Two-Year Safety and Efficacy of Inhaled Human Insulin (Exubera) in Adult Patients With Type 1 Diabetes

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OBJECTIVE — The purpose of this study was to evaluate the long-term (2-year) safety and efficacy of inhaled human insulin (Exubera [insulin human (rDNA origin)] inhalation powder) (EXU) in adult patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Patients were randomly assigned to receive EXU ($n = 290$) or subcutaneous (SC) insulin ($n = 290$), plus basal (intermediate- or long-acting) insulin. The primary end point was the annual rate of decline in pulmonary function (forced expiratory volume in 1 s [FEV_1] and carbon monoxide diffusing capacity [DL_{CO}]).

RESULTS — The mean ± SEM annual rates of change between months 0 and 24 were −0.051 ± 0.005 l/year with EXU and −0.034 ± 0.005 l/year with SC insulin (significant mean difference −0.017 ± 0.007 l/year [90% CI −0.028 to −0.005]) for FEV_1 and −0.437 ± 0.073 ml · min^{-1} · $mmHg^{-1}$ · $year^{-1}$ with EXU and −0.287 ± 0.065 ml · min^{-1} · $mmHg^{-1}$ · $year^{-1}$with SC insulin (nonsignificant mean difference −0.150 ml · min^{-1} · $mmHg^{-1}$ · $year^{-1}$ [−0.310 to 0.011]) for DL_{CO}. The mean annual rates of change in FEV_1 between months 3 and 24 were −0.041 ± 0.005 and −0.031 ± 0.006 l/year in the EXU and SC insulin groups, respectively (nonsignificant mean difference −0.011 l/year [−0.023 to 0.002]), indicating that the significant difference between the treatment groups in FEV_1 developed during the first 3 months and was not progressive thereafter. Adverse event profiles were similar except for a higher incidence of cough (usually mild and unproductive) in patients receiving EXU (37.6 vs. 13.1%) that decreased to 1.3% by month 24. Glycemic control was sustained in both groups (adjusted mean treatment difference in change from baseline A1C at month 24 0.25 ± 0.07% [0.13–0.37]). Although the overall hypoglycemic events were comparable between groups (4.0 vs. 3.8 events/subject-month), the incidence of severe hypoglycemic events was lower with EXU than with SC insulin (2.8 vs. 4.1 events/100 subject-months, risk ratio 0.67 [0.57–0.79]). Body weight increased to a significantly lesser extent with EXU (adjusted mean treatment difference −1.25 ± 0.36 kg [−1.85 to −0.66]).

CONCLUSIONS — Treatment group differences in lung function between EXU and SC insulin in adult patients with type 1 diabetes are small, develop early, and are nonprogressive for up to 2 years of therapy.

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Intensive insulin therapy reduces the risk of diabetes complications (1,2). However, insulin therapy is often delayed because of anxiety about injections, hypoglycemia, or weight gain (3–6). As a result, many type 1 and type 2 diabetic patients do not achieve treatment goals and continue to live with a risk of complications (7,8). If left unchecked, this failure to achieve glycemic control will place an increasing burden on global health care resources as the worldwide prevalence of diabetes escalates (9).

Pulmonary delivery of insulin may overcome some of the obstacles to intensive glycemic control by eliminating the need for prandial insulin injections. Inhaled human insulin (Exubera [insulin human (rDNA origin)] inhalation powder; Pfizer) (EXU) was approved for use in adult patients with type 1 or type 2 diabetes in the U.S. and European Union in January 2006. EXU has a time-action profile with onset of action closer to meals than subcutaneous (SC) regular insulin (10). Clinical trials have demonstrated that EXU is as effective and well tolerated as SC insulin in adult type 1 diabetic patients for up to 6 months (11–13).

Pulmonary function is an important aspect of the safety profile for medications delivered via the lungs. By using nonstandardized lung function testing, trials of EXU in adult type 1 diabetic patients identified small treatment group differences in lung function over 6 months, favoring SC insulin (12,13). A subsequent short-term (3-month) study in type 1 diabetic patients using standardized methodology showed that these differences occurred early and were not progressive after 2–4 weeks, were clinically insignificant, and resolved within 2 weeks of discontinuation of treatment (14).

