

In Patients Using Technosphere® Insulin, Variation in PPG Stayed Within ADA-recommended Targets Despite Large Variations in Glucose Load

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ABSTRACT

A Phase 2, single-center, open-label trial evaluated the effect of Technosphere® Insulin (TI) Inhalation Powder on PPG levels in T2DM patients ingesting meals with varied carbohydrate content. The trial was designed to determine if, once an optimal dose of TI is established for a patient based on a eucaloric diabetic meal, their optimal dose could be used safely regardless of variation in meal carbohydrate content.

Patients had ≤4 visits to optimize their TI doses to achieve a 1-hour PPG <150 mg/dL without hypoglycemia for breakfast (B) and lunch (L). Patients then underwent a meal challenge for 4 consecutive weeks with varied carbohydrate meal contents (50%, 100%, and 200% of calculated carbohydrates and no meal). Primary endpoints were changes in PPG excursions.

Five of 6 enrolled patients completed all 8 meal challenges. The 6th was lost to follow-up and did not complete 2 meal challenges (B-no meal, 200% carbohydrate). Baseline demographics were mean age 60.5 years (±6.8), duration of T2DM 12.3 years (±4.6), A1C 8.0% (±1.2), and BMI 31.6 kg/m² (±6.5). Five of 6 patients were treated with 15 U TI (~4 U sc RAA) for L and 4 of 6 with 15 U for B. The others used 30 U.

Maximum mean PPG excursions for 100% carbohydrate meals were modest (B: -13.7 mg/dL ±22; L: +10.0 mg/dL ±24), with similar results seen during 50% carbohydrate meals. The largest excursions occurred during 200% carbohydrate meals, which remained below ADA targets (B: +32.6 mg/dL ±33; L: +19.5 mg/dL ±18.5). Eleven patients took their usual TI dose, then had no meal. One patient began with an FPG of 97 mg/dL and blood glucose fell to 56 mg/dL at 60 minutes. For the other 10 meal challenges with no meals, the largest mean PPG excursion was -29 mg/dL ±10 at 90 minutes (B) and -33 mg/dL ±10.5 at 60 (L).

Preliminary results suggest that once an optimal dose of TI is determined, some patients can safely take their TI dose, ingest meals with a wide range of carbohydrate content, or even skip meals without severe hypoglycemia.

INTRODUCTION

- Technosphere® Insulin (TI) Inhalation Powder (AFREZZA™) is a pulmonary-delivered inhaled insulin formulation with an action profile similar to the physiological early insulin response.
- Designed as prandial insulin, its duration of action is sufficient to cover the meal-related rise in serum blood glucose and short enough to reduce the risk of potential postprandial hypoglycemia.
- The ADA recommends a peak 1- to 2-hour postprandial plasma glucose (PPG) of <180 mg/dL.¹
- Current data from studies conducted with TI confirm excellent subject acceptance of the technology.
- This clinical trial was designed to determine whether, once an optimal dose of TI is established for a patient with type 2 diabetes mellitus (T2DM) based on a eucaloric diabetic meal, the patient's optimal dose could be used safely regardless of variation in meal carbohydrate content.
- 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 TI for the control of hyperglycemia in adults with type 1 and 2 diabetes.
- TI is composed of recombinant human insulin adsorbed onto Technosphere® particles (formed with the excipient fumaric dikeTOPiperazine).
- 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 of approximately 14 minutes in subjects with T2DM.
- In clinical studies, most of the glucose-lowering effect of TI is delivered in the first 3 hours postdose, thereby potentially reducing the risk and incidence of hypoglycemia.

