# Use of Inhaled Insulin in a Basal/Bolus Insulin Regimen in Type 1 Diabetic Subjects

## A 6-month, randomized, comparative trial

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**OBJECTIVE** — Despite the demonstrated benefits of glycemic control, patient acceptance of basal/bolus insulin therapy for type 1 diabetes has been slow. We investigated whether a basal/bolus insulin regimen involving rapid-acting, dry powder, inhaled insulin could provide glycemic control comparable with a basal/bolus subcutaneous regimen.

**RESEARCH DESIGN AND METHODS** — Patients with type 1 diabetes (ages 12–65 years) received twice-daily subcutaneous NPH insulin and were randomized to premeal inhaled insulin ($n$ = 163) or subcutaneous regular insulin ($n$ = 165) for 6 months.

**RESULTS** — Mean glycosylated hemoglobin (A1C) decreased comparably from baseline in the inhaled and subcutaneous insulin groups (−0.3 and −0.1%, respectively; adjusted difference −0.16% [CI −0.34 to 0.01]), with a similar percentage of subjects achieving A1C <7%. Although 2-h postprandial glucose reductions were comparable between the groups, fasting plasma glucose levels declined more in the inhaled than in the subcutaneous insulin group (adjusted difference −39.5 mg/dl [CI −57.5 to −21.6]). Inhaled insulin was associated with a lower overall hypoglycemia rate but higher severe hypoglycemia rate. The overall hypoglycemia rate (episodes/patient-month) was 9.3 (inhaled) vs. 9.9 (subcutaneous) (risk ratio [RR] 0.94 [CI 0.91–0.97]), and the severe hypoglycemia rate (episodes/100 patient-months) was 6.5 vs. 3.3 (RR 2.00 [CI 1.28–3.12]). Increased insulin antibody serum binding without associated clinical manifestations occurred in the inhaled insulin group. Pulmonary function between the groups was comparable, except for a decline in carbon monoxide−diffusing capacity in the inhaled insulin group without any clinical correlates.

**CONCLUSIONS** — Inhaled insulin may provide an alternative for the management of type 1 diabetes as part of a basal/bolus strategy in patients who are unwilling or unable to use preprandial insulin injections.

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The long-term effects of meticulous glycemic control on microvascular complications of type 1 diabetes have been firmly established (1–3). Strict glycemic control is commonly achieved using basal/bolus insulin therapy involving intermediate- or long-acting insulin for basal control and multiple daily injections of preprandial short-acting insulin (4,5).

Patient acceptance of basal/bolus insulin regimens has been slow (6,7), perhaps because of the considerable burden of multiple injections for some (8,9). Inhaled insulin may provide an alternative for the management of type 1 diabetes as part of a basal/bolus strategy in patients who are unwilling or unable to use preprandial insulin injections. Results of a proof-of-concept study have suggested that inhaled insulin could replace preprandial subcutaneous insulin injections in type 1 diabetic subjects (10,11). A larger study demonstrating that inhaled insulin can provide glycemic control comparable with that of conventional subcutaneous insulin has reinforced this idea (12). Our study investigated whether a basal/bolus insulin regimen involving premeal inhaled, rapid-acting, dry-powder insulin plus twice-daily subcutaneous neutral protamine Hagedorn (NPH) insulin could provide comparable glycemic control comparable with that achieved with a basal/bolus subcutaneous insulin regimen of premeal regular insulin plus twice-daily NPH insulin in type 1 diabetic subjects.

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**Abbreviations:** FPG, fasting plasma glucose; IAb, insulin antibody; SMBG, self-monitoring of blood glucose.

