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

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OBJECTIVE — The purpose of this study was 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 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_1) and carbon monoxide diffusing capacity (DL_{CO}).

RESULTS — Small differences in FEV_1 favoring subcutaneous insulin developed during the first 3 months but did not progress. Adjusted treatment group differences in FEV_1 annual rate of change were −0.007 l/year (90% CI −0.021 to 0.006) between months 0 and 24 and 0.000 l/year (−0.016 to 0.016) during months 3–24. Treatment group differences in DL_{CO} annual rate of change were not significant. Both groups sustained similar reductions in A1C by month 24 (last observation carried forward) (EXU 7.7–7.3% vs. subcutaneous insulin 7.8–7.3%). Reductions in fasting plasma glucose (FPG) were greater with EXU than with subcutaneous insulin (adjusted mean treatment difference −12.4 mg/dl [90% CI −19.7 to −5.0]). Incidence of hypoglycemia was comparable in both groups. Weight increased less with EXU than with subcutaneous insulin (−1.3 kg [−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_1 and comparable sustained A1C improvement but lower FPG levels and less weight gain than seen in association with subcutaneous insulin in adults with type 2 diabetes.

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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 whose diabetes remains inadequately controlled with either monoagent or combination oral agent regimens (2–5). In addition, 6-month EXU therapy is at least comparable in efficacy to subcutaneous insulin therapy in type 2 diabetes (6).

Previous controlled studies of EXU in type 2 diabetic 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 long-term pulmonary safety of EXU versus subcutaneous 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 long-term efficacy of EXU versus subcutaneous insulin.

RESEARCH DESIGN AND METHODS

This is an ongoing, randomized, open-label, 5.5-year, parallel-group study in 84 centers in the U.S., 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 who had type 2 diabetes for at least 1 year, were aged 35–75 years, were receiving a stable subcutaneous insulin regimen for at least 2 months, and

had BMI ≤35 kg/m^2, A1C levels of 5.5–11%, and fasting plasma C-peptide concentrations ≥0.2 pmol/ml (≥0.6 ng/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 [FEV_1] <70% of predicted, carbon monoxide diffusing capacity [DL_{CO}] >120% or <70% of predicted, or total lung capacity [TLC] >130% or <70% of predicted) or if they had reported smoking in the previous 6 months. The predictive equations of Hankinson et al. (11), Crapo et al. (12), and Miller et al. (13) were used to establish baseline percent predicted lung function for FEV_1, TLC, and DL_{CO}, respectively. A 12% adjustment in TLC and DL_{CO} predicted values was applied for subjects of self-reported black race.

After a 4-week run-in, during which all patients optimized subcutaneous insulin use, patients were randomly assigned at week 0 to receive either subcutaneous 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 min before meals. The initial dose was based on body weight, and subsequent doses were adjusted to achieve blood glucose concentrations of 80–120 mg/dl before meals and 100–140 mg/dl at bedtime.

Primary end points were the annual rates of decline for FEV_1 and DL_{CO}. Pulmonary function tests were performed at screening, weekly for 3 weeks before randomized treatment was started and after 3, 6, 9, 12, 15, 18, 21, and 24 months of 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 used 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, MA) was used at all centers to minimize intermachine variability. All testing was performed according to American Thoracic Society guidelines (14,15). Data were collected centrally at Ferraris Respiratory (Louisville, CO) 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 before the first dose of study drug. Baseline insulin dose was the week 0 dose of subcutaneous 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; at weeks 3, 6, 12, and 18; at 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 treatment was started, and the TDI was established after 4 and 12 weeks of treatment and at 6, 12, 18, and 24 months.

