Two-Year Pulmonary Safety and Efficacy of Inhaled Human Insulin (Exubera) in Adult Patients with Type 2 Diabetes

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**Objective:** To evaluate the 2-year pulmonary safety of inhaled human insulin (Exubera; EXU) in 635 nonsmoking adults with type 2 diabetes.

**Research Design And Methods:** Patients were randomly assigned to receive prandial EXU or subcutaneous (SC) insulin (regular or short-acting), plus basal (intermediate- or long-acting) insulin. The primary end points were the annual rate of decline in forced expiratory volume in 1 s (FEV<sub>1</sub>) and carbon monoxide diffusing capacity (DL<sub>CO</sub>).

**Results:** Small differences in FEV<sub>1</sub> favoring SC insulin developed during the first 3 months, but did not progress. Adjusted treatment group differences in FEV<sub>1</sub> annual rate of change were −0.007 l/y (90% CI, −0.021 to +0.006) between months 0-24 and 0.000 l/y (90% CI, −0.016 to +0.016) during months 3-24. Treatment group differences in DL<sub>CO</sub> annual rate of change were not significant. Both groups sustained similar reductions in A1C by Month 24 LOCF (EXU: 7.7% to 7.3% vs SC insulin: 7.8% to 7.3%). Reductions in fasting plasma glucose (FPG) were greater with EXU than SC insulin (adjusted mean treatment difference −12.4mg/dl, 90% CI −19.7 to −5.0). Incidence of hypoglycemia was comparable in both groups. Weight increased less with EXU than with SC insulin (adjusted mean treatment difference −1.3kg, 90% CI −1.9 to −0.7). Adverse events were comparable, except for a higher incidence of mild cough and dyspnea with EXU.

**Conclusions:** Two-year prandial EXU therapy showed a small nonprogressive difference in FEV<sub>1</sub> and comparable sustained A1C improvement but lower FPG levels and less weight gain than SC insulin in adults with type 2 diabetes.
Inhaled human insulin (Exubera; EXU (insulin human [rDNA origin]) Inhalation Powder) is effective in patients with type 2 diabetes in whom glycemic control is not achieved with diet and exercise (1), and provides better glycemic control in patients who remain inadequately controlled on either mono- or combination oral agent regimens (2-5). In addition, 6-month EXU therapy is at least comparable in efficacy to subcutaneous (SC) therapy in type 2 diabetes (6).

Previous controlled studies of EXU in type 2 diabetes patients have shown slight but consistent treatment group differences in pulmonary function in favor of comparators, using nonstandardized lung function testing (3-6). These small differences occurred early, did not progress for up to 2-years, and were not clinically meaningful. However, these studies were not designed specifically to examine respiratory safety primary end points.

The aim of the present study was to provide a robust evaluation of the longterm pulmonary safety of EXU versus SC insulin. Adult patients with type 2 diabetes were evaluated by means of validated, highly standardized pulmonary function testing, trained coordinators, and centralized data collection (7-10). A secondary objective was to evaluate the longterm efficacy of EXU versus SC insulin.

RESEARCH DESIGN AND METHODS

This is an ongoing, randomized, open-label, 5.5-year, parallel-group study in 84 centers in the United States, Canada, and Brazil. Data from the first 2 years of treatment are reported here. The protocol was reviewed and approved by the independent local Institutional review boards of all participating centers, and all patients provided written informed consent. The study is being conducted in accordance with the ethical principles of the Declaration of Helsinki.

Patients with type 2 diabetes for at least 1 year, aged 35–75 years, who were receiving a stable SC insulin regimen for at least 2 months and had BMI ≤35kg/m², A1C levels of 5.5% to 11%, and fasting plasma C-peptide concentrations ≥0.2pmol/ml (≥0.6ng/ml), were eligible for inclusion. Patients were excluded if they had unstable diabetes or recurrent severe hypoglycemia, poorly controlled asthma, significant chronic obstructive pulmonary disease or other respiratory disease, abnormal lung function tests (forced expiratory volume in 1 s [FEV₁] <70% of predicted; carbon monoxide diffusing capacity [DLCO] >120% or <70% of predicted; total lung capacity [TLC] >130% or <70% of predicted), or had reported smoking in the previous 6 months. The predictive equations of Hankinson (11), Crapo (12), and Miller (13) were used to establish baseline percent predicted lung function for FEV₁, TLC, and DLCO, respectively. A 12% adjustment in TLC and DLCO predicted values was applied for subjects of self-reported black race.

