# Inhaled Technosphere Insulin Compared With Injected Prandial Insulin in Type 1 Diabetes: A Randomized 24-Week Trial

*Bruce W. Bode,[1] Janet B. McGill,[2] Daniel L. Lorber,[3] Jorge L. Gross,[4] P.-C. Chang,[5] and David B. Bregman,[6,7] for the Affinity 1 Study Group**

*Diabetes Care 2015;38:2266–2273 | DOI: 10.2337/dc15-0075*


## OBJECTIVE

**To compare the efficacy and safety of Technosphere insulin (TI) and insulin aspart in patients with type 1 diabetes.**

## RESEARCH DESIGN AND METHODS

**This open-label noninferiority trial compared the change in $HbA_{1c}$ from baseline to week 24 of prandial TI ($n$ = 174) with that of subcutaneous aspart ($n$ = 171), both with basal insulin, in patients with type 1 diabetes and $HbA_{1c}$ 7.5–10.0% (56.8–86.0 mmol/mol).**

## RESULTS

**Mean change in $HbA_{1c}$ in TI patients (–0.21% [–2.3 mmol/mol]) from baseline (7.94% [63.3 mmol/mol]) was noninferior to that in aspart patients (–0.40% [–4.4 mmol/mol]) from baseline (7.92% [63.1 mmol/mol]). The between-group difference was 0.19% (2.1 mmol/mol) (95% CI 0.02–0.36), satisfying the noninferiority margin of 0.4%. However, more aspart patients achieved $HbA_{1c}$ <7.0% (53.0 mmol/mol) (30.7% vs. 18.3%). TI patients had a small weight loss (–0.4 kg) compared with a gain (+0.9 kg) for aspart patients ($P$ = 0.0102). TI patients had a lower hypoglycemia event rate than aspart patients (9.8 vs. 14.0 events/patient-month, $P$ < 0.0001). Cough (generally mild) was the most frequent adverse event (31.6% with TI, 2.3% with aspart), leading to discontinuation in 5.7% of patients. Treatment group difference for mean change from baseline in forced expiratory volume in 1 s was small (40 mL) and disappeared upon TI discontinuation.**

## CONCLUSIONS

**In patients with type 1 diabetes receiving basal insulin, $HbA_{1c}$ reduction with TI was noninferior to that of aspart, with less hypoglycemia and less weight gain but increased incidence of cough.**


Intensive glycemic control often necessitates basal-bolus insulin treatment. However, hypoglycemia, weight gain, and the burden of multiple injections often lead to poor adherence (1). Hypoglycemia is considered the main limiting factor for optimizing glycemic control (2). Mild hypoglycemia may be inconvenient or frightening (3), whereas severe hypoglycemia can be life threatening (4). Lack of compliance with insulin therapy is a frequent problem in patients with type 1 diabetes due to pain and embarrassment associated with insulin injections (5). Concerns about weight gain also contribute to reduced adherence (6). An inhaled prandial insulin

*[1]Atlanta Diabetes Associates, Atlanta, GA*
*[2]Division of Endocrinology, Metabolism and Lipid Research, Washington University School of Medicine in St. Louis, St. Louis, MO*
*[3]New York Hospital Queens, New York-Presbyterian Healthcare System, Flushing, NY*
*[4]Centro de Pesquisas em Diabetes Ltda., Porto Alegre, Brazil*
*[5]MannKind Corporation, Paramus, NJ*
*[6]Sanofi, Bridgewater, NJ*
*[7]Department of Pathology, Albert Einstein College of Medicine, Bronx, NY*

*Corresponding author: Bruce W. Bode, bbode001@aol.com.*

*Received 13 January 2015 and accepted 15 June 2015.*

*Clinical trial reg. no. NCT01445951, clinicaltrials.gov.*

*This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-0075/-/DC1.*

*A slide set summarizing this article is available online.*

**A complete list of the Affinity 1 Study Group can be found in the Supplementary Data online.*



**See accompanying articles, pp. 2200, 2204, 2211, 2217, 2226, 2234, 2237, 2241, 2250, 2258, 2274, and 2282.**

with rapid kinetics may address some of these concerns and could provide important therapeutic options for individualized diabetes management.

Technosphere insulin (TI) (MannKind Corporation, Valencia, CA) is a dry powder formulation of regular human insulin adsorbed onto Technosphere microparticles for oral inhalation. The primary component of Technosphere particles is the excipient fumaryl diketopiperazine (FDKP), which is highly soluble in water at neutral and basic pH. Under acidic pH, FDKP undergoes intermolecular self-assembly and crystallizes into microparticles (median diameter ~2–2.5 μm) (7). Upon inhalation, these microparticles can reach the deep lung where they dissolve rapidly because of the physiological pH, allowing absorption of insulin and FDKP into the systemic circulation with a time to maximum serum insulin concentration of ~12–15 min (8,9). FDKP is excreted unchanged in the urine (10). TI is delivered through the Gen2 inhaler device. The Gen2, which replaced the previous device MedTone, is smaller, simpler, and more efficient (i.e., uses less TI than the MedTone inhaler to provide the same insulin exposure, and only one inhalation per cartridge is necessary).

The objective of the current study was to demonstrate noninferiority of TI delivered through the Gen2 inhaler in combination with basal insulin (TI-Gen2 group) to insulin aspart in combination with basal insulin (insulin aspart group) in its effect on $HbA_{1c}$ in patients with type 1 diabetes. In addition, the study compared the pulmonary safety in patients receiving TI when administered through the TI-Gen2 or TI-MedTone inhalers.

