

Reduced Incidence and Frequency of Hypoglycemia in an Integrated Analysis of Pooled Data from Clinical Trials of Subjects with Type 1 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 three Phase 2/3 clinical trials in subjects with type 1 diabetes mellitus inadequately controlled (HbA1c > 7.0% and ≤ 11.0%) with standard insulin regimens. **Materials and methods:** Subjects were randomized to one of 3 treatment regimens to achieve predefined glycemic goals: TI (n = 614) plus basal insulin; sc insulin (n = 599), which included insulin glargine plus aspart; or “usual care,” with insulin adjustments according to investigator discretion. A structured titration regimen was not enforced. When experiencing hypoglycemia-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 (age 38.4, 38.5 years; disease time since diagnosis 16.5, 16.6 years; baseline HbA1c 8.6%, 8.6%; BMI 26.1, 26.0 kg/m²). Subjects treated with TI had a lower incidence of hypoglycemia compared with subjects treated with other sc insulins: 75.9% vs 81.0% for total hypoglycemia; 75.6% vs 80.8% for mild/moderate hypoglycemia; and 24.3% vs 27.5% for severe hypoglycemia, with the comparison p values substantially in favor of TI for total hypoglycemia and mild/moderate hypoglycemia. For frequency, TI had a comparable (not statistically different) number of events, evaluated by event rate (number of events per 100 subject-months), with lower event rates for severe hypoglycemia in the TI group. When evaluated for subjects with blood glucose values ≤ 2 mmol/L, TI also was comparable (not statistically different) to sc insulin treatment with a lower event rate. **Conclusion:** TI, in combination with basal insulin, significantly reduced the incidence of total and mild/moderate hypoglycemia with a lower frequency of severe hypoglycemic events than sc insulin comparator under conditions of comparable glycemic control.

Hypoglycemia	Incidence (%)		Odds Ratio	Odds Ratio p Value	Event Rate per 100 Subject Months		Event Rate p Value
	TI + Basal Insulin	Comparator + Basal Insulin			TI + Basal Insulin	Comparator + Basal Insulin	
Mild/Moderate	75.6	80.8	0.743	0.0354	133.2	117.7	0.9097
Severe	24.3	27.5	0.826	0.1576	5.2	6.0	0.5901
Total	75.9	81.0	0.749	0.0413	138.6	124.1	0.9242

BACKGROUND AND AIMS

- The typical individual with type 1 diabetes (T1 DM) suffers an average of 43 symptomatic hypoglycemic events and at least one episode of severe hypoglycemia a year.¹
- New treatments are needed for patients with T1 DM that lower the risk for hypoglycemia, thus allowing for more effective insulin titration and improved glycemic control.²
- 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 9 to 15 minutes in subjects with T1 DM. 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 postdose, 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: TI + basal insulin (glargine or detemir) (n = 614); sc insulin (n = 599), insulin glargine plus aspart, or “usual anti-diabetic care” for subjects with T1 DM (including isophane insulin and aspart, lispro, detemir, and glargine analog insulins). A structured titration regimen was not enforced.
- Subjects in the TI group received TI 3-4 times per day before meals or snacks in combination with sc long-acting insulin QD or BID.

MATERIALS AND METHODS (CONT'D)

- 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 ≤ 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 + basal insulin with sc insulin comparator + basal insulin.

RESULTS

Baseline Characteristics:

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

Table 1. Baseline Characteristics of T1 DM Subjects (Safety Population)

	TI + Basal Insulin (N = 614)	SC Insulin Comparator (N = 599)
Age (Years)	38.4 ± 12.6	38.5 ± 12.5
Time Since Diagnosis (Years)	16.5 ± 11.2	16.6 ± 10.8
Baseline HbA1c (%)	8.6 ± 1.2	8.6 ± 1.2
BMI (kg/m ²)	26.1 ± 4.1	26.0 ± 3.9

Incidence of Hypoglycemia:

- Subjects treated with TI + basal insulin had a lower incidence of hypoglycemia and an improved odds ratio relative to sc insulin comparators for severe, mild/moderate, and total hypoglycemia, including those events with a BG ≤ 49 mg/dL (2.7 mmol/L) and ≤ 36 mg/dL (2.0 mmol/L) (Table 2).
- Treatment with TI is associated with a reduced risk for hypoglycemia relative to sc insulin comparators.

Table 2. Incidence of Hypoglycemia in T1 DM, TI vs SC Insulin Comparators (Safety Population)

	TI + Basal Insulin (N = 614)	SC Insulin Comparator (N = 599)	TI + Basal Insulin vs SC Insulin Comparators		
	n (%)	n (%)	Odds Ratio	95% CI	p Value
Mild/Moderate	464 (75.6)	484 (80.8)	0.743	[0.564, 0.980]	0.0354
Severe	149 (24.3)	165 (27.5)	0.826	[0.633, 1.077]	0.1576
Total	466 (75.9)	485 (81.0)	0.749	[0.567, 0.989]	0.0413
Subjects Requiring Assistance	22 (3.9)	18 (3.3)	1.193	[0.632, 2.249]	0.5862
With Glucose ≤ 49 mg/dL (≤ 2.7 mmol/L)	383 (62.4)	396 (66.1)	0.862	[0.677, 1.099]	0.2308
With Glucose ≤ 36 mg/dL (≤ 2.0 mmol/L)	145 (23.6)	157 (26.2)	0.904	[0.704, 1.159]	0.4260

RESULTS (CONT'D)

Hypoglycemia Event Rates:

TI and sc insulin treatment regimens had comparable (not statistically different) event rates; event rates for severe hypoglycemia and glucose ≤ 36 mg/dL (2.0 mmol/L) were lower for the TI group (Table 3).