The aim of the present study was to compare the long-term (2-year) safety and efficacy of EXU versus SC insulin in adult patients with type 1 diabetes using highly standardized pulmonary function tests, trained coordinators, and centralized data collection. This was a comparative trial designed to estimate the difference in annual rates of lung function decline between EXU and SC insulin.

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Abbreviations: DL_{CO}, carbon monoxide diffusing capacity; EXU, Exubera; FEV_1, forced expiratory volume in 1 s; FPG, fasting plasma glucose; LOCF, last observation carried forward; SC, subcutaneous; TLC, total lung capacity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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RESEARCH DESIGN AND METHODS

— This is an interim analysis of an ongoing randomized, open-label, 5.5-year, parallel-group study being performed at 65 centers in the U.S., Canada, Argentina, Mexico, and Brazil. Data from the first 2 years of randomized treatment are reported here, in view of the importance of communicating the pulmonary safety of EXU therapy. The protocol was reviewed and approved by the independent 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 1 diabetes, aged 18–65 years, who were receiving a stable insulin regimen for at least 2 months and had BMI ≤30 kg/m^2, A1C levels of 5.5–11%, and fasting plasma C-peptide concentrations ≤0.2 pmol/ml were included in the study. Patients were excluded if they had brittle 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%, or total lung capacity [TLC] >130 or <70%) or had reported smoking in the previous 6 months. The predicted equations of Hankinson et al. (15), Crapo et al. (16), and Miller et al. (17) were used to establish baseline percent predicted lung function for DL_{CO}, TLC, and FEV_1, respectively. A 12% race adjustment in TLC and DL_{CO} predicted values was applied for subjects whose self-reported race was black.

After a 4-week screening period during which all patients received SC insulin, patients were randomly assigned to receive either premeal EXU or SC insulin (regular insulin, insulin lispro, or insulin aspart) plus NPH insulin or Ultralente once or twice daily or insulin glargine once daily. Exactly 74% of subjects were using insulin lispro as their prandial insulin and >25% of subjects were using insulin glargine as their basal insulin. Randomization was performed using a computer-generated schedule. EXU was administered within 10 min before meals. The initial EXU dose was based on the patient's body weight, and subsequent doses were adjusted with blood glucose targets of 80–120 mg/dl before meals and 100–140 mg/dl at bedtime.

The primary end points were the annual rates of decline for FEV_1 and DL_{CO}. Comprehensive pulmonary function tests, including spirometry and DL_{CO}, were performed at screening (week −4) and at weeks −3, −2, −1, 0, and 12 and months 6, 9, 12, 15, 18, 21, and 24 during the study (where week 0 indicates the time of randomization). Baseline test values were defined as the means of the values obtained before the first dose of study drug after randomization. After each pulmonary function test, results were compared with each patient's baseline performance. Any subject who had a postbaseline decline of >15% in FEV_1, DL_{CO}, forced vital capacity, or TLC, in the absence of obvious intercurrent respiratory illness, had the test repeated. If on repeat testing an unexplained decrease of >15% persisted, a clinician was notified, and additional pulmonary evaluation was obtained. If a patient was identified as having an intercurrent respiratory illness at any time, the illness was treated before the pulmonary function test was performed or repeated.

Highly standardized methodology was used for the pulmonary function tests in this study (18). All study coordinators performing pulmonary function tests underwent a 2-day training session and were required to show theoretical and practical competencies before they performed any tests. The same type of lung function analyzer (Collins CPL; Collins Medical, Braintree, MA) was used at all centers to minimize interassay variability. All measurements were performed according to American Thoracic Society guidelines (19,20). Data were collected centrally at Ferraris Respiratory (Louisville, CO) and assessed for quality.

Safety was assessed by monitoring adverse events and clinical laboratory testing throughout the trial. 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.