## RESEARCH DESIGN AND METHODS

This study was a randomized, multicenter, 24-week trial. Adults ≥18 years old with type 1 diabetes for at least 12 months with $HbA_{1c}$ 7.5–10.0% (58.5–86.0 mmol/mol) participated in the U.S., Russia, Ukraine, and Brazil between February 2011 and May 2013. Inclusion criteria were nonsmoking for the preceding 6 months, BMI ≤38 kg/m$^2$, forced expiratory volume in 1 s ($FEV_1$) and forced vital capacity (FVC) ≥70% predicted (11), and stable insulin dose (<2 IU/kg/day) with fasting plasma glucose (FPG) <220 mg/dL for 3 months before screening. Exclusion criteria were significant pulmonary disease, significant abnormalities on chest X-ray, malignancy within 5 years, severe complications of diabetes, or two or more severe hypoglycemic episodes within 6 months.

This study was approved by appropriate independent ethics committees or institutional review boards and monitored by an independent Data Safety Monitoring Board. All patients provided written informed consent.

Randomization was stratified by region (U.S., Brazil, and Russia/Ukraine) and basal insulin (insulin glargine, insulin detemir, or NPH insulin) with block sizes of six. During a 4-week basal insulin optimization period, all patients continued their preenrollment basal insulin, converted their prandial insulin to insulin aspart, and titrated their dose of basal insulin every 3 days, targeting an FPG of 100–120 mg/dL. Patients reaching FPG <180 mg/dL at the end of this 4-week period were randomized 1:1:1 to TI-Gen2, TI-MedTone, or insulin aspart.

Patients randomized to insulin aspart continued the aspart dose used during basal optimization. Patients randomized to TI converted to a starting TI dose administered at the beginning of a meal or up to 20 min after starting a meal according to a conversion table based on 10 units TI-Gen2 per ~4 units insulin aspart (Supplementary Table 1). For the first 12 weeks of randomized treatment, prandial doses in each group were adjusted weekly. Patients randomized to insulin aspart targeted average premeal self-monitored blood glucose (SMBG) values of 100–120 mg/dL (Supplementary Table 2); patients randomized to TI targeted average 90-min postmeal SMBG values of 110–160 mg/dL (Supplementary Table 3). TI patients were instructed to take a supplemental dose (10 units TI) at the time of the reading if a 90-min postmeal SMBG value was ≥180 mg/dL. Aspart patients were also advised that additional dose adjustments may be made based on meal size, carbohydrate content, or SMBG results. Dosing was kept stable except for safety reasons during the final 12 weeks of randomized treatment. After 24 weeks of randomized treatment, patients converted back to insulin aspart and were followed for another 4 weeks to assess pulmonary safety.

The primary efficacy end point was change in $HbA_{1c}$ from the end of basal optimization (baseline) to week 24 in the TI-Gen2 and insulin aspart groups. Key secondary efficacy end points were the proportion of patients achieving $HbA_{1c}$ ≤7.0% (53.0 mmol/mol), proportion of patients achieving $HbA_{1c}$ ≤6.5% (47.5 mmol/mol), change in FPG from baseline to week 24, seven-point plasma glucose profile (before meals, 90 min after meals, and bedtime) based on SMBG values, and change in body weight.

The primary safety end point was change in $FEV_1$ from baseline to week 24 in the TI-Gen2 and TI-MedTone groups. Spirometry ($FEV_1$ and FVC) was performed according to American Thoracic Society and European Respiratory Society guidelines. Safety assessment also included incidence and event rates of hypoglycemia. Nonsevere hypoglycemia was defined as SMBG <70 mg/dL or symptoms of hypoglycemia; severe hypoglycemia was an event in which the assistance of another individual was required. Other safety assessments included adverse events (AEs), vital signs, electrocardiograms, laboratory values, and physical examinations. Anti-insulin antibody levels, measured using radioimmunoassay (Kronus, Star, ID), were reported in Kronus units.

Three hundred fourteen patients were targeted to be randomized to TI-Gen2 and insulin aspart groups, which would provide 90% power, using a one-sided α of 0.025 and an SD of 1.0 for a noninferiority design to test the difference in change from baseline to week 24 in $HbA_{1c}$ between the two groups. This assumes a noninferiority margin of 0.4% and a dropout rate of 15%.

The full analysis set, defined as all randomized patients, was used for efficacy analyses. The safety population, defined as patients who had at least one dose of study medication (based on treatments each subject received), was used for safety analyses. All analyses were predefined in the statistical analysis plan. No imputation was applied unless otherwise specified.

Noninferiority was assessed using a mixed-model repeated-measures (MMRM) analysis, with $HbA_{1c}$ measurement

as the dependent variable and explanatory variables of region, basal stratum, visit (categorical time), treatment, and visit by treatment as fixed effects; patient as a random effect; and baseline $HbA_{1c}$ as covariate. Sensitivity analyses were also performed to evaluate the impact of missing data. The primary safety comparison, change in $FEV_1$ from baseline to week 24 in the TI-Gen2 versus the TI-MedTone group, was analyzed using the MMRM model, with baseline pulmonary function test (PFT) value, height, and age as covariates; treatment, race, sex, visit (categorical time), and visit by treatment as fixed effects; and subject as a random effect.

## RESULTS

Patient disposition is shown in Supplementary Fig. 1. A total of 1,401 patients were screened for eligibility, 614 of whom entered the basal insulin optimization phase and 518 randomized (TI-Gen2 [*n* = 174], insulin aspart [*n* = 170], or TI-MedTone [*n* = 174]). Demographics and baseline characteristics are shown in Supplementary Table 4. Patient demographic and baseline characteristics were balanced among the groups. Mean baseline $HbA_{1c}$ was ~7.95% (~63.4 mmol/mol). Of the randomized patients, 130 (74.7%) in the TI-Gen2 group, 151 (88.8%) in the insulin aspart group, and 138 (79.3%) in the TI-MedTone group completed the 24-week treatment period. Dropout rates in the TI-Gen2, insulin aspart, and TI-MedTone groups were 25.3%, 11.2%, and 20.7%, respectively, primarily due to withdrawal of consent for personal reasons (e.g., moving, changing jobs) in all groups, whereas withdrawal because of an AE occurred only with TI (Supplementary Fig. 1).