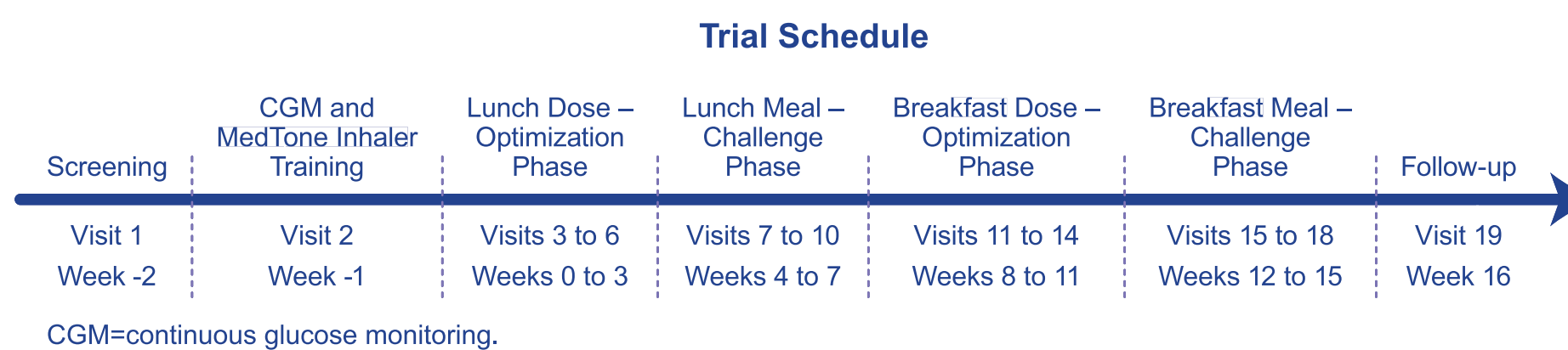
AIM

To evaluate the effect of TI on PPG levels in patients with T2DM following the ingestion of lunch or breakfast meals with varying carbohydrate content once patients have reached their optimal TI dose for each meal.

MATERIALS AND METHODS

- Phase 2, single-center, open-label, pharmacodynamic clinical trial
- Inclusion criteria
 - Nonsmoking patients ≥18 and ≤70 years of age with a clinical diagnosis of T2DM for ≥12 months with no change in antidiabetic regimen for at least 90 days prior to screening
 - Fasting plasma glucose of 80 to 140 mg/dL and A1C >6.5% and ≤10.0%
 - Body mass index of ≤40 kg/m²
 - Negative urine cotinine test, defined as ≤100 ng/mL
- Key exclusion criteria
 - Two or more severe hypoglycemic episodes within 6 months of screening or an episode of severe hypoglycemia between screening and baseline
 - Any hospitalization or emergency department visit due to poor diabetic control within 6 months of screening or between screening and baseline
 - Severe complications of diabetes mellitus, including symptomatic autonomic neuropathy; disabling peripheral neuropathy; active proliferative retinopathy; or nephropathy with renal failure, renal transplant, and/or dialysis
 - History of significant respiratory or cardiac disease, including chronic obstructive pulmonary disease, clinically proven asthma, congestive heart failure (New York Heart Association class III or IV), serious arrhythmia, and myocardial infarction
 - Uncontrolled hypertension with a systolic blood pressure of >180 mm Hg and/or diastolic blood pressure >110 mm Hg
 - Use of Symlin® (pramlintide acetate), Byetta® (exenatide), Exubera® (insulin human [rDNA origin]), or TI within the past 12 weeks
 - Major organ system diseases, including seizure disorder, renal or hepatic dysfunction or disease, cancer, active infection, anemia (hemoglobin value ≤10.5 g/dL for women or ≤11.5 g/dL for men)
 - Current or history of drug or alcohol abuse
- Following initial screening and continuous glucose monitoring and MedTone® inhaler training visits, patients underwent up to a maximum of 4 dose optimization visits and up to 4 meal challenge visits for lunch and then breakfast (Figure 1).

