

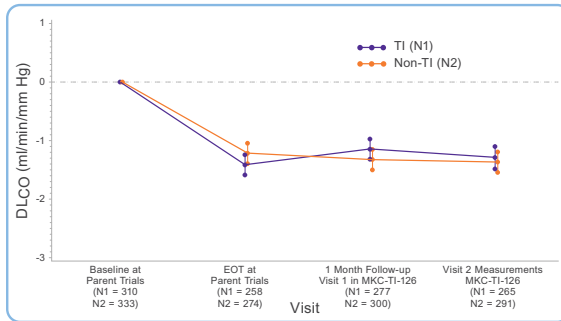
Pulmonary Function Tests Remain Similar in Patients Who Received Technosphere® Insulin and in Patients Currently Receiving Standard Antidiabetic Therapy

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ABSTRACT

Background and aims: Previous controlled clinical studies have demonstrated that regimens of basal insulin plus Technosphere® Insulin (TI) were as effective as basal insulin plus rapid-acting sc insulin in patients with diabetes. In previously reported studies, we have been unable to detect a consistent change in pulmonary function tests (PFTs). Small but clinically nonsignificant differences have been observed. This clinical trial was designed to assess the changes in pulmonary function after cessation of TI therapy and resumption of standard antidiabetic treatment in patients with type 1 or type 2 diabetes. **Materials and methods:** Adults with diabetes who participated in any of four controlled clinical trials of TI were invited to participate in this follow-up trial to evaluate changes in PFTs after completing the study and being switched to usual antidiabetic therapy without TI. Patients were followed for a total of 3 months after cessation of study therapy. PFTs were assessed at the end of the parent trial and 1 and 3 months after subjects completed the parent trial. **Results:** Of 649 patients in this study, 315 subjects (121 with type 1 diabetes, 194 with type 2 diabetes) received the antidiabetic regimen without prandial TI during the parent trials. Small, nonprogressive treatment group differences in mean changes from Baseline in forced expiratory volume in 1 second (FEV₁) and carbon monoxide diffusing capacity (DL_{CO}) observed during the comparative phase of the controlled trials disappeared when comparing the two groups at 3 months after cessation of TI therapy and resumption of standard antidiabetic therapy (FEV₁: -0.08 L in the TI group, -0.11 L in the non-TI group [p = 0.1388]; DL_{CO}: -1.29 mL/min/mm Hg in the TI group, -1.37 mL/min/mm Hg in the non-TI group [p = 0.9360]). In addition, there was no statistical difference in FEV₁ between the two groups when examining subjects with type 1 and type 2 diabetes (p = 0.6158 and p = 0.1795, respectively). **Conclusion:** These data suggest that the pattern and magnitude of PFT changes associated with the use of TI in subjects with type 1 and type 2 diabetes are not likely due to any structural alterations in the lungs and are not clinically meaningful.



BACKGROUND AND AIMS

MannKind Corporation is currently developing Technosphere® Insulin Inhalation Powder (TI) for the treatment of adult patients with diabetes mellitus. TI is an inhaled formulation of regular human insulin adsorbed onto Technosphere® particles with an action profile that closely mimics endogenous meal related insulin response. Previous controlled clinical studies have demonstrated that regimens of basal insulin plus prandial TI were as effective as basal insulin plus rapid-acting sc insulin in patients with diabetes. In previously reported studies, we have been unable to detect a consistent change in pulmonary function tests (PFTs). Small but clinically nonsignificant differences in the mean change from baseline in FEV₁, FVC and DL_{CO} between TI and comparator treatment groups have been observed. This clinical open-label trial was designed to assess the changes in pulmonary function after cessation of TI therapy and resumption of standard anti-diabetic treatment in patients with type 1 or type 2 diabetes.

