

Pulmonary Functions (Over 2 Years) in Diabetic Subjects Treated with Technosphere® Insulin or Usual Antidiabetic Treatment

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ABSTRACT

Background and aims: Technosphere® Insulin (TI) is a rapid-acting inhaled insulin with an action profile that mimics early meal-related insulin release. The goal of this multicenter study was to evaluate and compare changes in lung function in subjects with diabetes treated with TI or with usual antidiabetic treatment (UC). **Materials and methods:** Pulmonary function tests (PFTs), including forced expiratory volume in 1 second (FEV₁), forced vital capacity, total lung capacity, and carbon monoxide diffusing capacity (DL_{CO}), were prospectively followed over a 2-year period in subjects with type 1 and type 2 diabetes mellitus receiving TI (n = 730) or UC (n = 824), along with a cohort of nondiabetic subjects who did not receive any specific therapy (n = 145). **Results:** The treatment groups were similar for age (TI group: 50.8 ± 11.6 years; UC group: 50.4 ± 11.6 years; p = 0.40), gender distribution (p = 0.85), proportion of ethnic group composition (p = 0.93), and baseline PFT. Over 2 years, PFTs declined in all groups, including the non-diabetes group. TI was noninferior to UC for mean change in FEV₁ from Baseline to 24 months using Mixed Model Repeated Measure analysis with a prespecified noninferiority margin of 50 mL/year. After a slightly larger initial decline at the first post-Baseline assessment visit, annual rate of change (slope) in PFTs from Month 3 to Month 24 was not statistically different between the TI- and UC-treated subjects. Annualized change in FEV₁ between 3 to 24 months was -0.047 L/year for TI-treated subjects and -0.036 L/year for UC-treated subjects (difference between the treatment groups, 0.010 L/year [95% CI -0.003, 0.022]); DL_{CO} was -0.507 mL/min/mm Hg per year for TI-treated subjects and -0.455 mL/min/mm Hg per year for UC-treated subjects (difference between the treatment groups, 0.117 mL/min/mm Hg per year [95% CI -0.058, 0.292]). **Conclusion:** Small declines from Baseline in PFTs were observed in subjects with diabetes treated with TI and UC and also in subjects without diabetes. Observed differences between the TI and UC groups in the change from Baseline in FEV₁ and DL_{CO} were small, noted at the first post-Baseline assessment visit (3 months) and thereafter remained nonprogressive over 2 years of continuous therapy.

INTRODUCTION

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 human insulin adsorbed onto Technosphere® particles with an action profile that closely mimics endogenous meal-related insulin response. The development of pulmonary insulin as a promising alternative to subcutaneous (sc) insulin has further increased the need to understand pulmonary involvement in diabetes and pulmonary safety of chronic use of inhaled insulin. While pre-existing lung disease may affect the absorption and bioavailability of inhaled insulin, chronic use of inhaled insulin may potentially also affect pulmonary function. Subtle changes in pulmonary function have been reported in subjects with type 1 and type 2 diabetes treated with other inhaled insulin formulations.^{1,2,3}

The primary objective of this study was to examine changes in pulmonary functions associated with the antidiabetic treatment consisting of prandial TI (TI group) compared with usual antidiabetic treatment without TI (UC group) in subjects with diabetes over a 2-year period and also with subjects without abnormalities in glycemic control.

MATERIALS AND METHODS

This was a prospective, open-label, multi-center (investigational sites in North America, Europe, and Latin America) clinical trial in which subjects with type 1 or type 2 diabetes were randomized in a 1:1 ratio to receive either antidiabetic regimen consisting of prandial TI or antidiabetic regimen without TI for 24 months. Additionally, using an approximate 10:1 ratio, subjects with diabetes to subjects without abnormalities in glycemic control, were enrolled to examine the changes in lung functions over a 2-year period. Subjects without abnormalities in glycemic control did not receive any clinical study-specific treatment.

