency distributions (counts and percentages) were presented by treatment groups.

Safety Standards of the Sponsor were utilized to analyze and summarize the safety data. Laboratory, spirometry, AEs, and other safety data were subject to clinical review at the end of the study and were summarized by appropriate descriptive statistics.

## RESULTS

**Subject Disposition and Demography:** A total of 424 subjects were screened for the study, and 257 subjects were randomized and treated. One-hundred and thirty five (135) subjects were treated with Exubera (110 subjects [81.5%] completed the study), and 122 subjects were treated with Lantus (110 subjects [90.2%] completed the study). Table S1 summarizes subject disposition, subject discontinuations, and the number of subjects included in the efficacy and safety analyses. One subject (Lantus group) was not included in the safety lab analysis due to the fact that postbaseline labs were collected more than 1 day after the last dose of study medication.

## Table S1. Subject Disposition and Subjects Analyzed

| | Exubera | Lantus |
|---|---|---|
| **Number (%) of Subjects** | | |
| Screened, N = 424 | | |
| Assigned to study treatment | 135 | 122 |
| Treated | 135 | 122 |
| Completed | 110 (81.5) | 110 (90.2) |
| Discontinued: | 25 (18.5) | 12 (9.8) |
| Related to study drug: | 7 (5.2) | 3 (2.5) |
| AE | 3 (2.2) | 2 (1.6) |
| Lack of efficacy | 3 (2.2) | 0 |
| Other | 1 (0.7) | 1 (0.8) |
| Not Related to study drug: | 18 (13.3) | 9 (7.4) |
| AE | 5 (3.7) | 6 (4.9) |
| Other | 3 (2.2) | 2 (1.6) |
| Subject no longer willing to participate in study | 10 (7.4) | 1 (0.8) |
| Analyzed for efficacy: | | |
| Full analysis set | 134 (99.3) | 121 (99.2) |
| Analyzed for safety: | | |
| AEs | 135 (100.0) | 122 (100.0) |
| Laboratory data | 135 (100.0) | 121 (99.2) |

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

In both treatment groups, there were more males than female subjects. Most subjects were between the ages of 45 and 64 years old. The mean (SD) age was similar between groups (Exubera, 60.4 [8.8] years; Lantus, 62.1 [7.6] years). Most subjects were white, and weight and height were comparable between groups. The mean duration since diagnosis of diabetes was similar across treatment groups

