

# Inhaled Insulin Improves Glycemic Control When Substituted for or Added to Oral Combination Therapy in Type 2 Diabetes

## A Randomized, Controlled Trial

Julio Rosenstock, MD; Bernard Zinman, MD; Liam J. Murphy, MD; Stephen C. Clement, MD; Paul Moore, MD; C. Keith Bowering, MD; Rosa Hendler, MD; Shu-Ping Lan, MPH; and William T. Cefalu, MD

**Background:** Patients with type 2 diabetes who do not achieve glycemic control with oral agent therapy eventually require insulin.

**Objective:** To determine the effect on glycemic control of inhaled insulin alone or added to dual oral therapy (insulin secretagogue and sensitizer) after failure of dual oral therapy.

**Design:** Open-label, randomized, controlled trial.

**Setting:** 48 outpatient centers in the United States and Canada.

**Patients:** 309 patients with type 2 diabetes, no clinically significant respiratory disease, and hemoglobin A<sub>1c</sub> level of 8% to 11% who were receiving dual oral therapy.

**Measurements:** Primary end point was change in hemoglobin A<sub>1c</sub> level from baseline to 12 weeks. Secondary outcomes included hemoglobin A<sub>1c</sub> level less than 8% and less than 7%, hypoglycemia, weight, lipid levels, pulmonary function, insulin antibody binding, and adverse events.

**Intervention:** Inhaled insulin (Exubera; Pfizer Inc. [New York, New York], sanofi-aventis Group [Paris, France], and Nektar Therapeutics [San Carlos, California]), titrated to blood glucose, administered alone ( $n = 104$ ) or added to dual oral agents ( $n = 103$ ) versus oral therapy alone ( $n = 99$ ).

**Results:** Reductions in hemoglobin A<sub>1c</sub> level were greater with inhaled insulin. Adjusted treatment group differences for inhaled

insulin plus oral agents and inhaled insulin alone compared with continued oral agent therapy were  $-1.67$  percentage points (95% CI,  $-1.90$  to  $-1.44$  percentage points;  $P < 0.001$ ) and  $-1.18$  percentage points (CI,  $-1.41$  to  $-0.95$  percentage point;  $P < 0.001$ ), respectively. Hemoglobin A<sub>1c</sub> level less than 7% was achieved by 32% (inhaled insulin plus oral agents) and by 1% (oral agent therapy) of patients (adjusted odds ratio, 44.7 [CI, 6.0 to 335.2]). Hypoglycemia, mild weight gain, mild cough, and insulin antibodies were more frequent with inhaled insulin than with oral agent therapy alone. Pulmonary function was similar in all groups.

**Limitations:** This study evaluated only patients with hemoglobin A<sub>1c</sub> levels of 8% to 11%, did not compare inhaled insulin with other insulins or oral therapy except a dual regimen of secretagogue and sensitizer, and lasted only 12 weeks.

**Conclusions:** Inhaled insulin improved overall glycemic control and hemoglobin A<sub>1c</sub> level when added to or substituted for dual oral agent therapy with an insulin secretagogue and sensitizer. Consistent with other insulin therapies, hypoglycemia and mild weight gain occurred. Pulmonary function showed no between-group differences.

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For author affiliations, see end of text.

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The long-term benefits of good glycemic control are well-established for patients with type 1 and type 2 diabetes (1–9). In type 2 diabetes, the traditional treatment pathway generally involves the initiation of oral hypoglycemic agent therapy if lifestyle intervention is not effective (10). However, many patients will not achieve good glycemic control with oral agent therapy once insulin secretory capacity becomes insufficient (11). These patients must then receive insulin therapy to reduce the risk for diabetic complications. This usually involves the addition of basal insulin therapy to oral agents, although some studies suggest that insulin monotherapy is also effective (12–14).

The optimal strategy for insulin add-on therapy is yet to be determined. Both patients and physicians are often reluctant to initiate subcutaneous insulin therapy (15–19). Consequently, the pulmonary route is being investigated as an alternative, less invasive method of insulin administration. Human inhaled insulin (Exubera; Pfizer Inc. [New York, New York], sanofi-aventis Group [Paris, France], and Nektar Therapeutics [San Carlos, California]) is a dry

powder formulation and inhaler system currently in development (Figure 1).

Compared with injected regular insulin, inhaled insulin is more rapidly absorbed and eliminated and has a more rapid glucose-lowering effect (20). The pharmacodynamic profile of inhaled insulin has also been compared with the

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**Context**

Because inhaled insulin acts very rapidly and lasts as long as regular insulin, mealtime dosing could control postmeal hyperglycemia.

**Content**

The authors randomly assigned 309 patients whose type 2 diabetes was poorly controlled with oral therapy to receive inhaled insulin at mealtime, either alone or with oral therapy, or to continue oral therapy. Compared with oral agent therapy alone, inhaled insulin combination therapy and monotherapy reduced hemoglobin A<sub>1c</sub> level by 1.67 percentage points and 1.18 percentage points, respectively. Patients receiving inhaled insulin gained more weight and had more episodes of hypoglycemia.

**Conclusions**

Inhaled insulin is effective in patients whose oral agent therapy has failed. Using it alone is surprisingly effective despite its short duration of action.

—The Editors

rapid-acting insulin analogue insulin lispro and regular human insulin at equivalent doses in healthy volunteers. Inhaled insulin had a faster onset of action than both insulin lispro and regular insulin, with a duration of action longer than insulin lispro and similar to regular insulin (21). These characteristics predict that inhaled insulin is suitable for administration before meals to control postprandial glycemia.

In studies in patients with type 1 and type 2 diabetes, inhaled insulin has shown similar glycemic control to conventional subcutaneous regimens (22, 23). In addition, data from a small pilot study suggested that when oral agent therapy failed in patients with type 2 diabetes, adding premeal inhaled insulin to existing therapy significantly improved glycemic control (24). Our aim was to investigate whether monotherapy with inhaled insulin or therapy with inhaled insulin added to dual oral agent therapy can improve glycemic control in patients with type 2 diabetes, compared with those continuing a stable regimen of dual oral agent therapy. We also assessed the tolerability and safety of inhaled insulin therapy over a 3-month period.

**METHODS****Participants**

We screened male and female outpatients 35 to 80 years of age who had received a diagnosis of type 2 diabetes mellitus, as defined by the American Diabetes Association (ADA) (25), at least 1 year earlier at 48 centers in the United States and Canada. Patients were already attending the investigator's clinic or were recruited by physician referral.

For 2 months before the baseline lead-in period, pa-

tients were required to have been treated with a stable oral agent regimen involving 2 antidiabetic medications: 1 insulin secretagogue (a sulfonylurea or repaglinide) and 1 insulin sensitizer (a thiazolidinedione or metformin). In addition, patients were required to have a hemoglobin A<sub>1c</sub> level of 8% or greater at screening (week -4) and prerandomization (week -1) for eligibility. Exclusion criteria included hemoglobin A<sub>1c</sub> level greater than 11%; body mass index greater than 35 kg/m<sup>2</sup>; poorly controlled asthma; clinically significant chronic obstructive pulmonary disease or other clinically significant respiratory disease; smoking during the previous 6 months; abnormal pulmonary function at screening (carbon monoxide diffusing capacity < 75%, total lung capacity < 80% or > 120%, and FEV<sub>1</sub> < 70% of predicted); clinically significant major organ system disease; abnormal electrocardiogram; abnormalities on laboratory screening; systemic glucocorticoid therapy; known drug or alcohol dependence; previous inhaled insulin use; or pregnancy, lactation, or planned pregnancy. We also excluded patients with a predisposition to severe hypoglycemia (≥2 severe episodes within the past 6 months) or any hospitalization or emergency department visit due to poor diabetic control within the past 6 months.

