Efficacy and Safety of Inhaled Insulin (Exubera) Compared With Subcutaneous Insulin Therapy in Patients With Type 2 Diabetes

Results of a 6-month, randomized, comparative trial

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OBJECTIVE — Glycemic control using inhaled, dry-powder insulin plus a single injection of long-acting insulin was compared with a conventional regimen in patients with type 2 diabetes, which was previously managed with at least two daily insulin injections.

RESEARCH DESIGN AND METHODS — Patients were randomized to 6 months' treatment with either premeal inhaled insulin plus a bedtime dose of Ultralente ($n = 149$) or at least two daily injections of subcutaneous insulin (mixed regular/NPH insulin; $n = 150$). The primary efficacy end point was the change in HbA_{1c} from baseline to the end of study.

RESULTS — HbA_{1c} decreased similarly in the inhaled (−0.7%) and subcutaneous (−0.6%) insulin groups (adjusted treatment group difference: −0.07%, 95% CI −0.32 to 0.17). HbA_{1c} <7.0% was achieved in more patients receiving inhaled (46.9%) than subcutaneous (31.7%) insulin (odds ratio 2.27, 95% CI 1.24–4.14). Overall hypoglycemia (events per subject-month) was slightly lower in the inhaled (1.4 events) than in the subcutaneous (1.6 events) insulin group (risk ratio 0.89, 95% CI 0.82–0.97), with no difference in severe events. Other adverse events, with the exception of increased cough in the inhaled insulin group, were similar. No difference in pulmonary function testing was seen. Further studies are underway to assess tolerability in the longer term. Insulin antibody binding increased more in the inhaled insulin group. Treatment satisfaction was greater in the inhaled insulin group.

CONCLUSIONS — Inhaled insulin appears to be effective, well tolerated, and well accepted in patients with type 2 diabetes and provides glycemic control comparable to a conventional subcutaneous regimen.

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Although the long-term benefits of tight glycemic control have been shown in patients with both type 1 and type 2 diabetes (1–5), insulin therapy is often delayed or suboptimally implemented despite elevated HbA_{1c} levels, and a substantial number of patients remain poorly controlled (6).

Several factors contribute to the poor implementation of insulin therapy in the patient with type 2 diabetes, but the inconvenience and poor patient acceptability of a multiple daily injection regimen may play a major role (7). Currently, the majority of patients treated with insulin do not achieve recommended HbA_{1c} goals (8). Reliance on fixed-ratio premixed insulins for treatment of a significant proportion of the type 2 diabetic population may significantly constrain the ability to achieve target glycemia. More acceptable forms of insulin delivery are required to improve the implementation of insulin therapy aiming for recommended treatment goals.

A dry-powder insulin delivery system that permits noninvasive application of rapid-acting insulin via inhalation has been developed. The pulmonary route exploits the large vascular bed and permeability of the alveoli to deliver insulin directly into the bloodstream (9). Inhaled insulin provides a rapid-acting insulin for

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Abbreviations: DL_{CO}, carbon monoxide diffusing capacity; FEV_1, forced expiratory volume in 1 s; FPG, fasting plasma glucose; FVC, forced vital capacity; LOCF, last observation carried forward; PFT, pulmonary function test; PPG, postprandial plasma glucose; SMBG, self-monitoring of blood glucose; TLC, total lung capacity.

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

management of both type 1 and type 2 diabetes, and preliminary short-term studies have shown that inhaled insulin provides reproducible and effective control of meal-related glycemia (10–12).

The time-action profile of human regular insulin injected subcutaneously limits its ability to control postprandial glycemia. Its relatively slow onset of action does not reproduce the physiologic secretion profile of insulin in response to a meal (13), thus resulting in excessive postprandial hyperglycemia and increased risk of hypoglycemia before the next meal. A study (14) in healthy subjects showed inhaled insulin to have a rapid onset of action that was significantly faster than regular insulin and a duration of action between that of insulin lispro and regular insulin. It has also been shown (15) in patients with type 2 diabetes that inhaled insulin is rapidly and reproducibly absorbed. As such, inhaled insulin appears to match the physiologic needs for mealtime use.