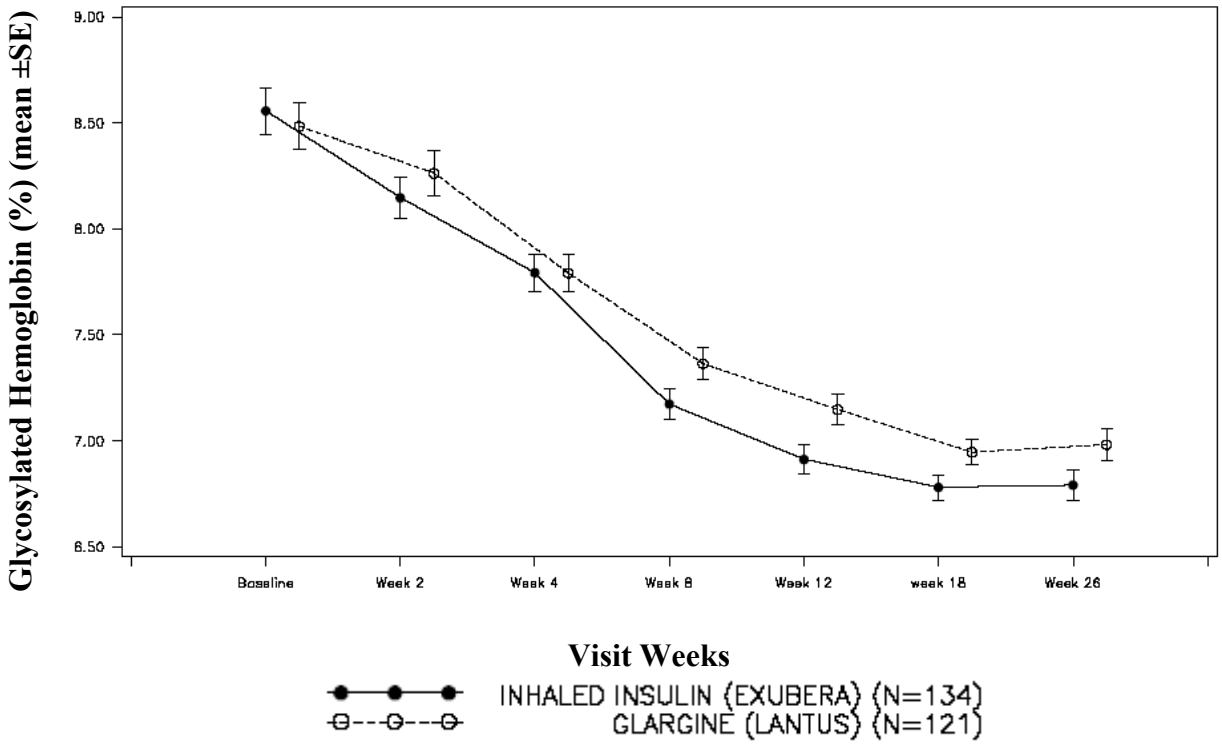
**Efficacy Results:** The primary evaluation was the comparison of $HbA_{1c}$ after 26 weeks of treatment with Exubera or Lantus. Table S2 provides descriptive statistics for $HbA_{1c}$ at Baseline, and at Weeks 2, 4, 8, 12, 18, and 26 and change from baseline at Weeks 2, 4, 8, 12, 18, and 26. $HbA_{1c}$ results over time are displayed graphically in Figure S1. The mean (SD) baseline HbA1c was similar across treatment groups (Exubera, 8.6% [1.29]; Lantus, 8.5% [1.21]). In both treatment groups, mean $HbA_{1c}$ was decreased from baseline at all weeks evaluated (Table S2 and Figure S1). The Exubera group demonstrated numerically greater decreases in $HbA_{1c}$ at all weeks compared to the Lantus group. At Week 26, the mean (SD) change for the Exubera group was -1.7% (1.19) compared to -1.4% (1.14) for the Lantus group. At this time, mean (SD) $HbA_{1c}$ for the Exubera group was 6.8% (0.73) and 7.0% (0.76) for the Lantus group.

## Table S2. Descriptive Statistics for $HbA_{1c}$

| | Exubera (N=134) | | Lantus (N=121) | |
|---|---|---|---|---|
| | **Actual (%)** | **Change from Baseline (%)** | **Actual (%)** | **Change from Baseline (%)** |
| Baseline | | | | |
| n | 134 | | 121 | |
| Mean (SD) | 8.6 (1.29) | | 8.5 (1.21) | |
| Median (Minimum, Maximum) | 8.3 (6.8-14.2) | | 8.2 (6.1-12.2) | |
| Week 2 | | | | |
| n | 128 | 128 | 108 | 108 |
| Mean (SD) | 8.1 (1.11) | -0.4 (0.40) | 8.3 (1.09) | -0.3 (0.40) |
| Median (Minimum, Maximum) | 7.8 (6.7-13.2) | -0.4 (-1.5-0.4) | 8.1 (6.5-12.6) | -0.3 (-1.6-0.6) |
| Week 4 | | | | |
| n | 126 | 134 | 111 | 121 |
| Mean (SD) | 7.8 (0.98) | -0.8 (0.61) | 7.8 (0.91) | -0.6 (0.58) |
| Median (Minimum, Maximum) | 7.5 (6.3-12.4) | -0.7 (-2.5-0.7) | 7.7 (5.7-10.5) | -0.5 (-2.6-0.3) |
| Week 8 | | | | |
| n | 121 | 134 | 112 | 121 |
| Mean (SD) | 7.2 (0.79) | -1.3 (0.86) | 7.4 (0.79) | -1.1 (0.85) |
| Median (Minimum, Maximum) | 7.0 (6.1-10.4) | -1.3 (-4.2-0.4) | 7.2 (5.2-10.4) | -0.9 (-3.8-0.8) |
| Week 12 | | | | |
| n | 113 | 134 | 108 | 121 |
| Mean (SD) | 6.9 (0.72) | -1.6 (1.08) | 7.1 (0.72) | -1.3 (0.99) |
| Median (Minimum, Maximum) | 6.8 (5.8-10.7) | -1.4 (-5.1-0.5) | 7.0 (5.3-9.8) | -1.2 (-4.3-0.8) |
| Week 18 | | | | |
| n | 114 | 134 | 105 | 121 |
| Mean (SD) | 6.8 (0.64) | -1.7 (1.16) | 6.9 (0.61) | -1.5 (1.11) |
| Median (Minimum, Maximum) | 6.7 (5.7-9.1) | -1.6 (-5.1-0.5) | 6.9 (5.4-9.4) | -1.4 (-4.8-0.6) |
| Week 26 | | | | |
| n | 107 | 134 | 106 | 121 |
| Mean (SD) | 6.8 (0.73) | -1.7 (1.19) | 7.0 (0.76) | -1.4 (1.14) |
| Median (Minimum, Maximum) | 6.7 (5.1-9.7) | -1.4 (-4.8-0.9) | 6.9 (5.4-10.8) | -1.3 (-5.0-0.9) |