Efficacy assessments including A1C, fasting plasma glucose (FPG), hypoglycemic events, insulin dose, and body weight were secondary end points. A1C and FPG were assessed at weeks −4, −1, 0, 6, and 12 and at months 6–24 at 3-month intervals. Body weight was assessed at weeks −4, −3, −2, −1, 0, 4, 8, 12, and 18 and at months 6–24 at 3-month intervals. Insulin dose was evaluated at every visit. Hypoglycemia was defined as one of the following: characteristic symptoms of hypoglycemia without a blood glucose check; characteristic symptoms of hypoglycemia with a blood glucose level ≤59 mg/dl; or any glucose measurement of ≤49 mg/dl, irrespective of whether symptoms were present. Hypoglycemia was defined as severe if all three of the following criteria from the Diabetes Control and Complications Trial (1) were met: *1*) any event requiring assistance by another individual with the ingestion of oral carbohydrate, glucagon injection, or intravenous glucose administration; *2*) any event involving a neurologic symptom (e.g., memory loss, confusion, seizure, or loss of consciousness); and *3*) any blood glucose measurement ≤49 mg/dl.

Statistical analysis

This trial was designed to estimate the difference in annual rates (slopes) of lung function decline between EXU and SC insulin. A random coefficients model (21), with a random intercept and slope associated with each patient, was fitted (using the PROC MIXED procedure in SAS) to the observed pulmonary function data to estimate the annual rate of decline for each treatment group, the treatment group difference (EXU − SC) in annual rates of decline, and the corresponding two-sided 90% CI. The model included terms for treatment, center, sex, time (in years), baseline pulmonary function data, age, and height. Missing pulmonary function test data were not imputed.

Additionally, a repeated-measures model was fitted to the change from baseline pulmonary function test data at each visit to estimate the mean change from baseline for each treatment group for each visit, the treatment group difference (EXU − SC) in change from baseline for each visit, and the corresponding 90% CI for each visit. Missing data at month 24 were imputed using the last observation carried forward (LOCF) algorithm.

Treatment group differences and corresponding two-sided 90% CIs for continuous secondary efficacy end points were estimated using a repeated-measures model similar to that described above. The hypoglycemic event risk ratio and associated two-sided 90% CI were estimated by a survival analysis counting process approach, with a term for treatment only.

Analyses for pulmonary function test data were performed for the full analysis set (FEV_1) of subjects and analyses for parameters of efficacy (A1C, FPG, hypoglycemia, and body weight) and insulin

