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ORIGINAL ARTICLES

Randomized Forced Titration to Different Doses of Technosphere® Insulin Demonstrates Reduction in Postprandial Glucose Excursions and Hemoglobin A1c in Patients with Type 2 Diabetes

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Abstract

Background:

Individuals with type 2 diabetes mellitus have impairments in early insulin release, resulting in increased postprandial glucose excursions and suboptimal glycemic control. Studies with Technosphere® Insulin (TI) indicate that it has rapid systemic absorption and a short duration of glucose-lowering activity, making it well suited for controlling postprandial glucose levels.

Methods:

The goal of this phase 2b, prospective, multicenter, double-blind, placebo-controlled study was to characterize the dose response of four different doses (equivalent to 3.6, 7.3, 10.9, and 14.6 U subcutaneous regular human insulin) of prandial TI or Technosphere powder alone administered before each of three meals daily, in combination with insulin glargine over an 11-week treatment period, in patients with type 2 diabetes and suboptimal glycemic control.

continued →

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Abbreviations: (AE) adverse event, (ATS) American Thoracic Society, ($AUC_{glucose}$) area under the glucose curve, (BG) blood glucose, (C_{max}) maximum plasma concentration, (DL_{CO}) lung diffusion capacity, (FBG) fasting blood glucose, (FEV_1) forced expiratory volume in 1 second, (FVC) forced vital capacity, (HbA1c) hemoglobin A1c, (HRCT) high-resolution computerized axial tomography, (MRI) magnetic resonance imaging, (PPG) postprandial glucose, (TI) Technosphere® Insulin

Keywords: diabetes, HbA1c, inhaled insulin, postprandial glucose, Technosphere Insulin

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Abstract cont.

Results:

The study enrolled 227 patients. In all dose groups, TI demonstrated statistically significant dose-dependent reductions in hemoglobin A1c (HbA1c) versus baseline (-0.4, -0.5, -0.5, and -0.6 for 3.6, 7.3, 10.9, and 14.6 U equivalents, respectively; $p < 0.05$ in all groups), as well as versus placebo or Technosphere powder alone (-0.40, -0.67, -0.70, and -0.78 for 3.6, 7.3, 10.9, and 14.6 U equivalents, respectively; $p < 0.04$ in all groups). It reduced the postprandial maximum glucose concentration within each treatment group (statistically significant in all but the TI 3.6 U-equivalent group) and reduced the postprandial area under the glucose curve (statistically significant for the TI 10.9 and 14.6 U-equivalent groups) versus placebo. There were no cases of severe hypoglycemia, while mild/moderate hypoglycemia was observed most frequently in the highest dosage groups, as expected. Rates of cough were low and comparable among all groups. No clinically relevant changes in pulmonary function tests, body weight, or high-resolution computerized axial tomography and magnetic resonance imaging were observed.

Conclusions:

This study demonstrated that, over 11 weeks, TI plus basal insulin glargine is well tolerated and results in dose-dependent reductions in postprandial glucose and HbA1c levels.

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Inroduction

The National Health and Nutrition Examination Survey 1999–2002 cohort demonstrated that only 42% of adults with diabetes achieved the American Diabetes Association goal of hemoglobin A1c (HbA1c) levels <7%.[1] These data underscore the need for alternative strategies to improve glycemic control in patients with diabetes. One strategy is to modify postprandial glucose (PPG) levels. Monnier and colleagues[2] reported that PPG excursions comprise 30 to 70% of the HbA1c level; other studies have suggested that reductions in PPG improve patient outcomes.[3–11] Impairments in early phase insulin release have been implicated in the elevation of PPG levels in patients with type 2 diabetes mellitus.[12–14] Current insulins do not have an onset rapid enough to replace this loss.[15] Agents that approximate this release should result in improvements in PPG levels.

Technosphere® technology represents a drug delivery platform that allows pulmonary administration of therapeutics currently administered by injection. It is based on the intermolecular self-assembly of a diketopiperazine molecule into microparticles called Technosphere particles. Technosphere Insulin (TI) particles are prepared using this technology and are optimized for inhalation into the deep lung. They have a uniform size distribution, >90% of the particles are in the respirable range (defined as >0.5 and <5.8 μm), and the average particle diameter is 2.5 μm. The particles dissolve rapidly at physiological pH.[16] The TI particles are delivered using a discreet, pocket-sized inhaler.