SD = standard deviation
Change from baseline values are based on LOCF value.

**Figure S1. Glycosylated $HbA_{1c}$, (%)**




Starting at Week 8, a numerically higher percentage of Exubera subjects achieved $HbA_{1c}$ <6.5% and<7.0% compared to the Lantus group. A numerically higher percentage of Exubera subjects achieved HbA1c <8.0% compared to the Lantus group at all time points evaluated.

Mean (SD) baseline fasting plasma glucose was numerically higher in the Exubera group (186.2 mg/dL [48.46]) compared to the Lantus group (188.4 mg/dL [42.38]). The mean change from baseline demonstrated numerically greater decreases for the Lantus group compared to the Exubera group. At Week 26, the mean (SD) change from baseline was -30.6 mg/dL (49.04) and -60.1 mg/dL (51.95) for the Exubera and Lantus groups, respectively.

Changes from baseline in mean average premeal blood glucose were numerically greater in the Lantus group compared to the Exubera group at all time points evaluated (Week 26: Exubera, -38.1 mg/dL; Lantus -50.7 mg/dL). Numerically greater decreases from baseline in postmeal blood glucose were also observed in the Exubera group compared to the Lantus group at all time points (Week 2: Exubera, -57.0 mg/dL; Lantus, -30.6 mg/dL and Week 26: Exubera, -64.5 mg/dL; Lantus -49.6 mg/dL). Mean change from pre to postmeal blood glucose was numerically lower in the Exubera group compared to the Lantus group at all time points evaluated (baseline: Exubera, 38.3 mg/dL; Lantus, 39.5 mg/dL and Week 26: Exubera, 11.4 mg/dL; Lantus, 39.0 mg/dL). The most marked change in the mean change from pre to postmeal blood glucose for the Exubera group was observed from baseline to Week 2. This initial decrease in mean change from pre to postmeal blood glucose was not

observed in the Lantus group. Mean changes from baseline in this parameter were numerically greater for the Exubera group compared to the Lantus group at all time points.

There were a numerically greater number of hypoglycemic events and a numerically larger crude event rate in the Exubera group, compared to the Lantus group. The highest incidence of hypoglycemic events for the Exubera group was observed during Week 8 (57 subjects) and the lowest incidence of hypoglycemic events (excluding baseline) was at Week 26 (26 subjects). One subject in each group was considered severe and both severe events occurred at Week 26. A numerically higher percentage of total hypoglycemic events occurred in the Lantus group compared to the Exubera group between the hours of Midnight to 9:00 AM, while the Exubera group had a numerically higher percentage of total events between 12:00 PM and 6:00 PM, with the largest difference occurring between 2:00 PM and 3:00 PM.

Mean changes from baseline in body weight were numerically higher in the Exubera group (1.5 kg at Week 12 and 2.2 kg at Week 26) compared to the Lantus group (0.8 kg at Week 12 and 1.1 kg at Week 26). Similar results were observed for BMI with similarity between groups at baseline and numerically higher change from baseline (0.5 and 0.7 $kg/m^2$ at Week 12 and Week 26 for Exubera; 0.3 and 0.4 $kg/m^2$ for Week 12 and Week 26 for Lantus).