The present study aimed to *1*) assess whether an insulin regimen involving pulmonary delivery of rapid-acting, dry-powder insulin plus a single injection of basal long-acting, subcutaneous insulin can provide glycemic control comparable to a conventional subcutaneous insulin regimen in a large cohort of patients with type 2 diabetes previously managed with at least two daily subcutaneous injections of insulin and 2) assess the tolerability of inhaled insulin over a 6-month period.

RESEARCH DESIGN AND METHODS

— Men and women (n = 520) diagnosed with type 2 diabetes for at least 1 year were screened at 39 centers in the U.S. and Canada. Inclusion criteria were age 35–80 years; stable subcutaneous insulin schedule involving two to three injections daily for at least 2 months before study entry and not receiving any oral antidiabetic agents; screening and prerandomization HbA_{1c} values of 6–11% inclusive, fasting plasma C-peptide >0.2 pmol/ml, and BMI ≤35 kg/m^2; willingness to perform self-monitoring of blood glucose (SMBG) and otherwise comply with the study protocol; and written informed consent.

Exclusion criteria included poorly controlled asthma, chronic obstructive pulmonary disease or other significant respiratory disease; smoking during the last 6 months; abnormal screening chest X-ray; abnormal pulmonary function at screening (carbon monoxide diffusing capacity [DL_{CO}] <75%, total lung capacity [TLC] <80 or >120%, and forced expiratory volume in 1 s [FEV_1] <70% of predicted); major organ system disease; clinically significant abnormalities on laboratory screening; concomitant therapy with systemic glucocorticoids; predisposition to severe hypoglycemia (two or more severe episodes within the past 6 months); any hospitalization or emergency room visit due to poor diabetic control within the past 6 months; insulin-pump therapy in the 2 months before screening or inhaled insulin in any clinical trial; and an insulin requirement of >150 units/day.

The study protocol was approved by the institutional review board at each center.

This was a phase 3, open-label, parallel-group, comparator study consisting of a screening visit, a 4-week baseline lead-in phase, and a 24-week randomized treatment phase. During the baseline period, patients received a subcutaneous insulin regimen consisting of two doses of mixed NPH/regular. If the patient had previously been treated with an insulin regimen consisting of mixed NPH/regular insulin before breakfast and supper, the patient continued with this regimen. Otherwise, the patient received an appropriate two-dose regimen based on insulin requirements and glycemic control before entering the study.

Three weeks before randomization, patients met a dietitian for instruction on a weight-maintaining diet, which they were to maintain for the study duration. Patients were also instructed to perform 30 min of moderate exercise at least three times each week. The importance of diet and exercise was reinforced at clinic visits. All patients received instruction in SMBG, which they were to perform four times daily: before breakfast, lunch, supper, and bedtime. Target glucose ranges were 80–140 mg/dl (4.4–7.8 mmol/l) before meals and 100–160 mg/dl (5.6–8.9 mmol/l) before bedtime.

Before randomization, patients received instruction regarding the use of the insulin inhalation device. Using a computer-generated randomization scheme, performed through interactive voice response technology, patients were randomized to receive an inhaled insulin regimen (n = 149) or continue receiving conventional subcutaneous therapy as described above for 24 weeks (n = 150). The inhaled insulin regimen consisted of premeal inhaled insulin plus a single bedtime dose of Ultralente insulin. Inhaled insulin was administered within 10 min of the start of each meal and given in one to two inhalations using a dry-powder aerosol delivery system (Nektar Therapeutics, San Carlos, CA). The insulin powder was packaged in foil blisters of 1- and 3-mg doses (1 mg is equivalent to 2–3 units of subcutaneous insulin) (11).

