

Basal/Bolus With Prandial Inhaled Technosphere® Insulin (TI) Plus Insulin Glargine QD vs Biaspart 70/30 Insulin BID in T2 DM Inadequately Controlled on Insulin With/Without Oral Agents

Luigi Gnudi¹, Daniel Lorber², Julio Rosenstock³, Campbell P. Howard⁴, Richard Petrucci⁴, David Shearer⁴, David Bilheimer⁴, Ping-Chung Chang⁴, David Kramer⁴, Peter C. Richardson⁴

¹Unit for Metabolic Medicine, Cardiovascular Division, King's College London, London, United Kingdom; ²Diabetes Care and Information Center of New York, Flushing, NY, United States; ³Dallas Diabetes and Endocrine Center, TX, United States; ⁴MannKind Corporation, Valencia, CA, United States



ABSTRACT

Background and aims: Technosphere® Insulin (TI) is a fast-acting inhaled insulin with a pharmacokinetic profile well suited for earlier control of postprandial plasma glucose (PPG). This randomized, active-control, parallel-group study compared the efficacy and safety of basal/bolus prandial TI plus bedtime glargine insulin (G) vs premixed biaspart 70/30 insulin BID (BPA 70/30) in type 2 diabetes mellitus inadequately controlled (HbA1c > 7.0% and ≤ 11.0%) despite insulin with or without oral antihyperglycemic therapy.

Materials and methods: Subjects were randomized to a 52-week course of TI+G (n = 334) or BPA 70/30 (n = 343) with insulin adjustments according to investigator discretion to achieve predefined glycemic goals but without enforcing a structured titration regimen. Primary outcome was change in HbA1c. Secondary objectives were proportion of subjects reaching specific HbA1c levels, PPG, and fasting plasma glucose (FPG). **Results:** Mean baseline characteristics were similar for TI+G and BPA 70/30 (age 55.9, 55.9 years; disease duration 13.1, 13.6 years; baseline HbA1c 8.7%, 8.7%; BMI 31.55, 31.07 kg/m²). HbA1c was reduced by 0.58% and 0.70% in the TI+G and BPA 70/30 groups (intent-to-treat last observation carried forward), respectively, and the proportion of subjects achieving HbA1c < 7.0% were comparable between treatments (22% vs. 27%). Mean FPG at week 52 was 7.8 mmol/L for the TI+G group and 8.7 mmol/L for the BPA 70/30 group, and the FPG change from baseline was 2.0 vs. 1.0 mmol/L (p = 0.0029). The absolute 1-h PPG (9.5 vs. 11.6 mmol/L; p < 0.0001) was significantly lower with TI+G. TI+G produced significantly less weight gain (0.9 vs. 2.5 kg; p = 0.0002) and significantly less mild/moderate and severe hypoglycemia (Table 1). The final insulin doses were TI, 198 U (approximately equivalent to 53 IU of rapid-acting insulin); G, 47 IU; and BPA 70/30, 88 IU. Mean changes from Baseline to Week 52 in forced expiratory volume, forced expiratory vital capacity, and carbon monoxide diffusing capacity were similar in the two groups.

Conclusion: TI+G vs BPA 70/30 resulted in comparable HbA1c reductions but lower 1-h PPG with less weight gain and less hypoglycemia.

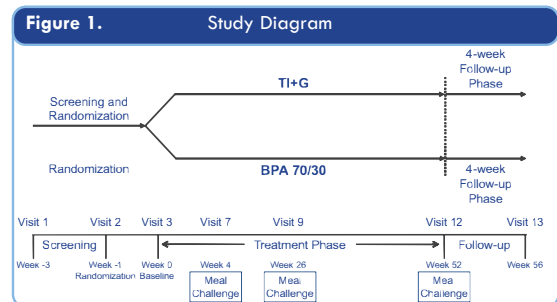
Category of Hypoglycemia	Incidence				Event Rates		
	TI+G	BPA 70/30	Odds Ratio	p Value	TI+G	BPA 70/30	p Value
Mild/Moderate (%)	48	69	0.417	<0.001	0.40 per subject-month	0.59 per subject-month	0.0029
Severe (%)	4	10	0.409	0.0066	0.72 per 100 subject-months	2.19 per 100 subject-months	0.0591
Total (%)	48	69	0.417	<0.001	0.41 per subject-month	0.61 per subject-month	0.0027