The mean of the 24-hour mean and of the 24-hour standard deviation of CGMS values were similar across treatment groups at baseline and at Week 26, however, due to the low number of subjects with available data, no conclusions could be drawn.

Change from baseline in hs-CRP and IL-6 was similar at Week 12 and Week 26 across treatment groups. At Week 12 and Week 26, changes from baseline in tat-complexes and soluble tissue factor differed between the Exubera and Lantus treatment groups, however, due to the low number of subjects with available data, no conclusions could be drawn.

**Other Results**: Due to the cancellation of the Exubera program, the results from the Diabetes DTSQs, DTSQc, PSIT-16, MHI-17, and EQ-5D were not summarized and were presented in listings only.

**Safety Results:** All-causality and treatment-related, treatment-emergent AEs are presented in Table S3.

**Table S3. Overview of All Causality and Treatment-Related, Treatment-Emergent Adverse Events – Safety Population**

| | All Causality | | Treatment Related | |
|---|---|---|---|---|
| | Exubera n (%) | Lantus n (%) | Exubera n (%) | Lantus n (%) |
| Subjects evaluable for adverse events | 135 | 122 | 135 | 122 |
| Number of adverse events | 262 | 215 | 147 | 76 |
| Subjects with adverse events | 109 (80.7) | 91 (74.6) | 96 (71.1) | 64 (52.5) |
| Subjects with serious adverse events | 8 (5.9) | 10 (8.2) | 2 (1.5) | 1 (0.8) |
| Subjects with severe adverse events | 7 (5.2) | 7 (5.7) | 3 (2.2) | 1 (0.8) |
| Subjects discontinued due to adverse events | 8 (5.9) | 6 (4.9) | 3 (2.2) | 2 (1.6) |
| Subjects with dose reduced or temporary discontinuation due to adverse events | 15 (11.1) | 5 (4.1) | 14 (10.4) | 5 (4.1) |

Includes data up to 1 day after the last dose of study drug.
Except for the number of AEs, subjects are counted only once per treatment in each row. Number of SAEs listed is according to the investigator's assessment.
MedDRA (v11.0) coding dictionary applied.

There were 4 deaths reported in this study (1 Exubera subject and 3 Lantus subjects). One subject in the Exubera group died on Day 135 of pancreatic carcinoma. In the Lantus group, 1 subject died on Day 233 due to metastatic colon cancer, 1 subject died on Day 216 due to adenocarcinoma pancreas, and 1 subject died on Day 197 due to pancreas neoplasm. None of these fatal events were considered related to treatment.

According to the Adverse Reaction Information System – global (ARISg) listing, a total of 9 Exubera subjects experienced 10 SAEs and 13 Lantus subjects experienced 23 SAEs. The majority of SAEs reported were not related to the study drug. All SAEs are represented by single occurrences with the exception of hypoglycemia (2 Exubera subjects and 1 Lantus subject) and anemia (2 Lantus subjects).

A total of 8 subjects in the Exubera group discontinued the study due to AEs compared to 6 subjects in the Lantus group. Of these, 6 subjects and 2 subjects were discontinued due to treatment related AEs in the Exubera and Lantus groups, respectively.

The percentage of subjects was numerically higher in the Exubera group compared to the Lantus group for all causality AEs (80.7% and 74.6%, respectively). There were a numerically higher percentage of treatment-related AEs in the Exubera group (71.1%) than the Lantus group (52.5%).

The most common all-causality AE reported in both groups was hypoglycemia, the percentage of which was numerically higher in the Exubera group (95 subjects [70.4%]) than the Lantus group (65 subjects [53.3%]). The only other AE reported in ≥10% of subjects was nasopharyngitis (13.3% of Exubera subjects and 16.4% of Lantus subjects). Other AEs reported by at least 4% of subjects in either treatment group included headache (5.2% of Exubera subjects and 2.5% of Lantus subjects), diarrhea (4.4% of Exubera subjects and 3.3% of Lantus subjects), edema peripheral (6.7% of Exubera subjects and 1.6% of Lantus subjects), back pain (4.4% of Exubera subjects and 3.3% of Lantus subjects), cough (6.7% of Exubera subjects and 1.6% of Lantus subjects), and dyspnea (4.4% of Exubera subjects and

0.8% of Lantus subjects). The majority of all-causality AEs were mild or moderate in both groups.