**Study Design**

This was an open-label, 12-week, parallel-group, multicenter, randomized study. The independent local institutional review boards of all participating centers approved the protocol. All patients provided written informed consent. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki.

Using a computer-generated randomization scheme, we randomly assigned eligible patients to receive premeal inhaled insulin (Exubera) plus their existing stable regimen of 2 oral agents (*n* = 102) (inhaled insulin plus 2 oral agents group), to receive a premeal inhaled insulin regimen (*n* = 105) (inhaled insulin monotherapy group), or to be in the comparator group and continue receiving their existing stable regimen of dual oral agent therapy (*n* = 102) (2 oral agents group). Randomization was not within center. A system of interactive voice-response technology assigned the randomization codes. The investigator dialed a central database, where the master randomization list was held, and answered a series of prompts (for example, protocol number and center identification), which determined the specific treatment group assignment.

At screening, 90%, 87%, and 90% of patients in the inhaled insulin plus 2 oral agents, inhaled insulin monotherapy, and 2 oral agents groups, respectively, were using metformin (mean dosage, approximately 2100 mg/d). Furthermore, 58%, 65%, and 63% of patients, respectively, were using glyburide (mean dosage, approximately 19 mg/d), and 27%, 23%, and 26% of patients, respectively, were using glipizide (mean dosage, approximately 20 mg/d). Five patients in the inhaled insulin plus 2 oral agents group, 3 patients in the inhaled insulin monotherapy

group, and 4 patients in the 2 oral agents group were using troglitazone (400 mg to 600 mg). Since troglitazone was withdrawn from the market while the study was in progress, we required patients who were receiving troglitazone ( $n = 4$ ) to switch to another thiazolidinedione. We recommended that patients who were receiving 400 mg or 600 mg of troglitazone switch to 4 mg of rosiglitazone or 30 mg of pioglitazone or to 8 mg of rosiglitazone or 45 mg of pioglitazone, respectively. Patients who switched from troglitazone therapy could continue participation in the study with no delay in study procedure schedules. Patients received dietary instruction in accordance with ADA recommendations (26). We also instructed patients to perform 30 minutes of moderate exercise at least 3 days per week, per ADA guidelines (27).

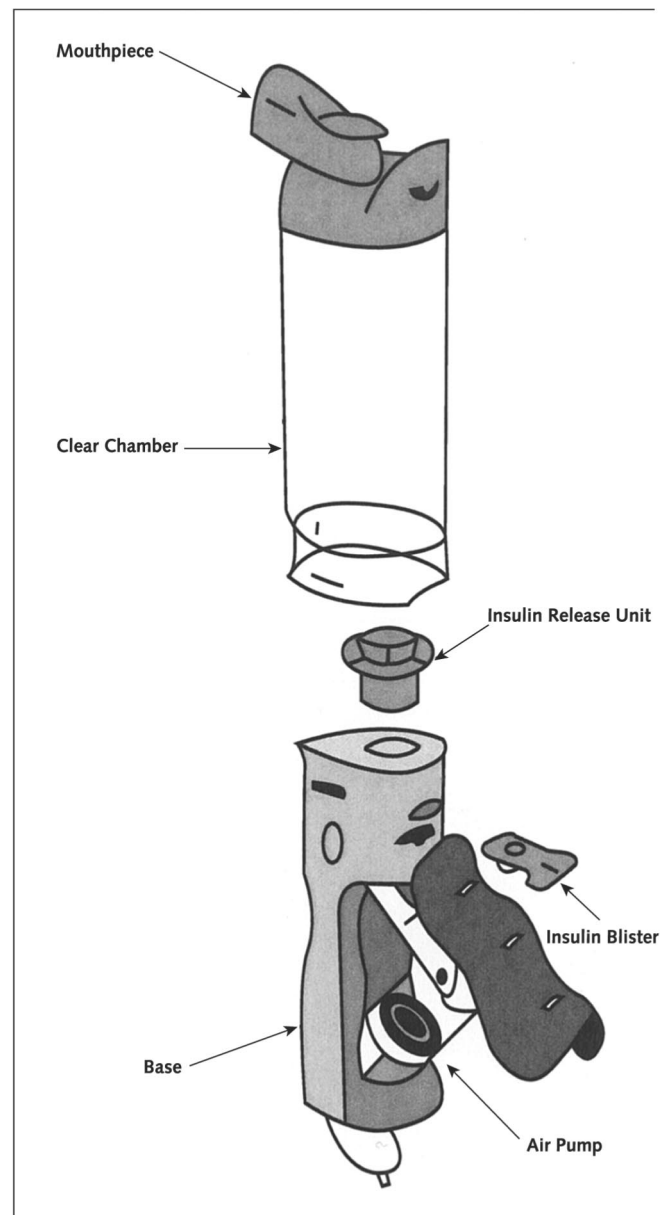
Inhaled insulin was administered within 10 minutes before meals. Before beginning the study, we trained patients in the appropriate procedure for inhalation of insulin. The insulin was available in 1-mg and 3-mg blister packs (1 mg is equivalent to approximately 2.5 U to 3.0 U of subcutaneously injected insulin). Typically, patients administered 1 or 2 inhalations for any given dose. We based initial recommended doses for inhaled insulin on factors such as the patient's weight and degree of glycemic control (Appendix 1, available at [www.annals.org](http://www.annals.org)). The doses of the oral agents were kept stable for the duration of the study.

We instructed patients to self-monitor blood glucose levels by using the Accu-Chek Complete glucometer (Roche Diagnostics, Basel, Switzerland) and to assess their blood glucose levels at least 4 times daily (before breakfast, lunch, and supper and at bedtime) with results recorded on a worksheet. Glycemic targets were 4.4 to 7.8 mmol/L (80 to 140 mg/dL) before breakfast, lunch, and supper and 5.6 to 8.9 mmol/L (100 to 160 mg/dL) at bedtime. Patients measured their blood glucose levels before administering insulin. We based recommended doses for prebreakfast, prelunch, and presupper inhaled insulin on review of the mean results for the prelunch, presupper, and bedtime self-monitored blood glucose levels, respectively, between clinic visits (Appendix 1, available at [www.annals.org](http://www.annals.org)). Doses of inhaled insulin could be altered according to guidelines in case the glucose concentrations were outside these ranges, in anticipation of a smaller or larger meal, or on an as-needed basis.

### Assessments

The primary efficacy end point was the change in hemoglobin A<sub>1c</sub> level from baseline to week 12. We measured hemoglobin A<sub>1c</sub> at screening and at weeks -1, 0, 6, and 12. We defined baseline hemoglobin A<sub>1c</sub> as the average of the week -1 and week 0 values (if either value was missing, baseline was the nonmissing value). Secondary efficacy end points included changes in fasting plasma glucose level and 2-hour postprandial glucose concentration and percentage of patients achieving acceptable (hemoglobin A<sub>1c</sub>

Figure 1. The inhaled insulin delivery system.