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

## RESEARCH DESIGN AND METHODS

— Men and women ($n$ = 419) with type 1 diabetes (defined by the American Diabetes Association as being of at least 1 year's duration and having a fasting plasma C-peptide level ≤0.2 pmol/ml) (13) were screened at 40 centers across the U.S. and Canada. Subjects met the following inclusion criteria: age 12–65 years, a stable insulin regimen (two or more injections daily for at least 2 months), $HbA_{1c}$ (A1C) levels of 6–11%, BMI ≤30 kg/m$^2$ at screening and before the randomization phase, a willingness to perform self-monitoring of blood glucose (SMBG), and written informed consent. Exclusion criteria included poorly controlled asthma; significant respiratory, renal, hepatic, or cardiac disease; smoking within 6 months; drug or alcohol dependence; significant insulin allergy; recurrent severe hypoglycemia; treatment with oral hypoglycemic agents, systemic glucocorticoid use, or insulin-pump therapy 2 months before screening; use of an inhaled insulin therapy in a previous clinical trial; insulin requirement >150 units/day; hospitalization or emergency room visit due to poor glycemic control within 6 months; or pregnancy, lactation, or planned pregnancy.

This was an open-label, 24-week, parallel-group, multicenter outpatient study. During the 4-week run-in period, subjects were transferred to the control treatment, comprised of premeal regular subcutaneous insulin plus twice-daily NPH insulin (total of four injections daily). Subjects were randomized to receive 24 weeks of treatment with premeal inhaled insulin (Exubera; Pfizer, New York, NY; sanofi-aventis Group, Bridgewater, NJ; and Nektar Therapeutics, San Carlos, CA) plus twice-daily NPH insulin or to continue the control treatment. Subjects received dietary instruction during the run-in period and at week 12 (14). All subjects were advised to perform 30 min of moderate exercise at least 3 days/week (15).

Inhaled insulin was administered within 10 min before meals as one to two inhalations of a dry-powder aerosol delivery system (Nektar) along with twice-daily subcutaneous NPH insulin (prebreakfast and bedtime). Insulin powder was packaged in foil blisters of 1- and 3-mg doses (1 mg is the equivalent of 2–3 units of subcutaneous insulin). Before treatment, subjects were trained in the appropriate procedure for insulin inhalation. Initial dosages were based on body weight and the known responses of equivalent subcutaneous dosages. Regular subcutaneous insulin was administered ~30 min preprandially.

Follow-up dosage recommendations were based on patient response. Subjects were instructed in SMBG and asked to test at least five times daily (before meals, 2 h postprandially, bedtime). Subjects' SMBG records were reviewed at clinic visits and mean values were calculated; target ranges were 4.4–6.7 mmol/l (80–120 mg/dl) before meals and 5.6–7.8 mmol/l (100–140 mg/dl) at bedtime. Factors considered in dosage selection included meal size, nutrient composition, time of day, premeal SMBG concentration, and recent or anticipated exercise.

### Assessments

The primary efficacy end point, the change in A1C from baseline to week 24, was measured at screening and weeks −1, 0, 6, 12, and 24. Secondary efficacy end points included changes in fasting and 2-h postprandial glucose concentrations and the percentage of subjects achieving an A1C <7% at week 24. Fasting plasma glucose (FPG) levels were measured at weeks −4, −1, 0, 12, and 24 after a minimum 8-h fast. Postprandial levels were assessed at weeks −1 and 24 after a standardized liquid formula meal (Boost; Mead Johnson, Evansville, IN; 480 kcal in 16 oz: 66 g carbohydrate, 29 g protein, 11 g fat). The incidence and severity of hypoglycemic events were recorded. Body weight was recorded at baseline and weeks 4, 8, 12, 16, 20, and 24 and lipid values were measured at weeks 0 and 24. Clinical laboratory tests, a 12-lead electrocardiogram, and a chest X-ray were performed at screening and week 24. IAbs were measured at weeks 0 and 24. Pulmonary function testing (spirometry, lung volumes, diffusion capacity) was performed at weeks −3 and 24; spirometry was also performed at week 12.

