

Comparative Efficacy and Safety of Technosphere® Insulin and a Rapid-Acting Analog Both Given with Glargine in Subjects with T1 DM in a 52-Week Study

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ABSTRACT

Background and aims: Technosphere® Insulin (TI) is a rapid-acting inhaled insulin with pharmacokinetics well suited for control of postprandial plasma glucose (PPG). This study compared the efficacy and safety of TI and a rapid-acting analog (RAA) both given at meals with insulin glargine, a long-acting analog (LAA). **Material and methods:** Subjects with type 1 diabetes mellitus and HbA1c > 7.0% and ≤ 11.0% were randomized to a 52-week course of basal LAA plus prandial TI (n = 301) or prandial RAA (n = 288). Prespecified efficacy endpoints included change in HbA1c, 1-h PPG, 2-h PPG, and fasting plasma glucose (FPG) following a standard meal challenge. Adverse events were monitored to compare safety profiles. **Results:** At the end of the 52-week treatment period, both groups experienced comparable reductions in HbA1c, and there were no significant differences in LAA doses between treatment groups. FPG levels and 1-h PPG values were significantly lower with TI than with RAA, and 2-h PPG levels were similar between both groups. The TI group had weight loss, whereas the RAA group gained weight, with the difference statistically significant. Finally, the TI group had a statistically significant reduction in the incidence of mild/moderate (odds ratio [OR]: 0.474; confidence interval [CI]: 0.0271, 0.831; p = 0.0091) and total hypoglycemia (OR: 0.488; CI: 0.278, 0.856; p = 0.0124). **Conclusion:** Compared with RAA in subjects with type 1 diabetes mellitus, TI in combination with LAA resulted in comparable HbA1c reductions; more favorable 1-h PPG and FPG; significantly less weight gain; and significantly less risk of hypoglycemia.

Parameter	TI + LAI	RAA + LAI	p Value or 95% CI
ΔHbA1c from Baseline (%)	-0.13 ± 0.06	-0.37 ± 0.06	0.08, 0.40 (ANCOVA)
ΔFPG from Baseline (mmol/L)	-2.0 ± 0.2	-1.1 ± 0.2	p = 0.0012 (MMRM)
Δ1-h PPG from Time 0 (mmol/L)	1.2 ± 0.3	2.3 ± 0.3	0.0022 (ANCOVA)
ΔWeight from Baseline (kg)	-0.5 ± 0.3	+1.4 ± 0.3	p < 0.0001 (ANCOVA)
Total hypoglycemia (%)	86.01	92.65	p = 0.0124 ^a
Mild/moderate hypoglycemia (%)	85.67	92.65	p = 0.0091 ^a
Severe hypoglycemia (%)	32.76	37.50	p = 0.2387 ^a
Hypoglycemia with plasma glucose ≤ 2.7 mmol/L (%)	4.2	4.7	p = 0.0232 ^a

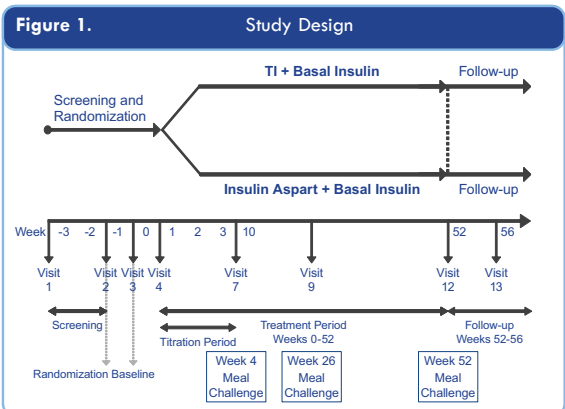
^a Treatment comparison statistics (p values) are from a logistic regression.

BACKGROUND AND AIMS

Providing physiologic mealtime insulin levels with respect to rapid onset and limited duration of action is needed for patients with type 1 diabetes. MannKind Corporation is currently developing the Technosphere® Insulin Inhalation System for the control of hyperglycemia in adults with diabetes. TI is composed of recombinant human insulin adsorbed onto Technosphere® particles made from fumaryl diketopiperazine 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 t_{max} of approximately 14 minutes in subjects with type 1 diabetes. Consequently, 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

This was a prospective, multi-country, multicenter, open-label, randomized, controlled clinical trial comparing glycemic control in subjects with T1 DM receiving basal insulin and prandial TI with subjects receiving basal insulin and subcutaneous (sc) RAA. Subjects entering the trial had an HbA1c > 7.0% and ≤ 11.0% and had been maintaining a treatment regimen of insulin ≤ 1.4 IU/kg/day. Prandial RAA in Prandial RAA in combination with once-daily basal insulin is considered standard of care for management of T1 DM and served as the internal control for this study. The trial was conducted in an open-label fashion because of the visibly different routes of treatment administration: inhalation for TI and sc injection for RAA.