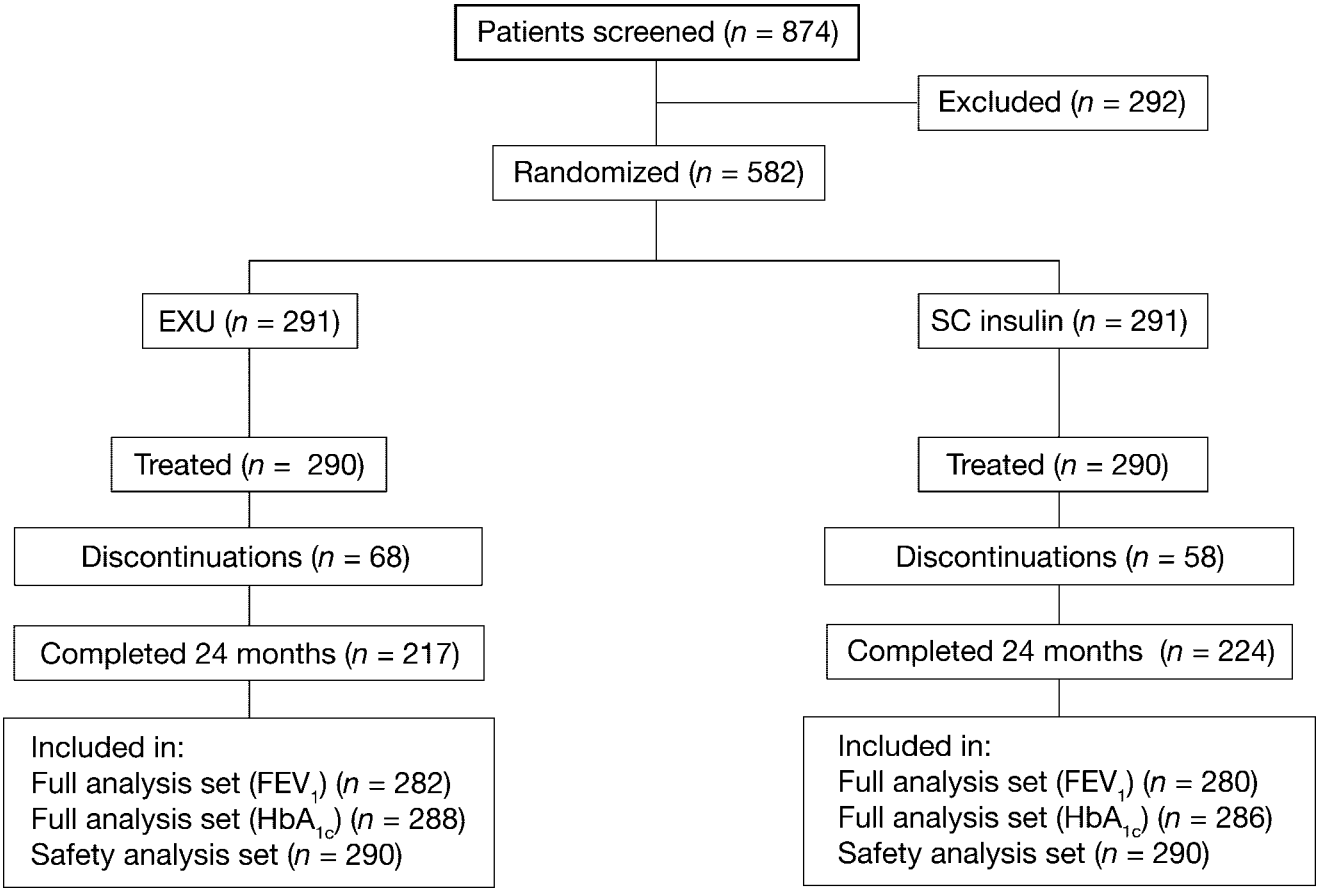

Figure 1—*Patient disposition. Analyses for pulmonary function test data were performed for the full analysis set (FEV_1) of subjects and analyses for parameters of efficacy (A1C, fasting plasma glucose, hypoglycemia, and body weight) and insulin doses were performed for the full analysis set (A1C). These sets include all patients who received at least one dose of study medication and had a baseline (FEV_1 or A1C, respectively) measurement and at least one postbaseline (FEV_1 or A1C, respectively) measurement. The general safety population, including all subjects who received at least one dose of study drug, was used to report adverse events.*

doses were performed for the full analysis set (A1C). For the repeated measures and descriptive analyses, these sets included all patients who received at least one dose of study medication and had a baseline measurement and at least one postbaseline (FEV_1 or A1C, respectively) measurement. For the annual rate of change for the pulmonary function test data, the full analysis set (FEV_1) was defined as all subjects who received at least one dose of study medication, had a baseline FEV_1 measurement, and had at least two postbaseline FEV_1 measurements. The general safety population, including all subjects who received at least one dose of study drug, was used to report adverse events.

It was estimated that a sample size of 190 patients per group would allow determination of the between-treatment group differences in lung function with a precision of ±25.3 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 SDs for the annualized rates of decline of 150 ml for FEV_1 and 2.5 ml · min^{-1} · $mmHg^{-1}$ for DL_{CO}.

RESULTS — A total of 582 patients were randomized, of whom 217 in the EXU group and 224 in the SC insulin group completed 2 years of treatment (Fig. 1). Demographic characteristics of the patients collected at screening were well matched between groups (Table 1).