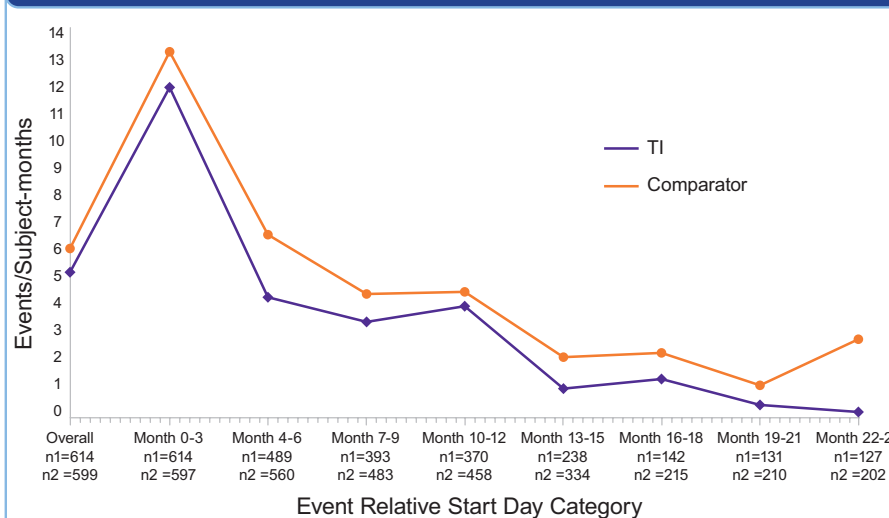
Table 3. Hypoglycemia Event Rates in T1 DM, TI vs SC Insulin Comparators (Safety Population)

Category	TI + Basal Insulin (N = 614)	SC Insulin Comparator (N = 599)
Total		
No. of Subjects at Risk	614	599
No. of Subjects w/Events (%)	466 (75.9)	485 (81.0)
No. of Events	8992	10161
Exposure Time (Subject-Month)	6487.7	8190.3
Event Rate (per 100 Subject-Month)	138.60	124.06
p value	0.9242	
Mild/Moderate		
No. of Subjects at Risk	614	599
No. of Subjects w/Events (%)	464 (75.6)	484 (80.8)
No. of Events	8639	9643
Exposure Time (Subject-Month)	6487.7	8190.3
Event Rate (per 100 Subject Month)	133.16	117.74
p value	0.9097	
Severe		
No. of Subjects at Risk	614	599
No. of Subjects w/Events (%)	149 (24.3)	165 (27.5)
No. of Events	335	494
Exposure Time (Subject-Month)	6487.7	8190.3
Event Rate (per 100 Subject-Month)	5.16	6.03
p value	0.5901	
Glucose ≤ 36 mg/dL (≤ 2.0 mmol/L)		
No. of Subjects at Risk	614	599
No. of Subjects w/Events (%)	145 (23.6)	157 (26.2)
No. of Events	317	470
Exposure Time (Subject-Month)	6487.7	8190.3
Event Rate (per 100 Subject-Month)	4.89	5.74
p value	0.5394	

Hypoglycemia Event Rates:

Severe hypoglycemic event rates increased during the initial drug titration period and then decreased over time in both treatment groups (Figure 1).

Figure 1. Severe Hypoglycemic Event Rates, Time Since Randomization, Subjects Treated with TI + Basal Insulin or SC Insulin Comparators (Safety Population)



CONCLUSIONS

In Subjects With T1 DM:

- The incidence and frequency of severe hypoglycemic events were lower with TI + basal insulin than with sc insulin comparator regimens in subjects with T1 DM. Severe hypoglycemic event rates decreased over time after the initial drug titration period.
- The incidence of non-severe (mild/moderate) hypoglycemia was significantly lower with TI + basal insulin than with sc insulin comparator regimens in subjects with T1 DM. Mild/moderate hypoglycemic event rates decreased over time after the initial drug titration period.
- The incidence of total hypoglycemia was significantly lower with TI + basal insulin than with sc insulin comparator regimens in subjects with T1 DM.
- There were fewer severe nocturnal hypoglycemic events in subjects treated with TI + basal insulin than with sc insulin comparator regimens: 0.6 vs 1.0 per 100 subject-months, respectively.

SUMMARY

- Under conditions of comparable HbA1c control, subjects treated with TI + basal insulin had a lower incidence of hypoglycemia and an improved odds ratio relative to sc insulin comparators for severe, mild/moderate, and total hypoglycemia, including those events with a BG ≤ 49 mg/dL (≤ 2.7 mmol/L) and ≤ 36 mg/dL (≤ 2.0 mmol/L).
- Treatment with TI + basal insulin is associated with a reduced risk for hypoglycemia relative to sc insulin comparators.

REFERENCES

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