Inhaled Technosphere Insulin Versus Inhaled Technosphere Placebo in Insulin-Naïve Subjects With Type 2 Diabetes Inadequately Controlled on Oral Antidiabetes Agents

*Julio Rosenstock,[1] Denise Franco,[2] Vadym Korpachev,[3] Brad Shumel,[4] Yuhui Ma,[5] Robert Baughman,[5] Nikhil Amin,[5] and Janet B. McGill,[6] for the Affinity 2 Study Group**

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OBJECTIVE

To investigate the efficacy and safety of prandial Technosphere inhaled insulin (TI), an inhaled insulin with a distinct time action profile, in insulin-naïve type 2 diabetes (T2D) inadequately controlled on oral antidiabetes agents (OADs).

RESEARCH DESIGN AND METHODS

Subjects with T2D with HbA_{1c} levels ≥7.5% (58.5 mmol/mol) and ≤10.0% (86.0 mmol/mol) on metformin alone or two or more OADs were randomized to add-on prandial TI (*n* = 177) or prandial Technosphere inhaled placebo (TP) (*n* = 176) to their OAD regimen in this double-blind, placebo-controlled trial. Primary end point was change in HbA_{1c} at 24 weeks.

RESULTS

TI significantly reduced HbA_{1c} by −0.8% (−9.0 mmol/mol) from a baseline of 8.3% (66.8 mmol/mol) compared with TP −0.4% (−4.6 mmol/mol) (treatment difference −0.4% [95% CI −0.57, −0.23]; $P < 0.0001$). More TI-treated subjects achieved an HbA_{1c} ≤7.0% (53.0 mmol/mol) (38% vs. 19%; $P = 0.0005$). Mean fasting plasma glucose was similarly reduced in both groups. Postprandial hyperglycemia, based on 7-point glucose profiles, was effectively controlled by TI. Mean weight change was 0.5 kg for TI and −1.1 kg for the TP group ($P < 0.0001$). Mild, transient dry cough was the most common adverse event, occurring similarly in both groups (TI, 23.7%; TP, 19.9%) and led to discontinuation in only 1.1% of TI-treated and 3.4% of TP-treated subjects. There was a small decline in forced expiratory volume in 1 s in both groups, with a slightly larger decline in the group receiving TI (TI, −0.13 L; TP, −0.04 L). The difference resolved after treatment discontinuation.

CONCLUSIONS

Prandial TI added to one or more OADs in inadequately controlled T2D is an effective treatment option. Mild, transient dry cough was the most common adverse event.

[1]*Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX*
[2]*CPCLIN Clinical Research Center, São Paulo, Brazil*
[3]*V.P. Komissarenko Institute of Endocrinology and Metabolism of AMS of Ukraine, Kiev, Ukraine*
[4]*Regeneron Pharmaceuticals, Tarrytown, NY*
[5]*MannKind Corporation, Paramus, NJ*
[6]*Division of Endocrinology, Metabolism and Lipid Research, Washington University School of Medicine, St. Louis, MO*

Corresponding author: Julio Rosenstock, juliorosenstock@dallasdiabetes.com.

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**A complete list of the Affinity 2 Study Group members can be found in the Supplementary Data online.*

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Most current treatment recommendations for type 2 diabetes (T2D) favor an incremental approach, beginning with lifestyle changes and metformin followed by combination therapy chosen according to HbA_{1c} response, side effect profile, hypoglycemia risk, weight changes, and cost (1). As β-cell function declines, most people ultimately require initiation of injectable insulin therapy (1,2).

Delays in starting insulin contribute to a "treat-to-failure" approach, whereby insulin is reserved as the treatment of last resort, leading to long periods of deleterious hyperglycemia and glucotoxicity in the intervals between treatment advancement and intensification. Time elapsed from diabetes diagnosis to the initiation of insulin therapy ranges from 7 to 10 years, with HbA_{1c} levels climbing to 9 or 10% (75 to 86 mmol/mol) by the time insulin is started (3–5).

Commonly cited barriers for both patients and providers to initiate insulin in a timely manner include fear of hypoglycemia, concerns about weight gain, resistance to or fear of injections, the inconvenience of lifestyle restrictions, and apprehension about the demands of the treatment regimen (6–9).