Men or women between 18 and 80 years of age, with a BMI < 42 kg/m², FEV₁ ≥ 70% of predicted, DL_{CO} ≥ 70% of predicted, and TLC ≥ 80% of predicted, who never smoked or who quit smoking within the 6-month period preceding the start of the clinical trial, with no evidence of any clinically relevant abnormalities by radiological examination of lungs at Screening were eligible to participate. Subjects with diabetes had a diagnosis of type 1 or type 2 diabetes for at least 2 years and an HbA1c ≥ 6.6% and ≤ 12.0%. Subjects without abnormalities in glycemic control had no history of diabetes and normal results from a formal GTT. Subjects were excluded if they had clinically relevant hepatic or renal disease or elevated liver enzymes or renal functions, an active respiratory infection, history of chronic obstructive pulmonary disease (COPD), asthma, other significant pulmonary disease, Grade III or IV congestive heart failure or myocardial infarction within the past 12 months or unstable angina, or

ENDPOINTS AND ANALYSES

history of malignancy within the 5 years preceding clinical trial entry or severe complications of diabetes, > 2 severe hypoglycemic episodes within 6 months of screening or an episode of severe hypoglycemia between Visit 1 and Visit 2 or any hospitalization or emergency room visit due to poor diabetic control within 6 months of screening; 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 practicing insufficient birth control were also excluded.

Study consisted of 7 clinic visits over a 24-month comparative treatment period. Pulmonary function tests (PFT), including spirometry, lung volumes (TLC), and DL_{CO} were performed according to current American Thoracic Society guidelines. All PFT laboratories received training and were required to meet the ATS/ERS defined standards for accuracy and reproducibility in PFT measurements. PFTs were obtained at Screening and Months 3, 6, 12, 18, and 24.

ENDPOINTS AND ANALYSES

The primary endpoint was the comparison between TI and UC treatment groups in the change in FEV₁ from Baseline to Month 24. Using the Mixed Model with Repeated Measure (MMRM) analysis for noninferiority test, (with trial group, visit, Baseline FEV₁ value, pooled site, and diabetes type as fixed factors), TI was to be considered noninferior to the UC group if the upper bound of the two-sided 95% CI for the treatment group difference (UC-TI) in the annualized mean change in FEV₁ from Baseline to end of study was no greater than 50 mL. Secondary endpoints included change in FVC, TLC, and DL_{CO} from Baseline at end of study.

RESULTS

A total of 2053 subjects (938 TI group, 951 in the UC group, and 164 in the nondiabetic group) were enrolled. Safety population was comprised of 923 subjects in TI group, 949 in UC group and 163 in nondiabetic group. The ITT Population in this trial was comprised of 1699 subjects, with 730 in the TI group, 824 in the UC group, and 145 in the nondiabetic group. A total of 475 (50.6%) subjects completed in the TI group, 662 (69.6%) completed in the UC group, and 127 (77.4%) completed in the nondiabetic group. As shown in Table 1, baseline characteristics were similar between the TI and UC treatment groups with respect to age, gender, race, weight, BMI, HbA1c (%), duration of diabetes, and history of smoking. Table 2 summarizes pulmonary function tests at baseline.

Baseline Characteristics	Category/Statistic	TI (n = 923)	Usual Care (n = 949)	Non-diabetes (n = 163)
Diabetes Type	Type 1 Diabetes	267 (28.9)	271 (28.6)	NA
	Type 2 Diabetes	656 (71.1)	678 (71.4)	NA
Gender, n (%)	Male	557 (60.3)	578 (60.9)	71 (43.6)
	Female	366 (39.7)	371 (39.1)	92 (56.4)
Race, n (%)	Caucasian	792 (85.8)	824 (86.8)	145 (89.0)
	Black	35 (3.8)	32 (3.4)	4 (2.5)
	Hispanic	59 (6.4)	56 (5.9)	11 (6.7)
	Asian	30 (3.2)	28 (3.0)	3 (1.8)
	Other	7 (0.8)	9 (0.9)	0 (0.0)
	Age (years)	Mean (± SD)	50.8 (11.55)	50.4 (11.62)
Age Group (years)	18-30	73 (7.9)	84 (8.9)	54 (33.1)
	31-49	276 (29.9)	287 (30.2)	71 (43.6)
	50-64	492 (53.2)	503 (53.0)	35 (21.5)
	65+	82 (8.9)	75 (7.9)	3 (1.8)
Weight (kg)	Mean (± SD)	87.66 (18.625)	87.53 (17.638)	74.35 (16.204)
BMI (kg/m ²)	Mean (± SD)	29.87 (5.366)	29.76 (5.035)	25.27 (4.494)
Baseline HbA1c (%)	Mean (± SD)	8.7 (1.39)	8.7 (1.38)	NA
Duration of Diabetes (years)	Mean (± SD)	11.9 (8.47)	11.8 (8.04)	NA
Past Smoker	Yes	277 (30.0%)	285 (30.0%)	29 (17.8%)