Table 1—*Patient characteristics at screening (week −4)*

	EXU	Subcutaneous insulin
Sex (male/female)	205/111 (65/35)	193/118 (62/38)
Race		
White	234 (74.1)	222 (71.4)
Black	28 (8.9)	28 (9.0)
Asian	6 (1.9)	6 (1.9)
Hispanic	38 (12.0)	42 (13.5)
Other	10 (3.2)	13 (4.2)
Age (years)	56.7 ± 9.2	55.5 ± 9.9
Weight (kg)	87.1 ± 14.8	88.3 ± 15.4
Height (cm)	171.0 ± 9.7	170.9 ± 10.1
BMI (kg/m^2)	29.6 ± 4.0	30.1 ± 3.9
A1C (%)	8.02 ± 1.26	8.15 ± 1.30
C-peptide (pmol/ml)	0.43 ± 0.37	0.36 ± 0.25
Time since diagnosis of diabetes (years)	13.7 (0.7–43.3)	13.7 (0.5–40.2)
FEV_1*		
Observed (liters)	2.91 ± 0.68	2.93 ± 0.71
Predicted (%)	90.9 ± 11.8	91.2 ± 12.6
DL_{CO}*		
Observed (ml · min^{-1} · mmHg^{-1})	24.17 ± 5.58	23.99 ± 5.72
Predicted (%)	92.3 ± 14.1	91.5 ± 12.7

Data are *n* (%), means ± SD, or mean (range). *FEV_1 and DL_{CO} test values at study entry were defined as the means of the values obtained at weeks −2 and −1.

Statistical analysis

This trial was designed to estimate the difference in annual rates (slopes) of lung function decline between EXU and subcutaneous insulin. The datasets, 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/year for FEV_1 and ±0.4 ml · min^{-1} · mmHg^{-1} · year^{-1} for DL_{CO}. This estimate was based on a two-sided 90% CI, assuming standard deviations for the annualized rates of decline of 150 ml for FEV_1 and 2.5 ml · min^{-1} · mmHg^{-1} for DL_{CO}. The precision was also based on the normal approximation of the test statistic for the comparison between two means.

RESULTS—A total of 635 patients were randomly assigned to either EXU (n = 319) or to subcutaneous insulin (n = 316). Three patients in the EXU group and five in the subcutaneous insulin group withdrew before receiving the study treatment. Of the remaining patients, 225 in the EXU group and 237 in the subcutaneous insulin group completed 2 years of treatment (supplemental Fig. A1, available in an online appendix at http://dx.doi.org/10.2337/dc08-0159). Demographics of the patients at screening are summarized in Table 1. The two groups were well matched in terms of demographic characteristics, duration of di-