MATERIALS AND METHODS

Adults with type 1 or type 2 diabetes who completed any one of the four prospective, open label, randomized, phase 3 trials of TI clinical development program [MKC-TI-009, MKC-TI-102, MKC-TI-103 or MKC-TI-030] were invited to participate in this follow-up trial to evaluate changes in pulmonary function tests (PFTs) after completion of the parent trial and reverting back to usual antidiabetic therapy as prescribed by their physicians. Patients were followed for a total of 3 months after cessation of the comparative treatment phase of the parent trials. The duration of the treatment phase varied from 3 to 24 months depending upon the parent trial. MKC-TI-009 was a randomized, controlled clinical trial in

MATERIALS AND METHODS (CONT'D)

subjects with type 1 diabetes comparing the efficacy and safety of prandial inhalation of TI with prandial rapid acting insulin and sc basal insulin (glargine) over a 52-week treatment period. In the MKC-TI-102 clinical trial, the efficacy and safety of prandial TI and basal insulin (glargine) was compared to a regimen of sc premixed insulin (BPA 70/30) therapy over a 52 week period in subjects with type 2 diabetes mellitus. MKC-TI-103 was a 24-week, controlled clinical trial to evaluate the efficacy and safety of prandial inhalation of TI alone or in combination with oral antidiabetic agents (Metformin and a secretagogue) in subjects with type 2 diabetes. MKC-TI-030 was a pulmonary safety trial of subjects with type 1 or 2 diabetes treated for a 24-month period with either a regimen of prandial TI with other antidiabetic agents (oral and/or sc insulins) or usual antidiabetic agents without prandial TI.

Key pulmonary inclusion criteria for the parent trials were: nonsmoking subjects (never smoked or quit smoking within 6 months of the Screening visit of the parent trial), FEV₁ ≥ 70% of predicted (NHANES III), DL_{CO} ≥ 70% of predicted (Miller's), and TLC ≥ 80% of predicted (Intermountain Thoracic Society-ITS). Subjects were excluded if they had evidence of clinically significant radiological abnormalities of the chest at screening, history of chronic obstructive pulmonary disease (COPD), asthma, or any other significant pulmonary disease, Grade III or IV congestive heart failure, myocardial infarction within the past 12 months, unstable angina, prior treatment with or participation in a clinical trial involving an inhaled insulin. Women who were pregnant, lactating or planning to become pregnant or women of childbearing potential not practicing adequate birth control measures were also excluded.

Pulmonary function tests (PFTs) were obtained at 1 month and 3 months after completion of the comparative phase of the parent trial. PFTs, including spirometry, lung volumes (TLC), and DL_{CO} were performed according to current American Thoracic Society (ATS) guidelines. All PFT laboratories received comprehensive training in pulmonary function testing and were required to meet 2005 ATS/ERS defined standards for acceptability and reproducibility of the PFT measurements.

ENDPOINTS AND ANALYSES

The primary endpoint was the comparison in the mean change from the Baseline of the parent trial to 3 months after completion of the trial in forced expiratory volume in one second (FEV₁) between subjects treated with TI (TI group) and subjects not treated with TI (Non-TI group) for their diabetes during the parent trial. Secondary endpoints included change in FEV₁, FVC, TLC, and DL_{CO} from the end of the parent trial to 3 months after the discontinuation of the study therapy. Analysis of Covariance (ANCOVA) with region and treatment groups as the class variables and baseline PFT value in the parent trials as continuous variable was used to compare the PFT changes between TI and Non-TI treatment groups. Adjusted (Least-Square) estimate of the mean difference along with its 2-sided 95% confidence intervals was calculated. All analyses were performed using SAS Version 8.2 or higher (SAS® Institute, Cary, NC, USA).

RESULTS

Of 649 patients in this study, 315 subjects (121 with type 1 diabetes, 194 with type 2 diabetes) received TI and 334 subjects (129 with type 1 diabetes, 205 with type 2 diabetes) received the antidiabetic regimen without prandial TI during the parent trials. A total of 632 patients completed the trial. Nine subjects in the TI and 8 subjects in Non-TI treatment groups were discontinued prematurely. As shown in Table 1, baseline characteristics were similar between the TI and Non-TI treatment groups in terms of age, gender, type and duration of diabetes.