The pulmonary inhaler consists of a reusable dry powder inhaler and unit-dose blisters containing insulin powder for inhalation. The system is designed to deliver the aerosolized powder to the small airways and alveoli to enable systemic insulin absorption. The pulmonary inhaler is solely mechanical, using no batteries or electronics, and requires only modest effort by the patient to operate. The chamber is transparent to allow the patient to see the insulin cloud after powder aerosolization. The inhaler measures approximately 16.5 cm in length when in the closed position and approximately 27.5 cm when in use (fully extended). The weight is approximately 6 oz (170 g). On the basis of experience from the clinical trial program, replacement of the insulin release unit is required every 2 weeks.

level < 8.0%) or good (hemoglobin A<sub>1c</sub> level < 7.0%) glycemic control at the end of the study. We measured fasting plasma glucose levels at weeks -4, -1, 0, and 12 in the laboratory after a fast of at least 8 hours. The standardized meal provided 480 kcal (66 g of carbohydrate, 29 g of

protein, and 11 g of fat) supplied by 450 g of a nutritional energy drink (Boost, Mead Johnson Nutritionals, Evansville, Indiana). We also analyzed patient-reported incidence and severity of hypoglycemic episodes, weight gain, and fasting lipid values. We recorded body weight at screening (week -4); baseline (week 0); and weeks 4, 8, and 12. We performed a full physical examination at screening and a brief physical examination, including throat and chest examination, at baseline before any inhaled insulin exposure and at weeks 4, 8, and 12. We performed 12-lead electrocardiography, chest radiography, and clinical laboratory tests at screening and week 12, and we measured insulin antibodies at weeks 0 and 12. We performed liver function tests monthly in patients who were using thiazolidinediones.

We performed comprehensive pulmonary function testing (spirometry, lung volumes, diffusion capacity, and oxygen saturation) at weeks -3 and 12 at investigative sites according to local procedures. We recorded adverse events (observed or self-reported) in all treated patients and classified events as mild, moderate, or severe.

We instructed patients to check blood glucose levels if they experienced symptoms of hypoglycemia. We defined hypoglycemia as having 1 of the following: characteristic symptoms of hypoglycemia with no blood glucose level measurement that resolved with food intake, subcutaneous glucagon, or intravenous glucose; characteristic symptoms of hypoglycemia with measured blood glucose level of 3.3 mmol/L or less ( $\leq 59$  mg/dL); or any measured blood glucose level of 2.7 mmol/L or less ( $\leq 49$  mg/dL). For an event to be classified as severe, patients had to meet the following criteria: inability to self-treat; at least 1 neurologic symptom; and a measured blood glucose level of 2.7 mmol/L or less ( $\leq 49$  mg/dL) or, if blood glucose level was not measured, reversal of the clinical symptoms by oral carbohydrates, subcutaneous glucagon, or intravenous glucose.

### Statistical Analysis

We needed a sample size of 89 patients per group to provide 80% to 90% power to detect at least a 0.7-percentage point difference in hemoglobin A<sub>1c</sub> level in the comparison between the inhaled insulin plus 2 oral agents group and the 2 oral agents group, or between the inhaled insulin monotherapy group and the 2 oral agents group.

For this superiority trial, the primary analysis population was the full analysis set, which we defined a priori in the protocol as all randomly assigned participants with a baseline hemoglobin A<sub>1c</sub> value and at least 1 postbaseline hemoglobin A<sub>1c</sub> value. We conducted analyses by using both baseline-carried-forward and last-observation-carried-forward approaches. The safety analyses included all participants who received at least 1 dose of the study drug.

For the primary efficacy end point, we fitted an analysis of covariance model with baseline hemoglobin A<sub>1c</sub> level as a continuous covariate and indicator variables for

center and treatment group to the change in hemoglobin A<sub>1c</sub> values from baseline to week 12. We used the step-down procedure for claiming statistical significance of the treatment effect (28). We assumed that the degree of glycemic control achieved in the inhaled insulin plus 2 oral agents group was greater than or equal to that of the inhaled insulin monotherapy group. The first test was to decide whether the treatment of the inhaled insulin plus 2 oral agents group was statistically significantly better than that of the 2 oral agents group. If not, then the analysis proceeded no further (and the study failed). If so, then the second test was to decide whether the treatment of the inhaled insulin monotherapy group was statistically significantly better than that of the 2 oral agents group. In each test, we considered statistical significance to be at an  $\alpha$  level of 0.05. This testing procedure protects the overall type 1 error rate of an  $\alpha$  level of 0.05 in multiple comparisons (29).

We assessed secondary continuous end points by using similar analyses. We analyzed the percentages of patients who reached a predefined hemoglobin A<sub>1c</sub> goal at week 12 by using logistic regression. For patients with hemoglobin A<sub>1c</sub> levels less than 7%, we used the Fisher exact test method for small samples because of the small cell size of the 2 oral agents group. We estimated the risk ratio for hypoglycemia by using the survival analysis counting process approach for recurrent events, which only included a term for treatment.

We estimated treatment group differences (inhaled insulin plus 2 oral agents vs. 2 oral agents or inhaled insulin monotherapy vs. 2 oral agents) in change from baseline in pulmonary function test variables at week 12 by using an analysis of covariance model. The model included terms for treatment and center and covariates that were known to have a physiologic relationship with pulmonary function, including baseline pulmonary function tests, age (in years), baseline height (in meters), and sex.

### Role of the Funding Sources

Pfizer Inc. and the sanofi-aventis Group funded this trial, supported trial management, implemented data collection, analyzed the data, and reviewed the manuscript before submission for publication. The funding sources performed statistical analyses in accordance with a predetermined statistical analysis plan. The investigators were not required by contract to make any revisions suggested by funding sources, and the funding sources did not control the decision to submit the manuscript for publication.

## RESULTS

### Patient Characteristics

Patient characteristics at study entry were similar among the treatment groups (Table 1). Of the 580 patients screened, 309 were randomly assigned to receive treatment (Figure 2). The main reasons for exclusion were