Technosphere Insulin has pharmacokinetic properties distinguishing it from other subcutaneous and inhaled insulins.[17] Previous studies demonstrate that TI has rapid systemic insulin absorption (time to maximum plasma concentration ≈15 minutes), fast onset of action (≈25–30 minutes), shorter duration of glucose-lowering activity (≈2–3 hours), and low within-subject variability, making it well suited for controlling PPG levels and potentially lowering the risk of hypoglycemia.[17–20] Furthermore, TI use results in minimal or no changes in body weight.[21] Because it is inhaled, TI may help overcome general resistance to insulin therapy by obviating the need for multiple daily injections.[22–26]

Restoration of early phase insulin decreases the glycemic response to a mixed meal,[12] but it is unclear whether this occurs in a dose-dependent way. The dose–response relationship is a critical aspect of the ability of an agent to reduce PPG. The goal of this double-blind, placebo-controlled study was to evaluate the dose–response relationship of four different doses of prandial TI or

Technosphere powder alone in combination with basal insulin glargine compared with baseline over an 11-week treatment period using a stepwise forced titration protocol in type 2 diabetes patients with suboptimal glycemic control.

Subjects and Methods

Patients

Inclusion criteria: Eighteen- to 80-year-old subjects with type 2 diabetes mellitus and inadequate glycemic control were enrolled in the study. To be eligible for study participation, subjects had to have a duration of diabetes >3 years and <20 years; HbA1c between 7 and 12%; a minimum of 2 months of treatment with a stable dose of ≥1 antihyperglycemic agent and/or basal insulin glargine therapy; fasting blood glucose (FBG) ≥108 mg/dl; C-peptide ≥0.5 nmol/liter; body mass index <38 kg/m^2; and baseline lung diffusion capacity (DL_{CO}), forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV_1) ≥75% of predicted normal based on spirometric reference values developed from the Third National Health and Nutrition Examination Survey.[27]

Exclusion criteria: Patients with acquired immunodeficiency syndrome; systemic autoimmune or collagen vascular disease; severe diabetes complications; significant hepatic or renal disease; histories of severe or multiple allergies, chronic obstructive, or other chronic pulmonary disease; major psychiatric disorders that would prevent participation; or myocardial infarction or stroke within the previous 6 months were excluded.

Study Protocol

The trial was designed to evaluate the dose response of force-titrated prandial TI compared with placebo (Technosphere powder alone) in subjects with type 2 diabetes who were controlled suboptimally. Subjects were randomized to receive a predetermined, fixed dose of TI or Technosphere powder alone as placebo, together with basal insulin glargine.

Subjects underwent a 16-week protocol comprising screening at week 1, a 4-week run-in period that included 2 weeks of single-blind placebo treatment, and an 11-week experimental period (**Figure 1**). At the screening visit and during the run-in period, demographic information was collected. Additionally, daily glucose readings and FBG and PPG levels were collected at scheduled standard meal challenges. The standardized liquid-ready meal was composed of 8 ounces of water, 14 grams of total fat, 45 grams of total carbohydrates, and 14 grams of protein for a total of 360 kilocalories. Patients were trained on the use of the MedTone® inhaler (MannKind Corporation, Valencia, CA), using Technosphere powder alone, and instructed to continue to use the inhaler with meals until the beginning of the experimental period. The inhaler—a hand-held, discreet, pocket-sized, breath-powered, high-resistance, dry powder device—was developed specifically for use with cartridges containing TI as a dry powder formulation.[19]

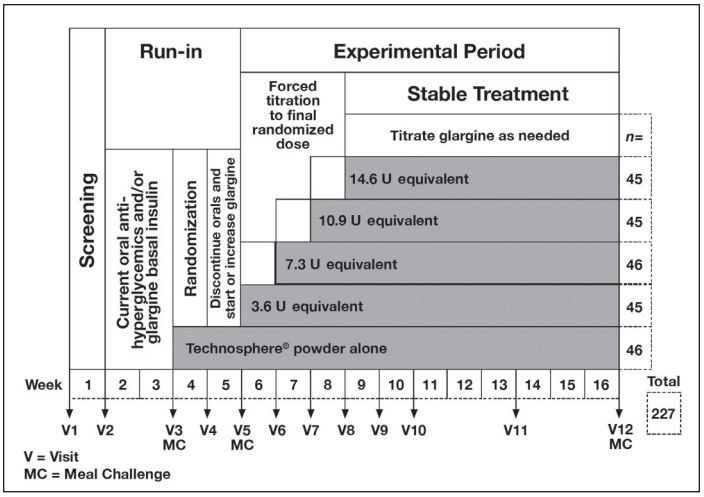

Figure 1. Study schedule.

One week before the experimental period, subjects discontinued their oral antihyperglycemic medication and initiated subcutaneous insulin glargine therapy at 10 IU once daily if they were not on it previously. For subjects previously receiving insulin glargine with oral hypoglycemic agents, their insulin glargine dose was raised by 5 IU. If they had been receiving insulin glargine without oral therapy, their dose was continued.