Initial recommended doses for inhaled insulin were based on the subject's weight, baseline subcutaneous insulin dose, and previous response to insulin. Administration of insulin, inhaled or injection, was preceded by SMBG, and the dose was adjusted weekly at the discretion of the investigator, based on SMBG results, to achieve target premeal glucose. Patients were also allowed to adjust doses when preprandial glucose was outside the above ranges, in anticipation of a smaller- or larger-than-usual meal or on an "as-needed" basis.

Assessments

The primary efficacy end point was the change in HbA_{1c} from baseline to week 24. HbA_{1c} was measured before randomization (at weeks −4 and −1) and at weeks 0, 6, 12, and 24. Mean HbA_{1c} from weeks −1 and 0 was taken as baseline. The percentage of patients achieving HbA_{1c} <7% at week 24 was also assessed. Other secondary efficacy end points included change in fasting plasma glucose (FPG) and 2-h postprandial plasma glucose (PPG) response (increment change in plasma glucose between 2-h postprandial and 30-min preprandial values). FPG was measured at weeks −4, −1, 0, 12, and 24, and PPG levels in response to a standard meal were measured at week −1 and at week 24 at the end of the treatment period. The meal test was conducted in the morning after an 8- to 10-h overnight fast and consisted of 16 oz of Boost (Mead Johnson Nutritionals, Evansville, IN), which provided 480 kcal (66 g carbohydrate, 29 g protein, and 11 g fat). Other end point comparisons included hypoglycemic events, body weight, fasting serum lipids, and pulmonary function tests (PFTs).

Patients were instructed to perform SMBG if they experienced symptoms of hypoglycemia and to record hypoglycemic episodes. Hypoglycemia was defined as

Table 1—*Demographic and clinical characteristics at study entry*

	Inhaled insulin	Subcutaneous insulin
n	149	149
Sex (M/F)	99/50	99/50
Age (years)	58.7 ± 9.5 (35–80)	56.2 ± 11.1 (23–78)
Duration of diabetes (years)	13.8 (0.4–59.0)	13.2 (0.9–43.4)
Weight (kg)		
Men	93.7 ± 13.4 (63–126)	91.5 ± 13.5 (65–123)
Women	82.3 ± 12.8 (59–115)	83.4 ± 12.4 (59–123)
Mean	89.9 ± 14.2	88.8 ± 13.7
BMI (kg/m^2)		
Men	29.9 ± 3.8 (21–38)	29.5 ± 3.6 (21–38)
Women	31.7 ± 5.1 (22–51)	31.1 ± 3.9 (22–38)
HbA_{1c} (%)	8.48 ± 1.24 (6.5–11.9)	8.47 ± 1.20 (5.8–11.6)
C-peptide (pmol/ml)	0.61 ± 0.41 (0.17–3.23)	0.58 ± 0.37 (0.07–2.81)
Short-acting insulin (units)	23.17 (1.0–92.0)	23.79 (4.0–110.0)
n	105	107
Long/intermediate-acting insulin (units)	41.27 (5.0–115.0)	41.66 (8.0–144.0)
n	112	117
Premixed short/intermediate-acting insulin (units)	61.79 (14.0–140.0)	49.03 (11.0–90.0)
n	39	36

Data are means ± SD.

typical symptoms without glucose measurement, but prompt resolution with food intake; typical symptoms with glucose concentrations of ≤59 mg/dl (≤3.3 mmol/l); or any glucose measurement of ≤49 mg/dl (≤2.7 mmol/l). For classification as severe hypoglycemia, all of the following criteria had to be met: *1*) the subject was unable to treat himself or herself, *2*) they exhibited neurological symptoms (memory loss, confusion, uncontrollable or irrational behavior, difficulty in awakening, seizure, or coma), and *3*) blood glucose ≤2.7 mmol/l or, if not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

Laboratory tests (complete blood count, urinalysis, and blood chemistries) were performed at screening and week 24 and measurement of insulin antibodies (semiquantitative radioligand binding assay) at weeks 0 and 24. Physical examinations (heart rate, blood pressure, and pharynx and chest examination) were performed throughout the study. All adverse events were recorded by the investigators. Using American Thoracic Society–certified methods, PFTs were performed in a pulmonary function laboratory with equipment available at each center. The full battery of PFTs, including forced vital capacity (FVC), FEV_1, TLC, and DL_{CO}, was conducted at weeks −3 and 24. Measurement of FVC and FEV_1 was also performed at week 12.