The mean change in $HbA_{1c}$ at week 24 was –0.21% (–2.3 mmol/mol) from a baseline of 7.94% (63.3 mmol/mol) for the TI-Gen2 group and –0.40% (–4.4 mmol/mol) from a baseline of 7.92% (63.1 mmol/mol) for the insulin aspart group based on MMRM analyses (Table 1). The between-group difference was 0.19% (2.1 mmol/mol) (95% CI 0.02–0.36), which satisfied the predefined noninferiority criterion (<0.4%). Assessment of the per-protocol population also supported noninferiority (Supplementary Table 5). $HbA_{1c}$ levels declined by ~0.6% in both groups during basal optimization, continued to decrease in the first 12 weeks of randomized treatment (slightly more in the insulin aspart group), and then remained stable during the 12-week stable dosing period (Fig. 1*A*).

During randomized treatment, the mean dose of daily basal insulin increased by ~5 units in the TI-Gen2 group (31.7 units at baseline to 36.8 units at week 12) and ~2 units in the

**Table 1—Key analyses and results (full analysis set)**

| | TI-Gen2 (*n* = 174) | Insulin aspart (*n* = 170) | Treatment difference |
|---|---|---|---|
| $HbA_{1c}$ (% [mmol/mol])* | | | |
| Baseline | 7.94 (63.3) | 7.92 (63.1) | |
| Week 24 | 7.73 (61.0) | 7.52 (58.7) | 0.19 (2.1) |
| Adjusted mean change | −0.21 (–2.3) | −0.40 (–4.4) | |
| 95% CI | –0.33 to –0.09 | –0.52 to –0.28 | 0.02 to 0.36 |
| $HbA_{1c}$ ≤7.0% (53.0 mmol/mol)† | | | |
| Incidence (%) | 24 (18.3) | 46 (30.7) | OR = 0.449 |
| 95% CI | | | 0.23 to 0.86 |
| | | | *P* = 0.0158 |
| $HbA_{1c}$ ≤6.5% (47.5 mmol/mol)† | | | |
| Incidence (%) | 10 (7.6) | 19 (12.7) | OR = 0.576 |
| 95% CI | | | 0.24 to 1.38 |
| | | | *P* = 0.2144 |
| FPG (mg/dL)* | | | |
| Baseline (SE) | 153.9 (5.3) | 151.6 (5.4) | |
| Adjusted mean change (SE) | −25.3 (7.6) | 10.2 (7.4) | −35.4 (10.6) |
| 95% CI | | | −56.3 to –14.6 |
| | | | *P* = 0.001 |
| Body weight, kg‡ | | | |
| Baseline (SE) | 75.5 (16.1) | 73.5 (15.3) | |
| Adjusted mean change (SE) | −0.4 (0.4) | 0.9 (0.4) | −1.3 (0.5) |
| 95% CI | | | −2.33 to –0.31 |
| | | | *P* = 0.0102 |
| All hypoglycemia§ | | | |
| Incidence (%) | 167 (96.0) | 170 (99.4) | *P* = 0.0621 |
| Event rate (events/patient-month) | 9.8 | 14.0 | *P* < 0.0001 |
| Severe hypoglycemia§ | | | |
| Incidence (%) | 32 (18.4) | 50 (29.2) | *P* = 0.0156 |
| Event rate (events/100 patient-months) | 8.1 | 14.5 | *P* = 0.1022 |

OR, odds ratio. *Assessed using MMRM analysis. †Assessed using logistic regression analysis. ‡Assessed using ANCOVA. §Incidence was based on the safety population, which was 174 for the TI-Gen2 group and 171 for the insulin aspart group. Incidence was assessed using logistic regression analysis. Event rate was assessed using negative binomial analysis.