Following a 4-week run-in, during which all patients optimized SC insulin, patients were randomized at Week 0 to receive either SC insulin (regular or a short-acting analog) or prandial EXU, both in combination with intermediate- or long-acting insulin (NPH insulin, Ultralente® or insulin glargine). Randomization was performed using a computer-generated schedule. EXU was administered within 10 minutes before meals. The initial dose was based on body weight, and subsequent doses were
adjusted to achieve blood glucose concentrations of 80 to 120 mg/dl before meals and 100 to 140 mg/dl at bedtime.

Primary end points were the annual rates of decline for FEV\textsubscript{1} and DL\textsubscript{CO}. Pulmonary function tests were performed at screening, weekly for 3 weeks before starting randomized treatment, and after 3, 6, 9, 12, 15, 18, 21, and 24 months' treatment. Baseline pulmonary function was defined as the means of the values obtained after screening and before randomization (Weeks -2 and -1). The pulmonary function tests employed validated, highly standardized, methodology (7-10). All study coordinators performing pulmonary function tests underwent a 2-day training session, and were required to show theoretical and practical competencies before performing any tests. The same type of lung function analyzer (Collins CPL, Collins Medical, Braintree, Massachusetts) was used at all centers in order to minimize inter-machine variability. All testing was performed according to American Thoracic Society guidelines (14-15). Data were collected centrally at Ferraris Respiratory (Louisville, Colorado), and assessed for quality.

Secondary end points for efficacy assessments included A1C, fasting plasma glucose (FPG), hypoglycemic events, insulin dose, and body weight. Baseline for A1C, FPG, and body weight was defined as the average of all measurements after screening and prior to the first dose of study drug. Baseline insulin dose was the Week 0 dose of SC insulin. Hypoglycemia and severe hypoglycemia were defined as described by Hollander et al (6).

Safety was assessed by monitoring adverse events and clinical laboratory testing. Serum samples for measurement of insulin antibodies were obtained at baseline and at weeks 3, 6, 12, and 18, month 6, and at 3-month intervals thereafter. Dyspnea was assessed in all patients by means of the baseline (BDI) and transition dyspnea index (TDI) (16). The BDI was established 1 week before starting treatment, and the TDI after 4 and 12 weeks' treatment, and at 6, 12, 18, and 24 months.

**Statistical Analysis**—This trial was designed to estimate the difference in annual rates (slopes) of lung function decline between EXU and SC insulin. The data sets, models, and procedures used have been described previously (17). It was estimated that a sample size of 243 patients per group would allow determination of the between-treatment group differences in the annual decline in lung function with a precision of ±22.4 ml/y for FEV\textsubscript{1} and ±0.4 ml/min/mm Hg/y for DL\textsubscript{CO}. This estimate was based on a 2-sided 90% CI, assuming standard deviations for the annualized rates of decline of 150 ml for FEV\textsubscript{1} and 2.5 ml/min/mm Hg for DL\textsubscript{CO}. The precision was also based on the normal approximation of the test statistic for the comparison between 2 means.

**RESULTS**

A total of 635 patients were randomized to either EXU (n = 319) or to SC insulin (n = 316). Three patients in the EXU group and 5 in the SC insulin group withdrew before receiving study treatment. Of the remaining patients, 225 in the EXU group and 237 in the SC insulin group completed 2 years of treatment (Figure A1, available in the Online Appendix at http://care.diabetesjournals.org). Demographics of the patients at screening are summarized in Table 1.
The 2 groups were well matched in terms of demographic characteristics, duration of diabetes, baseline lung function, and glycemic control. The majority of patients were on insulin lispro or insulin aspart at baseline (EXU, 65.9%; SC, 72.4%), and most were injecting 3 times per day. At randomization, 41.9% of EXU and 39.8% of SC patients were taking insulin glargine as their basal insulin.