The typical symptoms of hypoglycemia were discussed with the subjects and they were asked to perform SMBG whenever symptoms occurred. Hypoglycemia (modeled after Diabetes Control and Complications Trial criteria) (2) was defined as characteristic symptoms without SMBG measurement that promptly resolved with food intake, subcutaneous glucagon, or intravenous glucose; characteristic symptoms with SMBG <3.3 mmol/l (<60 mg/dl); or any SMBG measurement <2.8 mmol/l (<50 mg/dl) with or without symptoms. Severe hypoglycemia was defined as that *1*) requiring assistance by another, *2*) involving a neurological symptom (e.g., memory loss, confusion, irrational behavior, unusual difficulty waking, seizure, loss of consciousness), and *3*) associated with an SMBG measurement <2.8 mmol/l (<50 mg/dl) or, in the absence of an SMBG measurement, that which was reversible with oral carbohydrate, subcutaneous glucagon, or intravenous glucose.

### Sample size

To provide at least 80% power, 143 subjects per group were required. The sample size was designed to ensure that the upper limit of the two-sided 95% CI for the noninferiority criterion (difference in A1C change from baseline between treatment groups) would not be >0.5%. The sample size calculation was based on an assumed treatment difference of zero between groups. To account for a 10% dropout rate, 320 subjects (160 per group) were recruited.

### Statistical analysis

This trial was designed to test the noninferiority of inhaled insulin. Data were analyzed for the per-protocol (evaluable) population, defined as subjects who met all entry criteria, received at least half of their randomized treatment, and had a baseline and one or more evaluable postbaseline A1C assessments. If a week 24 A1C value was not available, the last evaluable postbaseline measurement was carried forward. Changes from baseline A1C were assessed using an ANCOVA model adjusted for baseline A1C, study center, and treatment group. The two-sided 95% CI was constructed based on this model and the noninferiority of inhaled insulin was concluded if the upper limit was <0.5% A1C.

A similar approach was used for all other continuous end points. The percent of subjects reaching A1C <7% at week 24 was analyzed using logistic regression. Survival analysis based on a counting process for analyzing recurrent hypoglycemic events was performed for RR estimates.