The most common treatment-related AE in either group was hypoglycemia (Exubera, 92 subjects [68.1%]; Lantus, 46 subjects [46.7%]). In the system organ class (SOC) of respiratory, thoracic and mediastinal disorders, treatment-related cough occurred in 9 subjects (6.9%) in the Exubera group and no subjects in the Lantus group and treatment related dyspnea occurred in 3 Exubera subjects (2.2%) and no Lantus subjects. The only other treatment related AE that was reported in at least 3% of subjects in either treatment group was edema peripheral (Exubera, 4 subjects [3.0%]; Lantus, 0 subjects).

Overall, the Exubera group had a numerically higher percentage subjects reporting pulmonary related AEs in the SOC of respiratory, thoracic and mediastinal disorders compared to the Lantus group (13.3% and 4.9%, respectively). The most common pulmonary AEs reported were nasopharyngitis (13.3% of Exubera subjects and 16.4% of Lantus subjects) and cough (6.7% of Exubera subjects and 1.6% of Lantus subjects). Treatment related pulmonary AEs included 1 subject each with pneumonia, upper respiratory tract infection, pharyngolaryngeal discomfort, dsyphonia, dsypnea exertional, and increased upper airway secretion; 9 subjects with cough, and 3 subjects with dyspnea. Only 1 of these subjects had a treatment related pulmonary AE that was severe (dyspnea). In the Lantus group, treatment related pulmonary AEs included 1 subject with mild nasopharyngitis. Three subjects discontinued due to pulmonary AEs.

Fifteen subjects (11.1%) in the Exubera group and 5 subjects (4.10%) in the Lantus group had dose reductions and/or temporary discontinuations due to AEs during this study. The majority of dose reductions and temporary discontinuations in the Exubera group and all of the dose reductions and temporary discontinuations in the Lantus group were due to events of hypoglycemia.

A total of 6 subjects (4.4%) in the Exubera group and 7 (5.7%) subjects in the Lantus group had significant changes from baseline in physical examination findings at the final visit which included weight gain, pneumonia, thoracic pain due to a traffic accident, low $FEV_1$, pitting edema in feet, papel with crista on the skin of head, heart rhythm changed-atrial fibrillation, red mouth and larynx, detachment of retina, edema of the lower leg, stress, and impotence.

Between the 2 treatment groups, the mean (SD) decreases in $FEV_1$ at Week 26 were small and identical (Exubera, -0.1 [0.41] L; Lantus, (-0.1 [0.28] L). No AEs related to $FEV_1$ were reported in either treatment group.

**CONCLUSIONS:**

- This study did not fully enroll (55% of targeted enrollment was achieved) due to the termination of marketing of Exubera by the Sponsor.

- The study showed that in subjects with type 2 diabetes mellitus, who failed on at least 2 oral agents, a numerical reduction in $HbA_{1c}$ was observed for both the Exubera

group and the Lantus group. Other measures of improvement in glycemic control were also observed for both treatment groups.

- Numerically, there were a greater number of reported hypoglycemic events and a larger crude event rate in the Exubera group, compared to the Lantus group.

- The most commonly reported pulmonary AEs in both groups were nasopharyngitis and cough.

- A total of 9 Exubera subjects experienced 10 SAEs and 13 Lantus subjects experienced 23 SAEs. The majority of SAEs reported were not deemed to be related to the study drug. All SAEs are represented by single occurrences with the exception of hypoglycemia (2 Exubera subjects and 1 Lantus subject) and anemia (2 Lantus subjects).

- There were 4 deaths reported in this study (1 Exubera subject and 3 Lantus subjects). None of the deaths in either treatment group were thought to be related to the study treatment.

- Decreases in $FEV_1$ at Week 26 were similar in the Exubera and Lantus groups. No AEs related to $FEV_1$ were reported in either treatment group.

- Based on overall and treatment-emergent AE summaries, Exubera was generally well tolerated in this study. Further, the AE profile was in agreement with that found in previous studies. These safety findings are consistent with the product labeling.