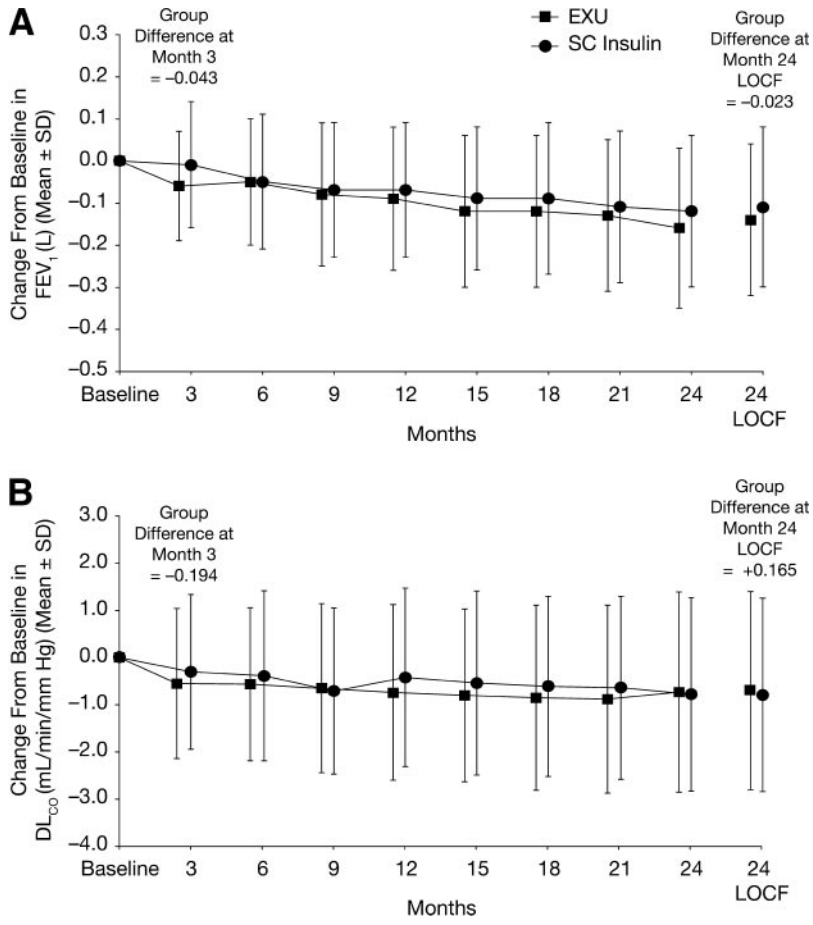

Figure 1—*Mean change in FEV_1 (A) and DL_{CO} (B) from baseline. Treatment group difference: EXU − subcutaneous insulin (SC).*

abetes, baseline lung function, and glycemic control. The majority of patients were using insulin lispro or insulin aspart at baseline (EXU 65.9%; subcutaneous insulin 72.4%), and most were injecting three times per day. At randomization, 41.9% of EXU and 39.8% of subcutaneous insulin patients were taking insulin glargine as their basal insulin.

Pulmonary function

Small decreases from baseline in FEV_1 were observed in both treatment groups (Fig. 1*A*). The mean ± SE changes in FEV_1 from baseline at 2 years (last observation carried forward [LOCF]) were -0.121 ± 0.013 l in the EXU group and -0.099 ± 0.012 l in the subcutaneous insulin group, giving an adjusted mean treatment difference (EXU − subcutaneous insulin) 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 rates of change for up to 24 months were -0.069 ± 0.006 l/year in the EXU group and -0.061 ± 0.006 l/year in the subcutaneous insulin group, giving an adjusted treatment group difference of −0.007 l/year (90% CI −0.021 to 0.006). From months 3 to 24, the corresponding figures were -0.058 ± 0.007 and -0.058 ± 0.006 l/year in EXU- and subcutaneous insulin–treated subjects, respectively (adjusted treatment group difference 0.000 l/year [90% CI −0.016 to 0.016]).

Mean changes in DL_{CO} are shown in Fig. 1*B*. At 2 years (LOCF), the changes from baseline were -0.661 ± 0.134 ml · min^{-1} · $mmHg^{-1}$ in the EXU group and -0.826 ± 0.130 ml · min^{-1} · $mmHg^{-1}$ in the subcutaneous insulin group, giving a mean treatment difference of 0.165 ml · min^{-1} · $mmHg^{-1}$ (90% CI −0.102 to +0.432). The adjusted annual rates of change in DL_{CO} for up to 24 months were -0.343 ± 0.067 ml · min^{-1} · $mmHg^{-1}$ · $year^{-1}$ in the EXU group and -0.385 ± 0.063 ml · min^{-1} · $mmHg^{-1}$ · $year^{-1}$ in the subcutaneous insulin group, giving a mean treatment difference of 0.042 ml · min^{-1} · $mmHg^{-1}$ · $year^{-1}$ (90% CI −0.109 to 0.193). The corresponding figures from months 3 to 24 were -0.192 ± 0.077 and -0.292 ± 0.071 ml · min^{-1} · $mmHg^{-1}$ · $year^{-1}$ in EXU and subcutaneous-treated subjects, respectively (mean treatment difference of 0.100 ml · min^{-1} · $mmHg^{-1}$ · $year^{-1}$ [90% CI −0.072 to 0.273]).