MATERIALS AND METHODS (CONT'D)

Meal challenge venous blood sampling times were: -30, 0, 30, 60, 90, 105, 120, 180, 240, 300, and 360 minutes. 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 RAA arm, subjects were instructed to inject the insulin 15 minutes prior to ingesting the liquid meal. Insulin glargine was used as basal insulin in this trial.

RESULTS

At Baseline, both groups were similar with respect to age, gender, BMI, HbA1c, FPG, and duration of T1 DM.

Primary Endpoint: Change From Baseline in HbA1c at Week 52

TI was noninferior to RAA: the 95% CI for the difference in change from Baseline was 0.11 to 0.38 in the ITT Population in a prespecified Mixed Model Repeated Measures (MMRM) analysis.

- HbA1c was significantly reduced in both treatment groups and the reduction was sustained over 52 weeks (Figure 2).
- HbA1c values in the TI arm fell to 8.21 ± 1.15% at Week 14 from a Baseline of 8.41 ± 0.92%; the reduction was maintained at Week 52 (8.20 ± 1.22%), p = 0.0281.
- HbA1c values in the RAA arm fell to 8.07 ± 1.09% at Week 14 from a Baseline of 8.48 ± 0.97%; the reduction was maintained at Week 52 (7.99 ± 1.07%), p < 0.0001.

- The overall mean daily dose of glargine was comparable in the 2 treatment groups, 32.4 ± 22.2 IU and 29.8 ± 12.8 IU for the TI and RAA groups, respectively.

TI + LAI was comparable to RAA + LAI in reducing HbA1c levels over 52 weeks of treatment.

Treatment Difference in Fasting Plasma Glucose

Mean FPG concentrations decreased significantly in the TI group compared to the RAA group, p = 0.0012 (ITT Population) over the 52-week treatment period (Figure 3) and as assessed by a prespecified Mixed Model Repeated Measure analysis.

- The LS Means change from Baseline was -2.0 ± 0.18 mmol/L in the TI group and -1.1 ± 0.18 mmol/L in the RAA group.
- Both treatment groups showed a continuous FPG reduction from Baseline over 52 weeks.

Baseline Characteristics	Category/Statistic	TI + LAI (n = 277)	RAA + LAI (n = 262)
Gender, number of subjects (%)	Male	146 (52.7)	136 (51.9)
	Female	131 (47.3)	126 (48.1)
Age (years)	Mean (± SD)	37.9 (13.1)	38.2 (13.3)
BMI (kg/m ²)	Mean (± SD)	26.07 (3.96)	26.17 (3.64)
HbA1c (%)	Mean (± SD)	8.4 (0.9)	8.5 (1.0)
Fasting plasma glucose (mmol/L)	Mean (± SD)	10.4 (4.7)	10.0 (4.8)
Duration of diabetes (years)	Mean (± SD)	18.1 (11.5)	18.7 (11.6)

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

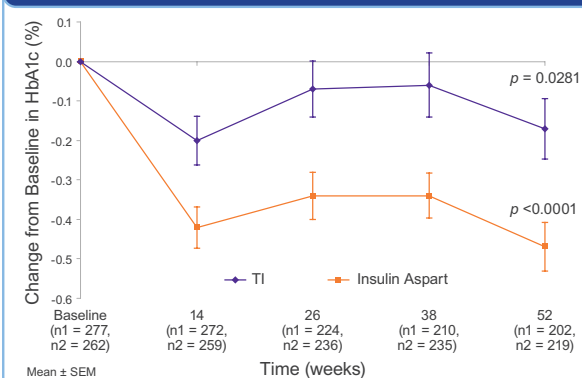
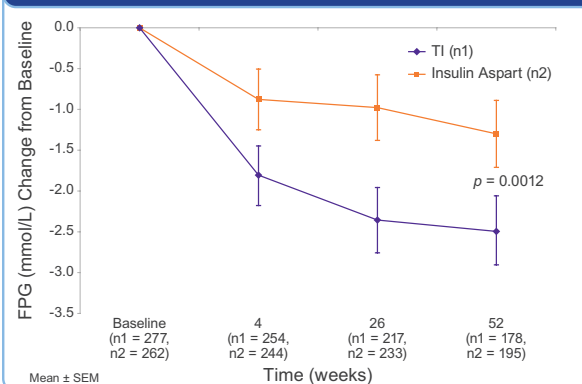