Demographic Characteristics		TI (N = 315)	Non-TI (N = 334)
Age (years)	Mean (SD)	50.4 (13.34)	51.6 (12.47)
Gender	Male (%)	173 (54.9)	188 (56.3)
	Female (%)	142 (45.1)	146 (43.7)
Diabetes Type	Type I (%)	121 (38.4)	129 (38.6)
	Type II (%)	194 (61.6)	205 (61.4)
Duration of Diabetes (years)	Mean (SD)	15.12 (9.61)	15.62 (9.97)

RESULTS (CONT'D)

Table 2 summarizes the antidiabetic agents and the duration of exposure during the comparative phase of the parent trials. Exposure to the study drugs varied from 3 months (MKC-TI-103) to as long as 24 months (MKC-TI-030).

	MKC-TI-009	MKC-TI-102	MKC-TI-103	MKC-TI-030	Total
Number of Subjects	169	138	22	320	649
Duration of exposure of the study drug in the parent trial	12 months	12 months	3 or 6 months	24 months	
TI Group	85 (50.3%)	69 (50.0%)	15 (68.2%)	146 (45.6%)	315 (48.5%)
TI Alone	—	—	1 (4.5%)	48 (15.0%)	49 (7.6%)
TI + Metformin	—	—	14 (63.6%)	35 (10.9%)	49 (7.6%)
TI + Glargine	85 (50.3%)	69 (50.0%)	—	63 (19.7%)	217 (33.4%)
Non-TI Group	84 (49.7%)	69 (50.0%)	7 (31.8%)	174 (54.4%)	334 (51.5%)
Metformin + Secretagogue	—	—	7 (31.8%)	8 (2.5%)	15 (2.3%)
Aspart + Glargine	84 (49.7%)	—	—	12 (3.8%)	96 (14.8%)
Premixed (BPA 70/30)	—	69 (50.0%)	—	—	69 (10.6%)
Usual Care without Insulin	—	—	—	33 (10.3%)	33 (5.1%)
Usual Care with Insulin	—	—	—	121 (37.8%)	121 (18.6%)

Both TI- and non-TI-treated subjects experienced a small decline in FEV₁, FVC, and lung diffusion capacity (DL_{CO}) from the baseline visit of the parent trial to the end of the safety follow-up (three months after completion of the parent trial); The difference between the two treatment groups in the mean change from Baseline visit of the parent trial to the 3-month follow-up visit in these PFT parameters were not significant (Table 3).

	FEV ₁ (L) Mean ± SE		FVC (L) Mean ± SE		DL _{CO} (mL/min/mm Hg) Mean ± SE	
	TI N = 315	Non-TI N = 334	TI N = 315	Non-TI N = 334	TI N = 315	Non-TI N = 334
Baseline Parent Trials	3.21 ± 0.74	3.23 ± 0.79	4.07 ± 0.94	4.11 ± 1.0	26.35 ± 6.31	26.69 ± 6.37
End of the Parent Trials	-0.12 ± 0.01	-0.10 ± 0.01	-0.11 ± 0.02	-0.08 ± 0.01	-1.41 ± 0.17	-1.22 ± 0.18
Visit 1 ^a	-0.09 ± 0.01	-0.09 ± 0.01	-0.10 ± 0.02	-0.09 ± 0.01	-1.14 ± 0.17	-1.32 ± 0.17
Visit 2 ^b	-0.08 ± 0.01	-0.11 ± 0.01	-0.09 ± 0.02	-0.10 ± 0.01	-1.29 ± 0.19	-1.37 ± 0.17
Change from BL to Visit 2 TI – Non-TI (95% CI) p value	0.03 (-0.008, 0.059) 0.1388		0.02 (-0.020, 0.059) 0.3367		0.02 (-0.471, 0.511) 0.9360	

^a 1 month after the end of the Parent Trial
^b 3 months after the end of the Parent Trial

Additionally, when analyzed separately for subjects with type 1 or type 2 diabetes, there was no statistical difference in the mean change from the Baseline of the parent trial to 3-month follow-up visit in FEV₁, FVC, and DL_{CO} between the two treatment groups. (Table 4).