Pulmonary function

Changes from baseline. Both treatment groups observed a decline from baseline in FEV_1 and DL_{CO} (Fig. 2). At month 3, the changes from baseline in FEV_1 were −0.047 l and −0.026 l in the EXU and SC insulin groups, respectively, giving a treatment group difference of −0.021 l [90% CI −0.041 to −0.002] in favor of SC insulin. At month 24 (LOCF), the equivalent changes from baseline in FEV_1 were −0.104 l and −0.082 l (treatment group difference −0.023 l [−0.044 to −0.002] in favor of SC insulin). For DL_{CO}, the month 3 changes from baseline were −1.112 and −0.425 ml · min^{-1} · $mmHg^{-1}$ in the EXU and SC insulin groups, respectively (treatment group difference −0.687 ml · min^{-1} · $mmHg^{-1}$ [−0.969 to −0.406] in favor of SC insulin). At month 24 (LOCF), the equivalent changes from baseline in DL_{CO} were −1.107 and −0.668 ml · min^{-1} · $mmHg^{-1}$ (treatment group difference −0.439 ml · min^{-1} · $mmHg^{-1}$ [−0.732 to −0.145] in favor of SC insulin). The differences between groups in the changes from baseline were small (<2% of baseline), occurred early (within 3 months), and did not progress for up to 2 years.

Annual rate of change. The mean ± SEM annual rates of change between months 0 and 24 in FEV_1 for the EXU and SC insulin groups were −0.051 ± 0.005 and −0.034 ± 0.005 l/year, respectively, giving a significant mean treatment differ-

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

	EXU	SC insulin
n	290	290
Men/women (%)	169/121 (58/42)	161/129 (56/44)
Race (%)		
White	254 (87.6)	261 (90)
Black	11 (3.8)	5 (1.7)
Asian	1 (0.3)	3 (1.0)
Hispanic	19 (6.6)	18 (6.2)
Other	5 (1.7)	3 (1.0)
Age (years)	37.6 ± 11.0	36.5 ± 11.6
Weight (kg)	74.8 ± 13.6	73.5 ± 13.3
Height (cm)	172.3 ± 9.7	171.2 ± 10.3
BMI (kg/m^2)	25.1 ± 3.0	25.0 ± 3.1
A1C (%)	7.8 ± 1.2	7.9 ± 1.2
C-peptide (pmol/ml)	0.15 ± 0.05	0.15 ± 0.05
Duration of diabetes (years)	18.4 (1.0–51.8)	17.4 (1.0–48.7)
FEV_1*		
Observed (l)	3.50 ± 0.76	3.47 ± 0.77
Predicted (%)	93.1 ± 10.8	93.2 ± 10.5
DL_{CO}*		
Observed (ml · min^{-1} · mmHg^{-1})	28.09 ± 6.22	27.20 ± 6.41
Predicted (%)	94.7 ± 13.2	92.2 ± 12.6

Data are means ± SD (range) unless otherwise indicated. *FEV_1 and DL_{CO} test values at study entry were defined as the means of the values obtained before the first dose of study drug after randomization.

ence of −0.017 ± 0.007 l/year [90% CI −0.028 to −0.005] in favor of SC insulin. Comparison of this annual rate of change in FEV_1 over the full 2 years of the study and between months 3 and 24 showed that the difference between the treatment groups developed during the first 3 months and was not progressive thereafter. The mean annual rate of change in FEV_1 between months 3 and 24 was −0.041 ± 0.005 l/year in the EXU group and −0.031 ± 0.006 l/year in the SC insulin group, giving a nonsignificant treatment group difference of −0.011 l/year [−0.023 to +0.002].

The mean annual rate of change in DL_{CO} was −0.437 ± 0.073 ml · min^{-1} · mmHg^{-1} · year^{-1} in the EXU group and −0.287 ± 0.065 ml · min^{-1} · mmHg^{-1} · year^{-1} in the SC insulin group, giving a nonsignificant mean treatment group difference of −0.150 ± 0.098 ml · min^{-1} · mmHg^{-1} · year^{-1} [90% CI −0.310 to +0.011]. The corresponding figures between months 3 and 24 were −0.111 ± 0.082 ml · min^{-1} · mmHg^{-1} · year^{-1} with EXU and −0.222 ± 0.073 ml · min^{-1} · mmHg^{-1} · year^{-1} with SC insulin, giving a nonsignificant mean treatment group difference of 0.111 ml · min^{-1} · mmHg^{-1} · year^{-1} [90% CI −0.070 to +0.292].