**Table 1. Patient Characteristics at Study Entry (All Patients Randomly Assigned and Treated)**

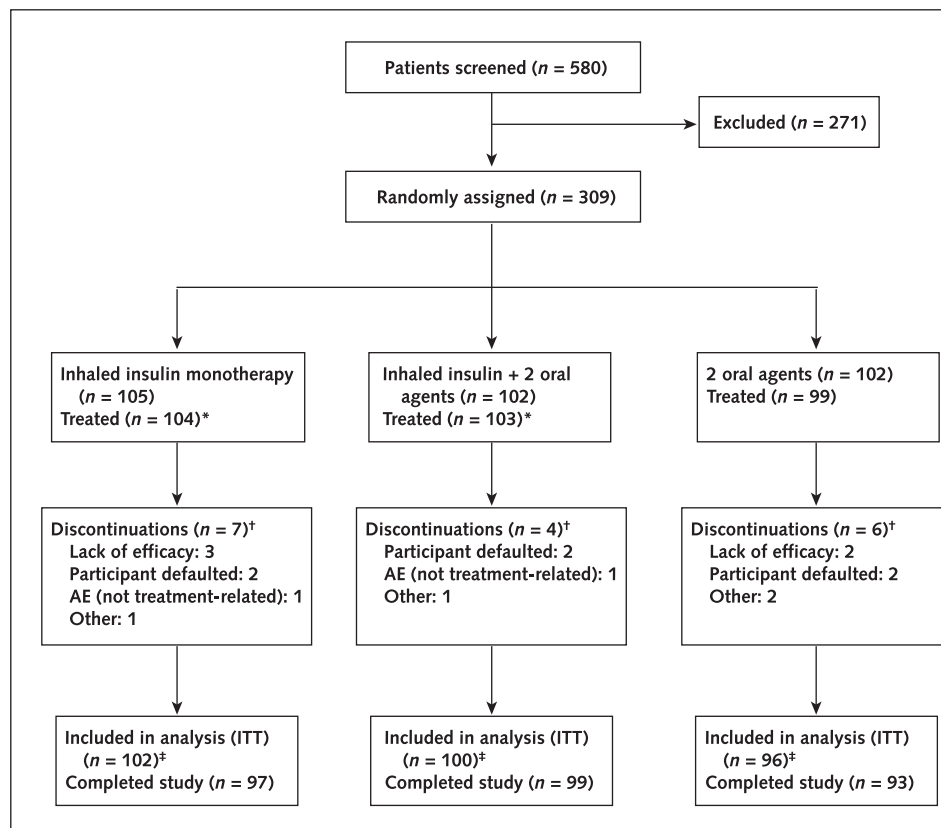
Characteristic	Inhaled Insulin plus 2 Oral Agents	Inhaled Insulin Monotherapy	2 Oral Agents
Mean age (SD) [range], y	58.3 (8.6) [38.0–77.0]	57.4 (9.2) [35.0–77.0]	56.4 (10.0) [33.0–80.0]
Men/women, n/n	65/37	75/30	62/37
Mean hemoglobin A <sub>1c</sub> level (SD) [range], %	9.48 (0.94) [7.70–11.70]	9.58 (0.87) [8.00–11.70]	9.56 (1.01) [7.20–11.80]
Mean C-peptide level (SD) [range], pmol/mL	1.08 (0.56) [0.26–3.30]	1.04 (0.54) [0.33–4.60]	1.05 (0.63) [0.23–5.50]
Mean weight (SD) [range], kg	88.9 (15.4) [46.0–127.0]	90.0 (15.6) [55.0–126.0]	87.9 (14.7) [49.0–121.0]
Mean body mass index (SD) [range], kg/m <sup>2</sup>	29.9 (3.7) [18.0–38.0]	30.2 (3.8) [22.0–39.0]	30.0 (4.0) [18.0–38.0]
Mean duration of diabetes [range], y	9.8 [1.0–37.0]	9.3 [1.8–25.0]	9.6 [1.3–32.8]
Randomly assigned and treated patients, n	102	105*	99†

\* One patient was randomly assigned to receive inhaled insulin monotherapy but received inhaled insulin plus 2 oral agents. This patient was excluded from efficacy analysis.  
 † Three of the 102 randomly assigned patients were never treated.

hemoglobin A<sub>1c</sub> values outside the inclusion criteria, abnormal pulmonary function test results or inability of the patients to perform the pulmonary function tests, and withdrawal of consent. Three patients who were randomly assigned to the 2 oral agents group dropped out before entering the active treatment phase of the trial. Therefore, 306 patients received study treatment. We excluded 2 patients randomly assigned to inhaled insulin plus 2 oral agents, 3 patients randomly assigned to inhaled insulin monotherapy, and 3 patients randomly assigned to the 2 oral agents group from the full analysis set because of miss-

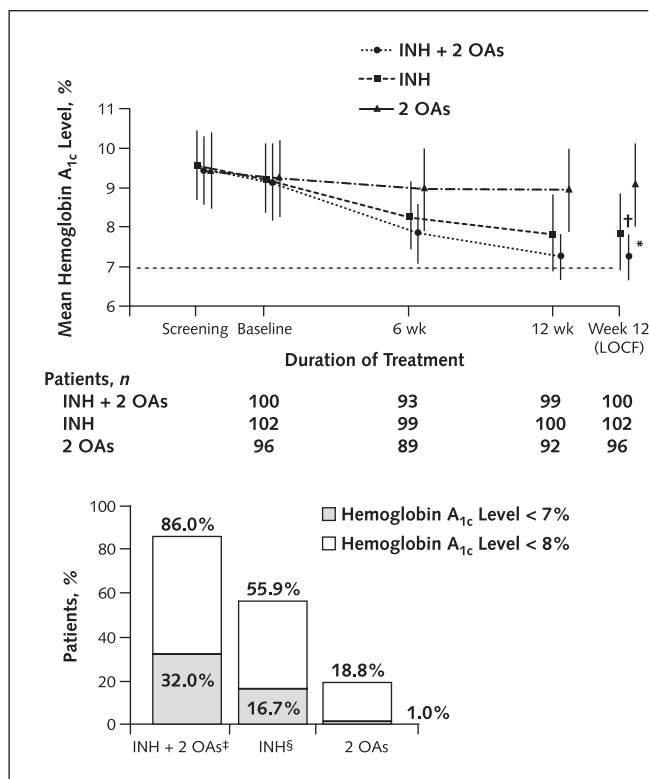
ing baseline or postbaseline data. Therefore, no differential dropout and potential bias occurred with respect to the patients who were excluded from the full analysis set. A total of 298 patients qualified for the full analysis, and 289 patients completed treatment (Figure 2). Four of 103 (3.9%) patients in the inhaled insulin plus 2 oral agents group, 7 of 104 (6.7%) patients in the inhaled insulin monotherapy group, and 6 of 99 (6.1%) patients in the 2 oral agents group discontinued the study. We considered 0 discontinuations in the inhaled insulin plus 2 oral agents group, 3 (2.9%) discontinuations in the inhaled insulin

**Figure 2. Flow of patients through the study.**



AE = adverse event; ITT = intention-to-treat. \*One patient was randomly assigned to receive inhaled insulin monotherapy but received inhaled insulin plus 2 oral agents. †Discontinuation from the study did not by itself exclude a patient from analysis. ‡Patients were excluded from the full analysis set for lack of baseline or postbaseline hemoglobin A<sub>1c</sub> values.

**Figure 3. Hemoglobin A<sub>1c</sub> values during 3 months of treatment (top) and patients reaching target hemoglobin A<sub>1c</sub> level at study end (bottom).**



**Top.** Mean (SD) hemoglobin A<sub>1c</sub> values during 3 months of treatment with inhaled insulin (INH) plus 2 oral agents (OAs), INH monotherapy, or 2 OAs. \*INH plus 2 OAs vs. 2 OAs adjusted difference at week 12 (last observation carried forward [LOCF]), -1.67 percentage points (95% CI, -1.90 to -1.44 percentage points). †INH vs. 2 OAs adjusted difference at week 12 (LOCF), -1.18 percentage points (CI, -1.41 to -0.95 percentage point). Numbers of patients analyzed at each time point by treatment group are shown below the graph. **Bottom.** Percentages of patients reaching target hemoglobin A<sub>1c</sub> values at study end with INH plus 2 OAs, INH monotherapy, or 2 OAs. ‡INH plus 2 OAs vs. 2 OAs adjusted odds ratio was 40.5 (CI, 17.0 to 96.9) for hemoglobin A<sub>1c</sub> level < 8% and 44.7 (CI, 6.0 to 335.2) for hemoglobin A<sub>1c</sub> level < 7%. §INH vs. 2 OAs adjusted odds ratio was 7.5 (CI, 3.6 to 15.5) for hemoglobin A<sub>1c</sub> level < 8% and 19.0 (CI, 2.5 to 145.8) for hemoglobin A<sub>1c</sub> level < 7%.

monotherapy group, and 2 (2.0%) discontinuations in the 2 oral agents group to be treatment-related (all due to lack of efficacy). No treatment-related discontinuations due to adverse events occurred in any group.