Basal insulin is commonly used as the initial insulin in subjects with T2D. The Treat-to-Target Trial (10) established basal insulin glargine as the therapy of choice in people with T2D inadequately controlled by oral antidiabetes agents (OADs), based on its comparable efficacy to NPH insulin but significantly lower rates of hypoglycemia. Basal insulin analogs offer simplicity in once-daily injection frequency and ease of dose titration. If properly and systematically titrated, basal insulin replacement has been shown to achieve target HbA_{1c} <7.0% in 50–60% of subjects. Injectable, rapid-acting prandial insulins can potentially achieve similar results but at the expense of more hypoglycemia and weight gain, greater insulin doses, and the inconvenience of thrice-daily injections (11).

Rapid-acting analog insulins (RAAs) have a faster onset and shorter duration of action than regular insulin, but the serum insulin concentrations after subcutaneous injection of RAAs do not return to baseline for ~6 h, often resulting in late postprandial hypoglycemia. In comparison, the endogenous insulin response to a meal peaks in ~30 min and returns to baseline within 2–3 h (12–15).

Technosphere inhaled insulin (TI) is a dry powder formulation of recombinant human insulin adsorbed onto Technosphere microparticles for oral inhalation. Fumaryl diketopiperazine (FDKP), a biologically inert excipient, forms the Technosphere particle matrix. Particles are prepared by a controlled, pH-induced crystallization process in which, at acidic pH, FDKP nanocrystals self-assemble into microparticles with a mean diameter of ~2.5 μm, ideal for inhalation into the deep lung (16,17). Insulin is bound noncovalently to the Technosphere microparticles. TI powder is delivered to the pulmonary tract via a proprietary breath-powered inhaler that provides reproducible insulin delivery. After inhalation, due to the prevailing physiological pH in the lungs, TI particles dissolve readily and both insulin and FDKP are rapidly absorbed into the systemic circulation. The insulin reaches a maximum blood concentration within 15 min with a duration of action of 2–3 h (18–20). This rapid kinetics may partly explain the more rapid suppression of endogenous hepatic glucose production noted with TI compared with an RAA (21).

The objective of the current study was to investigate the efficacy and safety of prandial inhaled TI in comparison with Technosphere inhaled placebo (TP) when added to the regimen of insulin-naïve subjects with T2D inadequately controlled on optimal/maximally tolerated doses of metformin alone or two or more OADs.

RESEARCH DESIGN AND METHODS

This 24-week, randomized, double-blind, placebo-controlled, international phase 3 study was conducted in multiple centers in Brazil, Russia, Ukraine, and the U.S. from 30 November 2011 to 17 June 2013 in accordance with the ethics principles of Good Clinical Practice as defined by the International Conference on Harmonisation and the Declaration of Helsinki. Independent ethics committees or institutional review boards approved the protocol, and all subjects gave written informed consent.

Insulin-naïve adults (≥18 years of age) with T2D for at least 12 months, poorly controlled with optimal or maximally tolerated doses of metformin monotherapy or two or more OADs and HbA_{1c} between 7.5% (58.5 mmol/mol) and 10.0% (86 mmol/mol), were eligible for inclusion. Participants were required to be nonsmokers for at least 6 months and have forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) ≥70% of predicted values (22).

Subjects using glucagon-like peptide 1 receptor agonists, thiazolidinediones, or weight loss drugs within the previous 3 months were excluded, as were those with two or more unexplained severe hypoglycemic episodes within 3 months of screening, a hospitalization or emergency room visit due to poor diabetes control within 6 months of screening, severe diabetes complications, significant pulmonary disease (e.g., chronic obstructive pulmonary disease, asthma, pulmonary fibrosis), known hypersensitivity to insulin or TI, and pregnant or breast-feeding women.

During the 6-week run-in, subjects continued their prestudy OAD regimen, were trained in use of glucose meters and self-monitoring of blood glucose (SMBG), and received standard diabetes education including nutritional and physical activity counseling. Participants with HbA_{1c} ≥7.5% (58.5 mmol/mol) and fasting plasma glucose (FPG) ≤270 mg/dL were then randomized 1:1 to inhaled TI (AFREZZA; MannKind Corporation, Valencia, CA) or TP (Technosphere particles without insulin, delivered via Gen2 inhaler). Randomization was stratified by region (North America, Latin America, and Eastern Europe) and OAD regimen (metformin only, metformin plus sulfonylurea, metformin plus dipeptidyl peptidase-4 inhibitor, metformin plus one or more OADs not specified above, and two or more OADs not including metformin).