Treatment group differences in the change from baseline in 1-s forced expi-

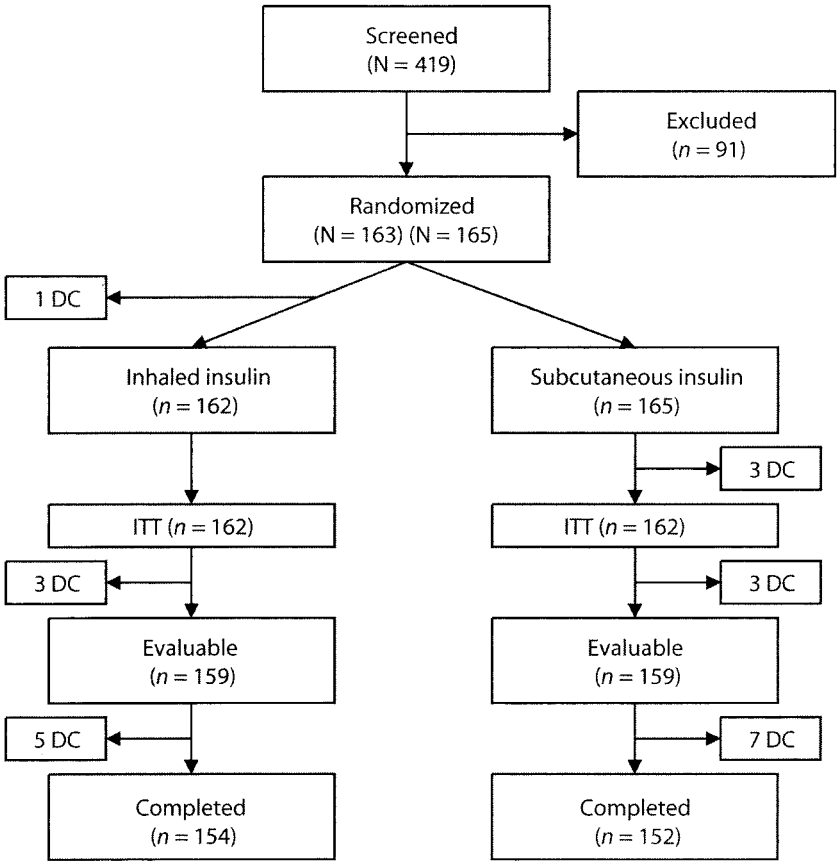


**Figure 1**—*Subject disposition. Subjects evaluable for efficacy did not have a major violation of the inclusion and exclusion criteria, had received at least half the protocol's required duration of treatments as assigned by the randomization scheme (12 out of 24 weeks), and had at least one evaluable postbaseline A1C assessment. At week 24, there were evaluable data for 318 individuals using last observation carried forward. A total of 306 individuals had a final A1C measurement at the end of 24 weeks. DC, discontinued; ITT, intent to treat.*

ratory volume ($FEV_1$) and forced vital capacity (FVC) were estimated at weeks 12 and 24 using repeated-measures ANCOVA. Treatment group differences in change from baseline in carbon monoxide–diffusing capacity ($DL_{CO}$) and total lung capacity (TLC) at week 24 were estimated using ANCOVA. These models were adjusted for treatment, study center, and covariates known to have a physiological association with pulmonary function (e.g., baseline pulmonary function tests, age, baseline height, sex). Data are given as means ± SD.

**RESULTS** — Of the 419 subjects screened, 328 were randomized to a treatment group. In the inhaled insulin group, 1 subject allocated to inhaled insulin was never treated; thus, 327 subjects received the study treatment. Of the 318 who were evaluable for efficacy, 2 discontinued the study for treatment-related reasons (1 had a moderate respiratory disorder attributed to preexisting airway hyperreactivity and 1 had a moderate liver enzyme level elevation) and 6 discontinued for administrative reasons (e.g., protocol violation, withdrawn consent, lost to follow-up). In all, 306 completed the treatment (Fig. 1). In the subcutaneous insulin group, 1 subject discontinued the study because of insufficient clinical response and 12 did not continue for non–treatment-related reasons (1 adverse event, 11 administrative reasons). Table 1 shows the subjects' baseline characteristics (~90% of the subjects were white; data not shown).

## Efficacy

At week 24, the mean A1C decreased from baseline comparably between groups. Mean observed A1C values at baseline and the end of the study were 8.0 ± 1.0 and 7.7 ± 1.0% (adjusted change from baseline −0.3%) in the inhaled group and 7.9 ± 1.0 and 7.8 ± 1.2% (adjusted treatment group difference −0.16% [CI −0.34 to 0.01]) in the subcutaneous group (Fig. 2*A*).

A1C <7.0% (16) was achieved by 23.3 and 22.0% of subjects in the inhaled ($n$ = 37) and subcutaneous ($n$ = 35) group, respectively (adjusted odds ratio 1.53 [CI 0.75–3.14]). From baseline to week 24, the mean adjusted change in FPG was −1.94 mmol/l (−35 mg/dl) in the inhaled group, whereas in the subcutaneous group, there was a slight increase in FPG (0.22 mmol/l [4 mg/dl]; adjusted treatment group difference −39.53 mg/dl [CI −57.50 to −21.56]) (Fig. 2*B*), despite an increased bedtime NPH dosage (Table 2). The mean adjusted change from baseline in 2-h postprandial concentration was −1.17 mmol/l (−21 mg/dl) and −0.78 mmol/l (−14 mg/dl) in the inhaled and subcutaneous groups, respectively (adjusted treatment group difference −6.78 mg/dl [CI −30.29 to 16.74]).