**Primary Outcomes**

At week 12, both inhaled insulin groups had statistically significantly greater reductions in mean hemoglobin A<sub>1c</sub> level than the 2 oral agents group. For the inhaled insulin plus 2 oral agents group, baseline hemoglobin A<sub>1c</sub> level of 9.2% (SD, 1.0%) decreased by 1.9 percentage points (SE, 0.1). For the inhaled insulin monotherapy group, baseline hemoglobin A<sub>1c</sub> level of 9.3% (SD, 0.9%) decreased by 1.4 percentage points (SE, 0.1). For the 2 oral agents group, baseline hemoglobin A<sub>1c</sub> level of 9.3% (SD,

1.0%) decreased by 0.2 percentage point (SE, 0.1) (Figure 3, top). The treatment group difference in mean adjusted hemoglobin A<sub>1c</sub> level was -1.67 percentage points (95% CI, -1.90 to -1.44 percentage points; P < 0.001) for the inhaled insulin plus 2 oral agents group and -1.18 percentage points (CI, -1.41 to -0.95 percentage point; P < 0.001) for the inhaled insulin monotherapy group relative to the 2 oral agents group. Thus, the superiority primary objectives of the study were met.

**Secondary Outcomes**

Hemoglobin A<sub>1c</sub> level less than 8.0% was achieved by 86 (86.0%) patients in the inhaled insulin plus 2 oral agents group, 57 (55.9%) patients in the inhaled insulin monotherapy group, and 18 (18.8%) patients in the 2 oral agents group. Adjusted odds ratios were 40.5 (CI, 17.0 to 96.9) and 7.5 (CI, 3.6 to 15.5) for the inhaled insulin plus 2 oral agents and inhaled insulin monotherapy groups, respectively, relative to the 2 oral agents group. Further improvement in glycemic control (hemoglobin A<sub>1c</sub> level < 7.0%) was achieved by 32 (32.0%) patients in the inhaled insulin plus 2 oral agents group, 17 (16.7%) patients in the inhaled insulin monotherapy group, and 1 (1.0%) patient in the 2 oral agents group (adjusted odds ratios, 44.7 [CI, 6.0 to 335.2] and 19.0 [CI, 2.5 to 145.8], respectively) (Figure 3, bottom).

At week 12, fasting plasma glucose levels and 2-hour postprandial glucose levels had greater reductions in the inhaled insulin plus 2 oral agents and inhaled insulin monotherapy groups than in the 2 oral agents group (Table 2, Figure 4). Mean body weight was similar at baseline. At week 12, the inhaled insulin plus 2 oral agents and inhaled insulin monotherapy groups showed greater increases in mean body weight than the 2 oral agents group (Table 2). The mean changes from baseline in fasting lipid levels were similar among the groups for total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels (Table 2), but levels of triglycerides decreased in both inhaled insulin groups and increased in the 2 oral agents group (Table 2).

The mean daily dose of inhaled insulin changed only slightly during the study. The mean doses for the inhaled insulin plus 2 oral agents and inhaled insulin monotherapy groups were 12.2 mg (SD, 7.6) and 23.7 mg (SD, 10.8), respectively, at week 6, compared with 13.1 mg (SD, 8.5) and 26.4 mg (SD, 13.3), respectively, at week 12.

**Safety and Tolerability**

The most commonly reported adverse event in the inhaled insulin groups was treatment-related hypoglycemia (Table 3). In addition to reported hypoglycemia, some other treatment-related adverse events (for example, asthenia, tremor, dizziness, sweating, and headache) may have been manifestations of mild hypoglycemia. Fewer patients in the dual oral agent therapy group experienced a treatment-related adverse event compared with the inhaled insulin groups. Three treatment-related severe adverse events

**Table 2. Change from Baseline to Week 12 in Secondary Outcome Measures\***

Variable	Inhaled Insulin plus 2 Oral Agents		Inhaled Insulin Monotherapy		2 Oral Agents		Adjusted Treatment Group Difference (95% CI)†	
	Baseline	Change from Baseline	Baseline	Change from Baseline	Baseline	Change from Baseline	Inhaled Insulin plus 2 Oral Agents vs. 2 Oral Agents	Inhaled Insulin Monotherapy vs. 2 Oral Agents
Mean FPG level (SD)								
<i>mmol/L</i>	10.8 (2.7)	-2.9 (0.2)	11.3 (2.4)	-1.3 (0.2)	11.3 (2.4)	0.06 (0.3)	-2.9 (-3.7 to -2.3)	-1.3 (-2.0 to -0.6)
<i>mg/dL</i>	195 (49)	-53 (4)	203 (43)	-23 (4)	203 (44)	1 (5)	-53 (-66 to -41)	-24 (-36 to -11)
Mean 2-h PPG level (SD)								
<i>mmol/L</i>	16.2 (36.1)	-4.4 (0.3)	16.7 (3.1)	-3.7 (0.3)	16.7 (3.0)	-0.2 (0.4)	-4.2 (-5.2 to -3.2)	-3.4 (-4.4 to -2.5)
<i>mg/dL</i>	291 (65)	-79 (6)	300 (56)	-66 (6)	300 (54)	-3 (7)	-76 (-93 to -58)	-62 (-79 to -45)
Mean total cholesterol level (SD)								
<i>mmol/L</i>	4.98 (0.96)	-0.03 (0.06)	5.01 (1.02)	0.02 (0.06)	4.84 (1.04)	0.10 (0.06)	-0.13 (-0.30 to 0.03)	-0.08 (-0.25 to 0.08)
<i>mg/dL</i>	192 (37)	-1 (2)	193 (39)	1 (2)	187 (40)	4 (2)	-5 (-12 to 1)	-3 (-10 to 3)
Mean LDL cholesterol level (SD)								
<i>mmol/L</i>	2.89 (0.80)	0.10 (0.06)	3.02 (0.84)	0.12 (0.06)	2.78 (0.81)	0.03 (0.06)	0.08 (-0.09 to 0.25)	0.09 (-0.08 to 0.27)
<i>mg/dL</i>	112 (31)	4 (2)	116 (32)	4 (2)	107 (31)	1 (2)	3 (-4 to 10)	4 (-3 to 10)
Mean triglycerides level (SD)								
<i>mmol/L</i>	2.29 (1.47)	-0.44 (0.09)	2.12 (1.24)	-0.61 (0.09)	2.40 (1.78)	0.18 (0.09)	-0.61 (-0.86 to -0.37)	-0.78 (-1.03 to -0.54)
<i>mg/dL</i>	203 (130)	-39 (8)	188 (110)	-54 (8)	213 (157)	15 (8)	-54 (-76 to -33)	-69 (-91 to -48)
Mean HDL cholesterol level (SD)								
<i>mmol/L</i>	1.04 (0.28)	0.06 (0.02)	1.04 (0.29)	0.12 (0.02)	0.98 (0.27)	0.03 (0.02)	0.03 (-0.02 to 0.09)	0.10 (0.04 to 0.15)
<i>mg/dL</i>	40 (11)	2 (1)	40 (11)	5 (1)	38 (11)	1 (1)	1 (-1 to 3)	4 (1 to 6)
Mean body weight (SD), <i>kg</i>	88.6 (15.5)	2.7 (0.3)	89.5 (15.8)	2.8 (0.3)	88.0 (15.4)	0.0 (0.3)	2.7 (1.9 to 3.6)	2.8 (1.9 to 3.6)
Mean FEV <sub>1</sub> (SE), <i>L</i>	2.96 (0.68)	-0.12 (0.02)	3.01 (0.64)	-0.10 (0.02)	2.97 (0.75)	-0.07 (0.02)	-0.05 (-0.11 to 0.01)	-0.03 (-0.09 to 0.03)
Mean FVC (SE), <i>L</i>	3.75 (0.91)	-0.10 (0.03)	3.80 (0.83)	-0.06 (0.03)	3.72 (0.96)	-0.05 (0.03)	-0.05 (-0.12 to 0.02)	-0.01 (-0.09 to 0.06)
Mean DL <sub>CO</sub> (SE), <i>mL/min per mm Hg</i>	25.10 (6.43)	-1.17 (0.31)	24.86 (6.08)	-1.20 (0.32)	25.12 (6.60)	-0.46 (0.34)	-0.70 (-1.56 to 0.16)	-0.73 (-1.60 to 0.13)
Mean TLC (SE), <i>L</i>	5.97 (1.33)	-0.11 (0.05)	5.90 (1.13)	-0.04 (0.05)	5.80 (1.31)	-0.05 (0.05)	-0.06 (-0.19 to 0.07)	0.01 (-0.12 to 0.14)

\* DL<sub>CO</sub> = diffusing lung capacity for carbon monoxide; FPG = fasting plasma glucose; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PPG = postprandial plasma glucose; TLC = total lung capacity.