TI powder was dispensed in cartridges containing premeasured doses of 10 or 20 units. Each 10-unit and 20-unit dose of inhaled TI approximates 4 and 8 units of subcutaneous insulin, respectively. At randomization, all subjects were started on a 10-unit dose of TI or TP per meal. During the first 12 weeks of treatment, study drug was titrated weekly based on SMBG levels to target 90-min postprandial glucose levels of 110–160 mg/dL, and patients could take a supplemental dose if 90-min postprandial glucose was ≥180 mg/dL according to a treatment algorithm (Supplementary Table 1). During the final 12 weeks of treatment, dosing was to remain stable and to be adjusted for safety reasons only. Open-label rescue

therapy, in addition to study treatment, was provided for subjects whose FPG exceeded prespecified thresholds. After completion of 24 weeks of treatment, participants converted back to usual care and were followed for another 4 weeks.

The primary efficacy end point was mean change in HbA_{1c} from baseline (randomization) to week 24. Key secondary efficacy end points were 7-point plasma glucose profiles (based on SMBG values taken immediately before every meal, 90 min after the meal, and at bedtime), the proportion of subjects achieving $HbA_{1c} \leq 7.0\%$ (53.0 mmol/mol) and $\leq 6.5\%$ (47.5 mmol/mol) at week 24, change in FPG and body weight from baseline to week 24, proportion of subjects who received rescue therapy, and time to rescue during the randomized treatment period.

Safety was assessed by between-group comparisons of adverse events (AEs), vital signs, 12-lead electrocardiograms, clinical laboratory values, and physical examination findings. Other safety assessments included pulmonary function tests (PFTs), hypoglycemic events, serum anti-insulin immunoglobulin G concentrations, and cough. Spirometry (FEV_1 and FVC) was performed at baseline, at weeks 12 and 24, and at a follow-up visit (4 weeks after discontinuation of the study drugs). Spirometry was performed according to American Thoracic Society and European Respiratory Society recommendations (23) and only at certified laboratories. Nonsevere hypoglycemia was defined as SMBG $<$70 mg/dL and/or symptoms of hypoglycemia relieved by carbohydrates; severe hypoglycemia was an event in which third-party assistance was required. Information related to cough including cough frequency, severity, duration, characteristics, and temporal relation to the inhalation of the dry powder was collected on a special cough-specific case report form at all visits throughout the study.

Statistical Analyses

The primary analysis population for efficacy was the full analysis set comprising all randomized subjects. The per-protocol population included all randomized subjects who completed randomized treatment and were protocol compliant. The safety population comprised randomized participants who received at least one dose of study medication.

The primary end point of change in HbA_{1c} was assessed using a mixed-model repeated-measures (MMRM) analysis with terms of region, OAD stratum, visit (categorical time in weeks), treatment, and interaction of treatment by visit. To account for the repeated HbA_{1c} measurements within a subject across the visits, an autoregressive (first-order) covariance structure was used. For evaluation of the impact of missing data on the efficacy results, sensitivity analyses of pattern mixture models were used to simultaneously model whether a subject was a "study completer" versus a "noncompleter" by including an indicator variable for study noncompleters as a predictor in the regression model of the primary end point and examine the interaction with key study covariates of treatment group and visit (a categorical variable in weeks). Proportions of subjects that reached HbA_{1c} targets of $\leq 7.0\%$ or $HbA_{1c} \leq 6.5\%$ were compared using logistic regression analysis between treatment groups. Seven-point glucose profiles were summarized using descriptive statistics. Body weight changes were compared using ANCOVA at the significance level of 0.05. Mean FPG was summarized over time, and the difference between treatments at week 24 was evaluated using MMRM. The proportion of subjects who received rescue therapy was compared between groups, and time-to-rescue was analyzed using the Kaplan-Meier estimator and log-rank test. Change in FEV_1 was analyzed using the MMRM model with baseline FEV_1 value, height, age, gender, visit, and interaction of treatment by visit. To account for the repeated FEV_1 measurements within a subject across the visits, we used an autoregressive (first-order) covariance structure.

The planned sample size was 328 to achieve 246 subjects with evaluable efficacy data (assuming a 25% dropout rate). This sample size was estimated by assuming the treatment difference of 0.5% with an SD of 1.2 and a one-sided α of 0.025, which would provide 90% power to test the primary efficacy end point.

RESULTS

Subject disposition is shown in Supplementary Fig. 1. Of 1,379 screened participants, 479 completed the run-in phase and 353 were randomized to TI (n = 177) or TP (n = 176). Demographics and baseline characteristics were balanced between treatment groups (Supplementary Table 2). Mean age was 56.7 years, and mean BMI was $\sim$32 kg/m^2 in both groups. For the TI and TP groups, 54% and 58% were females with a mean diabetes duration of 9.7 and 9.2 years, respectively. Mean baseline HbA_{1c} was 8.26% (66.8 mmol/mol) and 8.35% (67.8 mmol/mol) in the TI and TP groups, respectively. Approximately 65% of participants in both groups were on a combination of metformin and sulfonylurea and 24% were on metformin alone, with the remaining 11% on other types of combinations of two or more OADs. In the TI group, 150 (84.7%) completed the 24-week treatment period compared with 139 (79.0%) in the placebo group.