BACKGROUND AND AIMS

- Physiologic mealtime insulin levels with a rapid onset and limited duration of action will be needed eventually for the management of patients with type 2 diabetes.
- MannKind Corporation is currently developing Technosphere® Insulin (TI) Inhalation Powder for the control of hyperglycemia in adults with diabetes.
- TI is composed of recombinant human insulin adsorbed onto Technosphere® particles (formed with the excipient, fumaric dikeketopiperazine powder).
- TI particles are ideally sized for inhalation into the deep lung. Once inhaled, TI dissolves immediately upon contact with the lung surface and the insulin is rapidly absorbed into the systemic circulation with a time to maximum observed concentration (t_{max}) of approximately 14 minutes in subjects with type 2 diabetes.
- In clinical studies, most of the glucose-lowering effect of TI is delivered in the first 3 hours postdose, thereby potentially reducing the risk for and the incidence of hypoglycemia.
- Our aim is to compare the efficacy and safety of TID prandial TI plus insulin glargine QD as a basal/bolus regimen vs Biaspart 70/30 insulin BID in T2 DM inadequately controlled on previous insulin +/- oral agents.

STUDY DESIGN

- Prospective, multinational, multicenter, open-label, randomized, controlled trial.
- 654 subjects with type 2 diabetes, comparing a basal/bolus regimen of subcutaneous (sc) basal insulin glargine QD in combination with inhaled prandial TI vs sc premix of intermediate-acting and rapid-acting insulin (BPA 70/30) BID.



MATERIALS AND METHODS

Inclusion Criteria

- Type 2 diabetes subjects entering the trial had an HbA1c > 7.0% and < 11.0% and were receiving insulin.
- Prior use of sc insulin 2-3 times daily ± allowed oral antihyperglycemic agents.
- Subjects were allowed to continue specified oral antidiabetic agents that they were using at trial entry (ie, metformin or thiazolidinediones [TZD]).

Insulin Adjustments

- The starting TI doses for each subject were selected to replace 50% of the subject's total daily sc insulin dose with a corresponding TI dose.
- TI doses were divided over the main daily meals and adjusted based on home glucose monitoring.
- The remaining 50% of the total sc insulin dose was replaced with basal insulin adjusted based on home glucose monitoring.
- Dosing for subjects in the BPA 70/30 group was adjusted based on fasting and presupper home glucose monitoring.
- Insulin adjustments were made at the investigators discretion with no enforcement of a structured insulin algorithm in either insulin group.

Glycemic Control Assessments

- HbA1c was measured at Screening, Week 0 (Baseline), and Weeks 14, 26, 38, and 52.
- Meal challenge tests were performed at Weeks 4, 26, and 52.
 - Venous blood was drawn at -30 and 0 minutes premeal and at 30, 60, 90, 105, 120, 180, 240, 300, and 360 minutes postmeal.
 - A standardized liquid meal (12 ounces Boost Plus®, Novartis) was used for the meal challenge.
 - Within 90 seconds of inhalation of TI, subjects immediately began ingesting the liquid meal.
 - In the BPA 70/30 arm, subjects were instructed to inject the insulin 15 minutes prior to ingesting the liquid meal.

RESULTS

Study Demographics

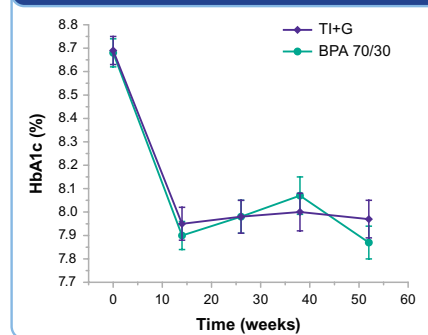
At Baseline, both groups were similar with respect to age, gender, BMI, HbA1c, FPG, and duration of type 2 diabetes.

Baseline Characteristics	Category/Statistic	TI+G (n = 323)	BPA 70/30 (n = 331)
Gender, number of subjects (%)	Male	163 (50.5)	146 (44.1)
	Female	160 (49.5)	185 (55.9)
Age (years)	Mean	56 ± 11	56 ± 10
BMI (kg/m ²)	Mean	31.6 ± 5	31.1 ± 5
HbA1c (%)	Mean	8.7 ± 1.1	8.7 ± 1.1
Fasting Plasma Glucose (mmol/L)	Mean	9.4 ± 3.7	9.8 ± 3.7
Duration of Diabetes (years)	Mean	13.1 ± 7	13.6 ± 8

Primary Endpoint

- The mean change from Baseline (Week 0) to Week 52 in HbA1c was the primary endpoint.
- TI+G was noninferior to BPA 70/30 with a mean treatment difference of 0.06% in the ITT Population.
- In the TI+G arm, the change from Baseline (8.7 ± 1.1%) was -0.66 ± 0.08%.
- In the BPA 70/30 arm, the change from Baseline (8.7 ± 1.1%) was -0.72 ± 0.07%.
- At Week 52, there was a sustained and statistically comparable reduction from Baseline in HbA1c for both treatment arms (p = 0.5782 by Mixed Model Repeated Measures [MMRM]).
- The percent of subjects with an end-of-study HbA1c < 6.5%, < 7.0%, and < 8.0% was not statistically different between the TI+G and BPA 70/30 treatment groups.