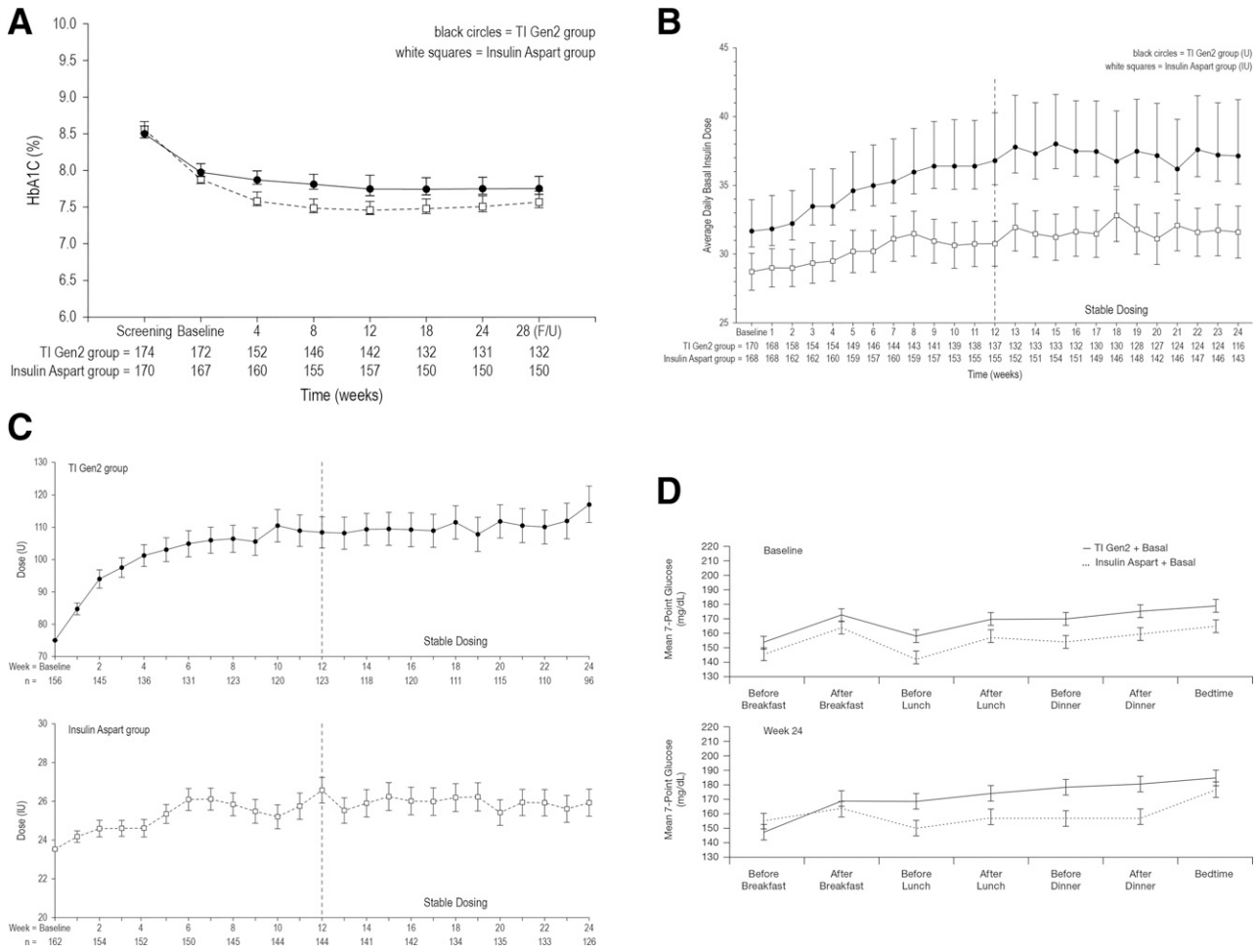


**Figure 1—**Mean change over time in $HbA_{1c}$ from screening to posttreatment (*A*), average daily dose of basal insulin in the TI-Gen2 and insulin aspart groups (*B*), mean daily dose of prandial insulin in the TI-Gen2 and insulin aspart groups (*C*), and mean seven-point glucose profiles at baseline and week 24 (*D*). Full analysis set is presented with SE bars. F/U, follow-up.

insulin aspart group (28.7 units at baseline to 30.8 units at week 24) (Fig. 1*B*). The mean daily prandial insulin aspart dose started at 23.5 IU at randomization and increased 9.1% during the first 12 weeks of randomized treatment. The mean daily prandial dose in the TI-Gen2 group was 75.0 units at randomization (10-unit cartridge of TI-Gen2 = ~4 units of rapid-acting insulin analog [RAA]) (Supplementary Table 1). The dose increased to 107.4 units at week 12 and then remained stable for the next 12 weeks (Fig. 1*C*). Approximately 60% of patients in each treatment group took at least one supplemental dose in addition to their meal-associated doses; however, overall supplemental dosing was infrequent.

At week 24, the adjusted mean change in FPG levels was –25.3 mg/dL with TI-Gen2 and 10.2 mg/dL with insulin aspart. The treatment difference in FPG change from baseline to week 24 was statistically significant in favor of TI-Gen2 (–35.4 mg/dL, $P = 0.001$) (Table 1).

For the secondary end point of $HbA_{1c}$ goal attainment, more insulin aspart patients (46 [30.7%]) reached $HbA_{1c}$ targets of ≤7.0% (53.0 mmol/mol) than TI-Gen2 patients (24 [18.3%], $P = 0.0158$) (Table 1). The between-group difference in attaining $HbA_{1c}$ ≤6.5% (47.5 mmol/mol) was not statistically significant.

At baseline, seven-point glucose profiles were higher at every time point for the TI-Gen2 group than for the insulin aspart group; this difference was also seen at week 24, except for a lower pre-breakfast value in the TI-Gen2 group (Fig. 1*D*). A progressive increase in SMBG values throughout the day was noted for both groups at baseline and week 24; this increase was greater in the TI-Gen2 group. TI patients had a small weight loss (–0.4 kg) compared with a gain (+0.9 kg) for aspart patients ($P = 0.0102$) (Table 1).

The proportions of patients reporting at least one AE were higher with TI-Gen2 and TI-MedTone (101 of 174 [58.0%] and 104 of 173 [60.1%], respectively) than with insulin aspart (74 of 171 [43.3%]). AEs occurring in ≥2% of patients are shown in Supplementary Table 6. AEs were mostly mild or moderate. Rates of serious AEs were low in all groups (TI-Gen2, 5 of 174 [2.9%]; TI-MedTone, 9 of 173 [5.2%]; insulin aspart, 7 of 171 [4.1%]). Discontinuations due to AEs occurred with TI only (TI-Gen2, 16 of 174 [9.2%]; TI-MedTone, 9 of 173 [5.2%]). One patient in the insulin aspart group died of accidental drowning, which was considered unlikely related to the study drug. Excluding hypoglycemia, cough was the most

frequent AE and reported by a higher percentage of the TI-Gen2 (55 of 174 [31.6%]) and TI-MedTone (39 of 173 [22.5%]) patients than the insulin aspart patients (4 of 171 [2.3%]). Regardless of the inhaler, cough was predominantly a mild, dry, intermittent (66–69%) or single-defined event (23–27%) and occurred within 10 min after inhalation of the dry powder. Cough led to study discontinuation in 15 patients (TI-Gen2, 10 of 174 [5.7%]; TI-MedTone, 5 of 173 [2.9%]) and was severe in 3 (TI-Gen2, 2 of 174 [1.1%]; TI-MedTone, 1 of 173 [0.6%]). Cough resolved when TI was discontinued. In both the TI-Gen2 and TI-MedTone groups, the percentage of patients reporting new-onset cough was highest in the first week after treatment initiation (19.5% and 13.3%, respectively) and then decreased to 4.1% and 2.3%, respectively, during week 2, and to 0% and 0.5%, respectively, by week 8.