At baseline and weeks 6, 12, 20, and 24, patients were requested to complete a self-administered Quality of Life and Treatment Satisfaction Questionnaire (Phase V Technologies, Wellesley Hills, MA) addressing satisfaction, preference, and quality of life.

Statistical methods

This comparative trial was designed to test the "noninferiority" of an inhaled insulin regimen relative to a subcutaneous insulin regimen with respect to change in HbA_{1c} from baseline to week 24. Analysis was performed for the per-protocol (assessable) population, a subset of the intention-to-treat population. The population that could be evaluated included subjects who did not have a major violation of the inclusion/exclusion criteria, had received at least one-half of the protocol-required duration of treatments (12 of 24 weeks), had a baseline HbA_{1c} measurement, and had at least one assessable postbaseline HbA_{1c} assessment (≥75% of the elapsed time since the previous assessment). The primary efficacy end point was the change in HbA_{1c} from baseline to week 24. If the week 24 HbA_{1c} value was not available, the last assessable value was carried forward (last observation carried forward [LOCF]). An ANCOVA model, with baseline HbA_{1c} as a continuous covariant and indicator variables for center and treatment group, was fitted to the week 24 change from baseline HbA_{1c} values. The 95% CI for the comparison of inhaled and subcutaneous insulin was derived from this model. Noninferiority of the inhaled insulin regimen to the subcutaneous insulin regimen was concluded if the upper limit of the 95% CI for the difference was <0.5% HbA_{1c}, as specified in the protocol. A similar analysis approach was used for all other end points, except for the hypoglycemic event rate ratio, which was estimated using the survival analysis counting process approach for recurrent events and included a term for treatment only, and percentage reaching HbA_{1c} goal, which was estimated using logistic regression. Multivariate ANCOVA was used to test the overall null hypothesis of no treatment differences by analyzing the Quality of Life and Treatment Satisfaction scale changes from baseline to week 24 (LOCF).

Treatment group differences (inhaled-subcutaneous) in change from baseline in FEV_1 and FVC were estimated at each assessment time point (weeks 12 and 24) using a repeated measures ANCOVA model. The treatment group differences in change from baseline in DL_{CO} and TLC at week 24 were estimated using an ANCOVA model. These models included terms for treatment and center and covariates known to have a physiologic relationship with pulmonary function, including baseline PFT, age (years), baseline height (meters), and sex.

RESULTS — Characteristics of the study participants at study entry are given in Table 1. The groups were well matched for all baseline characteristics. Both groups used only subcutaneous insulin at baseline, and the use of short- and long/intermediate-acting insulins at baseline was similar between treatment groups (Table 1). Daily insulin use in both groups trended slightly higher from week 6 to week 24 (inhaled group: short acting, 15.0 and 16.6 mg at weeks 6 and 24, respectively, and long acting, 34.0 and 37.9 units, respectively; subcutaneous group: short acting, 24.0 and 25.5 units, respectively, and intermediate acting, 50.1 and 52.3 units, respectively). As the inhaled insulin regimen involved only one daily injection of long-acting Ultralente along with premeal short-acting insulin, the