Efficacy

Glycemic control was sustained and comparable in both groups (Fig. 2*A*). The mean treatment group difference in A1C at month 24 was small (Table 2) and was consistent with noninferiority using criteria similar to those used in earlier EXU efficacy trials (upper bound of CI ≤0.5%). Although the mean observed values of FPG were comparable at baseline, decreases in FPG were consistently greater with EXU than with subcutaneous insulin at all subsequent time points (Fig. 2*B*; Table 2). Body weight increased in both groups, but the weight gain increase was significantly attenuated with EXU compared with subcutaneous insulin (Fig. 2*C*; Table 2).

The incidence of hypoglycemic events declined over time and was slightly lower with EXU than with subcutaneous insulin, with a 22% risk reduction (0.8 vs. 1.0 events per subject-month, respectively; risk ratio 0.78 [90% CI 0.75-0.80]). The incidence of severe hypoglycemic events was similar with EXU and subcutaneous insulin (0.4 vs. 0.6 events per 100 subject-months, respectively; 0.68 [0.44–1.06]).

Safety

A total of 2,126 adverse events occurred in 315 (99.7%) patients in the EXU group, and 2,069 events occurred in 303 (97.4%) patients in the subcutaneous insulin group. Overall, 22 patients (7%) in the EXU group and 4 (1.3%) in the subcutaneous insulin group discontinued treatment because of adverse events (Fig. A1). 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

