

# Reduced Incidence and Frequency of Hypoglycemia in an Integrated Analysis of Pooled Data from Clinical Trials of Subjects with Type 2 Diabetes Using Prandial Inhaled Technosphere® Insulin

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## ABSTRACT

**Background and aims:** Technosphere® Insulin (TI) is a rapid-acting insulin with a pharmacokinetic profile well suited for early control of postprandial plasma glucose. This integrated analysis includes the pooled data from six phase 2/3 clinical trials in subjects with type 2 diabetes mellitus inadequately controlled (HbA1c  $\geq 6.6\%$  and  $\leq 12.0\%$ ) despite insulin with or without oral antihyperglycemic therapy.

**Materials and methods:** Subjects were randomized to treatment regimens to achieve predefined glycemic goals: TI (N = 1795) or sc insulin (N = 942), which included biphasic insulin aspart 70/30, or insulin aspart and "usual care," with insulin adjustments according to investigator discretion in five trials and forced titration in one trial. A structured titration regimen was not enforced. When experiencing hypoglycemic-like symptoms, subjects were instructed to confirm the event with a blood glucose reading. Subjects experiencing a severe hypoglycemic episode were required to report the details of third-party assistance (if needed), the presence of neurologic symptoms, and the specifics of treatment.

**Results:** Mean baseline characteristics were similar for TI and sc insulin comparator (age 56.2, 55.6 years; disease time since diagnosis 10.8, 12.4 years; baseline HbA1c 8.8%, 8.8%; BMI 31.1, 31.1 kg/m<sup>2</sup>). Subjects treated with TI experienced statistically significantly fewer hypoglycemic episodes in regard to both incidence and frequency compared with subjects treated with sc insulins. For incidence, significantly fewer subjects reported hypoglycemia with TI: 31.8% vs 49.6% for total hypoglycemia; 31.6% vs 49.4% for mild/moderate hypoglycemia; and 2.8% vs 7.5% for severe hypoglycemia, with the three comparison p values  $<0.0001$ . For frequency, TI also had significantly fewer events, evaluated by event rate (number of events per 100 subject months): 23.9 vs 38.8 for total hypoglycemia ( $p <0.0001$ ); 23.2 vs 37.3 for mild/moderate hypoglycemia ( $p <0.0001$ ); and 0.66 vs 1.37 for severe hypoglycemia ( $p <0.0184$ ). **Conclusion:** TI, often in combination with a basal insulin, consistently reduced the incidence and frequency of both mild/moderate and severe hypoglycemic events under conditions of comparable glycemic control. The reduction in the risk of hypoglycemia in patients with type 2 diabetes under inadequate control may facilitate the introduction of insulin therapy.

Hypoglycemia	Incidence (%)		Odds Ratio	Odds Ratio p Value	Event Rate per 100 Subject Months		Event Rate p Value
	TI	SC Insulin			TI	SC Insulin	
Mild/Moderate	31.6	49.4	0.466	$<0.0001$	23.2	37.3	$<0.0001$
Severe	2.8	7.5	0.359	$<0.0001$	0.66	1.37	0.0184
Total	31.8	49.6	0.466	$<0.0001$	23.9	38.8	$<0.0001$

## INTRODUCTION

- Fear of hypoglycemia is a common deterrent to the initiation of insulin in patients with type 2 diabetes (T2 DM).<sup>1</sup> Once insulin therapy is initiated, concerns about risk of hypoglycemia as well as the actual episodes themselves often limit insulin dosing, thereby preventing adequate blood glucose (BG) control.<sup>2</sup>
- A recent report found that insulin-treated patients with T2 DM experience ~1.64 episodes of hypoglycemia per year, with 0.35 of these episodes per patient per year (~5 episodes per year) being considered severe hypoglycemic events.<sup>3</sup>
- New treatments are needed for patients with T2 DM that lower the risk for hypoglycemia, thus allowing for more effective insulin titration and improved glycemic control.
- MannKind Corporation is developing the Technosphere® Insulin Inhalation System for the control of hyperglycemia in adult patients with diabetes. 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. As a result of the rapid absorption, the metabolic effects of TI achieve maximum effect substantially earlier than has been reported for other insulins. In clinical studies, the majority of the glucose-lowering effect of TI is delivered in the first 3 hours post-dose, thereby reducing the risk for and the incidence of hypoglycemia.