At the beginning of the experimental period, double-blind treatment was initiated. The titration targets were four TI doses: 14, 28, 42, and 56 U equivalents per the amount of insulin loaded in the cartridges, or 3.6, 7.3, 10.9, and 14.6 U equivalents to subcutaneous regular human insulin based on a relative bioavailability of 26% reported in a previous study.[17] All subjects randomized to TI began treatment at 3.6 U equivalent with each meal. Over the following weeks, those in the higher TI dose groups were titrated weekly in 3.6 U-equivalent increments until they achieved their final, randomization-determined dose of 7.3, 10.9, or 14.6 U equivalent to be administered prior to each meal (**Figure 1**), unless symptomatic hypoglycemia [blood glucose (BG) <63 mg/dl] was confirmed. For confirmed hypoglycemia, the glargine dose was reduced

by 10 IU daily. Subjects randomized to the Technosphere powder alone group continued to use the inhaler as instructed in the run-in phase and then continued to receive Technosphere powder alone for the remainder of the study.

Blinding was maintained in all groups whereby all TI and Technosphere powder alone doses were delivered in the same number of cartridges containing either TI or Technosphere powder alone. Subjects were instructed to inhale the study drug (TI or Technosphere powder alone) within 1 minute before the first mouthful of food of each regular meal and to record FBG levels in the morning and BG levels before and 2 hours after each meal in their patient diaries. All testing was repeated at the end of the 11-week treatment period.

All subjects received insulin glargine during the double-blind, experimental treatment period. Doses were adjusted to provide sufficient basal insulin effect to control FBG levels at <160 mg/dl.

As part of the study protocol, all subjects underwent a 2-hour diabetes education program regarding the pathophysiology of the disease, nutritional management, physical activity, and medical management in controlling BG and preventing diabetic complications. All subjects were trained on BG measurement and were provided with a glucose meter, test strips, and a patient diary; in addition, they were instructed on documenting BG and hypoglycemic events and appropriate responses, such as ingestion of glucose-containing food. Hypoglycemia was defined as recognizable symptoms and/or a BG concentration <63 mg/dl. Severe hypoglycemia was defined as an episode requiring glucagon injection, glucose infusion, or third-party assistance.

All patients underwent baseline pulmonary function tests and high-resolution computerized axial tomography (HRCT) or magnetic resonance imaging (MRI). The scans were reviewed by a central reading laboratory. Evaluations consistent with the American Thoracic Society (ATS) recommendations for equipment quality control were performed on all equipment prior to subject testing. An audit of the pulmonary function testing data was done poststudy to confirm adherence to ATS reporting standards.

Written informed consent was obtained from all patients prior to study enrollment. Institutional review board and independent ethics committees for all participating centers and countries provided study approval.

Study End Points, Sample Size, and Statistical Analysis

The primary efficacy measures were change in HbA1c of each randomized dose from baseline over the experimental period and change from baseline of HbA1c compared with change from baseline of placebo. Secondary efficacy measures included change in mean PPG excursions during 0–300 minutes of a standardized meal challenge at the end of the experimental period, as assessed by area under the glucose curve ($AUC_{glucose}$) and maximum plasma concentration (C_{max}). Changes for each randomized dose from the placebo group were also analyzed for the aforementioned efficacy measures. Safety variables were assessed, including incidence of hypoglycemia, cough, and change in pulmonary function tests. DL_{CO} values were corrected for serum carboxyhemoglobin levels and serum hemoglobin.

The primary analysis was the comparison of the change from baseline of TI to the change from baseline of placebo for each of the TI groups. As only a decrease in HbA1c is relevant, a one-sided test is appropriate. Given this, a sample size of 36 in each group has 80% power to detect a difference in means of 0.6, assuming that the common standard deviation is 1.0 using a two-group *t* test with a one-sided significance level of 0.05. To account for a 10–20% dropout rate, 260 subjects were recruited.

Summary statistics are expressed as mean ± standard deviation. A two-sided Student's *t* test was used to compare efficacy end points, except for HbA1c, where one-sided tests were employed. A step-down procedure involving a series of two-sample one-sided *t* tests was used in multiple comparisons between means of the TI and Technosphere powder alone groups in the primary end point analysis of HbA1c. This procedure did not adjust for the multiple comparisons between TI group means and Technosphere powder alone, comparing the highest dose group with Technosphere powder alone first, and only comparing the next dose group when the previous comparison reached significance at 0.05. Analysis of covariance was performed to adjust for differences in insulin glargine use and baseline HbA1c, FBG, or PPG levels. Safety data were analyzed using descriptive statistics. Statistical significance was set at $p < 0.05$. All analyses were performed using SAS Version 8.2 or later (SAS Institute, Cary, NC).

Per the study design, the study was powered to examine the dose response empirically based on clinical end points. A formal statistical dose–response analysis was not performed.

Results

Study Population

A total of 357 subjects completed screening tests in 32 centers in Bulgaria, the Czech Republic, Germany, and The Netherlands. Of these, 227 subjects constituted the safety population and were randomized in a double-blind manner to four TI groups (n = 181) and Technosphere powder alone (n = 46). Subjects receiving TI were randomized to parallel cohorts that would dose escalate in a stepwise manner (in an increment of 3.6 U equivalent) to different final dosing levels of TI (3.6, 7.3, 10.9, or 14.6 U equivalent) per prespecified forced titration to be administered before each meal. The intent-to-treat population included 212 subjects; the per-protocol population included 190 subjects. Because experimental results from the latter two populations were similar, only data from the intent-to-treat population are reported here.