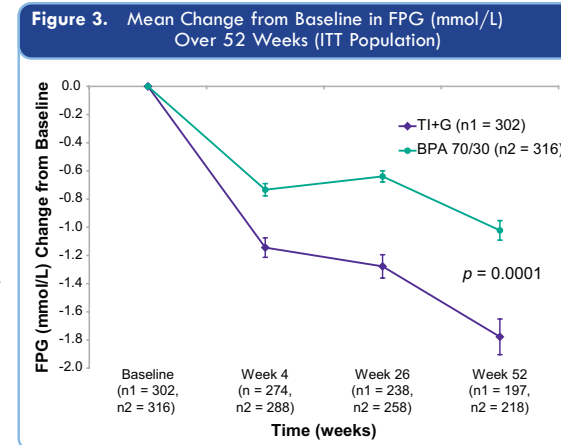
Figure 2. Mean Change from Baseline in HbA1c Over 52 Weeks (ITT Population)



RESULTS (CONT'D)

Fasting Plasma Glucose

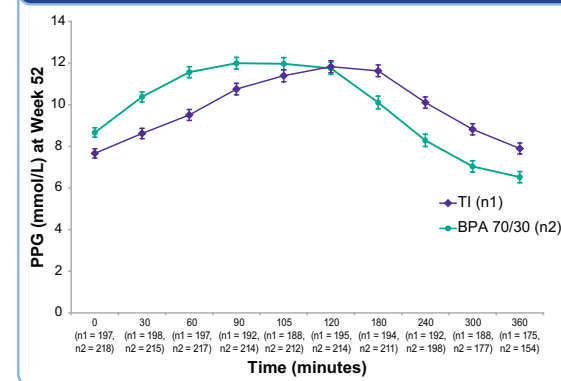
- Over the 52-week treatment period, mean FPG levels decreased significantly in the TI+G group compared to the BPA 70/30 group (Figure 3).
- The Least Square Means FPG change from Baseline was -1.5 ± 0.17 mmol/L in the TI+G arm vs -0.7 ± 0.17 mmol/L in the BPA 70/30 arm, p = 0.0001.
- Mean FPG values at Week 52 were 7.8 ± 3.11 mmol/L and 8.7 ± 3.33 mmol/L in the TI+G and BPA 70/30 arms, respectively.
- The change from Baseline was significantly different between groups in favor of TI+G at Weeks 4, 26, and 52; p = 0.0029 at Week 52.



Postprandial Glucose Control After a Meal Challenge

- Early postprandial control after a meal challenge was better in the TI+G arm with a slower rise in mean PPG and lower 1-hour PPG values at all of the meal challenges.
- At Week 52, the 1-hour postdose change from Time 0 was significantly different between groups (p < 0.0001), 2.1 ± 0.17 mmol/L in the TI+G arm compared to 3 ± 0.17 mmol/L in the BPA 70/30 arm.
- The absolute values at 60 minutes postdose (Week 52) were lower in the TI+G vs the BPA 70/30 group, 9.5 ± 3.67 mmol/L and 11.6 ± 3.89 mmol/L, respectively.
- Mean PPG profile in the TI+G group had a slower rise in plasma glucose concentrations, a lower mean 1-hour PPG concentration, a lower AUC₀₋₁₂₀, and a slower decline to Baseline compared to subjects in the BPA 70/30 group (Figure 4).
- Mean PPG profile in the BPA 70/30 group showed a greater AUC₀₋₁₂₀ and a more rapid and steep descent to Baseline that might have accounted for the higher incidence of hypoglycemia at meal challenges and throughout the trial.

Figure 4. Postprandial Glucose Control After a Meal Challenge at Week 52 (ITT Population)



Insulin Doses

In the TI+G arm, the mean total daily dose (TDD) of TI increased substantially over time and was 198 ± 74 U at Week 52 (equivalent to 53 ± 20 IU of sc insulin); the average daily dose of insulin glargine was 47 IU. In the BPA 70/30 arm, the final mean TDD was 88 ± 48 IU. The mean daily dose of TZDs and metformin was similar between treatment groups.