At week 24, the TI group had a significantly greater reduction from baseline in mean HbA_{1c} than the TP group (adjusted mean changes from baseline -0.82% [-9.0 mmol/mol] and -0.42% [-4.6 mmol/mol], respectively; treatment difference -0.40% [-4.4 mmol/mol] with 95% CI -0.57, -0.23 [-6.2, -2.5]; $P < 0.0001$) (Table 1). Sensitivity analyses, using pattern mixture models, showed that the missing data did not alter the primary analysis conclusion. Glycemic improvement (HbA_{1c}) was noted in the TI group as early as week 2; the differences versus placebo continued to increase through week 12 and then stabilized during the subsequent 12 weeks of the stable dosing period (Fig. 1*A*).

The mean $\pm$ SD total daily starting dose (at week 1) of TI was 35 $\pm$ 14 units (10-unit cartridge of TI provides $\sim$4 IU s.c. insulin) and 35 $\pm$ 10 units for TP. During the 12-week titration period, mean total daily dose increased and reached 109 $\pm$ 58 units in the TI group and 164 $\pm$ 84 units in the TP group at week 12 distributed before each meal. For the next 12 weeks of the stable dosing period, the mean total daily dose remained relatively stable, reaching 115 $\pm$ 65 units in TI-treated and 169 $\pm$ 97 units in TP-treated subjects at week 24. Approximately 35.3% of subjects in the TI group took at least one supplemental dose compared with 45.5% of subjects in the TP group.

The 7-point glucose profiles in the TI group show clinically meaningful reductions in postmeal glucose values at weeks 12 and 24 compared with

Table 1—Efficacy end points and treatment group differences at week 24 (full analysis set)

		TI (n = 177)	TP (n = 176)	Treatment difference (TI − TP) at week 24
HbA_{1c}, %	Baseline (SE) [baseline value in mmol/mol]	8.25 (0.06) [67.2]	8.27 (0.06) [67.2]	
	Adjusted mean change (SE) [adjusted mean change in mmol/mol]	−0.82 (0.06) [−9.0]	−0.42 (0.06) [−4.6]	−0.40 (0.09) [−4.4][a]
	95% CI; P			−0.57, −0.23 [−6.2, −2.5]; <0.0001
HbA_{1c} ≤7.0% [53.0 mmol/mol]	Incidence, n (%)	57 (37.7)	27 (19.0)	
	Odds ratio (95% CI); P			2.726[b] (1.55, 4.80); 0.0005
HbA_{1c} ≤6.5% [47.5 mmol/mol]	Incidence, n (%)	24 (15.9)	6 (4.2)	
	Odds ratio (95% CI); P			4.361[b] (1.70, 11.17); 0.0021
FPG, mg/dL	Baseline (SE)	175.91 (2.97)	175.19 (2.99)	
	Adjusted mean change (SE)	−11.20 (3.78)	−3.78 (3.86)	−7.42 (5.400)[c]
	95% CI; P			−18.03, 3.18; 0.1698
Body weight, kg	Baseline (SE)	90.15 (1.29)	90.79 (1.31)	
	Adjusted mean change (SE)	0.49 (0.33)	−1.13 (0.35)	1.62 (0.365)[d]
	95% CI; P			0.90, 2.34; <0.0001

n is the number of randomized patients. For analysis of secondary efficacy end points, P values were provided for descriptive purposes only. [a]Adjusted means, 95% CI, and P value are based on the MMRM analysis with covariance autoregressive (first-order) structure and the following model: HbA_{1c} = baseline HbA_{1c} + region + pooled OAD stratum + visit + treatment + treatment * visit. [b]Odds ratio, 95% CI, and P value are derived from logistic regression analysis with treatment, pooled OAD stratum, region, and baseline HbA_{1c} in the model. Percentages are based on number of subjects who have valid measurement at week 24 within corresponding baseline category. Subjects who received rescue therapy during the treatment phase are considered as nonresponders at week 24. [c]Adjusted means, 95% CI, and P value are based on the MMRM analysis with covariance autoregressive (first-order) structure and the following model: FPG = baseline FPG + region + pooled OAD stratum + visit + treatment + treatment * visit. [d]Adjusted means, 95% CI, and P value are based on the ANCOVA analysis with the following model: change from baseline in weight = baseline weight + region + change in HbA_{1c} at week 24 + pooled OAD stratum + treatment.

baseline, resulting in a flattened prandial glycemic profile compared with placebo (Fig. 1*B* and *C*). Four weeks after study treatment was stopped, the 7-point glucose profile in the TI group reverted back to the baseline pattern (Fig. 1*D*).