## MATERIALS AND METHODS

- Subjects were randomized to the following treatment regimens and insulin adjustments were made according to investigator discretion in 5 trials and forced titration in 1 trial: TI (N = 1795) or sc insulin (N = 942), which included biphasic aspart (BPA) 70/30 BID, insulin aspart TID, and "usual antidiabetic care with insulin".
- Subjects in the TI group received TI 3-4 times per day before meals or snacks, alone or in combination with sc insulin glargine QD.
- Mild/moderate hypoglycemia was defined as a BG  $< 63$  mg/dL (3.5 mmol/L) or hypoglycemia-like symptoms.
- Severe hypoglycemia was defined as a BG  $\leq 36$  mg/dL (2.0 mmol/L) or when all 3 of the following occurred simultaneously – subject required the assistance of another person; AND subject exhibited at least 1 cognitive neurological symptom (memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, seizure, loss of consciousness); AND a measured BG  $< 49$  mg/dL (2.7 mmol/L), or, in the absence of a BG measurement, clinical symptoms were reversed by oral carbohydrates, sc glucagon or intravenous glucose administration. Or in some smaller trials, events that required glucagon injections, glucose infusions, or third party assistance.
- An integrated analysis of hypoglycemia using pooled data from the active-controlled Phase 2/3 trials (similarity of trial design and continuous exposure to study treatment of  $> 14$  days) was performed comparing TI with sc insulin comparators.

## RESULTS

### Baseline Characteristics:

At baseline, both treatment groups were similar with respect to age, BMI, HbA1c, and duration of type 2 diabetes (Table 1).

	TI (N = 1795)	SC Insulin Comparator (N = 942)
Age (years)	56.2 $\pm$ 8.7	55.6 $\pm$ 8.9
Time Since Diagnosis (years)	10.8 $\pm$ 6.7	12.4 $\pm$ 7.3
Baseline HbA1c (%)	8.8 $\pm$ 1.3	8.8 $\pm$ 1.3
BMI (kg/m <sup>2</sup> )	31.1 $\pm$ 4.8	31.1 $\pm$ 4.9

### Incidence of Hypoglycemia:

- Subjects treated with TI had a lower incidence of hypoglycemia than sc insulin comparators in all assessed categories, with statistically significant differences for total, mild/moderate, and severe hypoglycemia, including those events with a BG  $\leq 49$  mg/dL ( $\leq 2.7$  mmol/L) and  $\leq 36$  mg/dL ( $\leq 2.0$  mmol/L) (Table 2).

	TI (N = 1795)	SC Insulin Comparator (N = 942)	TI vs. SC Insulin Comparators		
			Odds Ratio	95% CI	p Value
Mild/Moderate	567 (31.6)	465 (49.4)	0.466	[0.395, 0.550]	$<0.0001$
Severe	50 (2.8)	71 (7.5)	0.359	[0.247, 0.520]	$<0.0001$
Total	570 (31.8)	467 (49.6)	0.466	[0.395, 0.550]	$<0.0001$
With Cognitive Neurological Symptom	7 (0.7)	13 (1.7)	0.429	[0.170, 1.080]	0.0724
With Glucose $\leq 49$ mg/dL ( $\leq 2.7$ mmol/L)	301 (16.8)	270 (28.7)	0.501	[0.414, 0.607]	$<0.0001$
With Glucose $\leq 36$ mg/dL ( $\leq 2.0$ mmol/L)	47 (2.6)	70 (7.4)	0.372	[0.258, 0.537]	$<0.0001$

## RESULTS (CONT'D)

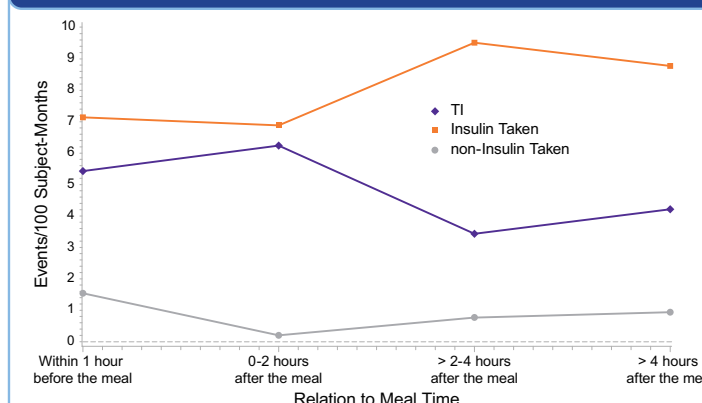
### Hypoglycemia Event Rates

Subjects treated with TI had significantly lower hypoglycemia event rates than sc insulin comparators with respect to total, mild/moderate, and severe hypoglycemia, as well as subjects with BG  $\leq 36$  mg/dL ( $\leq 2.0$  mmol/L).