Over 24 weeks, all groups had small declines from baseline in mean $FEV_1$ (TI-Gen2, –0.07 L; TI-MedTone, –0.08 L; insulin aspart, –0.04 L). The decline was greater in the inhaled insulin groups, but this difference resolved by the follow-up visit 4 weeks after discontinuation of treatment (Fig. 2). A similar pattern was seen in FVC results (data not shown).

The hypoglycemia event rate, regardless of severity, as well as the incidence of severe hypoglycemia was lower in the TI-Gen2 group than in the insulin aspart group ($P < 0.0001$ and 0.0156, respectively) (Table 1). Over the course of the study, the event rate for severe hypoglycemia was 44% lower in the TI-Gen2 group (8.1 vs. 14.5 events/100 patient-months for TI vs. insulin aspart), but the difference was not statistically significant ($P = 0.1022$). Both nonsevere and severe hypoglycemia event rates in the TI-Gen2 group were consistently lower regardless of the achieved $HbA_{1c}$ value at week 24 (Fig. 3*A* and *B*) and after adjustment for $HbA_{1c}$ change from baseline to week 24 (Fig. 3*C*). Similarly, the hypoglycemia rate was lower in the TI group after $HbA_{1c}$ was added to the statistical model used in the data analysis (Supplementary Table 7). Furthermore, the timing of the hypoglycemia events with TI paralleled its rapid kinetics; hypoglycemia event rates within 2 h postmeal were comparable between TI and insulin aspart but were two- to threefold higher in the insulin aspart group >2–5 h after meals (Fig. 3*D*).

At week 24, median insulin antibody levels increased in the TI-Gen2 group (9.3 to 30.9 Kronus units/mL from baseline to week 24) and the TI-MedTone group (8.6 to 41.1 Kronus units/mL from baseline to week 24) and remained unchanged in the insulin aspart group (8.7 and 8.9 Kronus units/mL from baseline to week 24). No differences were seen in the type or incidence of AEs or changes in $HbA_{1c}$ in patients at the top 10th percentile of insulin antibody increase and the overall trial population. There were no clinically meaningful changes in other laboratory values, vital signs, physical examinations, or electrocardiogram results.

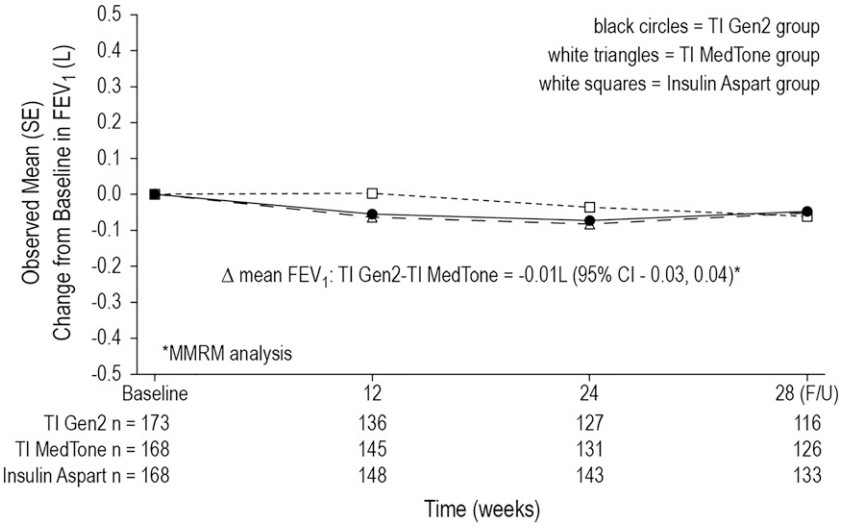


**Figure 2**—$FEV_1$ test results from baseline to week 28 follow-up (MMRM). Safety population. F/U, follow-up.

## CONCLUSIONS

The results of this trial demonstrate that a regimen of prandial TI in combination with basal insulin is noninferior to a standard regimen of basal insulin plus prandial RAA for reducing $HbA_{1c}$ in patients with type 1 diabetes. The mean reduction in $HbA_{1c}$ was greater in the insulin aspart group than in the TI group, and more patients in the insulin aspart group achieved $HbA_{1c}$ goals of ≤7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol). Certain factors may have contributed to these differences. The trial compared a basal-bolus regimen using a novel inhaled agent (TI) to that of a standard-of-care injectable comparator (insulin aspart) under conditions that would optimize the comparator treatment regimen. After randomization, the insulin aspart group continued the basal-bolus regimen that all patients received during basal optimization. Approximately 40% of patients used insulin aspart in clinical practice (before trial entry). In comparison, the inhaled insulin group switched to an unfamiliar regimen and titration scheme (based on 90-min postprandial rather than premeal SMBG values). Study design elements, including a new titration scheme along with less insulin available 2–5 h after the meal with inhaled insulin, could account for this $HbA_{1c}$ difference. Optimization of the basal dose could potentially decrease this difference between inhaled insulin and RAA.