Significantly more TI-treated subjects reached HbA_{1c} targets of ≤7.0% (53.0 mmol/mol) (38% vs. 19%; P = 0.0005) and HbA_{1c} ≤6.5% (47.5 mmol/mol) (16% vs. 4%; P = 0.0021) compared with TP-treated subjects (Table 1).

At week 24, the adjusted mean change in FPG levels was −11 mg/dL with TI and −4 mg/dL with TP; the difference was not statistically significant (−7.4 mg/dL [95% CI −18.0, 3.2], P = 0.1698) (Table 1).

Over the 24-week treatment period, there was a modest mean weight increase of 0.5 kg in the TI group versus a mean loss of 1.1 kg in the TP group. Over the 24-week treatment period, mean change from baseline in body weight favored TP (treatment group difference of 1.6 kg, $P < 0.0001$) (Table 1).

Fewer subjects in the TI group (12 of 177 [6.8%]) received rescue therapy than in the TP group (17 of 176 [9.7%]) during the study. The median time to rescue therapy was not significantly different between the groups (95 days in the TI group vs. 85 days in the TP group).

The proportion of subjects reporting at least one AE was 61.0% (108 of 177) in the TI group and 51.1% (90 of 176) in the TP group (Table 2). Most AEs in both groups were mild or moderate in intensity. There were no deaths during the study. Rates of serious AEs were low in both groups (TI, n = 5 [2.8%]; TP, n = 9 [5.1%]). There were no respiratory serious AEs. Discontinuations owing to AEs were infrequent and comparable between the groups (TI, 4.0%; TP, 5.1%). The most common reason for early discontinuation in both groups was withdrawal of consent by participants for personal and social reasons.

Apart from hypoglycemia, cough was the most common AE, occurring with similar frequency in the TI (42 of 177 [23.7%]) and TP (35 of 176 [19.9%]) groups. In both groups, cough was predominantly intermittent or a single defined episode, nonproductive, mild or moderate in severity, and occurred within 10 min after inhalation of the dry powder. The percentage of subjects with new-onset cough was highest in the first week after initiation of the dry powder therapy and then tended to diminish over time. Cough leading to study discontinuation was uncommon (TI, 2 of 177 [1.1%]; TP, 6 of 176 [3.4%]). In participants who discontinued owing to cough, cough resolved within 1–2 days after the discontinuation of TI or TP. None of the cough treatment-emergent adverse events were considered serious.

Mean values for FEV_1 were normal and similar in both treatment groups at baseline (TI, 2.9 L [97.6% of predicted]; TP, 2.8 L [97.7% of predicted] (Supplementary Table 3). Over 24 weeks, both groups experienced small declines from baseline in mean FEV_1 (TI, −0.13 L; TP, −0.04 L) (treatment group difference −0.09 L [95% CI −0.12, −0.05]). This small treatment group difference resolved by week 28 (4 weeks after stopping treatment), by which time the mean FEV_1 value in the TI group returned to levels similar to the TP group (Fig. 2). Results for FVC were consistent with the FEV_1 results.

The incidence and event rate of all and severe hypoglycemia were higher in the TI group than in the TP group. The incidence of all hypoglycemia in the TI and TP groups was 67.8% vs. 30.7%, respectively ($P < 0.0001$), and the incidence of severe hypoglycemia was 5.7% vs. 1.7% (P = 0.0943). Event rates for all hypoglycemia in TI- and TP-treated subjects were