Twenty-two subjects discontinued prematurely from the study: 6 (13.0%) in the Technosphere powder alone group and 16 (8.8%) in the TI groups. Reasons for discontinuation included treatment-related adverse event (AE; suspected drug hypersensitivity, n = 1), protocol violation (n = 3), patient decision (n = 11) because of refusal to use basal insulin (n = 2) or monitor sufficient glucose levels (n = 1), time constraints (n = 4), lack of glycemic control (n = 2) and other causes (n = 2), physician decision (n = 1), and other reasons (n = 6). Of the 227 patients entering the study, 205 subjects completed (Technosphere powder alone: 40 subjects; TI 3.6 U equivalent: 42; TI 7.3 U equivalent: 41; TI 10.9 U equivalent: 41; TI 14.6 U equivalent: 41).

Baseline HbA1c, FBG, and 2-hour PPG levels were similar between TI and Technosphere powder alone groups. Other baseline demographic, physical examination, laboratory, and radiographic data were similar among all groups (**Table 1**).

Before entering the study, subjects used a variety of oral agents, mainly metformin and sulphonylureas (**Table 1**). Only a few subjects were using an insulin regimen.

Table 1.
Baseline Demographics (Mean ± SD)[a]

Parameter	Technosphere powder alone (n = 46)	TI 3.6 U equivalent (n = 45)	TI 7.3 U equivalent (n = 46)	TI 10.9 U equivalent (n = 45)	TI 14.6 U equivalent (n = 45)	TI total[a] (n = 181)	Overall total[a] (n = 227)
Gender (female:male)	25:21	23:22	18:28	20:25	18:27	79:102	104:123
Age (years)	59 ± 9	58 ± 9	57 ± 8	60 ± 9	55 ± 8	58 ± 9	58 ± 9
Weight (kg)	85.5 ± 12.4	85.1 ± 16.4	89.7 ± 16.8	84.2 ± 11.7	88.8 ± 16.8	87.0 ± 15.6	86.7 ± 15.0
BMI (kg/m^2)	29.9 ± 3.5	30.0 ± 5.1	30.7 ± 4.2	29.4 ± 3.3	30.0 ± 4.3	30.0 ± 4.2	30.0 ± 4.1
Diabetes duration (years)	10 ± 5	9 ± 5	9 ± 4	10 ± 5	9 ± 5	9 ± 5	9 ± 5
HbA1c (%)[b]	9.2 ± 1.3	9.3 ± 1.5	8.8 ± 1.5	8.7 ± 1.3	9.2 ± 1.4	9.0 ± 1.4	9.0 ± 1.4
Fasting blood glucose (mg/dl)	190.8 ± 57	182.2 ± 58.9	179.5 ± 47.7	179.5 ± 48.9	179.5 ± 50.1	180 ± 49.8	182.2 ± 51.3
Medication, n (%)							
Acarbose	6 (13.0)	2 (4.4)	2 (4.3)	5 (11.1)	2 (4.4)	11 (6.1)	17 (7.5)
Insulin glargine	8 (17.4)	8 (17.8)	5 (10.9)	7 (15.6)	15 (33.3)	35 (19.3)	43 (18.9)
Human insulin	5 (10.9)	2 (4.4)	2 (4.3)	4 (8.9)	2 (4.4)	10 (5.5)	15 (6.6)
Rapid-acting analogs	5 (10.9)	2 (4.4)	2 (4.3)	4 (8.9)	2 (4.4)	10 (5.5)	15 (6.6)
Metformin	36 (78.3)	34 (75.6)	37 (80.4)	35 (77.8)	35 (77.8)	141 (77.9)	177 (78.0)
Meglitinides	7 (15.2)	4 (8.9)	4 (8.7)	5 (11.1)	4 (8.9)	17 (9.4)	24 (10.5)
Thiazolidinediones	11 (23.9)	10 (22.2)	7 (15.2)	9 (20.0)	10 (22.2)	33 (19.9)	47 (20.7)
Sulfonylurea	37 (80.4)	40 (88.9)	37 (80.4)	36 (80.0)	35 (77.8)	148 (81.8)	185 (81.5)
Other	1 (2.2)	0 (0.0)	1 (2.2)	1 (2.2)	1 (2.2)	3 (1.7)	4 (1.8)

[a] TI total is defined as all the treatment groups combined. Overall total is defined as treatment groups and control group (Technosphere powder alone) combined.

[b] HbA1c baseline data are from week 5.

Efficacy

Treatment with TI lowered HbA1c values over the 11-week treatment period. Mean reductions in HbA1c from baseline were statistically significant for all treatment groups and increased with increasing TI doses (**Tables 2** and **3**). The greatest reduction from Technosphere powder alone was seen in the TI 14.6 U-equivalent group (0.78%; **Figure 2** and **Table 3**).