**Pulmonary Function**—Small decreases from baseline in FEV\(_1\) were observed in both treatment groups (Figure 1A). The mean change (±SE) in FEV\(_1\) from baseline at 2 years (LOCF) was \(-0.121 ± 0.013\) l in the EXU group and \(-0.099 ± 0.012\) l in the SC insulin group, giving an adjusted mean treatment difference (EXU-SC) of \(-0.023\) l (90% CI, \(-0.047\) to +0.002). These mean differences were not driven by outlier EXU-treated subjects with large declines in FEV\(_1\) (data not shown). Comparison of the mean annualized rates of change in FEV\(_1\) from baseline to month 24 and from months 3 to 24 showed that the treatment group difference occurred during the first 3 months of treatment and did not progress thereafter. Specifically, the mean annual rate of change for up to 24 months was \(-0.069 ± 0.006\) l/y in the EXU group and \(-0.061 ± 0.006\) l/y in the SC insulin group, giving an adjusted treatment group difference of \(-0.007\) l/y (90% CI, \(-0.021\) to +0.006). From months 3 to 24, the corresponding figures were \(-0.192 ± 0.077\) ml/min/mm Hg/y in the EXU group and \(-0.292 ± 0.071\) ml/min/mm Hg/y, in EXU and SC-treated subjects, respectively (mean treatment difference of 0.100 ml/min/mm Hg/y (90% CI, –0.072 to +0.273)).

**Efficacy**—Glycemic control was sustained and comparable in both groups (Figure 2A). The mean treatment group difference in A1C at Month 24 was small (Table 2), and was consistent with non-inferiority using criteria similar to those employed in earlier EXU efficacy trials (upper bound of CI ≤0.5%). While the mean observed values of FPG were comparable at baseline, decreases in FPG were consistently greater with EXU than with SC insulin at all subsequent time points (Figure 2B, Table 2). Body weight increased in both groups, but the weight gain increase was significantly attenuated with EXU when compared with SC insulin (Figure 2C, Table 2).

The incidence of hypoglycemic events declined over time and was slightly lower with EXU than SC insulin with a 22% risk reduction (0.8 versus 1.0 events/subject-month, respectively; risk ratio 0.78, 90% CI, 0.75 to 0.80). The incidence of severe hypoglycemic events was similar with EXU and SC insulin (0.4 versus 0.6 events/100 subject-months, respectively; risk ratio 0.68, 90% CI, 0.44 to 1.06).
**Safety**—A total of 2126 adverse events occurred in 315 (99.7%) patients in the EXU group, and 2069 events occurred in 303 (97.4%) patients in the SC insulin group. Overall, 22 patients (7%) in the EXU group and 4 (1.3%) in the SC insulin group discontinued treatment because of adverse events (Figure A1, Online Appendix). Twelve of the adverse events resulting in discontinuation in the EXU group were judged to be treatment-related and included cough (n=7), asthma exacerbation (n=3), weight gain (n=1), and dyspnea (n=1). None of the adverse events that resulted in discontinuation in the SC group were treatment-related.

The adverse event profiles of the 2 groups were comparable, except for a higher incidence of cough in EXU-treated patients. The incidence of cough was highest during the first 3 months of treatment in the EXU group (23.1%), and decreased during subsequent 3-month periods (Table A1, Online Appendix). Dyspnea was reported in 5.4% of EXU-treated patients (2.5% treatment-related) and 3.5% (0.3% treatment-related) of patients receiving SC insulin. Mean (± SD) BDI total scores were 10.99 ± 1.70 and 11.05 ± 1.65, respectively, and mean changes in TDI total scores at 2 years were –0.10 ± 0.63 and –0.01 ± 0.75, respectively.

Ninety-eight subjects in each treatment group underwent high resolution computerized tomography (HRCT) of the thorax at baseline and at least one post-baseline visit. For subjects with normal baseline scans, the incidence of abnormal HRCT results was comparable between treatment groups at Month 24. For subjects with abnormal baseline scans, no additional worsening of HRCT results occurred in EXU subjects at Month 24 (Table A2, Online Appendix).

Median insulin antibody concentrations at baseline were 1.05 µU/ml in both groups. At 2 years, the median changes from baseline were 10.6 µU/ml in the EXU group and 0.0 µU/ml in the SC insulin group. No correlation between insulin antibodies and A1C, FPG, frequency of hypoglycemia, or insulin doses was observed.

The current status of EXU, including the change in labeling regarding lung carcinoma, is summarized in the Pfizer Statement in the Online Appendix.

**CONCLUSIONS**

This is the first report of long-term pulmonary safety in insulin-using type 2 diabetes patients on EXU. Using highly sensitive and precise validated methods to assess pulmonary function (7-10), small, clinically nonmeaningful, treatment group differences in the change in FEV\(_1\) during the first 3 months of treatment favoring SC insulin were identified, confirming previous findings with EXU in type 2 diabetes patients (3-6). Most notably, the between-group differences did not increase after 3 months for up to 2 years, and pulmonary function declined at similar rates in both groups during months 3 to 24, reflecting the age- or diabetes-related decline in pulmonary function (18). The mechanism of the early treatment effect of EXU on FEV\(_1\) is unknown and remains under study. No significant difference in the annual rate of change in DL\(_{CO}\) was observed between the two treatment groups.