Category	TI + Basal Insulin (N = 614)	SC Insulin Comparator (N = 599)
<b>Total</b>		
No. of Subjects at Risk	1795	942
No. of Subjects w/Events (%)	570 (31.8)	467 (49.6)
No. of Events	3653	4862
Exposure Time (Subject-Month)	15305.2	12536.9
Event Rate (Per 100 Subject-Month)	23.9	38.8
p value	$<0.0001$	
<b>Mild/Moderate</b>		
No. of Subjects at Risk	1795	942
No. of Subjects w/Events (%)	567 (31.6)	465 (49.4)
No. of Events	3545	4679
Exposure Time (Subject-Month)	15305.2	12536.9
Event Rate (Per 100 Subject-Month)	23.2	37.3
p value	$<0.0001$	
<b>Severe</b>		
No. of Subjects at Risk	1795	942
No. of Subjects w/Events (%)	50 (2.8)	71 (7.5)
No. of Events	101	172
Exposure Time (Subject-Month)	15305.2	12536.9
Event Rate (per 100 Subject-Month)	0.66	1.37
p value	0.0184	
<b>Cognitive Neurological Symptoms</b>		
No. of Subjects at Risk	979	787
No. of Subjects w/Events (%)	7 (0.7)	13 (1.7)
No. of Events	7	19
Exposure Time (Subject-Month)	12763.8	11675.8
Event Rate (per 100 Subject-Month)	0.05	0.16
<b>Glucose <math>\leq 36</math> mg/dL (<math>\leq 2.0</math> mmol/L)</b>		
No. of Subjects at Risk	1795	942
No. of Subjects w/Events (%)	47 (2.6)	70 (7.4)
No. of Events	97	167
Exposure Time (Subject-Month)	15305.2	12536.9
Event Rate (per 100 Subject-Month)	0.63	1.33
p value	0.0187	

For the category of subjects at risk for cognitive neurological symptoms, analyses covered only some of the Phase 3 studies – where the safety data bases could be queried for this category. For other categories of hypoglycemia, event rates were calculated from all pooled, active controlled studies, so the number of subjects at risk was larger (Table 3).

Figure 1. Mild/Moderate Hypoglycemia Event Rates in Relation to Meal Time, TI vs SC Insulin Comparator (Safety Population)

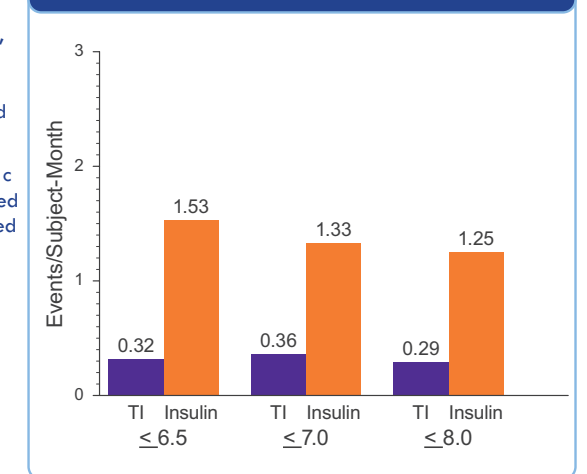


## RESULTS (CONT'D)

### Hypoglycemia Event Rate Based on End-of-Trial HbA1c Category and Treatment

- Event rates of total hypoglycemia, when stratified by end-of-trial HbA1c levels, were always markedly lower in subjects treated with TI vs sc insulin comparators.
- Thus, at equivalent levels of HbA1c control, TI has a markedly improved hypoglycemic risk profile compared to sc insulin comparators.

Figure 2. Event Rate of Hypoglycemia for Subjects Based on End-of-Trial HbA1c Category and Treatment (ITT Population)



## CONCLUSIONS

### In Subjects With T2 DM:

- The incidence and frequency of severe hypoglycemic events were significantly lower with TI than with sc insulin comparator regimens in subjects with T2 DM.
- The incidence and frequency of nonsevere (mild/moderate) hypoglycemic events were significantly lower with TI than with sc insulin comparator regimens in subjects with T2 DM.
- The incidence and frequency of total hypoglycemic events were significantly lower with TI than with sc insulin comparator regimens in subjects with T2 DM.
- There were fewer nocturnal hypoglycemic events, for both severe and mild/moderate, in subjects treated with TI than with sc insulin comparator regimens: 2.2 vs 4.6 per 100 subject-months, respectively, for mild/moderate event rates and 0.1 vs 0.2 per 100 subject-months, respectively, for severe event rates.

## SUMMARY

Under conditions of comparable HbA1c control, the incidence and frequency of hypoglycemic events in TI-treated subjects were significantly lower than the sc insulin comparator treatment in subjects with T2 DM.

## REFERENCES

1. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes*. 2008;57:3169-76.
2. Editorial. Glycemic Control and Hypoglycemia. *Diabetes Care*. 2008;31(10):2072-2076.
3. Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, Band MM, Reekie G, Leese GP; DARTS/MEMO Collaboration. Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. *Diabet Med*. 2005 Jun;22(6):749-55.