Technosphere Insulin treatment significantly reduced PPG excursions after a mixed meal, as assessed by reductions in mean postprandial glucose concentration and C_{max} values (**Figure 3**) within each treatment group. Over the 11-week treatment period, dose-dependent and statistically significant mean reductions from baseline were seen in postprandial $AUC_{glucose}$ at 0–300 minutes for

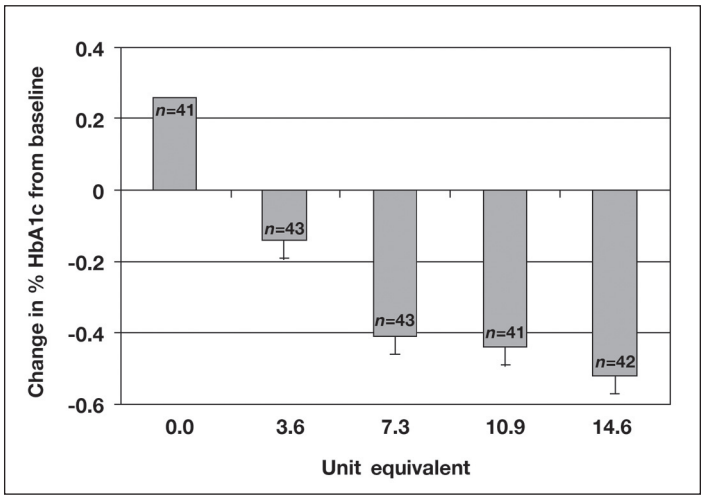

Figure 2. Changes in HbA1c by treatment group. *p* values: TI 3.6 U equivalent: $p = 0.034$; TI 7.3 U equivalent: $p = 0.001$; TI 10.9 U equivalent: $p < 0.001$; 14.6 U equivalent: $p < 0.001$.

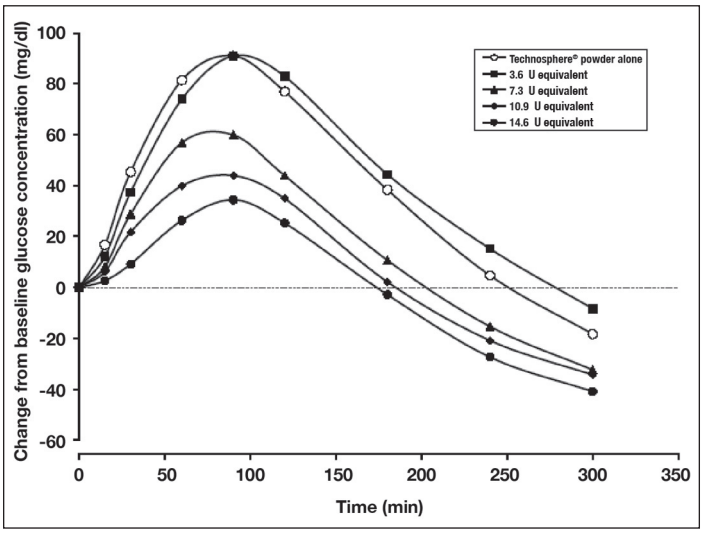

Figure 3. Change in mean postprandial glucose concentration (mg/dl) (baseline corrected) and C_{max} (baseline corrected) for each treatment group.

Table 2.
HbA1c (%), Change from Baseline

	Technosphere powder alone (*n* = 41)	TI 3.6 U equivalent (*n* = 43)	TI 7.3 U equivalent (*n* = 43)	TI 10.9 U equivalent (*n* = 41)	TI 14.6 U equivalent (*n* = 42)
HbA1c baseline	8.7 ± 1.3	8.9 ± 1.4	8.6 ± 1.4	8.7 ± 1.2	8.8 ± 1.2
HbA1c at week 11	8.9 ± 1.3	8.6 ± 1.3	8.1 ± 1.3	8.2 ± 1.2	8.2 ± 1.3
Change from baseline	0.2 ± 0.9	-0.4 ± 1.2	-0.5 ± 1.2	-0.5 ± 0.9	-0.6 ± 1.1
p value	0.098	0.050	0.004	0.002	0.001

Table 3.
Change in HbA1c (%), Corrected for Baseline HbA1c, and Basal Insulin[a]

	Technosphere powder alone (*n* = 41)	TI 3.6 U equivalent (*n* = 43)	TI 7.3 U equivalent (*n* = 43)	TI 10.9 U equivalent (*n* = 41)	TI 14.6 U equivalent (*n* = 42)
Change (%) (CI, LS mean)	0.26 (-0.08, 0.6)	-0.14 (-0.46, 0.19)	-0.41 (-0.75, 0.07)	-0.44 (-0.75, -0.11)	-0.52 (-0.84, -0.19)
Change from Technosphere powder alone	-	-0.40	-0.67	-0.70	-0.78
p value vs Technosphere powder alone	-	0.04	0.001	0.001	<0.001

[a] Least-squares (LS) mean, the model-adjusted mean ANCOVA, includes the main effects of treatment group, baseline HbA1c, site, time-adjusted glargine exposure (TALE), and interaction effect of TALE × treatment group. *p* values for each treatment group vs Technosphere powder alone are based on a one-sided *t* test.

the 7.3, 10.9, and 14.6 U-equivalent groups ($p \leq 0.001$ for these groups; **Table 4**).