Figure 3. Mean Change from Baseline in FPG (mmol/L) Over 52 Weeks (ITT Population)



RESULTS (CONT'D)

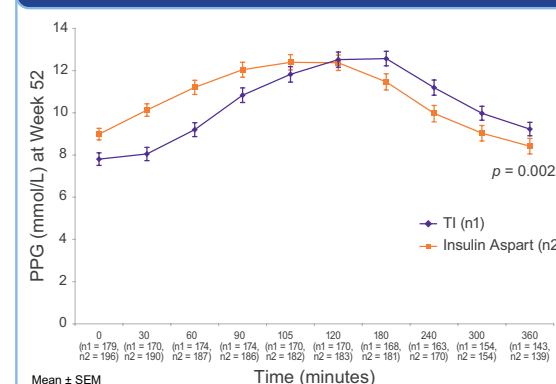
- The mean within-group FPG change from Baseline at Week 52 was statistically significant for both treatment groups: p < 0.0001 for the TI group, p = 0.0018 for the RAA group.
- The difference in FPG between treatments cannot be attributed to basal insulin because the overall mean daily insulin glargine dose was similar between groups: 32.4 IU and 29.8 IU for the TI and RAA groups, respectively.

TI+LAI provided a statistically significant lower FPG than RAA+LAI over 52 weeks.

Postprandial Glucose Control after a Meal Challenge at Week 52

Early postprandial glucose control was significantly better in the TI group with a slower rise in mean PPG and lower mean 1-h PPG concentrations as compared to the RAA group (Figure 4).

Figure 4. Postprandial Plasma Glucose (mmol/L) at a Meal Challenge, Week 52 (ITT Population)



- At Week 52, the 60 minute PPG change from Time 0 was 1.2 ± 0.3 mmol/L in the TI group compared to 2.3 ± 0.3 mmol/L in the RAA group, p = 0.0022 (ANCOVA). The absolute PPG concentrations at 60 minutes were 9.2 mmol/L in the TI group compared to 11.2 mmol/L in the RAA group.

- At 120 minutes after dosing, mean PPG concentrations were similar between the TI group (12.5 mmol/L) and the RAA group (12.4 mmol/L).

- The range of PPG values after 120 minutes post-dose was lower in the RAA group, as was the mean change from Baseline, consistent with the higher number of overall and severe hypoglycemic events in that time period for RAA-treated subjects at all of the meal challenges (Table 3).

Early postprandial glucose control was significantly better in the TI group.

Treatment Difference in Body Weight

Subjects in the TI group lost an average of 0.5 ± 0.3 kg over the 52-week treatment period, compared to an average gain of 1.4 ± 0.3 kg in the RAA group (ITT Population) (Figure 5).

- The treatment difference was -1.8 kg and was statistically significant by a prespecified ANCOVA analysis (p < 0.0001).
- The mean body weight loss in the TI group was not statistically significant (p = 0.1102), but the mean body weight gain in the RAA group was significant (p < 0.0001).

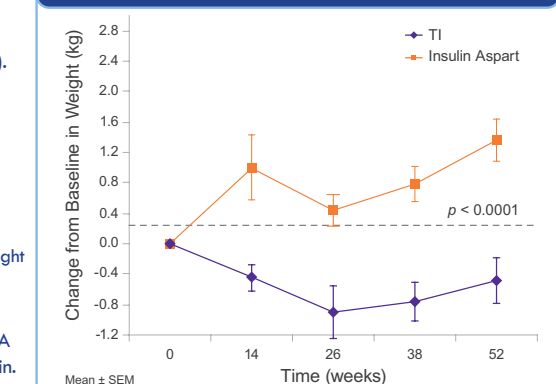
TI + LAI was weight neutral while RAA + LAI was associated with weight gain.