Body weight increased comparably in both groups (1.3 and 1.5 kg in the inhaled

**Table 1**—*Characteristics of randomized subjects at study entry*

| | Inhaled insulin | Subcutaneous insulin |
|---|---|---|
| $n$ randomized and treated | 162 | 165 |
| Age (years) | 29.3 ± 14.5 (12–65) | 29.7 ± 14.7 (11–65) |
| Sex (male/female) | 85/77 | 89/76 |
| A1C (%) | 8.24 ± 1.08 (6.40–11.10) | 8.2 ± 1.16 (6.00–11.50) |
| C-peptide (pmol/ml) | 0.07 ± 0.03 (0.07–0.26) | 0.07 ± 0.03 (0.07–0.23) |
| Weight (kg) | 70.1 ± 14.9 (36–119) | 70.8 ± 15.4 (34–116) |
| BMI (kg/m$^2$) | 24.3 ± 3.4 (17–32) | 24.4 ± 3.7 (15–35) |
| Duration of diabetes (years) | 12.9 (1.0–50.0) | 14.6 (1.0–49.0) |

Data are means ± SD (range).

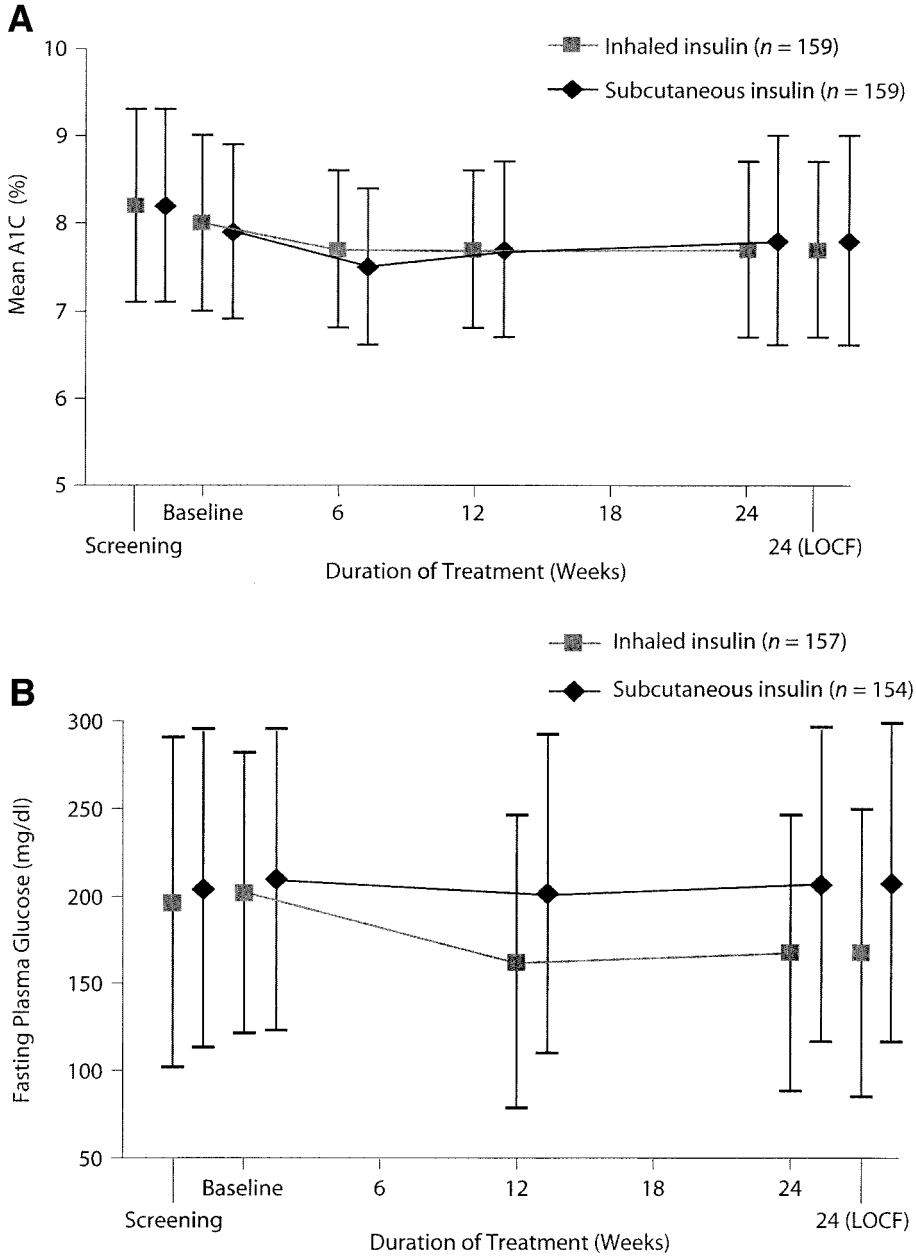


**Figure 2—**A: *A1C during 6 months' treatment with a basal/bolus inhaled insulin regimen versus a basal/bolus subcutaneous insulin regimen. Data are means ± SD.* B: *Fasting plasma glucose concentration during 6 months' treatment with a basal/bolus inhaled insulin regimen versus a basal/bolus subcutaneous insulin regimen. 1 mg/dl = 0.0555 mmol/l. Data are means ± SD. LOCF, last observation carried forward.*

and subcutaneous groups, respectively; adjusted treatment group difference −0.19 kg [CI −0.91 to 0.53]). The week 24 median changes from baseline in fasting lipid parameters for the inhaled and subcutaneous groups, respectively, were as follows: total cholesterol, −4.0 vs. 5.0 mg/dl; HDL cholesterol, −4.5 vs. 1.0 mg/dl; LDL cholesterol, −1.5 vs. 3.0 mg/dl; and triglycerides, 6.0 vs. 6.0 mg/dl.

Insulin dosages in the two groups were comparable at baseline and increased slightly over the study period (Table 2).