FIGURE 1



- During the dose optimization visits, patients received a meal challenge utilizing 100% carbohydrate content, defined as 50 g of carbohydrates and a breakdown of calories in a ratio of 40% carbohydrates, 30% protein, and 30% fat content.
- Only patients achieving the optimal dose of 1-hour PPG level <150 mg/dL without 2- to 3-hour PPG hypoglycemia proceeded to the meal challenge phase.
- During the meal challenge visits, patients received varied carbohydrate content with their optimal dose of TI: Visit 7, 50% of the carbohydrate content; Visit 8, without a meal (only if deemed safe by the principal investigator); Visit 9, 200% of the carbohydrate content; Visit 10, 150% of the carbohydrate content (only if significant hyperglycemia was noted during the 200% meal challenge).
- Patients with T2DM began taking TI as their prandial insulin at Visit 3 and took TI with meals on a daily basis throughout the course of the clinical trial.
- The primary endpoint was the change in the minimum and maximum PPG and area under the glucose concentration curve from 0 to 240 minutes, based on venous-drawn blood glucose concentrations, measured at -30, 0, 30, 60, 90, 105, 120, 180, and 240 minutes following each meal challenge.

RESULTS

Patients

- Five of the 6 enrolled T2DM patients completed all 8 meal challenges for lunch and breakfast (Table 1).