† Adjusted mean difference between inhaled insulin groups (inhaled insulin monotherapy or inhaled insulin plus 2 oral agents) and 2 oral agents in change from baseline and 95% CI are based on the primary model with terms for treatment, center, age, height, and sex.

occurred in the inhaled insulin plus 2 oral agents group (asthenia, diarrhea, and tremor), 3 occurred in the inhaled insulin monotherapy group (hypoglycemia, dizziness, and sweating), and 4 occurred in the 2 oral agents group (constipation, diarrhea, flatulence, and hypesthesia).

In the inhaled insulin plus 2 oral agents, inhaled insulin monotherapy, and 2 oral agents groups, 477, 365, and 14 hypoglycemic events occurred, respectively. The rates of overall hypoglycemia (episodes per participant-month) were 1.7 and 1.3 in the inhaled insulin plus 2 oral agents and inhaled insulin monotherapy groups, respectively, and 0.1 in the 2 oral agents group. This translated into a risk ratio of 32 (CI, 19 to 54) for inhaled insulin plus 2 oral agents and 24 (CI, 14 to 42) for inhaled insulin monotherapy relative to the 2 oral agents group. One severe hypoglycemic episode was reported in the inhaled insulin monotherapy group.

Overall, 12 of 103 (12%) patients in the inhaled insulin plus 2 oral agents group, 15 of 104 (14%) patients in the inhaled insulin monotherapy group, and 2 of 99 (2%) patients in the 2 oral agents group reported at least 1 episode of cough, which was generally mild and decreased in

incidence and prevalence during the study, and no patient discontinued therapy because of cough.

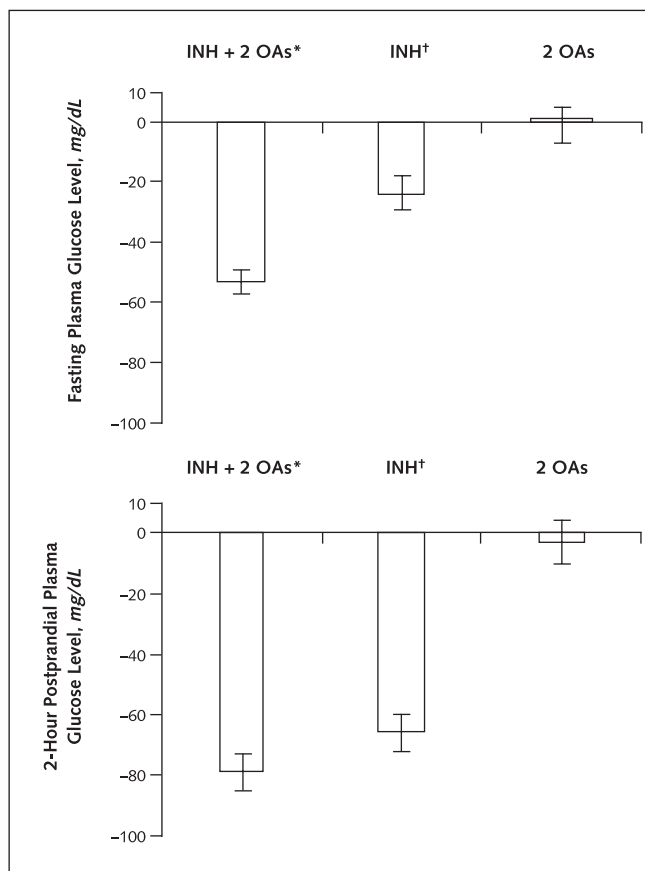
Pulmonary function tests showed no statistically significant between-group differences for FEV<sub>1</sub>, FVC, total lung capacity, or carbon monoxide diffusing capacity (Table 2).

We observed increased insulin antibody serum binding in the inhaled insulin groups. At week 12, the mean change in percentage binding from baseline was 2.89% (SD, 6.08%), 6.14% (SD, 12.41%), and 0% (SD, 0%) for the inhaled insulin plus 2 oral agents, inhaled insulin monotherapy, and 2 oral agents groups, respectively. The higher antibody levels observed in the inhaled insulin groups were not associated with allergic adverse events, and increased insulin antibody binding did not affect glycemic control, hypoglycemic events, inhaled insulin dose requirements, or pulmonary function.

**DISCUSSION**

A large clinical trial program assessed the efficacy and safety of inhaled insulin in patients with type 1 or type 2

**Figure 4.** Adjusted mean change in fasting plasma glucose concentration (top) and 2-hour postprandial glucose concentration (bottom) from baseline to study end after 12 weeks of treatment.



**Top.** Adjusted mean change in fasting plasma glucose concentration with inhaled insulin (INH) plus 2 oral agents (OAs), INH monotherapy, or 2 OAs. \*Adjusted difference at week 12, -2.9 mmol/L (-53 mg/dL) (95% CI, -3.7 mmol/L [-66 mg/dL] to -2.3 mmol/L [-41 mg/dL]). †Adjusted difference at week 12, -1.3 mmol/L (-24 mg/dL) (CI, -2.0 mmol/L [-36 mg/dL] to -0.6 mmol/L [-11 mg/dL]). **Bottom.** Adjusted mean change in 2-hour postprandial glucose concentration from baseline to study end after 12 weeks of treatment with INH plus 2 OAs, INH monotherapy, or 2 OAs. \*Adjusted difference at week 12, -4.2 mmol/L (-76 mg/dL) (CI, -5.2 mmol/L [-93 mg/dL] to -3.2 mmol/L [-58 mg/dL]). †Adjusted difference at week 12, -3.4 mmol/L (-62 mg/dL) (CI, -4.4 mmol/L [-79 mg/dL] to -2.5 mmol/L [-45 mg/dL]).

diabetes. In patients with type 1 diabetes, inhaled insulin showed similar decreases in mean hemoglobin A<sub>1c</sub> level compared with subcutaneous insulin in studies of 6 months' duration (22, 30). In patients with type 2 diabetes, treatment for 6 months with inhaled insulin or subcutaneous insulin also resulted in similar improvements in glycemic control (23). The results of a 2-year study demonstrated the efficacy and long-term pulmonary safety of inhaled insulin in combination with an oral agent regimen in patients with type 2 diabetes (31). Finally, we offered continued, open-label inhaled insulin therapy to patients who completed the randomized, controlled clinical trials.

Four-year data from these extension studies show that inhaled insulin can be used to maintain long-term glycemic control in patients with type 1 or type 2 diabetes (32).