## Safety and tolerability

The overall hypoglycemia rate (episodes per patient-month) was lower in the inhaled than in the subcutaneous group (9.3 vs. 9.9; RR 0.94 [CI 0.91–0.97]) (Table 3). The rate of severe hypoglycemia (episodes per 100 patient-months) was higher in the inhaled group (6.5 vs. 3.3; RR 2.00 [CI 1.28–3.12]), with the four subjects receiving inhaled insulin accounting for 27 (46.6%) of the episodes, 22 of which occurred within the first 12 weeks of treatment. All subjects experiencing hypoglycemia events completed the study. Details of the hypoglycemia episodes are included in an online appendix (available at http://care.diabetesjournals.org).

The overall frequency and nature of adverse events were comparable between groups. Cough was reported more often in the inhaled group (25 vs. 7%) but was generally mild and decreased over the study period (incidence from 17 [10.5%, weeks 0–4] to 4 [2.6%, weeks 20–24]; prevalence from 18 [11.1%] to 15 [9.7%] at study end).

Inhaled insulin–treated subjects developed increased serum insulin antibody (IAb) binding. At week 24, median binding was 28% in the inhaled group and 4% in the subcutaneous group. The mean change from baseline in the percent of IAb

**Table 2—*Mean insulin dosages during study***

| | Inhaled insulin | | | | | Subcutaneous insulin | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Prebreakfast | | Prelunch | Presupper | Bedtime | Prebreakfast | | Prelunch | Presupper | |
| | Short-acting | NPH | (short-acting) | (short-acting) | (NPH) | Short-acting | NPH | (short-acting) | (short-acting) | Bedtime (NPH) |
| Baseline | 8.3 ± 4.7 | 18.1 ± 12.2 | 6.6 ± 4.5 | 9.5 ± 5.0 | 17.1 ± 9.2 | 8.6 ± 4.8 | 17.2 ± 10.5 | 7.1 ± 4.3 | 9.7 ± 4.9 | 17.3 ± 9.2 |
| Week 6 | 3.1 ± 1.7* | 19.4 ± 12.8 | 2.7 ± 1.7* | 3.8 ± 1.8* | 17.7 ± 10.2 | 8.7 ± 5.1 | 17.6 ± 10.9 | 6.9 ± 4.9 | 10.3 ± 5.2 | 19.0 ± 10.0 |
| Week 12 | 3.2 ± 1.8* | 20.4 ± 13.2 | 3.0 ± 1.7* | 4.1 ± 1.9* | 17.4 ± 10.1 | 8.4 ± 5.3 | 17.7 ± 11.2 | 6.8 ± 5.1 | 10.8 ± 5.4 | 19.4 ± 10.5 |
| Week 24 | 3.3 ± 1.9* | 21.2 ± 12.8 | 3.3 ± 1.8* | 4.2 ± 1.9* | 16.9 ± 10.3 | 8.9 ± 5.8 | 18.0 ± 11.6 | 7.0 ± 4.5 | 10.9 ± 5.4 | 19.8 ± 11.1 |