Consistently less hypoglycemia was observed in TI patients than in insulin aspart patients. The greatest difference was observed in the >2–5-h period after the meal. This analysis of hypoglycemia rate as a function of time after a meal indicates that the lower hypoglycemia rate associated with TI resulted from its rapid kinetics. Maximum plasma drug concentration occurs sooner with TI (12–15 min) than with RAA (45–60 min) (8,12–14). Similarly, the time to return to baseline drug concentration (180 min vs. >300 min) and time to baseline glucose lowering effect (240 min vs. 300–360 min) is also less with TI than with RAA. $HbA_{1c}$ reduction

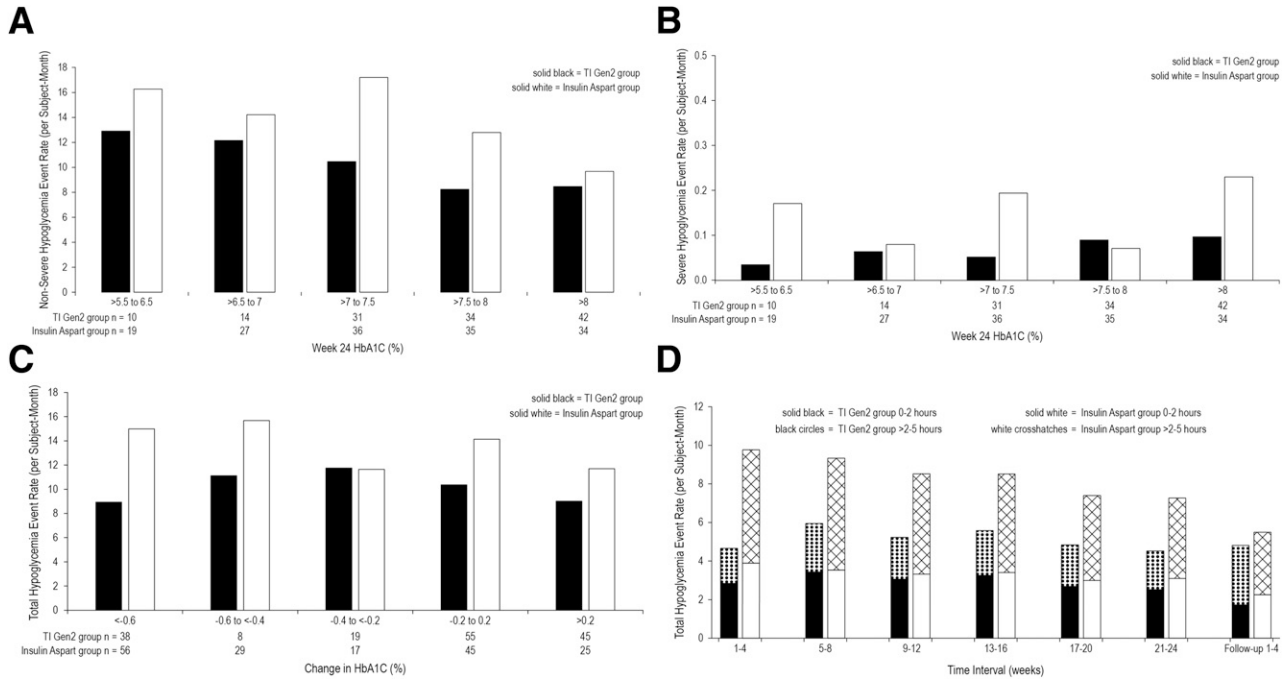


**Figure 3—**Analyses of hypoglycemia. Event rates of nonsevere and severe hypoglycemia by $HbA_{1c}$ category at week 24 (*A* and *B*), total hypoglycemia as a function of change in $HbA_{1c}$ from baseline to week 24 (*C*), and total hypoglycemia as a function of time after a meal throughout the trial (*D*). Full analysis set. Based on negative binomial analysis to account for patient effect and exposure time.

was 0.19% less in the TI group than in the insulin aspart group. However, the hypoglycemia advantage of TI over insulin aspart was maintained, even after adjusting for the different levels of achieved $HbA_{1c}$ at week 24 and when including change from baseline in $HbA_{1c}$ in the statistical model. Thus, the small between-group difference in $HbA_{1c}$ reduction favoring the insulin aspart group could not entirely explain the beneficial effect on hypoglycemia seen with TI. Rather, at least a part of the hypoglycemia advantage is likely to result from the more rapid kinetics of TI. Although a small $HbA_{1c}$ reduction was seen in both groups, a small weight reduction was seen in the TI-Gen2 group, whereas a statistically significant weight gain occurred for the insulin aspart group. Although the mechanism is not known with certainty, reduced concern about hypoglycemia may lead to less "defensive" eating (15).

There was a decrease in FPG for the TI-Gen2 group compared with an increase in the insulin aspart group. Again, the mechanism is not known, but it has been observed previously with TI and with another inhaled insulin (16,17). A canine model suggested that it might be due to better peripheral glucose utilization after delivery of inhaled insulin (18). Except for the prebreakfast (FPG) value, seven-point glucose values were greater for the TI-Gen2 group than for the insulin aspart group at all other points. SMBG values increased throughout the day in both treatment groups.

During the 24-week randomized treatment period, basal insulin doses increased in both the TI-Gen2 and the insulin aspart groups but increased by 3 units more in the TI-Gen2 group. This finding is not unexpected because duration of action of TI is shorter than that of insulin aspart. The need to increase the dose of the basal insulin in a basal-bolus regimen was similarly observed when RAAs with a relatively shorter time action profile compared with regular human insulin were introduced in the basal-bolus treatment regimen (19–21). When basal insulin dose was included in the statistical model used for assessing the change in $HbA_{1c}$, noninferiority of the TI group relative to the insulin aspart group was maintained (Supplementary Table 8). Patients in both the TI-Gen2 and the insulin aspart groups continually titrated their prandial insulin doses during the first 12 weeks of the randomized treatment period. There was a greater increase in the TI dose partly because the protocol-recommended conversion ratio (one 10-unit cartridge of TI per 4 units insulin aspart) was intentionally conservative to maximize safety during the switch from injected to inhaled insulin.