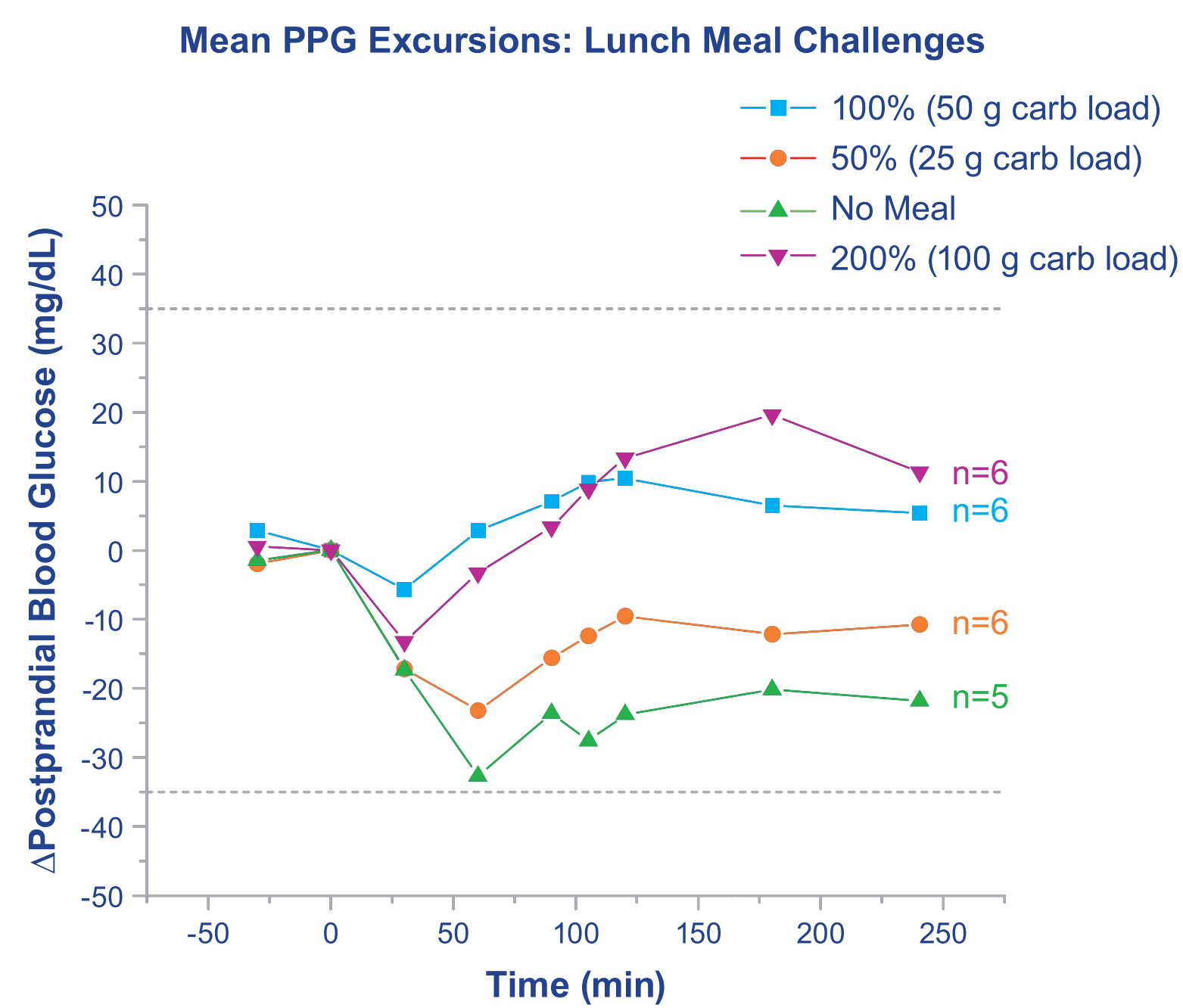
TABLE 1

Baseline Patient Demographics and Optimized TI Dose						
Subject	Age (y)	Duration of Diabetes (y)	Baseline A1C (%)	Baseline BMI (kg/m ²)	TI Optimized Dose (U): Lunch	TI Optimized Dose (U): Breakfast
A	71	20	6.5	25	15	15
B	54	12	8.9	33	15	15
C	52	6	9.8	28	15	15
D	61	14	7.2	40	15	15
E	63	10	7.7	26	15	30
F	62	12	7.8	38	30	30

BMI=body mass index; TI=Technosphere® Insulin.

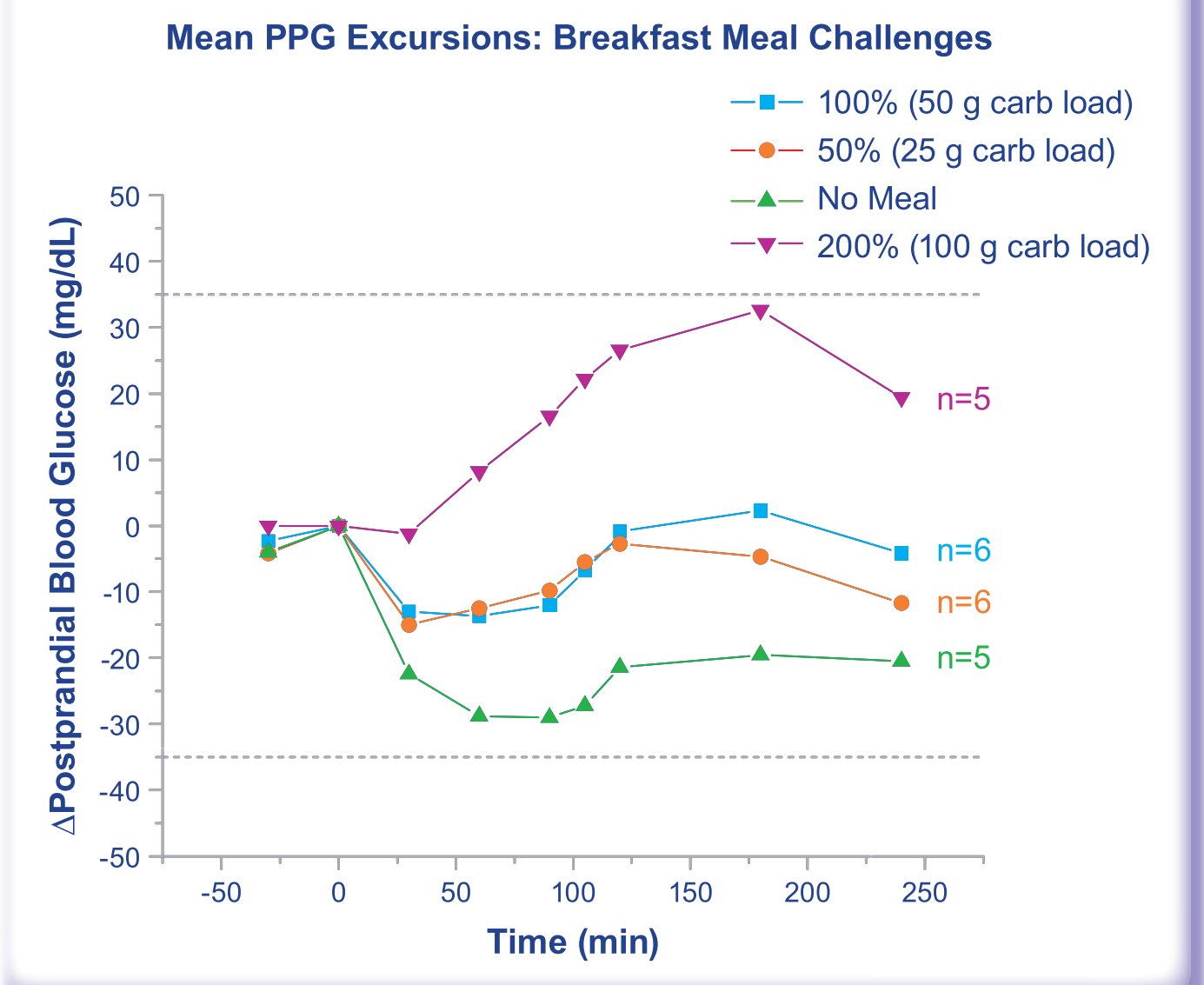
- Baseline demographics were mean age 60.5 years (±6.8), duration of T2DM 12.3 years (±4.6), A1C 8.0% (±1.2), and body mass index 31.6 kg/m² (±6.5).
- Five of 6 patients were treated with 15 U TI (~4 U subcutaneous rapid-acting insulin analog) for lunch and 4 of 6 with 15 U for breakfast. The remaining patients used 30 U of TI.
- Primary endpoint: Mean PPG levels.
- Mean PPG excursions for the lunch and breakfast meal challenges are depicted in Figure 2 and Figure 3, respectively.