Data are means ± SD. *mg; all other doses in IU.

**Table 3—*Hypoglycemic episodes***

| | Inhaled insulin | Subcutaneous insulin |
|---|---|---|
| *n* | 159 | 159 |
| Overall episodes | | |
| Subjects with episode | 158 (>99) | 158 (>99) |
| Total episodes | 8,348 | 8,832 |
| Episodes/patient-month* | 9.3 | 9.9 |
| Inhaled/subcutaneous risk ratio | 0.94 (0.91–0.97) | |
| Severe episodes | | |
| Subjects with episode | 25 (15.7)† | 22 (13.8) |
| Total episodes | 58† | 29 |
| Episodes/100 patient-months* | 6.5† | 3.3 |
| Inhaled/subcutaneous risk ratio | 2.00 (1.28–3.12) | |

Data are *n* (%) or risk ratio (95% CI). *Crude event rate. †Four subjects accounted for 46.6% of the severe events in the inhaled insulin group.

binding was 23.03 ± 15.69 and 0.85 ± 3.76 in the inhaled and subcutaneous groups, respectively. Higher antibody levels did not have any apparent clinical consequences. Pulmonary function tests demonstrated no between-group differences for changes in $FEV_1$, FVC, or TLC (Table 4). A greater mean decrease in $DL_{CO}$ of −0.75 (from 26.40 to 25.65 ml · $min^{-1}$ · $mmHg^{-1}$) was observed for the inhaled group compared with −0.23 (from 27.07 to 26.8 ml · $min^{-1}$ · $mmHg^{-1}$) in the subcutaneous group, without any clinical correlates.

**CONCLUSIONS** — This study was the first to compare premeal inhaled and subcutaneous insulin in basal/bolus insulin therapy in type 1 diabetic patients. Several previous studies have shown that basal/bolus insulin combinations effectively improve metabolic control (17–20). The fast-onset action of inhaled insulin is similar to that of rapid-acting insulin analogs. By improving patient compliance, noninvasive delivery of rapidly absorbed insulin could be beneficial for mealtime insulin administration.

Our results showed that in combination with twice-daily basal injections of NPH insulin, both inhaled and subcutaneous insulin regimens provided comparable glycemic control over 6 months in terms of A1C reduction and postprandial glycemic control. These findings are analogous to and complement those of recent studies comparing inhaled and conventional subcutaneous insulin regimens in type 1 and type 2 diabetes (12,21). It should be noted that in our study and others, the insulin dosages probably were not always maximized, despite subjects' not achieving protocol target values.

The inhaled insulin group had a greater FPG reduction despite similar bedtime NPH dosages. Although the reasons for this are not clear, it is possible that *1*) the FPG decrease with inhaled insulin relates to IAbs functioning as a repository that slowly releases insulin (22) (however, no correlation between insulin binding and FPG has been observed to date with this preparation) or *2*) the inhalation of insulin may increase insulin sensitivity or reduce endogenous glucose release (23,24).

Inhaled insulin was associated with a lower overall hypoglycemia rate but higher severe hypoglycemia rate. As described in the online appendix, four subjects accounted for nearly half of the severe events in the inhaled group. Most of these occurred early in the study, and the subjects completed the study without continued severe hypoglycemia.