This study included a direct comparison of pulmonary function in patients receiving TI through the Gen2 or MedTone inhalers. The changes in both $FEV_1$ and FVC observed during treatment with either inhaler were small. No association was noted with either $FEV_1$ or FVC changes and mean TI dose, age, sex, race, or cough status; mean changes in $FEV_1$ and FVC were driven not by a small number of subjects with large changes (outliers) but by slight shifts in distribution because of a large number of subjects with small changes (data not shown). Furthermore, the changes reversed after discontinuing TI treatment. The changes to $FEV_1$ and FVC were unlikely to be clinically significant. The higher incidence of cough with the Gen2 inhaler was most likely a result of the greater amount of powder being inhaled in a single inhalation with Gen2, whereas with MedTone, the amount of powder inhaled per dose is distributed over two inhalations. Overall, the pulmonary findings in this study are

consistent with data collected throughout the TI development program describing the pulmonary tolerability and safety of TI (12). All adults, whether they have diabetes, demonstrate a decline in pulmonary function with age. There is some evidence that the decline in pulmonary function in patients with diabetes is greater than that of the general population (22). In clinical trials of TI of up to 2 years duration, small (40 mL or ~1–1.5%) nonprogressive treatment group differences in PFT decline are observed, which disappear after TI is discontinued. These results suggest that the observed changes in PFTs are of limited clinical significance. Longer studies (>5 years) are being conducted to evaluate PFT changes associated with long-term use of TI.

The potential impact of dropouts on the noninferiority analysis was assessed using multiple statistical models. First, the analysis method (MMRM) is a preferred model for addressing missing data (23,24). Analyses performed based on the completers population or the conventional last observation carried forward imputation method confirmed the conclusion from the primary MMRM analysis based on the full analysis set. Furthermore, sensitivity analyses, such as pattern mixture and multiple imputation analyses, concluded that the impact of missing data is insignificant to the conclusion of noninferiority. Importantly, in all analyses, the average $HbA_{1c}$ level was maintained with the TI regimen over the 24-week randomized treatment period, with no clinically significant loss of glycemic control. During the 4-week follow-up phase after patients converted back to prandial insulin aspart, mean $HbA_{1c}$ levels were maintained with no clinically significant change in the rate of hypoglycemia, although the difference in hypoglycemia rate between TI and aspart started to diminish (Supplementary Fig. 2).

Patients receiving TI experienced an increase in insulin antibodies, but higher antibody levels were not associated with adverse clinical outcomes. The increase in antibody levels has been reported with inhaled insulin and is probably associated with the lungs' immunological properties (25).

In summary, this 24-week study showed that a regimen of prandial TI-Gen2 in combination with basal insulin led to noninferior reductions in glycemic parameters, with weight neutrality and less hypoglycemia compared with subcutaneous aspart. However, TI-Gen2 enabled fewer patients to achieve $HbA_{1c}$ <7.0% (53.0 mmol/mol) (18.3% with TI-Gen2 vs. 30.7% with aspart), most likely due to higher glucose levels in the late postprandial period 2–5 h postinhalation. The change in FPG from baseline to week 24 was –25.3 mg/dL with TI-Gen2 vs. 10.2 mg/dL with aspart. TI was associated with a higher incidence of (generally mild) cough (31.6% with TI-Gen2 vs. 2.3% with aspart), which also contributed to discontinuations due to AEs occurring with TI only (TI-Gen2, 16 of 174 [9.2%]; TI-MedTone, 9 of 173 [5.2%]). Thus, TI is an option for prandial insulin in patients with type 1 diabetes who have concerns about hypoglycemia or injection burden. A trial to evaluate long-term pulmonary safety will be conducted.

**Acknowledgments.** The authors thank all the patients who participated in the trial as well as the following current and former MannKind Corporation employees for expert contributions to trial conduct and analysis: I. Battles, D. Gash, Y. Ma, L. Ming, S. Suh, and G. Tonelli. Medical writing assistance was provided by F. Martino of FPM Communications, LLC (North Brunswick, NJ).

**Funding.** B.W.B.'s employer (Atlanta Diabetes Associates) received grant and research support from the National Institutes of Health.

**Duality of Interest.** This study was funded by MannKind Corporation. Sanofi has a worldwide license for TI from MannKind Corporation. Technosphere and MedTone are registered trademarks of MannKind Corporation. B.W.B. is a stock/shareholder of Aseko (formerly Glytec); received consulting honoraria from Halozyme, Janssen, Medtronic, Novo Nordisk, Sanofi, Tandem Diabetes Care, and Valeritas; and belongs to speakers' bureaus for AstraZeneca, Dexcom, GlaxoSmithKline, Insulet, Janssen, Eli Lilly, Medtronic, Merck, Novo Nordisk, Sanofi, and Valeritas, and grant and research support was received by his employer (Atlanta Diabetes Associates) from Abbott, Biodel, Bristol-Myers Squibb/Amylin, Dexcom, GlaxoSmithKline, Halozyme, Janssen, Eli Lilly/Boehringer Ingelheim, MacroGenics, MannKind Corporation, Medtronic, Novo Nordisk, Sanofi, and Valeritas. J.B.M. has participated in advisory panels for AstraZeneca, Merck, Janssen, Abbott, Novo Nordisk, McNeil, Sanofi, and Eli Lilly/Boehringer Ingelheim; has received consulting honoraria from MannKind Corporation; received research support from MannKind Corporation, Andromeda, Novartis, Sanofi, Novo Nordisk, and Takeda; and belongs to the speakers' bureau for Janssen. D.L.L. has participated in advisory panels for Merck, Eli Lilly/Boehringer Ingelheim, Novo Nordisk, and Roche; is a board member and stock/shareholder of Biodel; received consulting honoraria from Merck, Novo Nordisk, and Roche; has received research support from MannKind Corporation, Janssen, Novo Nordisk, Boehringer Ingelheim, and Merck; and belongs to speakers' bureaus for Novo Nordisk and Janssen. J.L.G. received consulting honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, and Novo Nordisk and research support from Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Novo Nordisk. P.-C.C. is an employee of MannKind Corporation. D.B.B. was an employee of MannKind Corporation at the time the trial was performed. Medical writing assistance was funded by MannKind Corporation. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** B.W.B., J.B.M., D.L.L., and J.L.G. contributed to the conduct of the study; data acquisition, analysis, and interpretation; and review and approval of the manuscript. P.-C.C. contributed to the study design; data acquisition, analysis, and interpretation; and review and approval of the manuscript. D.B.B. contributed to the data analysis and interpretation and review and approval of the manuscript. P.-C.C. and D.B.B 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.