Small treatment group differences in mean changes from baseline in forced expiratory volume in 1 second (FEV₁) – Figure 1 and carbon monoxide diffusing capacity (DL_{CO}) – Figure 2 observed during the comparative phase of the controlled trials disappeared when comparing the two groups at 3 months after cessation of TI therapy and resumption of standard antidiabetic treatment.

RESULTS (CONT'D)

	FEV ₁ (L) Mean ± SE		FVC (L) Mean ± SE		DL _{CO} (mL/min/mm Hg) Mean ± SE	
	TI N = 121	Non-TI N = 129	TI N = 121	Non-TI N = 129	TI N = 121	Non-TI N = 129
Baseline Parent Trials Mean ± SD	3.56 ± 0.75	3.54 ± 0.84	4.46 ± 0.95	4.46 ± 1.02	28.74 ± 7.09	28.42 ± 6.48
Change from BL to Visit 2 Mean (L)	-0.07	-0.08	-0.08	-0.11	-1.74	-1.26
TI – Non-TI (95% CI) p value	0.01 (-0.041, 0.070) 0.6158		0.03 (-0.036, 0.095) 0.3792		-0.48 (-1.301, 0.349) 0.2563	
	FEV ₁ (L) Mean ± SE		FVC (L) Mean ± SE		DL _{CO} (mL/min/mm Hg) Mean ± SE	
	TI N = 194	Non-TI N = 205	TI N = 194	Non-TI N = 205	TI N = 194	Non-TI N = 205
Baseline Parent Trials Mean ± SD	2.98 ± 0.63	3.06 ± 0.75	3.79 ± 0.83	3.92 ± 0.97	24.91 ± 5.29	25.73 ± 6.31
Change from BL to Visit 2 Mean (L)	-0.09	-0.12	-0.10	-0.12	-0.99	-1.43
TI – Non-TI (95% CI) p value	0.03 (-0.013, 0.071) 0.1795		0.01 (-0.039, 0.059) 0.6856		0.30 (-0.313, 0.915) 0.3350	

Figure 1. Mean FEV₁ (L) Over Time (Safety Population)

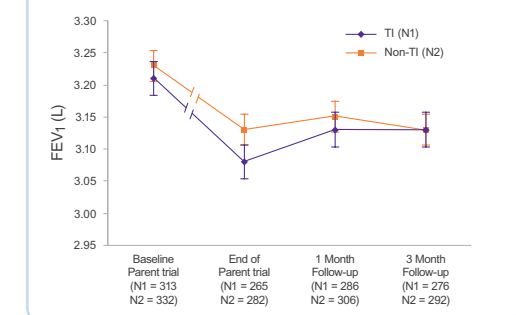
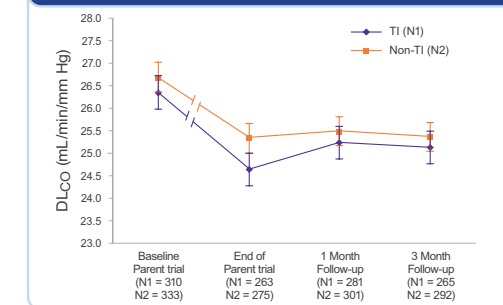


Figure 2. Mean DL_{CO} (mL/min/mm Hg) Over Time (Safety Population)



CONCLUSIONS

- Small treatment group difference in the mean change from baseline in pulmonary function tests (FEV₁, FVC, and DL_{CO}) associated with the use of Technosphere® Insulin disappears upon cessation of Technosphere® Insulin therapy, irrespective of the duration of exposure.
- The pattern and magnitude of PFT changes associated with the use of TI in subjects with type 1 and type 2 diabetes are not likely to be due to any structural alterations in the lungs and unlikely to be clinically meaningful.