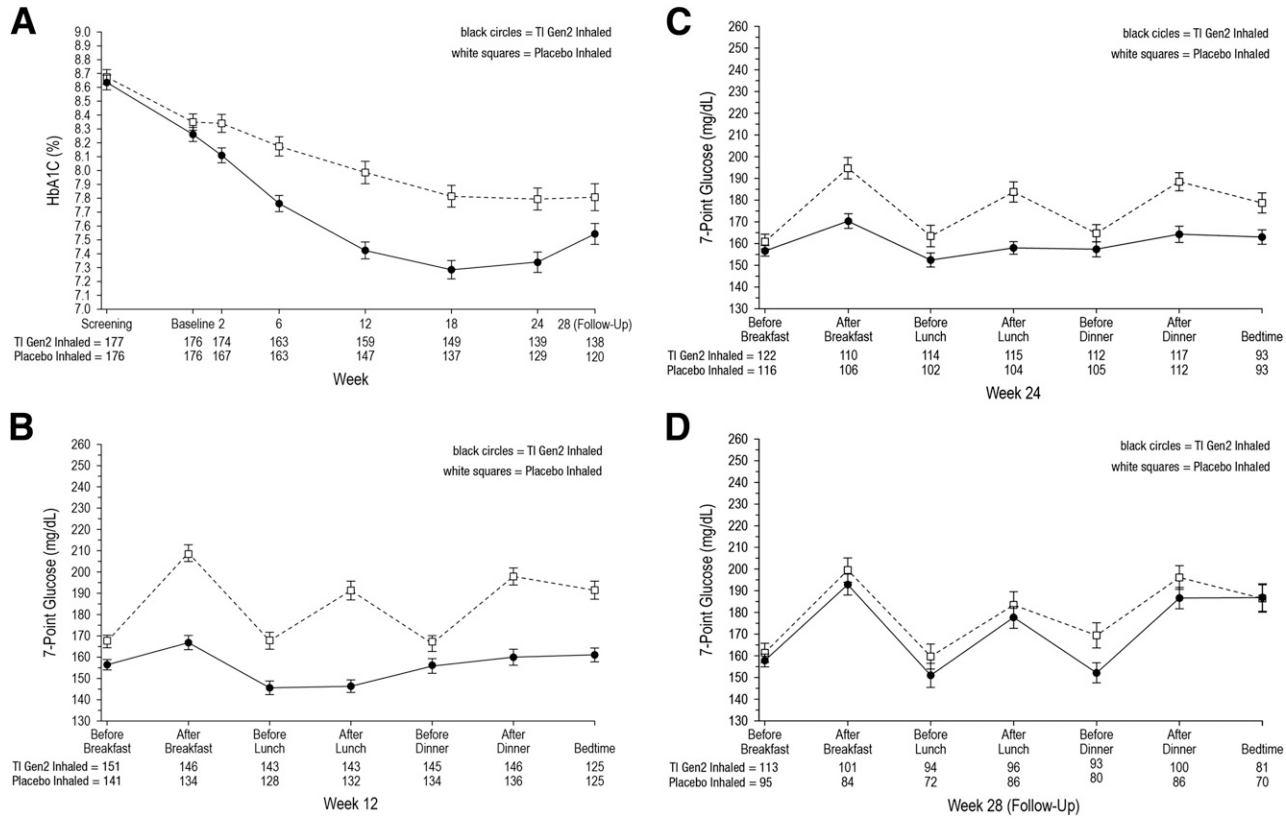

Figure 1—Mean (SE) HbA_{1c} levels over the 24-week treatment period (*A*); 7-point glucose profiles at week 12 (*B*) and week 24 (*C*) and at posttreatment at week 28, 4 weeks after stopping treatment (*D*). Full analysis set. SE bars.

1.16 and 0.50 events per subject-month, respectively ($P < 0.0001$). Although event rates for severe hypoglycemia were numerically greater in the TI group (2.37 events per 100 subject-months) than the TP group (0.60 events per 100 subject-months), this did not reach statistical significance ($P = 0.2024$), probably due to few events (Supplementary Table 4). Of note, the frequency of severe hypoglycemia in the TI group was influenced disproportionately by one subject who reported nine episodes of severe hypoglycemia over a 4-week period early in the trial. This individual completed the study without further incident.

A post hoc exploratory analysis was conducted to assess the impact of background OAD use on the incidence of hypoglycemia. The event rate for subjects taking TI and metformin alone was similar to that for subjects taking TP and metformin plus a sulfonylurea (TI + metformin, 0.62 events per subject-month; TP + metformin + sulfonylurea, 0.68 events per subject-month), suggesting that the hypoglycemia associated with TI is similar to that of a sulfonylurea (Supplementary Table 4).

There were no clinically meaningful changes in the TI and placebo groups in other laboratory values, serum anti-insulin immunoglobulin G concentrations, vital signs, physical examinations, or electrocardiogram results.