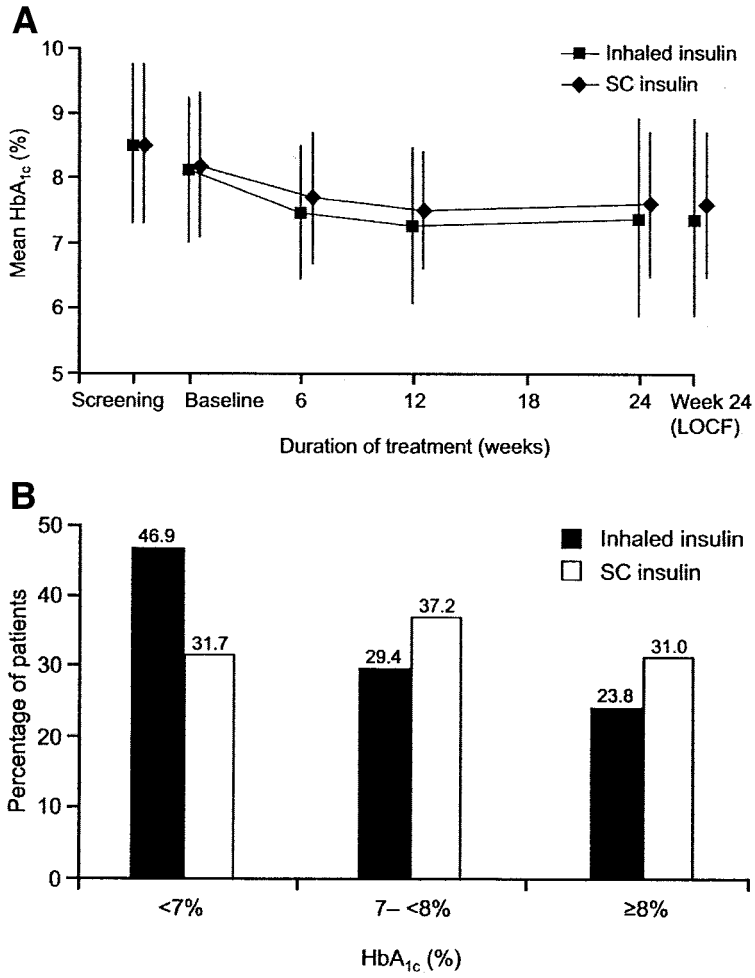

Figure 1—A: *HbA_{1c} (mean ± SD) during treatment with inhaled (■) versus subcutaneous (◆) insulin at screening* (n = *141 and 145, respectively), baseline* (n = *143 and 145), and weeks 6* (n = *137 and 130), 12* (n = *143 and 145), and 24* (n = *134 and 140*). B: *Percentage of patients achieving defined levels of HbA_{1c} at week 24 (LOCF) with inhaled (■,* n = *143) versus subcutaneous (□,* n = *145) insulin.*

basal-to-bolus ratio was shifted (i.e., less basal and more bolus insulin) relative to the subcutaneous group, where two daily doses of both intermediate- and short-acting insulin were used.

Of the 299 patients enrolled, 1 withdrew consent after randomization. In the inhaled group, 3 patients discontinued for reasons related to study treatment (two adverse events and one insufficient clinical response), and 12 subjects discontinued for administrative reasons (e.g., protocol violation or withdrawn consent). Two subjects in the inhaled group died of causes unrelated to treatment (one of metastatic esophageal cancer and one of esophageal bleeding of unknown etiology). In the subcutaneous insulin group, one subject discontinued for insufficient clinical response and two subjects discontinued due to adverse events not considered related to the study drug. Six subjects in the subcutaneous group discontinued for administrative reasons.

Mean change in HbA_{1c}

Mean HbA_{1c} decreased similarly in the two treatment groups (Fig. 1*A*). After 24 weeks of treatment, mean HbA_{1c} levels decreased from 8.1% at baseline to 7.4% (−0.7%) at week 24 in patients receiving inhaled insulin. Patients receiving subcutaneous showed a decrease from 8.2 to 7.6% (−0.6%). The difference between the adjusted mean changes from baseline for the two treatments (inhaled-subcutaneous) was −0.07% (95% CI −0.32 to 0.17). Thus, the upper limit of the 95% CI was <0.5 (the prespecified noninferiority margin), showing that the two treatment regimens are statistically comparable.