The annualized decline in FEV\(_1\) in both the EXU and SC insulin groups between months 3-24 (–0.058 l/y) was greater than that reported in the general population (≤ 0.040 l/y) (19-20), adding to the growing literature suggesting that
Reduced lung function is a chronic complication of type 2 diabetes. In a prospective study of 125 type 2 diabetes patients, FEV$_1$ decreased by a mean of 0.071 l/y (21), and preliminary studies have reported histopathologic changes in the lungs of patients with diabetes (22-23). Although respiratory dysfunction is rarely a presenting complaint (24), further studies are warranted to understand the impact of diabetes on lung function.

One of the limitations of this study is that the treatment targets were not met and it is conceivable that the mean A1C of 7.3% would have been lower if a more structured insulin titration algorithm was used. Despite comparable levels of longterm A1C control and slightly less hypoglycemia, EXU therapy was associated with greater reductions in FPG levels and significantly less weight gain than SC insulin over 2 years. This FPG finding has been observed in previous EXU studies (6, 17) and may be related to EXU pharmacokinetics such that prandial use reduces late post-prandial hyperglycemia after dinner, improves overnight glucotoxicity and reduces hepatic glucose production.

Adverse events in the two treatment groups were similar except for a higher incidence of cough in the EXU group during the first 3–6 months of treatment, the incidence decreasing during subsequent 3-month periods. Cough tended to occur within minutes after inhalation, was usually mild in severity, and seldom productive. Dyspnea was rare in both groups, although the incidence was higher in EXU-treated patients than in those receiving SC insulin. The majority of dyspnea episodes were mild, and the index scores indicate that patients seldom experienced dyspnea during everyday activities, and no clinically significant increases in dyspnea occurred during treatment (25).

For subjects who underwent HRCT scans, the incidence of abnormal HRCT results was comparable between treatment groups and did not worsen up to Month 24.

Insulin antibody formation was more marked after administration of EXU than after SC insulin administration, a finding consistent with previous studies (26). However, antibody formation in response to EXU was not correlated with glycemic control, insulin dose, hypoglycemic episodes, change in FEV$_1$, or tolerability (26-27). Recently, in a 3-month, highly standardized, type 1 diabetes study, no association was found between the time course of changes in lung function and antibody responses, either at the beginning or upon discontinuation of EXU therapy (28).

In summary, two-year prandial EXU therapy showed a small nonprogressive difference in FEV$_1$ and comparable sustained A1C improvement but lower FPG levels and less weight gain than SC insulin in adults with type 2 diabetes.

ACKNOWLEDGMENTS

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We would like to thank all the patients, investigators (see Online Appendix), and coordinators who took part in this study.
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**Figure legends**

**Figure 1:** Mean change in FEV₁ (A) and DL_{CO} (B) from baseline. FEV₁, forced expiratory volume in 1 second; DL_{CO}, carbon monoxide diffusing capacity; LOCF, last observation carried forward. Treatment group difference = EXU-SC.

**Figure 2:** Adjusted mean adjusted change in A1C (A), fasting plasma glucose (B), and body weight (C) from baseline. LOCF, last observation carried forward.
### Table 1: Patient Characteristics at Screening (Week -4).

<table>
<thead>
<tr>
<th></th>
<th>EXU</th>
<th>SC Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females, n (%)</td>
<td>205/111 (65/35)</td>
<td>193/118 (62/38)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>234 (74.1)</td>
<td>222 (71.4)</td>
</tr>
<tr>
<td>Black</td>
<td>28 (8.9)</td>
<td>28 (9.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (1.9)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>38 (12.0)</td>
<td>42 (13.5)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (3.2)</td>
<td>13 (4.2)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>56.7 ± 9.2</td>
<td>55.5 ± 9.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87.1 ± 14.8</td>
<td>88.3 ± 15.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.0 ± 9.7</td>
<td>170.9 ± 10.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.6 ± 4.0</td>
<td>30.1 ± 3.9</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.02 ± 1.26</td>
<td>8.15 ± 1.30</td>
</tr>
<tr>
<td>C-peptide (pmol/ml)</td>
<td>0.43 ± 0.37</td>
<td>0.36 ± 0.25</td>
</tr>
<tr>
<td>Time since diagnosis of diabetes (y)</td>
<td>13.7 (0.7–43.3)</td>
<td>13.7 (0.5–40.2)</td>
</tr>
<tr>
<td>FEV₁⁺</td>
<td></td>
<td></td>
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<tr>
<td>Observed (l)</td>
<td>2.91 ± 0.68</td>
<td>2.93 ± 0.71</td>
</tr>
<tr>
<td>Predicted (%)</td>
<td>90.9 ± 11.8</td>
<td>91.2 ± 12.6</td>
</tr>
<tr>
<td>DL₃₀⁺</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed (ml/min/mmHg)</td>
<td>24.17 ± 5.58</td>
<td>23.99 ± 5.72</td>
</tr>
<tr>
<td>Predicted (%)</td>
<td>92.3 ± 14.1</td>
<td>91.5 ± 12.7</td>
</tr>
</tbody>
</table>