The increased IAb binding seen with inhaled insulin did not have recognizable clinical consequences, and there was no relation between it and the frequency of severe hypoglycemia. The impact, if any, of circulating antibodies on pharmacodynamic response to absorbed insulin requires further study.

With the exception of cough and severe hypoglycemia, tolerability was generally comparable between groups. Although one subject discontinued the study because of respiratory symptoms during inhaled insulin therapy, this event was attributed to preexisting airway hyperreactivity and the subject's pulmonary function tests were stable. Regarding pulmonary function overall, a greater rate of decline in $DL_{CO}$ (adjusted mean decrease of −0.791 ml · $min^{-1}$ · $mmHg^{-1}$) was noted in the inhaled group. Any clinical effect or possible mechanistic or methodological basis for this small difference remains unclear, although considerable test variability may be expected because of the complexity of the measurement process (25,26). Additional studies using high-quality machines and standardized laboratory personnel training are being conducted to collect more robust data.

These results suggest that inhaled in-

**Table 4—*Pulmonary function test results***

| | Inhaled insulin | | | Subcutaneous insulin | | | Adjusted inhaled/subcutaneous difference | 95% CI |
|---|---|---|---|---|---|---|---|---|
| | *n* | Baseline | Change from baseline (week 24 or LOCF) | *n* | Baseline | Change from baseline (week 24 or LOCF) | | |
| $FEV_1$ (l) | 162 | 3.288 ± 0.779 | −0.016 ± 0.256 | 160 | 3.384 ± 0.784 | 0.008 ± 0.244 | −0.037 | −0.084 to 0.010 |
| FVC (l) | 162 | 4.016 ± 1.006 | 0.029 ± 0.309 | 160 | 4.101 ± 1.034 | 0.022 ± 0.270 | −0.007 | −0.060 to 0.046 |
| TLC (l) | 157 | 5.519 ± 1.356 | 0.047 ± 0.522 | 152 | 5.608 ± 1.399 | 0.083 ± 0.543 | −0.058 | −0.161 to 0.045 |
| $DL_{CO}$ (ml · $min^{-1}$ · $mmHg^{-1}$ | 154 | 26.404 ± 6.885 | −0.750 ± 3.882 | 149 | 27.068 ± 6.868 | −0.229 ± 3.337 | −0.791 | −1.466 to −0.117 |

Data are means ± SD. $DL_{CO}$, carbon monoxide diffusing capacity; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; LOCF, last observation carried forward; TLC, total lung capacity.

sulin therapy is as effective as regular subcutaneous insulin and is well tolerated in individuals with type 1 diabetes. Thus, inhaled insulin may provide an alternative to subcutaneous insulin in the management of type 1 diabetes as part of a basal/bolus strategy in patients who are unwilling or unable to use preprandial insulin injections.

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**APPENDIX** — Study investigators: M. Larissa Aviles-Santa, Eugene Barrett, C. Keith Bowering, Stuart Brink, William Cefalu, Jean-Louis Chiasson, Kenneth Copeland, Larry Deeb, Joan Dimartino-Nardi, Stephen Duck, Mark Feinglos, Wei Feng, Barbara Feuerstein, Satish Garg, John E. Gerich, Hertzel C. Gerstein, David Goldstein, Irving Gottesman, Morey Haymond, Rosa Hendler, Kenneth Hershon, Irl B. Hirsch, Nicolas Jospe, Francine R. Kaufman, Mary Korytkowski, Mark Kummer, Sam Lerman, Ellis Levin, Rodney Lorenz, Jennifer B. Marks, Kusiel Perlman, Leslie Plotnick, Philip Raskin, Edmond Ryan, Paul Saenger, Desmond Schatz, Robert Sherwin, Jay S. Skyler, Martha Spencer, William V. Tamborlane Jr, Philip Walravens, Ruth S. Weinstock, Sandra Werbel, Darrell Wilson, Jean-François Yale, Bernard Zinman.

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