Sixty-seven patients (47%) receiving inhaled insulin achieved HbA_{1c} <7% by week 24, compared with 46 patients (32%) receiving subcutaneous insulin. The adjusted odds ratio (inhaled-subcutaneous) of achieving versus not achieving HbA_{1c} <7% was 2.27 (95% CI 1.24–4.14). The distribution of HbA_{1c} values in both groups is shown in Fig. 1*B*.

FPG and PPG

FPG decreased from 152 mg/dl (8.44 mmol/l) at baseline to 132 mg/dl (7.33 mmol/l) at week 24 in those receiving inhaled insulin compared with 158 mg/dl (8.77 mmol/l) to 149 mg/dl (8.27 mmol/l) in the subcutaneous group. The difference between the adjusted mean changes from baseline was −15.9 mg/dl in favor of inhaled insulin (95% CI −26.6 to −5.2).

The treatment groups were comparable in terms of change from baseline in the 2-h PPG concentration at week 24. In patients receiving inhaled insulin treatment, 2-h PPG decreased from 244 mg/dl (13.5 mmol/l) at baseline to 221 mg/dl (12.3 mmol/l) at week 24, compared with a reduction from 252 mg/dl (14.0 mmol/l) to 231 mg/dl (12.8 mmol/l) in patients receiving subcutaneous treatment. The difference between adjusted mean changes from baseline was −9.41 mg/dl (95% CI −26.9 to 8.0).

Hypoglycemia

In the inhaled insulin group, 109 (76.2%) patients experienced a total of 1,104 hypoglycemic events: a crude event rate of 1.40 events per subject-month. One hundred four patients (71.7%) in the subcutaneous insulin group experienced a total of 1,278 events: a crude event rate of 1.57 events per subject-month. This represents a risk ratio (inhaled/subcutaneous) for any hypoglycemic event of 0.89 (95% CI 0.82–0.97), indicating that there is a lower risk of hypoglycemia associated with inhaled insulin. There were very few severe hypoglycemic events in either treatment group. Only four events in the inhaled group were classed as severe (crude event rate 0.5/100 subject-months) and one event in the subcutaneous group (0.1/100 subject-months).

Body weight and lipid profile

After 24 weeks, mean body weight in the inhaled insulin group remained stable at 90.5 kg. However, there was an increase in body weight in the subcutaneous treatment group (89.2 kg at baseline, 90.6 kg at week 24). The adjusted mean treatment

Table 2—*PFT results in subjects with a baseline and at least one postbaseline PFT measurement*

PFT parameter	Inhaled insulin			Subcutaneous insulin			Adjusted inhaled-subcutaneous difference in change from baseline at week 24 (95% CI)*
	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24	
n	149	140	136	149	141	142	
FEV_1 (l)	2.840 ± 0.669	2.765 ± 0.651	2.789 ± 0.665	2.980 ± 0.683	2.915 ± 0.648	2.910 ± 0.644	0.000 (−0.048 to 0.048)
n	149	140	136	149	141	142	
FVC (l)	3.587 ± 0.832	3.527 ± 0.820	3.548 ± 0.867	3.734 ± 0.907	3.670 ± 0.824	3.657 ± 0.814	0.025 (−0.041 to 0.090)
n	149	—	134	149	—	139	
TLC (l)	5.717 ± 1.167	—	5.730 ± 1.196	5.837 ± 1.190	—	5.786 ± 1.240	0.044 (−0.080 to 0.168)
n	146	—	135	147	—	140	
DL_{CO} (ml · min^{-1} · mmHg^{-1})	23.554 ± 5.248	—	22.760 ± 5.650	24.100 ± 5.447	—	23.390 ± 5.501	−0.403 (−1.166 to 0.360)

Data are means ± SD, unless noted otherwise. *For adjusted mean treatment group difference in change from baseline at week 24.

group difference was −1.29 kg (95% CI −1.98 to −0.59).