**Prior Presentation.** Parts of this study were presented in abstract form at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014.

## References

1. Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. Lancet 1997;350:1505–1510

2. Cryer PE. Hypoglycemia in type 1 diabetes mellitus. Endocrinol Metab Clin North Am 2010;39:641–654

3. Jacqueminet S, Masseboeuf N, Rolland M, Grimaldi A, Sachon C. Limitations of the so-called "intensified" insulin therapy in type 1 diabetes mellitus. Diabetes Metab 2005;31:4S45–4S50

4. American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl. 1):S14–S80

5. Peyrot M, Rubin RR, Kruger DF, Travis LB. Correlates of insulin injection omission. Diabetes Care 2010;33:240–245

6. Peyrot M, Skovlund SE, Landgraf R. Epidemiology and correlates of weight worry in the multinational Diabetes Attitudes, Wishes and Needs study. Curr Med Res Opin 2009;25:1985–1993

7. Leone-Bay A, Grant M. Technosphere/insulin: mimicking endogenous insulin release. In *Modified-Release Drug Delivery Technology*. Vol. 2, 2nd ed. Rathbone M, Hadgraft J, Roberts M, Lane M, Eds. New York, Informa Healthcare USA, Inc., 2008, p. 673–679

8. Boss AH, Petrucci R, Lorber D. Coverage of prandial insulin requirements by means of an

ultra-rapid-acting inhaled insulin. J Diabetes Sci Technol 2012;6:773–779
9. Richardson PC, Boss AH. Technosphere insulin technology. Diabetes Technol Ther 2007;9 (Suppl. 1):S65–S72
10. Potocka E, Cassidy JP, Haworth P, Heuman D, van Marle S, Baughman RA Jr. Pharmacokinetic characterization of the novel pulmonary delivery excipient fumaryl diketopiperazine. J Diabetes Sci Technol 2010;4: 1164–1173
11. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179–187
12. Neumiller JJ, Campbell RK, Wood LD. A review of inhaled Technosphere insulin. Ann Pharmacother 2010;44:1231–1239
13. Rave K, Heise T, Heinemann L, Boss AH. Inhaled Technosphere insulin in comparison to subcutaneous regular human insulin: time action profile and variability in subjects with type 2 diabetes. J Diabetes Sci Technol 2008;2: 205–212
14. Bosi E, Scavini M, Ceriello A, et al.; PRISMA Study Group. Intensive structured self-monitoring of blood glucose and glycemic control in non-insulin-treated type 2 diabetes: the PRISMA randomized trial. Diabetes Care 2013;36:2887–2894
15. Hollander PA. Insulin detemir for the treatment of obese patients with type 2 diabetes. Diabetes Metab Syndr Obes 2012;5:11–19
16. Rosenstock J, Lorber DL, Gnudi L, et al. Prandial inhaled insulin plus basal insulin glargine versus twice daily biaspart insulin for type 2 diabetes: a multicentre randomised trial. Lancet 2010;375:2244–2253
17. Skyler JS, Weinstock RS, Raskin P, et al.; Inhaled Insulin Phase III Type 1 Diabetes Study Group. Use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic subjects: a 6-month, randomized, comparative trial. Diabetes Care 2005;28:1630–1635
18. Edgerton DS, Cherrington AD, Neal DW, et al. Inhaled insulin is associated with prolonged enhancement of glucose disposal in muscle and liver in the canine. J Pharmacol Exp Ther 2009;328:970–975
19. Ciofetta M, Lalli C, Del Sindaco P, et al. Contribution of postprandial versus interprandial blood glucose to $HbA_{1c}$ in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. Diabetes Care 1999;22:795–800
20. Del Sindaco P, Ciofetta M, Lalli C, et al. Use of the short-acting insulin analogue lispro in intensive treatment of type 1 diabetes mellitus: importance of appropriate replacement of basal insulin and time-interval injection-meal. Diabet Med 1998;15:592–600
21. Tamás G, Marre M, Astorga R, Dedov I, Jacobsen J, Lindholm A; Insulin Aspart Study Group. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. Diabetes Res Clin Pract 2001;54:105–114
22. Davis WA, Knuiman M, Kendall P, Grange V, Davis TME; Fremantle Diabetes Study. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care 2004;27:752–757
23. Panel on Handling Missing Datain Clinical Trials; National Research Council. *The Prevention and Treatment of Missing Data in Clinical Trials*. Washington, DC, National Academies Press, 2010
24. Siddiqui O, Hung HM, O'Neill R. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat 2009;19:227–246
25. Fineberg SE, Kawabata TT, Krasner AS, Fineberg NS. Insulin antibodies with pulmonary delivery of insulin. Diabetes Technol Ther 2007; 9(Suppl. 1):S102–S110