Our study, which we believe to be the first study providing data for inhaled insulin use when dual oral agent therapy fails in patients with type 2 diabetes, also demonstrates that inhaled insulin is an effective agent to improve glycemic control on the basis of hemoglobin A<sub>1c</sub> level, fasting and postprandial glucose levels, and triglyceride levels. The value of inhaled insulin seems greater when it is used in combination with oral agents, as indicated by improvements in hemoglobin A<sub>1c</sub> values from 9.2% to 7.3%. As well as improving postprandial glucose control, premeal inhaled insulin reduced fasting plasma glucose concentrations, thus seeming to have a glucose-lowering effect that extends beyond the postprandial period. Although the reasons for this effect remain unclear, this has been a consistent finding in other inhaled insulin studies in patients with both type 1 and type 2 diabetes, regardless of the concomitant diabetes medication (22, 23).

During our 3-month study, inhaled insulin therapy was well-tolerated. In particular, we did not observe statistically significant differences in pulmonary function among the treatment groups. Although insulin inhalation was associated with an increase in treatment-related respiratory adverse events, these events were mostly mild cough with no associated discontinuation of therapy. Inhaled insulin therapy was also associated with a propensity for mild weight gain, which is consistent with insulin therapy in general, compared with oral agents.

As expected, and consistent with their improved glycemic control, patients in the inhaled insulin plus 2 oral agents group and the inhaled insulin monotherapy group had more hypoglycemic events than those in the dual oral agent therapy group. The definition of severe hypoglycemia in our trial was consistent with the Diabetes Control and Complications Trial Research Group criteria for severe hypoglycemia (1). Severe hypoglycemia is relatively rare in patients with type 2 diabetes without predisposing risk factors (6). Only 1 patient reported a severe hypoglycemic

**Table 3. Treatment-Related Adverse Events Experienced by More than 5% of Patients**

Patients with Adverse Event	Inhaled Insulin plus 2 Oral Agents (n = 103), n (%)	Inhaled Insulin Monotherapy (n = 104), n (%)	2 Oral Agents (n = 99), n (%)
Asthenia	21 (20)	24 (23)	4 (4)
Headache	6 (6)	7 (7)	0 (0)
Hypoglycemia	78 (76)	69 (66)	8 (8)
Total events	477	365	13
Severe events	0	1	0
Dizziness	11 (11)	24 (23)	3 (3)
Nervousness	3 (3)	6 (6)	0 (0)
Tremor	36 (35)	33 (32)	5 (5)
Increased cough	7 (7)	5 (5)	0 (0)
Sweating	18 (18)	21 (20)	3 (3)

episode, and the patient completely recovered. No patient discontinued therapy because of hypoglycemia.

Patients treated with inhaled insulin develop increased insulin antibody titers. This phenomenon was investigated because a large pool of insulin antibodies might blunt free insulin excursions and result in postprandial hyperglycemia (33) and, second, might release free insulin from a large pool of antibody-bound insulin at inappropriate times, thus increasing the likelihood of hypoglycemia, especially overnight (34). However, the increase in insulin antibodies seen with inhaled insulin did not seem to have any clinical consequences. A recent pooled analysis of antibody response to inhaled insulin in patients with type 1 or type 2 diabetes found no evidence to date that insulin antibodies are associated with adverse clinical consequences in trials of inhaled insulin (35). Stoeber and Palmer (34) have reviewed the potential implications of elevated insulin antibody levels.

Limitations of our study include the open-label study design, a defined patient sample, and a comparator group that did not intensify oral agent treatment. We included only patients with hemoglobin A<sub>1c</sub> levels between 8% and 11% and a body mass index less than 35 kg/m<sup>2</sup>. We cannot, therefore, extend any conclusions from our trial to patients who do not meet these criteria. However, the patient group studied in our trial represents a large population found in clinical practice. Inhaled insulin was available in nominal 1-mg and 3-mg blister packs, and the smallest possible dose adjustment was 1 mg (a single 1-mg blister of inhaled insulin is approximately equal to 2.5 U to 3.0 U of a standard subcutaneous insulin dose). By adjusting the inhaled insulin dose by as little as 1 mg if necessary in response to self-monitored blood glucose levels (Appendix 1, available at [www.annals.org](http://www.annals.org)), patients can attain a relatively stable insulin dose by week 4 (24). However, patients who are thought to be particularly sensitive to insulin may need to receive lower doses of inhaled insulin and titrate it cautiously. A further limitation of our study was that the trial findings can only be discussed in relation to the agents used in our study because we did not randomly assign patients to a study group that used an additional third oral agent or added injected insulin. Nonetheless, the results show that for patients with type 2 diabetes who have poor glycemic control with a stable regimen of dual oral agent therapy, the introduction of premeal inhaled insulin therapy provides better glycemic control, more frequently achieves target hemoglobin A<sub>1c</sub> levels, and is well-tolerated over 3 months. This is accomplished with inhaled insulin as monotherapy or, more effectively, as an addition to existing oral agent therapy and does not require any supplementation with injected insulin. The addition of premeal inhaled insulin resulted in statistically significant decreases in both fasting plasma glucose and 2-hour postprandial glucose levels. These reductions achieve a more physiologic approach to overall glycemic control.

Guidelines recommend that patients with type 2 dia-

betes who do not achieve adequate control with oral agent therapy alone should start receiving insulin therapy (36–38). Previous studies have shown that inhaled insulin is associated with greater treatment satisfaction than subcutaneous insulin in patients with type 1 or type 2 diabetes (39–41) and, in fact, may increase the acceptance of insulin in patients with type 2 diabetes whose diet and exercise regimen, oral agent therapy, or both fail (42). Any measure that facilitates initiation of insulin therapy is, therefore, likely to be of benefit in these patients.

Ongoing studies are examining the long-term safety of inhaled insulin. However, to date, various clinical studies of inhaled insulin in patients with diabetes suggest that this route of delivery is well-tolerated (22, 23, 30–32) and preferred by patients (39–42). Noninvasive insulin delivery methods may increase acceptance of insulin, thus facilitating better glycemic control and improved long-term treatment outcomes in patients with type 2 diabetes.

From Dallas Diabetes and Endocrine Center at Medical City, Dallas, Texas; University of Toronto and Samuel Lunenfeld Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada; University of Manitoba, Winnipeg, Manitoba, Canada; Georgetown University, Washington, DC; Austin Diagnostic Clinic, Austin, Texas; University of Alberta and Royal Alexandra Hospital, Edmonton, Alberta, Canada; Yale University School of Medicine, New Haven, and Pfizer Global Research and Development, Groton, Connecticut; and Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana.

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**Requests for Single Reprints:** Julio Rosenstock, MD, Dallas Diabetes and Endocrine Center, 7777 Forest Lane, Suite C618, Medical City Dallas, Dallas, TX 75230; e-mail, juliorosenstock@dallasdiabetes.com.

Current author addresses and author contributions are available at [www.annals.org](http://www.annals.org).

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**Current Author Addresses:** Dr. Rosenstock: Dallas Diabetes and Endocrine Center, 7777 Forest Lane, Suite C618, Medical City Dallas, Dallas, TX 75230.

Dr. Zinman: Department of Medicine, Mount Sinai Hospital, L 5-024, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada.

Dr. Murphy: Department of Internal Medicine, University of Manitoba, 820 Sherbrook Street, Winnipeg, Manitoba R3A 1R8, Canada.

Dr. Clement: Department of Endocrinology, Georgetown University Hospital, Building D, Room 232, 4000 Reservoir Road NW, Washington, DC 20007.

Dr. Moore: Austin Diagnostic Clinic, 12221 MoPac Expressway North, 2nd Floor, South Entrance, Austin, TX 78758-2483.