No differences in serum lipid parameters were seen between the two groups. After 24 weeks of treatment, the median changes from baseline in lipid parameters in the inhaled and subcutaneous insulin groups, respectively, were total cholesterol, 0 and 3 mg/dl (0.0 and 0.08 mmol/l); HDL cholesterol, 0 and 1 mg/dl (0.0 and 0.03 mmol/l); LDL cholesterol, −3 and 0 mg/dl (−0.08 and 0.0 mmol/l); and triglycerides, 3.5 and 8.0 mg/dl (0.04 and 0.09 mmol/l).

Safety and tolerability

The frequency and nature of adverse events, with the exception of cough, were comparable between the two treatment groups. A total of 126 patients in the inhaled insulin group and 118 patients in the subcutaneous insulin group experienced adverse events (including the hypoglycemic events discussed above) that were possibly or probably related to the treatment regimen. The majority of these were mild or moderate. Treatment-related adverse events experienced by >10% of patients in the inhaled insulin group were tremor (43 patients, 29%), asthenia (27 patients, 18%), sweating (25 patients, 17%), and dizziness (23 patients, 15%). All of these adverse events are symptoms compatible with hypoglycemia. Treatment-related adverse events experienced by >10% of patients in the subcutaneous group were tremor (40 patients, 27%), sweating (29 patients, 20%), asthenia (21 patients, 14%), and dizziness (19 patients, 13%). All-cause cough was experienced by 21% (32 of 149) of patients in the inhaled insulin treatment group compared with 2% (3 of 149) in the subcutaneous group. Cough was judged as mild to moderate in the inhaled group and decreased in incidence over the study period; the median duration of the period of increased cough was 2.0 weeks. There were six treatment-related severe adverse events reported in the inhaled insulin group; three hypoglycemia, one hyperglycemia, one neuralgia, and one anxiety. There was one treatment-related severe adverse event in the subcutaneous group (unconsciousness associated with hypoglycemia).

The incidence of clinical laboratory abnormalities was similar between the two treatment groups. Forty-three of 135 patients (32%) in the inhaled group had at least one laboratory test abnormality compared with 56 of 142 patients (39%) in the

subcutaneous group. The most frequent laboratory abnormalities were in urinalysis (increases in urine glucose, urine white blood cells, and hyaline casts).

Inhaled insulin–treated patients developed increased insulin antibody serum binding. Median percentage binding was 5.0 and 1.5% (below the level of quantitation) in the inhaled and subcutaneous groups, respectively. Levels of antibodies did not correlate to HbA_{1c}, insulin dose, or incidence of hypoglycemia, and there was no association with adverse events or pulmonary function.

Mean changes in FVC, FEV_1, TLC, and DL_{CO} were small and comparable between the two treatment groups (Table 2).

Treatment satisfaction and quality of life

The mean overall satisfaction score improved significantly for the inhaled group ($P < 0.0001$) and worsened slightly for the subcutaneous group. All satisfaction subscales (advocacy, burden, convenience, efficacy, flexibility, general satisfaction, hassle, interference, pain, preference, side effects, and social) showed similar favorable effects associated with inhaled insulin treatment (all $P < 0.0001$). The quality-of-life scale and subscales of health perception and symptom interference also showed favorable improvements for inhaled compared with subcutaneous treatment ($P < 0.05$).

CONCLUSIONS — The results of this study show that inhaled insulin provides glycemic control comparable to a conventional insulin regimen in patients with type 2 diabetes, as assessed by the changes in HbA_{1c} from baseline to week 24. The actual decrease in HbA_{1c} in both treatment groups at week 24 was modest; however, such a change would be expected to reduce the development and/or progression of diabetes complications, as shown in the U.K. Prospective Diabetes Study (3,4). Moreover, the study was designed to demonstrate equivalence and was not target driven. Nevertheless, a greater proportion of patients in the inhaled insulin group reached the American Diabetes Association goal of $HbA_{1c} < 7\%$ (16). The addition of premeal inhaled insulin reduced both FPG and PPG levels. Although both basal and postprandial glucose contribute to glucose exposure, the relative importance of each has been debated (17) and may depend on the severity of diabetes (18). Interestingly, FPG decreased more in the inhaled group than in the subcutaneous group. The bedtime administration of Ultralente basal insulin in the inhaled insulin group may have contributed to lower FPG.