Statistically significant reductions in $AUC_{glucose}$ were also seen between Technosphere powder alone and the 10.9 and 14.6 U-equivalent groups ($p = 0.028$ and 0.008, respectively; **Figure 4** and **Table 4**).

For baseline-corrected postprandial C_{max} (the observed maximum glucose concentration), statistically significant mean reductions from baseline in each treatment group were 28.08 ± 42.12 mg/dl for 7.3 U equivalent ($p = 0.007$), 40.86 ± 56.88 mg/dl for 10.9 U equivalent ($p < 0.001$), and 40.32 ± 46.98 mg/dl for 14.6 U equivalent ($p < 0.001$). Comparing the treatment groups with Technosphere powder alone demonstrated differences that were statistically significant for the TI groups [-26.1 mg/dl for 7.3 U equivalent ($p = 0.009$), -38.7 mg/dl for 10.9 U equivalent ($p < 0.001$), and -38.34 mg/dl for 14.6 U equivalent ($p < 0.001$)].

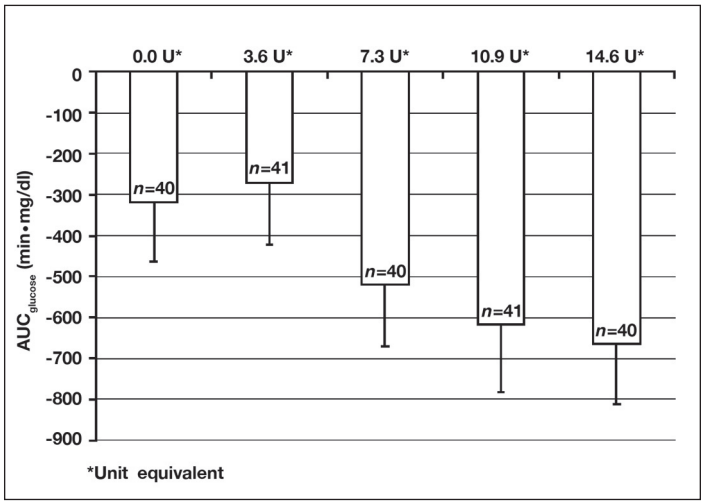

Figure 4. Magnitude of dose-dependent reduction in mean postprandial $AUC_{glucose}$ from baseline for each treatment group. $AUC_{glucose}$ changes from baseline: TI 3.6 U equivalent: p = NS; TI 7.3 U equivalent: p = NS; TI 10.9 U equivalent: $p = 0.028$; TI 14.6 U equivalent: $p = 0.008$.

All five treatment groups had mean decreases in FBG over the 11-week treatment period: -7.3 mg/dl for Technosphere powder alone group and -21.4, -18.6, -3.2, and -8.5 mg/dl for the 3.6, 7.3, 10.9, and 14.6 U-equivalent TI groups. However, none of the decreases in the TI groups were significantly different from baseline or from the decrease observed in the Technosphere powder alone group.

There were no differences in the mean glargine dose between the TI groups (the Technosphere powder alone group started at 19 ± 10 IU and was 29 ± 13 IU at study end). Across the TI groups, the starting mean glargine dose was 20 ± 12 IU [range 19 ± 10 IU (3.6 U equivalent) to 22 ± 13 IU (14.6 U equivalent)], whereas the mean dose at study end was 27 ± 14 IU [range 26 ± 12 IU (3.6 U equivalent) to 30 ± 13 IU (14.6 U equivalent)].

Safety

The number of subjects reporting hypoglycemia ranged from 9 in the Technosphere powder alone group to 15 in the 14.6 U-equivalent group (**Table 5**). No episodes of severe hypoglycemia were reported in this study, and no subject withdrew because of hypoglycemia. Patients randomized to the highest TI doses experienced more hypoglycemic events than those randomized to Technosphere powder alone or to the lowest two TI doses.