Table 3. Events of Hypoglycemia During Meal Challenges (Safety Population)

Treatment	< 2.0 mmol/L	< 2.7 mmol/L	< 3.5 mmol/L
TI + LAI			
Total Events	10	64	208
> 0-120 minutes	5	34	123
> 120-360 minutes	5	30	85
RAA + LAI			
Total Events	18	83	230
> 0-120 minutes	5	18	69
> 120-360 minutes	13	65	161

An event of hypoglycemia < 3.6 mg/dL is also included in < 4.9 mg/dL and < 6.3 mg/dL.

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



RESULTS (CONT'D)

Treatment Difference in Hypoglycemia

- Fewer TI + LAI-treated subjects experienced hypoglycemic events during the trial, with a statistically significant difference in the number of TI+LAI-treated subjects reporting all hypoglycemic events compared to RAA + LAI-treated subjects (Table 4).
- Event rates in each category of hypoglycemia were similar between treatments (Table 5).
- Hypoglycemia event rates were higher in both treatment groups during dose titration at the beginning of the study and declined after doses began to stabilize in the later part of the study.

Incidence	TI (n = 293) n (%)	Insulin Aspart (n = 272) n (%)	TI vs Insulin Aspart		
			Odds Ratio	95% CI	p Value
All hypoglycemia events	252 (86.0)	252 (92.7)	0.488	(0.278, 0.856)	0.0124
Mild/moderate hypoglycemia	251 (85.7)	252 (92.7)	0.474	(0.271, 0.831)	0.0091
Hypoglycemia with plasma glucose ≤ 2.7 mmol/L	223 (76.1)	228 (83.8)	0.615	(0.404, 0.936)	0.0232
Severe hypoglycemia	96 (32.8)	102 (37.5)	0.812	(0.575, 1.148)	0.2387
Hypoglycemia requiring assistance	16 (5.4)	13 (4.8)	1.151	(0.543, 2.439)	0.7140
Hypoglycemia with cognitive neurologic symptoms	22 (7.5)	12 (4.4)	1.759	(0.853, 3.627)	0.1262

Table 5. Hypoglycemia Event Rates Over 52 Weeks (Safety Population)

	TI (n = 293)	Insulin Aspart (n = 272)	p Value
Total Hypoglycemia Event Rates			
Subjects with events, n (%)	252 (86.01)	252 (92.65)	
Event rate (number of events/subject-month)	1.81	1.85	0.1094
Severe Hypoglycemia Event Rates			
Subjects with events, n (%)	96 (32.76)	102 (37.50)	
Event rate (number of events/subject-month)	0.08	0.10	0.1839
Nonsevere Hypoglycemia Event Rates			
Subjects with events, n (%)	251 (85.67)	252 (92.65)	
Event rate (number of events/subject-month)	1.72	1.75	0.1424

Hypoglycemia: < 63 mg/dL (3.5 mmol/L) or relevant symptoms alleviated by caloric intake
Severe Hypoglycemia: Required glucagon injection, glucose infusion or assistance from another person

- The mild/moderate hypoglycemic event rate was highest during the Month 0-3 period for both TI and RAA (2.84 per subject-month versus 3.38 per subject-month, respectively). During the Month 10-12 period, the event rates were 1.52 per subject-month and 1.38 per subject-month for the TI and RAA groups, respectively.

- In the TI group, the event rates for severe hypoglycemia did not rise over the course of the trial while the mean daily TI dose increased over 52 weeks.

Pulmonary Safety Profile

Pulmonary safety monitoring was performed throughout the trial and at follow-up. There were no differences in the observed mean changes from Baseline to Week 52 in FEV₁, FVC, and TLC between the TI and RAA groups. Overall, observed mean changes from Baseline to Week 52 in tested pulmonary parameters for either treatment group were small.

CONCLUSIONS

- TI + LAI was comparable to RAA + LAI in reducing HbA1c levels over 52 weeks of treatment.
- TI + LAI provided a statistically significant lower FPG and 1-h PPG and significantly less total hypoglycemia in the context of weight neutrality.
- Total and severe hypoglycemia event rates decreased over the course of the trial in TI + LAI-treated subjects despite a concurrent increase in daily TI doses.
- Body weight difference between groups was statistically significant (p < 0.0001) with a treatment difference of -1.8 kg.
- Mean change from Baseline (Week 0) in body weight was not statistically significant for the TI arm (p = 0.1102), while mean body weight gain for the insulin aspart arm was significant (p < 0.0001).
- Based on the results from this trial, subjects with T1 DM treated with sc insulin can be safely and effectively transferred to TI in combination with basal insulin, achieving clinical benefits in FPG and weight.