Table 3. PPG AUC Parameters (mmol/L·hr) at Week 52 (ITT Population)

PPG AUC ₀₋₃₆₀ minutes	TI+G	BPA 70/30
0-120 minutes	19.3	22.1
120-360 minutes	40.4	34.6
0-360 minutes	59.8	56.7

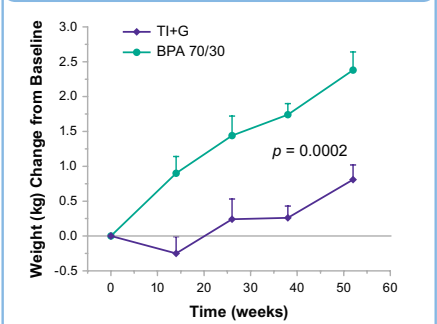
AUCs were calculated based on the linear trapezoidal rule
AUC = Area under the concentration versus time curve

RESULTS (CONT'D)

Body Weight

- Weight gain was significantly less during treatment with TI+G than during treatment with BPA 70/30 (Figure 5).
- In the TI+G arm, subjects gained a LS Mean of 0.9 ± 0.3 kg vs 2.5 ± 0.3 kg in the BPA 70/30 arm (p = 0.0002).
- Body weight treatment difference of 1.6 ± 0.4 kg (ITT Population by ANCOVA).

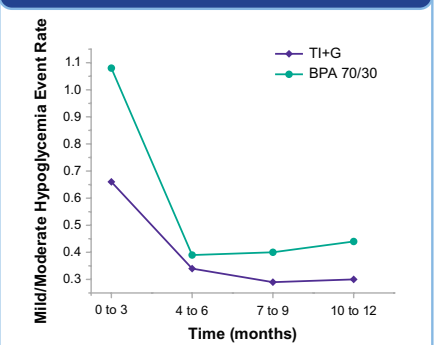
Figure 5. Mean Change from Baseline in Body Weight (kg) Over 52 weeks (ITT Population)



Hypoglycemia

- 48% of subjects treated with TI+G reported any hypoglycemic events while 69% of BPA 70/30-treated subjects reported episodes of hypoglycemia (OR = 0.417; p < 0.001).
- A significantly lower percentage of subjects treated with TI+G (14 subjects, 4%) reported protocol-defined severe hypoglycemia than those treated with BPA 70/30 (33 subjects, 10%) (OR = 0.409; p = 0.0066).
- The hypoglycemia event rate was highest over the first 3 months of the study in both groups (0.67 per subject-month vs 1.13 per subject-month, respectively, for TI+G and BPA). A similar pattern was observed for severe hypoglycemia rates. During this period, the mean daily TI+G dose was titrated up while the mild-to-moderate hypoglycemia event rates decreased over the same time period (Figure 6).
- In the BPA 70/30 group, the mean daily insulin doses increased over the first 3 months of the trial but the mild-to-moderate hypoglycemia event rate was higher than in the TI+G group.
- Because both treatment groups demonstrated comparable glucose control over the first 3 months of the study (Figure 1), the data indicate that the inherent hypoglycemia risk during study drug titration was lower in TI+G-treated subjects.
- BPA 70/30-treated subjects reported more nocturnal severe hypoglycemic events than did TI+G-treated subjects.
- A total of 9 (2.7%) subjects reported 14 severe nocturnal events in the BPA 70/30 group; in the TI+G group, 1 (0.3%) subject reported 3 events.

Figure 6. Mild and Moderate Hypoglycemia Event Rates by Time Since Randomization (Safety Population)



Pulmonary Safety Profile

Pulmonary safety monitoring was performed throughout the trial and at follow-up. No statistically significant differences between the 2 treatment groups were noted in the mean change from Baseline in FEV₁, FVC or DL_{CO} at Week 52, the end of the treatment period.

CONCLUSIONS

- New treatments are needed for type 2 diabetes that will improve glycemic control with a lower risk for weight gain and hypoglycemia.
- In this trial, TI+G proved to be an effective therapy, with a significantly lower risk for weight gain and hypoglycemia than the widely used twice-daily premixed insulin analog BPA 70/30.
- Treatment with TI+G provided sustained glycemic efficacy over 52 weeks that was comparable to twice-daily premixed insulin analog BPA 70/30.
- Both insulin groups achieved a significant reduction from baseline in HbA1c that could have been greater had a structured insulin algorithm been consistently followed.
- Compared with the twice-daily premixed insulin analog BPA 70/30, the improvements in glycemic control with TI+G had significantly lower 1-hour PPG, significantly better FPG control, significantly less weight gain, and significantly less overall and severe hypoglycemia.