Table 2—Patients with AEs (safety population)

	TI	TP
Treated patients	177 (100.0)	176 (100.0)
At least one AE	108 (61.0)	90 (51.1)
Severe AEs	5 (2.8)	11 (6.3)
Serious AEs[a]	5 (2.8)	9 (5.1)
Drug-related AEs	48 (27.1)	42 (23.9)
AEs leading to discontinuation of trial drug	7 (4.0)	9 (5.1)
Cough events	42 (23.7)	35 (19.9)
All hypoglycemic events	120 (67.8)	54 (30.7)
Severe hypoglycemic events	9 (5.1)	3 (1.7)

Data are *n* (%). [a]In TI group, serious AEs: 2 myocardial infarction, 1 urinary tract infection, 1 hypoglycemia, and 1 rectal carcinoma. Only hypoglycemia was considered related to the study drug. In TP group: 1 myocardial infarction, 1 angina pectoris, 1 coronary disease, 1 humerus fracture, 1 squamous cell carcinoma of the palate, 1 ischemic stroke, 1 back pain, 1 angioneurotic edema (due to ACE inhibitor), and 1 skull malformation. Only ischemic stroke was considered related to the study drug.

CONCLUSIONS

In insulin-naïve subjects with T2D inadequately controlled on one or more OADs, addition of prandial TI resulted in significant HbA_{1c} reductions and target HbA_{1c} attainment, meaningful decreases in postprandial blood glucose excursions, and minimal weight gain. These results provide the basis for prandial TI as a viable option for those who

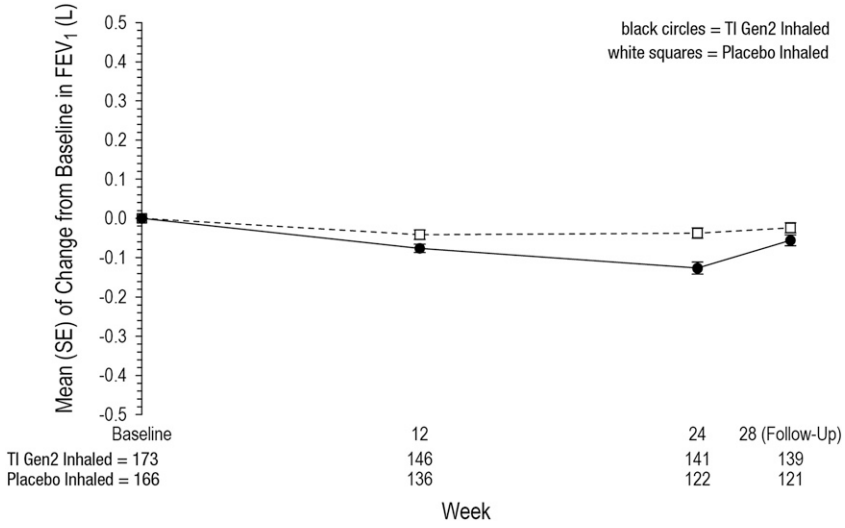

Figure 2—Mean FEV_1 change from baseline to week 28 follow-up (MMRM). Safety population.

require initiation of insulin but are reluctant to accept injectable therapy.

Addition of prandial TI, as a first insulin in the treatment regimen of subjects with T2D failing a maximally tolerated dose of one or more OADs, effectively reduced HbA_{1c} by 0.8% (−9.0 mmol/mol) from a baseline of 8.3% (67 mmol/mol). In the 4T study of injected insulin (24), with patients with T2D receiving maximal tolerated doses of metformin plus sulfonylurea, the HbA_{1c} after 1 year in patients receiving injected prandial insulin aspart was 7.2%. The HbA_{1c} after 1 year in patients receiving basal insulin detemir was 7.6%, and 7.3% for patients receiving biaspart premixed insulin, while in the current study it was 7.4%. It is conceivable that more rigorous titration regimens would have resulted in lower HbA_{1c} reductions. Indeed, the APOLLO study (11) used a far more aggressive insulin titration regimen and the final HbA_{1c} from a baseline of 8.7% was 7.0% and 6.8% for basal insulin glargine once daily and the prandial insulin lispro three times a day, respectively, but at the expense of significantly more hypoglycemia with the prandial insulin (5.2 vs. 24.0 events/patient/year).

HbA_{1c} reduction observed in the TI group was likely achieved mainly by the abatement of postprandial hyperglycemia, as there was no significant change in FPG. The time-action profile of TI with its rapid onset and short duration of action provided effective control of postmeal glucose excursions as reflected by 7-point blood glucose profiles. Postprandial hyperglycemia is a significant component of overall glycemic control and contributes to overall glycemia, especially in people with mild hyperglycemia where the contribution of postprandial hyperglycemia appears to exceed that of FPG (25–28).