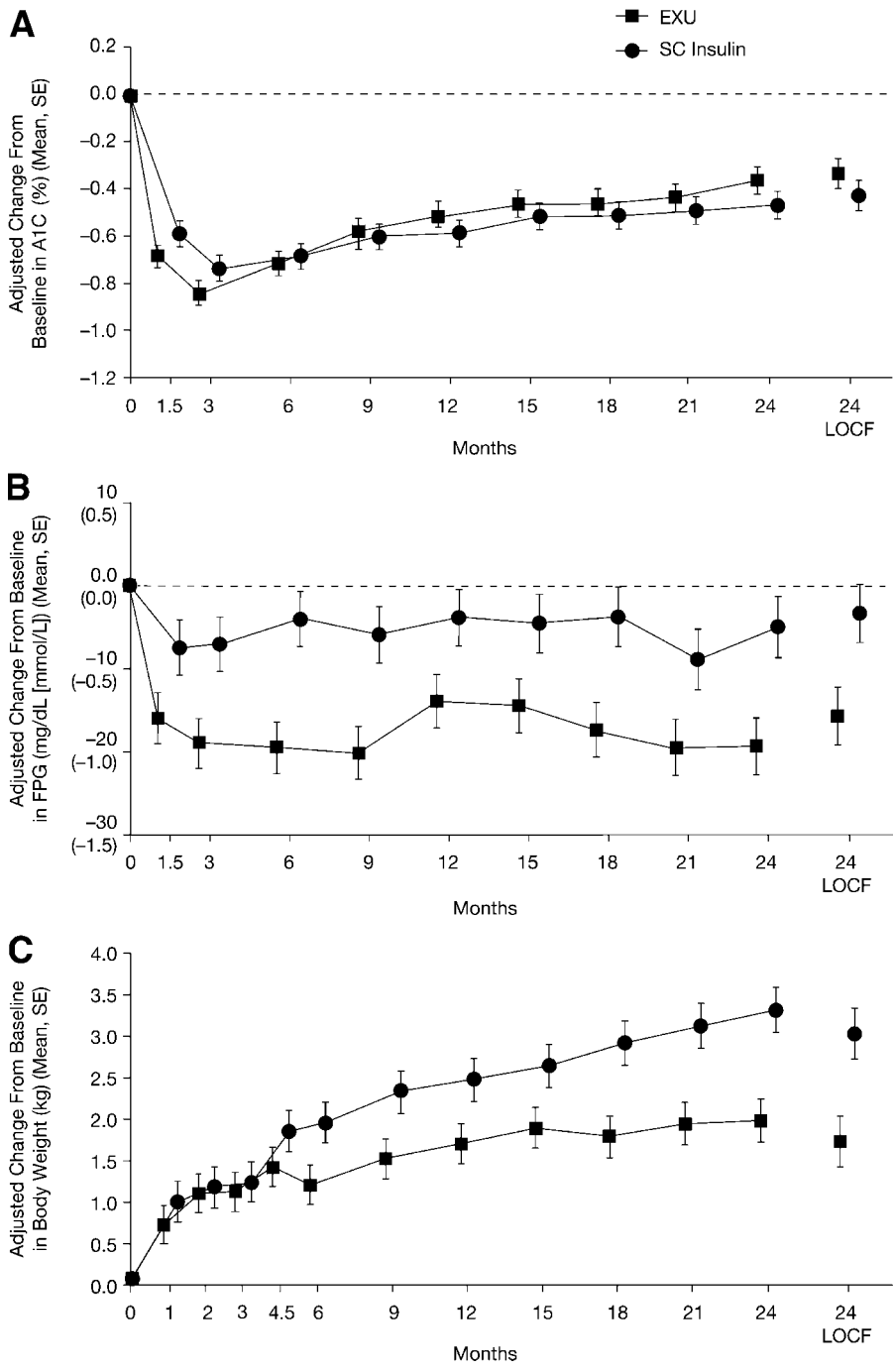

Figure 2—*Adjusted mean adjusted change in A1C* (A)*, FPG* (B)*, and body weight* (C) *from baseline.*

the subcutaneous group were treatment related.

The adverse event profiles of the two 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, available in the 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 subcutaneous insulin. Mean ± SD BDI total scores were 10.99 ± 1.70 and 11.05 ± 1.65, respectively, and 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 subjects in the EXU group at month 24 (Table A2, available in the 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 subcutaneous insulin group. No correlation between insulin antibodies and A1C, FPG, frequency of hypoglycemia, or insulin doses was observed.

CONCLUSIONS —This is the first report of long-term pulmonary safety in insulin-using type 2 diabetic patients receiving 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 subcutaneous insulin were identified, confirming previous findings with EXU in type 2 diabetic 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 an 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 subcutaneous insulin groups between months 3 and 24 (−0.058 l/year) was greater than that reported in the general population (≤0.040 l/year) (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 diabetic patients, FEV_1 decreased by a mean of 0.071 l/year (21), and histopathological changes have been reported in the lungs of patients with diabetes in preliminary studies (22,23). Although respiratory dysfunction is rarely a presenting complaint (24), further studies are warranted to understand the impact of diabetes on lung function.

Table 2—*Changes in A1C, FPG, insulin dose, and body weight from baseline (week 0)*

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

Data are means ± SD or means (90% CI). 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 after randomization. The baseline insulin dose was the week 0 dose of subcutaneous insulin. *During the comparative phase, the short-acting insulin was EXU and was measured in milligrams; 1 mg is equivalent to ~2–3 units of subcutaneously injected fast-acting human insulin.

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 long-term A1C control and slightly less hypoglycemia, EXU therapy was also associated with greater reductions in FPG levels and significantly less weight gain than subcutaneous 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 postprandial 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, with incidence decreasing during subsequent 3-month periods. Cough tended to occur within minutes after inhalation, was usually mild in severity, and was seldom productive. Dyspnea was rare in both groups, although the incidence was higher in EXU-treated patients than in those receiving subcutaneous insulin. The majority of dyspnea episodes were mild, and the index scores indicate that patients seldom experienced dyspnea during everyday activities and that 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 subcutaneous insulin administration, a finding consistent with those of 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 on discontinuation of EXU therapy (28).

In summary, 2-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 seen in association with subcutaneous insulin in adults with type 2 diabetes.

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