Data are means ± SD (range). BMI, body mass index; A1C, glycated hemoglobin; FEV₁, forced expiratory volume in 1 s; DL₃₀, carbon monoxide diffusing capacity. *FEV₁ and DL₃₀ test values at study entry were defined as the means of the values obtained at Weeks -2, and -1.
Table 2: Changes in A1C, Fasting Plasma Glucose, Insulin Dose, and Body Weight from Baseline (Week 0).

<table>
<thead>
<tr>
<th></th>
<th>EXU (n = 314)</th>
<th>SC insulin (n = 303)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.66 ± 1.12</td>
<td>7.77 ± 1.11</td>
</tr>
<tr>
<td>2 years LOCF</td>
<td>7.33 ± 1.31</td>
<td>7.32 ± 1.22</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−0.33 ± 1.04</td>
<td>−0.45 ± 1.13</td>
</tr>
<tr>
<td>Adjusted mean treatment difference</td>
<td>0.09, 90% CI −0.04 to +0.23</td>
<td></td>
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<tr>
<td><strong>FPG, mg/dl</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>151.2 ± 44.6</td>
<td>148.2 ± 46.1</td>
</tr>
<tr>
<td>2 years LOCF</td>
<td>135.6 ± 53.4</td>
<td>147.1 ± 61.3</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−15.67 ± 57.31</td>
<td>−1.06 ± 68.04</td>
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<tr>
<td>Adjusted mean treatment difference</td>
<td>−12.4, 90% CI −19.7 to −5.0</td>
<td></td>
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<tr>
<td><strong>Average daily insulin dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>27.4 U ± 19.6</td>
<td>26.9 U ± 16.0</td>
</tr>
<tr>
<td>2 years</td>
<td>15.8 mg† ± 10.2</td>
<td>34.6 U ± 21.8</td>
</tr>
<tr>
<td>Intermediate-/Long-acting insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>43.2 U ± 22.2</td>
<td>44.0 U ± 22.9</td>
</tr>
<tr>
<td>2 years</td>
<td>46.4 U ± 28.5</td>
<td>50.0 U ± 29.1</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87.1 ± 14.8</td>
<td>88.4 ± 15.4</td>
</tr>
<tr>
<td>2 years LOCF</td>
<td>88.8 ± 15.3</td>
<td>91.4 ± 16.2</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.7 ± 4.7</td>
<td>3.0 ± 5.2</td>
</tr>
<tr>
<td>Adjusted mean treatment difference</td>
<td>−1.3, 90% CI −1.9 to −0.7</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SD. A1C, glycated hemoglobin; FPG, fasting plasma glucose; LOCF, Last observation carried forward. †During the comparative phase, the short-acting insulin was EXU and measured in mg; 1 mg is equivalent approximately to 2-3 units of subcutaneously injected fast-acting human insulin. Baseline A1C, FPG, and body weight were defined as the average of all measurements after the screening date and prior to the first dose of study drug post-randomization. Baseline insulin dose was the Week 0 dose of SC insulin.
Figure 1

A

Group Difference at Month 3 = -0.043

Group Difference at Month 24 LOC = -0.023

Change From Baseline in FEV₁ (Mean ± SD)

Baseline 3 6 9 12 15 18 21 24 24

Months

B

Group Difference at Month 3 = -0.194

Group Difference at Month 24 LOC = +0.165

Change From Baseline in DLCO (mL/min/mm Hg) (Mean ± SD)

Baseline 3 6 9 12 15 18 21 24 24

Months
Figure 2

A. Adjusted Change From Baseline in A1C [mg/dL] (Mean, SE)

B. Adjusted Change From Baseline in FPG (mg/dL) (Mean, SE)

C. Adjusted Change From Baseline in Body Weight (kg) (Mean, SE)