A unique feature of this insulin trial was the adoption of a double-blind, placebo-controlled design. Interestingly, subjects in the inhaled placebo group who continued their OADs also showed a meaningful HbA_{1c} reduction during the course of the study. Such a response may be attributable to the introduction of close monitoring and regular medical supervision during the trial in this insulin-naïve population with T2D who may have had previous low treatment compliance and limited glucose monitoring. Knowledge of their true glycemic status during the study and the perception of receiving additional inhaled medicine may have prompted some participants to make more effective lifestyle changes including better treatment adherence, improved eating habits, and exercise, a hypothesis supported by the weight loss observed in the placebo group. Insulin-naïve people with T2D exposed to a highly structured SMBG regimen have been reported to achieve HbA_{1c} reductions of up to −1.2% (−13.1 mmol/mol) (29–31).

Current treatment guidelines stress a patient-centric approach to therapy selection that takes into consideration multiple factors including glucose-lowering efficacy, cost, potential side effects, comorbidities, hypoglycemia risk, and patient preference. Prompt intensification of treatment with a second OAD or injectables with either a glucagon-like peptide 1 receptor agonist and/or insulin is recommended if HbA_{1c} targets are not achieved within 3 months of metformin monotherapy. Usually, basal insulin as the initial insulin is added to the regimen when adequate control is not achieved with OADs. Trials comparing basal insulin to prandial insulin therapy in T2D have found that prandial therapy was at least as effective as basal insulin in terms of lowering HbA_{1c}, but basal insulin was associated with fewer hypoglycemic episodes (11,24). Less hypoglycemia risk is one of the main reasons basal insulin is the preferred initial treatment, in addition to the obvious preference of once-daily injection instead of multiple prandial injections (10,11,24). A previous trial in subjects with T2D, comparing TI plus insulin glargine with twice-daily biaspart insulin, demonstrated lower rates of hypoglycemia, especially delayed hypoglycemia (2–4 h after the dose), and less weight gain in TI-treated subjects (32), probably due to the shorter duration of action of TI. Predictably, in this placebo-controlled trial, the incidence of hypoglycemia was higher in the insulin-treated subjects than the inhaled placebo group.

Treatment with TI was well tolerated. Cough was the most common AE, most likely due to stimulation of the cough reflex by inhalation of a dry powder. Indeed, the value of our study, which makes it unique, was that we used an inhaled placebo that allowed us to demonstrate that the cough is produced not by the insulin but probably by the excipient. In both groups, cough was predominantly transient, intermittent, and dry and occurred within 10 min of inhalation. Cough resulting in withdrawal from the study was uncommon; in cases where subjects discontinued owing to cough, notably, cough resolved within 24–48 h after cessation of the dry powder inhalation. The incidence of cough, 23.7% in the TI group and 19.9% in the TP group, was similar to what has been reported with other inhaled insulins (32–34).

Respiratory AEs were common in both groups. Nasopharyngitis, influenza, upper-respiratory infections (but not bronchitis), oropharyngeal pain, and throat irritation occurred with greater

frequency in the TI group. None of these events were serious.

There was a slightly greater decline in measures of pulmonary function in the TI group compared with the TP group. However, the mean decline in FEV_1 in the TI group was 130 mL (<5% of the baseline value) and returned toward baseline 4 weeks after treatment ended. These small changes, which disappeared after discontinuation of TI and were not associated with clinical findings, are unlikely to be clinically meaningful. Of note, in the overall TI development program, including a 2-year pulmonary safety study in people with type 1 or type 2 diabetes (35), treatment group differences in changes from baseline in PFTs between TI-treated and comparator-treated subjects were small, were noted early at treatment initiation, remained nonprogressive over 2 years of continuous therapy, and resolved when TI was discontinued. The magnitude and pattern of PFT changes are reassuring in that the observed changes are unlikely to be due to permanent structural changes in the lungs.

A major limitation of the placebo-controlled design is the absence of an active comparison with more standard regimens usually introduced at the stage of disease progression studied in this trial.

In conclusion, the addition of inhaled prandial TI in insulin-naïve subjects with T2D inadequately controlled on OADs is an effective, well-tolerated, and patient-friendly intervention that may help to overcome some of the barriers and clinical inertia associated with initiation of insulin therapy in the management of T2D.

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Author Contributions. J.R., D.F., V.K., and J.B.M. contributed to the conduct of the study; contributed to the acquisition, analysis, and interpretation of data; and reviewed and approved the manuscript. B.S., Y.M., R.B., and N.A. contributed to the design and conduct of the study; contributed to the acquisition, analysis, and interpretation of data; and reviewed and approved the manuscript. Y.M., R.B., and N.A. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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