Table 4.
Postprandial $AUC_{glucose}$ (min·mg/dl)

	Technosphere powder alone (n = 41)	TI 3.6 U equivalent (n = 44)	TI 7.3 U equivalent (n = 43)	TI 10.9 U equivalent (n = 41)	TI 14.6 U equivalent (n = 42)
AUC at baseline	3858.6 ± 1057.25	3666.2 ± 1035.83	3384.4 ± 1013.07	3666.1 ± 979.95	3507.9 ± 853.05
AUC at week 11	3532.0 ± 780.78	3308.7 ± 954.46	2921.6 ± 863.51	3050.4 ± 1002.14	2888.5 ± 852.34
Change from baseline	-318.2 ± 924.96	-270.6 ± 971.97	-519.7 ± 948.20	-615.8 ± 1059.68	-665.6 ± 924.67
p value vs baseline[a]	0.064	0.078	0.001	<0.001	<0.001
Difference from Technosphere powder alone	-	47.6	-201.5	-297.6	–347.4
p value vs Technosphere powder alone[b]	-	-	0.070	0.028	0.008

[a] One-sample t test for differences within treatment group.
[b] Two-sample t test for comparison between treatment group and Technosphere powder alone (based on step-down procedures).

Cough was reported by 10 subjects in the Technosphere powder alone group and by 4–12 subjects in the TI groups (**Table 5**). No subjects withdrew from the study due to an occurrence of cough.

As shown in **Table 6**, changes in pulmonary function parameters (FVC, FEV_1, and DL_{CO}) were minimal during the study period.

No dose-dependent or other notable changes in body weight were reported at the end of the 11-week treatment period (0.2 ± 3.1 kilograms in the Technosphere powder alone group; -0.3 ± 2.2, 1.0 ± 5.7, 0.7 ± 2.7, and 0.6 ± 2.5 kilograms in the respective TI groups; $p = 0.30$). Any changes observed in laboratory testing (hematology, chemistry, urinalysis, and lipids) were minimal. Two subjects (one each in the 3.6 U- and 7.3 U-equivalent groups) developed anemia during the study. In the first, anemia occurred during the middle of the study and was classified as moderate and possibly related to either the study drug or a common cold. The study drug was not discontinued and the anemia resolved without treatment. In the second subject, who had a medical history of hemophilia A, anemia occurred at the end of the study (last laboratory assessment) and was classified as mild and possibly related to the study drug, but there was no subsequent follow-up information. A third subject in the 7.3 U-equivalent group had anemia at week 1, prior to treatment initiation, but completed the study. Hematocrit and hemoglobin values declined slightly throughout the study, and the anemia was classified as not being related to the study drug.

Table 5.
Hypoglycemia and Cough Events in the Safety Population[a]

Statistic	Technosphere powder alone (n = 224)	TI 3.6 U equivalent (n = 171)	TI 7.3 U equivalent (n = 119)	TI 10.9 U equivalent (n = 79)	TI 14.6 U equivalent (n = 40)
Hypoglycemia (No. of subjects)	9	11	10	13	15
Hypoglycemia (No. of events)	16	20	16	36	69
Hypoglycemia event rate[b,c]	0.08	0.13	0.14	0.39	0.88
Cough (No. of subjects)	10	10	12	4	6
Cough events	28	33	22	4	11
Cough event rate[c]	0.15	0.21	0.20	0.04	0.14

[a] Hypoglycemic events with missing occurrence dates are excluded.
[b] None of the hypoglycemic events were severe.
[c] Event rate: number of events/total subject months; total subject month: total exposure time, days/30.3.

Table 6.
Pulmonary Studies in the Safety Population[a]

	Technosphere powder alone (n = 42)	TI 3.6 U equivalent (n = 45)	TI 7.3 U equivalent (n = 45)	TI 10.9 U equivalent (n = 44)	TI 14.6 U equivalent (n = 44)
FEV_1 (liter) baseline	2.92 ± 0.65	2.91 ± 0.68	3.03 ± 0.84	2.94 ± 0.83	3.06 ± 0.69
FEV_1 (liter) change from baseline	-0.09 ± 0.20	-0.05 ± 0.18	-0.04 ± 0.16	-0.06 ± 0.17	-0.04 ± 0.26
FVC (liter) baseline	3.80 ± 0.86	3.75 ± 0.87	3.90 ± 1.15	3.84 ± 1.05	3.84 ± 0.81
FVC (liter) change from baseline	-0.10 ± 0.17	0.00 ± 0.21	0.01 ± 0.18	-0.07 ± 0.23	-0.03 ± 0.36
DL_{CO} (ml/mm Hg/min) baseline	24.39 ± 6.00	25.41 ± 6.37	25.51 ± 7.18	25.59 ± 5.84	26.49 ± 6.29
DL_{CO} (ml/mm Hg/min) change from baseline	0.61 ± 2.87	-1.00 ± 1.71	-0.05 ± 3.09	-0.37 ± 2.19	-0.48 ± 3.03

[a] Values are changes from the baseline value compared with subject's actual measurement at last visit.

Electrocardiographic parameters (pulse rate, corrected QTc, and heart rate), HRCT, and MRI findings showed no significant changes over the treatment period and were comparable among all groups. Abnormal but not clinically significant findings for HRCT and MRI were reported in about 14.5% of the total safety population (n = 227) at baseline and 12.8% at the conclusion of the study.