FIGURE 2



RESULTS (CONTINUED)

FIGURE 3



- Overall, the range of PPG excursions for all lunch and breakfast meal challenges was narrow (-35 mg/dL to 35 mg/dL).
- Maximum mean PPG excursions for 100% carbohydrate meals were modest (lunch: +10.0 mg/dL ±24; breakfast: -13.7 mg/dL ±22), with similar results seen during 50% carbohydrate meals.
- The largest excursions occurred during 200% carbohydrate meals, which remained below ADA targets (lunch: +19.5 mg/dL ±18.5; breakfast: +32.6 mg/dL ±33).
- On eleven occasions (5 breakfasts and 6 lunch), 6 patients took their usual TI dose, then had no meal. One patient began with a fasting plasma glucose of 97 mg/dL, which fell to 56 mg/dL at 60 minutes.
- For the other 10 meal challenges with no meals, the largest mean PPG excursion was -33 mg/dL ±10.5 at 60 minutes (lunch) and -29 mg/dL ±10 at 90 minutes (breakfast).

CONCLUSIONS

- New treatments are needed for patients with T2DM that will improve glycemic control and lower the risk of weight gain and hypoglycemia.
- In this trial, PPG excursions were minimal with an acceptable TI dose and were generally similar across a wide range of carbohydrate content, with the exception of the 200% carbohydrate load, in which there was a somewhat higher excursion for the breakfast meal challenge.
- Preliminary results suggest that once an optimal dose of TI is determined, some patients could safely take their TI dose, ingest meals with a wide range of carbohydrate content, or even inadvertently skip meals without developing severe hypoglycemia.

REFERENCE

1. Standards of medical care in diabetes—2010. *Diabetes Care*. 2010;33(Suppl 1):S11-S61.