Adverse events

Both treatments were well tolerated during the study. A total of 1,939 adverse events occurred in 290 (100%) patients in the EXU group, and 1,844 events occurred in 289 (99.7%) patients in the SC insulin group. Ten treatment-related adverse events resulted in discontinuation in the EXU group: mild-to-moderate cough (n = 7), dyspnea (n = 2), and raised insulin antibody levels (n = 1). One treatment-related adverse event resulted in discontinuation in the SC group (severe hypoglycemia).

The adverse event profiles in the two groups were similar except for a higher incidence of cough in patients receiving EXU (37.6 vs. 13.1%). The incidence of cough was highest during the first 3 months of treatment in the EXU group (26.6%) and decreased during subsequent 3-month periods to 1.3% during months 21–24. The highest incidence of cough in the SC insulin group (7.6%) was seen during months 0–3; during months 21–24 the incidence of cough in this group was 0.4%. Cough was predominantly mild to moderate and nonproductive and usually developed within seconds or minutes after inhalation. Patients with cough did not experience excessive declines in FEV_1.

Median insulin antibody levels were 4.50 vs. 4.15 μU/ml at baseline and 64.50 vs. 3.85 μU/ml after 2 years in the EXU and SC insulin groups, respectively. The increase in insulin antibodies in EXU-treated patients was maximal at 12 months and subsequently declined. There were no clinical manifestations of the increased antibodies observed in this study.

Efficacy

Glycemic control was sustained in both treatment groups: A1C changed from 7.4 and 7.5% at baseline (week 0) to 7.5 and 7.3% in the EXU and SC insulin groups, respectively (Table 2). The mean treatment group difference in A1C at month 24 was small (0.25 ± 0.07% [90% CI 0.13–0.37]) and was consistent with noninferiority using criteria similar to those used in earlier EXU efficacy trials (upper bound of CI ≤0.5%). Decreases in FPG were consistently greater with EXU: the mean treatment difference at 2 years LOCF was −17.11 ± 6.60 mg/dl [−27.98 to −6.23]. In addition, there was significantly less weight gain with EXU versus SC insulin (adjusted mean treatment group difference −1.25 ± 0.36 kg [−1.85 to −0.66]).

The overall incidence of hypoglycemic events was comparable in the EXU and SC treatment groups (4.0 and 3.8 events/subject-month, respectively). Hypoglycemia was reported by 96.9 and 98.3% of the EXU- and SC insulin-treated patients, respectively. The incidence of severe hypoglycemic events was significantly lower with EXU versus SC insulin (2.8 vs. 4.1 events/100 subject-months, respectively); the EXU-to-SC risk ratio was 0.67 [90% CI 0.57–0.79], corresponding to a 33% reduction in risk with EXU. Severe hypoglycemia was reported by 24.5 and 29.3% of the EXU and SC insulin-treated patients, respectively.

CONCLUSIONS

— This study confirms the long-term (2-year) pulmonary safety and efficacy of EXU therapy in adult type 1 diabetic patients. Consistent with previously published short-term data (11–14), the present study demonstrates that EXU therapy is equally as effective in maintaining glycemic control as SC insulin while generally having a similar safety profile and minimal impact on lung function.

The primary focus of this study was the long-term pulmonary safety of EXU, which was assessed by means of standardized methodology. Although FEV_1 and