Five subjects had serious AEs all considered not related to the study drug or device; all completed the study. Seven subjects withdrew from the study because of treatment-emergent AEs. One subject in the 7.3 U-equivalent group had a toothache that was not considered related to the drug or device. One subject was randomized to the 10.9 U-equivalent group but only received Technosphere powder alone as part of inhaler training as a consequence of early termination. This subject had a history of cold urticaria reported as ongoing at trial entry, but no record of hypersensitivity to insulin. He developed canker sores and urticaria on the fingertips 2 days after the first and only dose of Technosphere powder alone. The canker sores and urticaria improved significantly without treatment by day 5, but new canker sores appeared at the same time, prompting the decision to withdraw this subject from the study. The subject was not rechallenged and never received TI. This was the only suspected hypersensitivity reaction reported in this trial. Four subjects, two in the 3.6 U-equivalent group, one subject randomized to the 7.3 U-equivalent group, and one in the 10.9 U-equivalent group, withdrew for hyperglycemia; one subject in the 14.6 U-equivalent group withdrew consent during the placebo run-in period because of AEs and dissatisfaction with BG readings. One subject randomized to Technosphere powder alone had a myocardial infarction ≥1 month after the study conclusion, and two subjects suffered from muscular skeletal injuries prior to the beginning of the experimental period. None of these three events were considered to be related to the drug or device. No deaths were reported in this study.

Discussion

Early phase insulin release is impaired in patients with type 2 diabetes, resulting in increased PPG excursions and suboptimal overall glycemic control.[12–14] In contrast to available insulin formulations, TI has rapid absorption suitable for the replacement of early physiologic insulin release and an appropriate duration of action to reduce the risk of hypoglycemia.[17,18,20]

This study was designed to examine the effect of four fixed doses of TI on HbA1c and PPG indices compared with Technosphere powder alone, a vehicle control. TI plus basal insulin glargine resulted in dose-dependent HbA1c reductions. Significant reductions in HbA1c were seen after 8–11 weeks of therapy at the final randomized doses. As anticipated, the reductions in HbA1c increased as the dose of TI increased. In addition to reducing HbA1c, TI plus basal insulin glargine resulted in a decrease in PPG indices. Maximal PPG level changes from baseline were reduced by ≈50% with the 14.6 U equivalent, with total glucose exposure reduced by ≈20%. At the end of the trial, there was no difference in average glargine dosing between TI and Technosphere powder alone, demonstrating that changes in HbA1c and reductions in PPG excursions were not the sole result of the insulin glargine.

It is important to note that the study was designed as a forced titration dose–response study, not a treat-to-goal study. Subjects were randomized to receive a fixed dose of TI at the end of the titration. As such, the dose of TI was not optimized for the individual patient. In addition, the follow-up period may not have been long enough to observe the full HbA1c-lowering effect of the study drug.

There was a statistically and clinically significant reduction in HbA1c in the TI 3.6 U-equivalent dose group. The lack of apparent effect on PPG excursion in this group may be the result of the relatively low-calorie meal used in the study. When such a meal is ingested, TI may cause a partial substitution of endogenous insulin release rather than augmenting the response. Over the course of the study, when meal content is not restricted, endogenous insulin alone may not control PPG and TI will be additive to the endogenous response.

The study population was type 2 diabetes patients who were not taking any medications except for a basal insulin. This excluded any interference of sulphonylureas with insulin secretion and metformin with hepatic glucose production. However, it is conceivable that TI will exhibit similar pharmacodynamic properties when given in addition to oral treatment, for example, with metformin, thiazolidinediones, or even sulphonylureas, without basal insulin.

Technosphere Insulin plus basal insulin glargine was well tolerated, with very few clinically relevant AEs. An increase in the number of hypoglycemia events occurred as the TI dose was increased. This would be expected in a forced titration study, as the dose administered was predetermined and was not individualized based on clinical need. The baseline HbA1c levels were relatively

high, which may account for the low incidence of hypoglycemia observed in this study in combination with the short duration of the glucose-lowering activity of TI. The AE rate for cough was low and led to no study discontinuations. Additionally, the number of subjects experiencing cough dropped for each consecutive treatment period, as subjects became accustomed to the inhalation of TI. There were no clinically meaningful changes in body weight and lung function over the treatment period.

Although all randomized subjects received Technosphere, the quantitative exposure to Technosphere during the study period varied between the respective randomized doses as well as within each dosing group. In addition, as there was no simultaneous control group that did not receive Technosphere or TI during the study, no inference can be drawn as to the effect of Technosphere on pulmonary functions. Clinical studies are in progress that will address the pulmonary safety of TI.

To date, no other inhaled insulins have published any dose–response studies with which to compare the results of this study. As more studies become available, there may be an opportunity to identify the potential impact early insulin release may have on dose-dependent responses.

In summary, this study demonstrated that an 11-week course of TI plus basal insulin glargine is well tolerated and results in dose-dependent reductions in HbA1c and PPG. Additional clinical trials are in progress to confirm the long-term safety and efficacy of TI in reducing HbA1c and PPG levels.

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