Overall, inhaled insulin was well tolerated. The risk of a hypoglycemic event was lower in the inhaled group compared with the subcutaneous group, which is consistent with results from a previous study (12). As inhaled insulin is delivered systemically via the lungs, it is important to assess possible pulmonary adverse events. Cough of mild-to-moderate severity was observed with a greater frequency in the inhaled insulin group, although its incidence decreased as the study progressed, and no patient withdrew due to cough. In the present study, inhaled insulin treatment was not associated with adverse effects on pulmonary function parameters of FEV_1, FVC, TLC, or DL_{CO}. Long-term studies are underway to assess any potential effect more conclusively. Changes in lung function initially observed in a long-term extension study of the Exubera Phase III program remained small and nonprogressive. Furthermore, controlled discontinuation of Exubera in a subset of those patients resulted in lung function gains of similar magnitude to the initial small decrease (19).

Insulin antibodies with both animal and human insulins have previously been reported (20). In the present study, inhaled insulin–treated patients developed increased insulin antibody serum binding, but there was no correlation with parameters of clinical efficacy such as HbA_{1c}, FPG, or hypoglycemia. Further analyses of combined data from a number of 3- to 6-month and extension studies (21) with inhaled insulin showed that antibody levels plateau after ~12 months and also demonstrated no relation to efficacy measures or to pulmonary or other adverse events.

Both physicians and patients are often hesitant to initiate insulin therapy for several reasons. Weight gain has been a major concern (22), as has injection-related anxiety and/or phobia, all of which impede the timely use of insulin in patients with type 2 diabetes (23). During the present study, a greater increase in body weight occurred in patients who received subcutaneous insulin (1.4 kg) compared with inhaled insulin (no change). In a previous shorter study (11) in type 2 diabetes, inhaled insulin was not associated with increases in body weight. Whether the more physiologic insulin profile associated with inhaled insulin may have prevented weight gain remains to be established. Although the majority of patients in the present study had a BMI <35 kg/m^2 to minimize any confounding factors associated with excessively high insulin doses, experience with inhaled insulin use is also being gained in patients with more severe levels of obesity (24,25).

Reluctance to taking insulin by patients and reluctance to prescribe insulin by physicians contribute to poor glycemic control in many patients with type 2 diabetes, resulting in poor quality of life, greater risk for micro- and macrovascular complications, and increased long-term economic costs. By allowing the implementation of intensive insulin therapy with a noninvasive delivery system, inhaled insulin may allow patients to regard insulin therapy as a more positive treatment option. Although this was an open-label study in which patients volunteered to receive a novel therapeutic agent, a significantly higher level of patient satisfaction was seen with inhaled insulin. Many factors are likely to influence satisfaction; however, in the present study, the overall score as well as that of all satisfaction subscales favored inhaled insulin. Any effect of novelty with a new delivery system on satisfaction is likely to have diminished by the end of the study, and other studies show that that improved satisfaction with inhaled insulin peaks after 6 weeks, remains constant to 24 weeks (26), and is maintained after 1 year of continuous therapy (27). Therefore, the availability of inhaled insulin might help improve acceptance of insulin therapy by both patients and physicians.

In conclusion, this study demonstrated that inhaled insulin treatment in type 2 diabetes was effective, well tolerated, and comparable in glycemic control to a conventional subcutaneous insulin regimen. Ongoing studies will establish the long-term safety of inhaled insulin, but results from this 6-month study, together with those of other clinical studies of inhaled insulin (10–12), suggest that it may prove a novel and well-accepted treatment approach for the management of many patients with diabetes.

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Editor's note. The results of the self-administered Quality of Life and Treatment Satisfaction Questionnaire for this study were previously published (28). The results across all populations of diabetic patients evaluated by the Quality of Life and Treatment Satisfaction Questionnaire in the Exubera studies will be presented in a subsequent report.

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