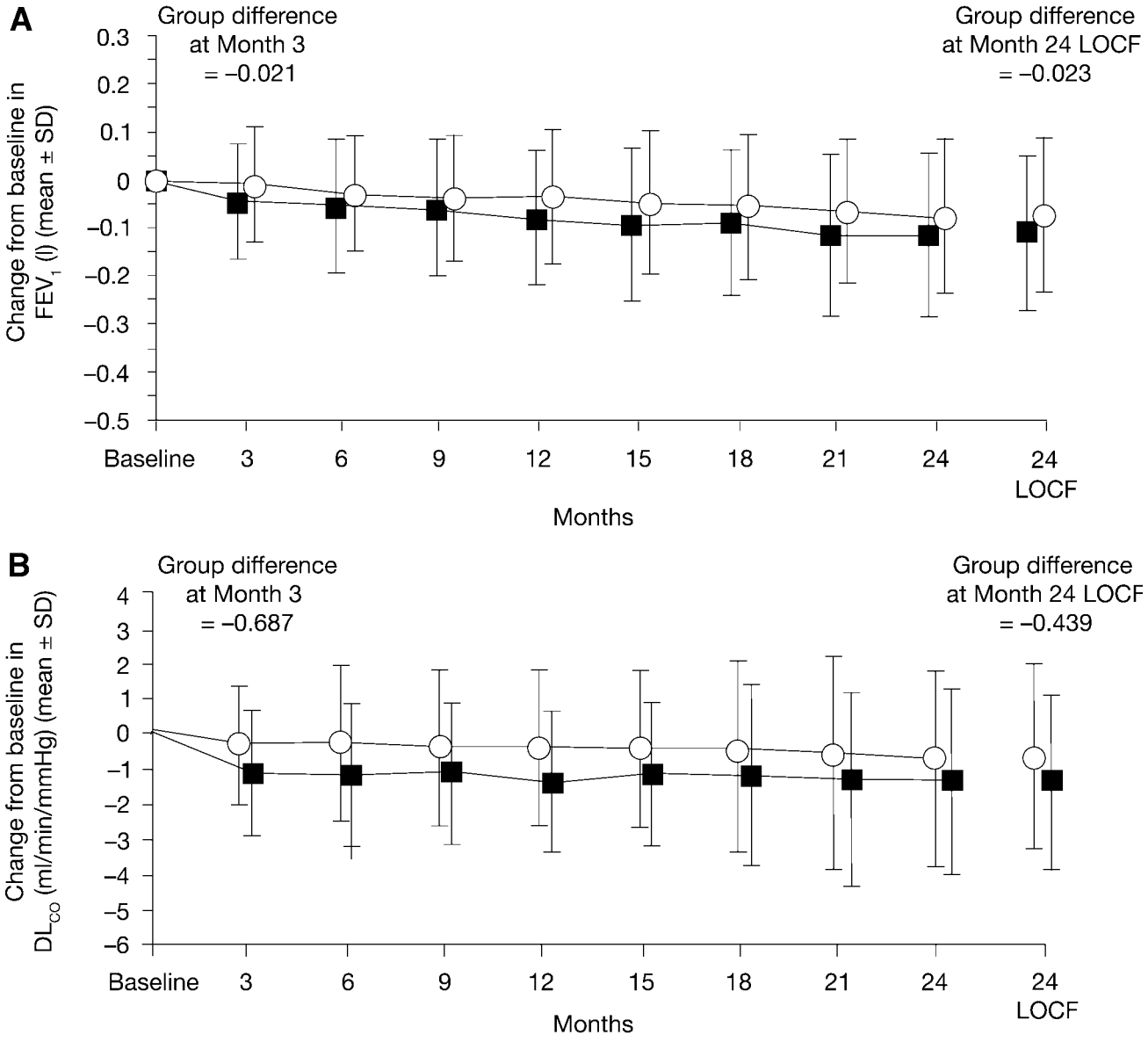

Figure 2—*Mean ± SD change from baseline in FEV_1 (A) and DL_{CO} (B). Treatment group difference = EXU − SC. Although FEV_1 and DL_{CO} declined in each group during the course of the study, differences between the two treatment groups remained small (<2% of baseline), developed early (during the first 3 months), and did not progress further for up to 2 years.* ■*, EXU;* ○*, SC insulin.*

DL_{CO} declined in each group during the course of the study, the only statistically significant difference in the annual rate of change between the two treatment groups was in FEV_1 during the first 3 months of treatment, and this did not progress further. These results complement those previously reported from a short-term (3-month) highly standardized study of EXU in type 1 diabetes; in that study differences also occurred early and were not progressive after 2–4 weeks, were clinically insignificant, and resolved within 2 weeks of treatment discontinuation (14). The mechanism of the treatment effect of EXU on lung function is currently unknown and remains under study.

That pulmonary function was observed to decline at similar rates with both EXU and SC insulin during months 3–24 is reflective of the normal age-related decline in pulmonary function (22). Interestingly, a recent pooled analysis of FEV_1 data from 22 EXU trials including 3,766 patients with type 1 or type 2 diabetes identified baseline FEV_1 and age as important covariates in predicting the rate of FEV_1 decline; the type of diabetes was not a factor (23).