Dr. Bowering: Multidisciplinary Diabetic Foot Clinic, Royal Alexandra Hospital, 10240 Kingsway Avenue, Edmonton, Alberta T5H 3V9, Canada.

Dr. Hendler: Department of Internal Medicine, Yale University School of Medicine, Fitkin 1, 333 Cedar Street, PO Box 208020, New Haven, CT 06520-8020.

Ms. Lan: Pfizer Inc., MS 6025-A4269, 50 Pequot Avenue, New London, CT 06320.

Dr. Cefalu: Pennington Biomedical Research Center, Louisiana State University, 6400 Perkins Road, Baton Rouge, LA 70808.

**Author Contributions:** Conception and design: J. Rosenstock, B. Zinman.

Analysis and interpretation of the data: J. Rosenstock, B. Zinman, S.-P. Lan.

Drafting of the article: J. Rosenstock, W.T. Cefalu.

Critical revision of the article for important intellectual content: J. Rosenstock, B. Zinman, L.J. Murphy, P. Moore, C.K. Bowering, R. Hendler, S.-P. Lan, W.T. Cefalu.

Final approval of the article: J. Rosenstock, B. Zinman, L.J. Murphy, S.C. Clement, P. Moore, C.K. Bowering, R. Hendler, W.T. Cefalu.

Provision of study materials or patients: J. Rosenstock, B. Zinman, L.J. Murphy, S.C. Clement, P. Moore, C.K. Bowering, R. Hendler, W.T. Cefalu.

Statistical expertise: S.-P. Lan.

Obtaining of funding: J. Rosenstock, B. Zinman.

Administrative, technical, or logistic support: J. Rosenstock, B. Zinman.

Collection and assembly of data: J. Rosenstock, S.C. Clement, B. Zinman.

## APPENDIX 1: INHALED INSULIN DOSING REGIMEN

### Initial Premeal Inhaled Insulin Dose

Inhaled insulin was available in 1-mg and 3-mg dose blister packs. Each inhalation used 1 blister. Typically, patients administered 1 to 2 inhalations per dosing session (**Appendix Table 1**).

For simplicity and convenience of dosing, each dosing session used 1 of 5 dose levels. Generally, doses in excess of 2 inhalations of the 3-mg strength were not to be used. However, if the investigator felt that another dose level was required for optimal care of a particular patient, the case was reviewed with the sponsor clinician, who could grant approval for such doses on a case-by-case basis.

Patients administered the initial dose of inhaled insulin just before breakfast under observation at the study site. The patient remained at the site until the investigator verified the response to the insulin dose. We adjusted doses for each patient on the basis of glucose level response.

**Appendix Table 2** presents approximate guidelines for ini-

**Appendix Table 1. Inhaled Insulin Dose Levels**

Dose Level	Inhalations ("Blisters"), n	
	1-mg Strength	3-mg Strength
1	1	—
2	2	—
3	—	1
4	1	1
5	—	2

tial premeal inhaled insulin doses based on body weight. These doses are only rough guidelines. As with injected insulin, other factors considered in dose selection included meal size and nutrient composition, time of day (for example, higher insulin requirement in the morning), premeal blood glucose concentration, and recent or anticipated exercise. Patients who were thought to be particularly sensitive to injected insulin started receiving lower doses of inhaled insulin and titrated it cautiously.

### Inhaled Insulin Dose Titration

At all times in the trial, each patient had an individualized recommended insulin dose for each dosing time. All study participants receiving the inhaled insulin regimens were to perform home glucose level monitoring at least 4 times daily: just before breakfast, lunch, and supper and at bedtime. Patients recorded glucose level results in a worksheet that we provided to them. To set recommended doses, we reviewed patients' glucose level records at each clinic visit and calculated the mean glucose level values. The goal glucose level range was 4.4 to 7.8 mmol/L (80 to 140 mg/dL) before meals and 5.5 to 8.9 mmol/L (100 to 160 mg/dL) at bedtime. We based recommended doses for prebreakfast, prelunch, and presupper inhaled insulin on review of the mean results for the prelunch, presupper, and bedtime glucose values, respectively. If typical glucose values at any testing time were outside the goal ranges before meals and at bedtime, we recommended a new insulin dose for the preceding dosing period (for example, a high presupper mean glucose level required an upward adjustment of the prelunch inhaled insulin dose) (**Appendix Table 3**).

The patient used the recommended dose when the self-measured premeal glucose level was within the target range. In the event of lower (<4.4 mmol/L [ $<80$  mg/dL]) or higher (>10.0 mmol/L [ $>180$  mg/dL]) glucose levels at the time of dosing, the patient could adjust the dose down or up by 1 inhalation of the

**Appendix Table 2. Guidelines for Initial Premeal Inhaled Insulin Doses Based on Body Weight**

Body Weight	Premeal Inhaled Dose Inhalations, n	
	1 mg	3 mg
30–44 kg	1	—
45–59 kg	2	—
60–79 kg	—	1
80–99 kg	1	1
>100 kg	—	2

**Appendix Table 3. Recommendations for Insulin Dose Titration for Patients Receiving the Inhaled Insulin Regimens**

Average Plasma Glucose Level Outside Target Range	Target Range, mmol/L (mg/dL)	Insulin Dose Adjusted
Prelunch	4.4–7.8 (80–140)	Prebreakfast (inhaled)
Presupper	4.4–7.8 (80–140)	Prelunch (inhaled)
Bedtime	5.5–8.9 (100–160)	Presupper (inhaled)

1-mg strength of inhaled insulin. A minor deviation from the recommended dose (for example, by 1 inhalation of 1-mg strength) could also be considered in anticipation of a smaller or larger meal.

In addition to premeal dosing, inhaled insulin could be administered on an as-needed basis (for example, with an afternoon snack or at bedtime), if warranted on the basis of high home blood glucose level test results. A bedtime dose of 1 or 2 inhalations of 1-mg strength of inhaled insulin could be considered if the bedtime glucose level exceeded 10.0 mmol/L (180 mg/dL). Patients determined whether to take a bedtime inhaled insulin dose by the bedtime glucose level. The bedtime dose of inhaled

insulin, because of its short activity–time course, was not titrated to the next morning’s prebreakfast glucose level.

## APPENDIX 2: STUDY INVESTIGATORS

Jeanine Albu, M. Larissa Aviles-Santa, Gordon Bailey, Eugene Barrett, André Bélanger, Richard Bergenstal, Sheldon Berger, Judson Black, Lawrence Blonde, C. Keith Bowering, Seth Braunstein, Arnold Brickman, Vasti Broadstone, Veronica Catanese, William T. Cefalu, M. Arthur Charles, Stephen C. Clement, Mayer Davidson, Michael Davidson, Jerry Drucker, Mark Ettinger, David Gardner, John Gerich, Hertzell Gerstein, Robert Goldstein, Rosa Hendler, Kenneth Hershon, Priscilla Hollander, Carol Joyce, Charles Kilo, Lawrence Leiter, Sam Lerman, Seymour Levin, Heather Lochnan, Adi Mehta, Joseph Milburn, Paul Moore, Liam J. Murphy, William Petit Jr., Philip Raskin, Marc Rendell, Matthew Riddle, Daeyoung Roh, Sid Rosenblatt, Julio Rosenstock, Stuart Ross, Richard Rowe, Edmond Ryan, Manuel Sainz de la Pena, Sherwyn Schwartz, Robert Sherwin, Jay Skyler, David Smith, Allen Sussman, Robert Tannenber, Stuart Weiss, Sandra Werbel, and Bernard Zinman.