Glycemic control was sustained during 2 years in both treatment groups. FPG concentrations were lower in the EXU than in the SC insulin group at every study time point. This latter finding is consistent with previous observations in type 1 (12,13) and type 2 diabetic patients (24); the reason is unclear at present and is the subject of ongoing investigations but may be due to the improved postprandial glucose concentrations at bedtime and/or possibly the prolonged action of pulmonary insulin in this formulation.

Weight gain is a frequent and undesirable effect of insulin therapy and is an important concern of patients (6). In this study, EXU resulted in significantly less weight gain than SC insulin. It is possible that the pharmacokinetic profile of EXU (10) results in reduced hyperinsulinemia and, thus, less weight

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

	EXU	SC insulin
n	288	286
A1C (%)		
Baseline	7.4 ± 1.1	7.5 ± 1.1
2 years LOCF	7.5 ± 1.1	7.3 ± 1.2
Change from baseline	0.1 ± 0.9	−0.2 ± 1.0
Adjusted treatment difference	0.25 ± 0.07 (0.13–0.37)	
FPG (mg/dl)		
Baseline	170.1 ± 67.2	166.9 ± 59.6
2 years LOCF	156.8 ± 77.8	173.5 ± 81.0
Change from baseline	−13.3 ± 97.9	6.6 ± 97.8
Adjusted treatment difference	−17.11 ± 6.60 (−27.98 to −6.23)	
Insulin dose		
Short-acting insulin (units)		
Baseline	22.6 ± 13.3	23.9 ± 14.4
2 years	14.7 ± 9.1*	25.4 ± 16.7
Intermediate-/long-acting insulin (units)		
Baseline	30.8 ± 13.5	33.3 ± 15.9
2 years	31.8 ± 19.4	36.2 ± 18.2
Body weight (kg)		
Baseline	75.1 ± 13.6	73.8 ± 13.1
2 years LOCF	75.9 ± 13.6	75.8 ± 13.8
Change from baseline	0.8 ± 4.2	2.0 ± 4.6
Adjusted treatment difference	−1.25 ± 0.36 (−1.85 to −0.66)	

Data are presented as means ± SD or adjusted mean ± SEM (95% CI). *During the comparative phase, EXU was measured in milligrams; 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 before the first dose of the study drug after randomization. Baseline insulin dose was the week 0 measurement.

gain in the setting of comparable A1C and incidence of hypoglycemia.

The adverse event profiles of EXU and SC insulin were similar except for a higher incidence of cough with EXU during the first 3 months of treatment. This cough tended to occur within seconds to minutes of dosing and was usually mild and nonproductive; the incidence decreased during subsequent 3-month periods.

In this study we found that insulin antibody formation was more marked after administration of EXU than after SC insulin administration, a finding consistent with previously published EXU trials (25). In addition, there were no clinical manifestations of the increased antibodies observed in this study. This result is supported by previous studies that have shown that antibody formation in response to EXU does not appear to have any clinical relevance, as there are no correlations between antibody formation and glycemic control, insulin dose, the small changes observed in FEV_1 or DL_{CO}, hypoglycemic episodes, or allergies (14,25,26). The design of the present study did not permit a detailed analysis of the onset and time course of the development of the antibody response in relation to the changes in lung function. This was recently accomplished, however, in a 3-month, highly standardized, type 1 diabetes study in which it was found that there is a dissociation between the time course of the changes in lung function and the antibody responses, both at the beginning and upon discontinuation of EXU therapy (14).

Patients' unwillingness or inability to comply with multiple daily insulin injection regimens may be a barrier to acceptance of intensive insulin therapy (27). Although not examined in the present study, several trials assessing patients' treatment preferences have shown preferences for EXU over SC insulin (28,29). Taken together with the demonstrated long-term efficacy and safety data obtained in the present study, these patient preference results suggest that EXU may increase the acceptance of insulin therapy in type 1 diabetic patients.

In summary, the results of this study indicate that treatment group differences in lung function between EXU and SC insulin in adult patients with type 1 diabetes are small, develop early, and are nonprogressive for up to 2 years of therapy.

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