Parameter	Category/Statistic	TI	Usual Care	Non-diabetes
FEV ₁ (L)	n	920	940	149
	Mean (± SD)	3.24 (0.741)	3.29 (0.789)	3.66 (0.904)
FVC (L)	n	920	940	149
	Mean (± SD)	4.12 (0.955)	4.20 (1.016)	4.61 (1.073)
TLC (L)	n	702	782	139
	Mean (± SD)	5.94 (1.132)	6.05 (1.235)	6.22 (1.216)
DL _{CO} (mL/min/mm Hg)	n	713	788	140
	Mean (± SD)	26.60 (5.686)	27.09 (6.095)	28.31 (7.104)

SD = standard deviation; NA = not applicable

RESULTS (CONT'D)

Primary Endpoint

Over 2 years, small declines from Baseline in FEV₁ were observed in all groups, with the smallest change in subjects without diabetes. Observed least square mean treatment difference (UC-TI) in change in FEV₁ from Baseline to Month 24 was 0.037 L. Using an MMRM model for a noninferiority analysis, the upper limit of the model adjusted 95% CI for the treatment group difference (UC-TI) in the change from Baseline in FEV₁ was less than 50 mL per year (100 mL for 2 years), demonstrating that the TI group was noninferior to the UC group. The results in the PP Population were comparable to the ITT Population (Table 3).

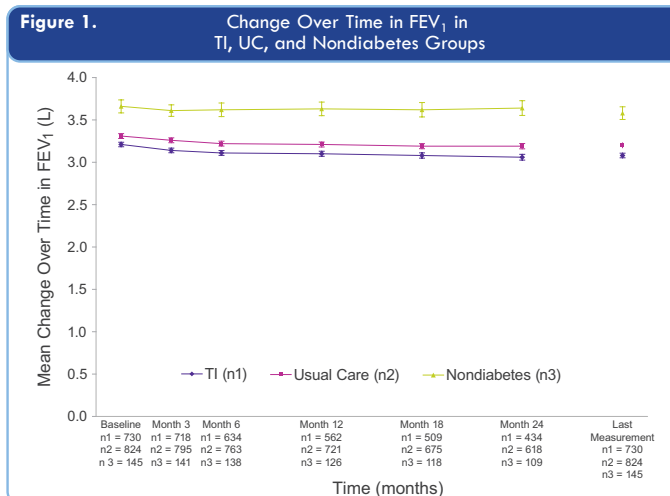
Population	Difference in LSM (± SE) Usual Care - TI	95% CI*
ITT Population		
All subjects with diabetes	0.037 (0.0119)	(0.014, 0.060)
Type 1 subjects with diabetes	0.045 (0.0220)	(0.002, 0.088)
Type 2 subjects with diabetes	0.037 (0.0142)	(0.009, 0.064)
PP Population		
All subjects with diabetes	0.038 (0.0122)	(0.014, 0.062)
Type 1 subjects with diabetes	0.048 (0.0218)	(0.005, 0.090)
Type 2 subjects with diabetes	0.036 (0.0149)	(0.007, 0.065)

* 95% CI is based on Mixed Model Repeated Measure analysis with trial group, visit, baseline FEV₁ value, pooled site, and diabetes type (in analysis of all subjects) as fixed factors. Noninferiority is achieved if the upper limit of the model adjusted 95% CI for the treatment difference (UC - TI) in annualized change is no greater than 50 mL/year (100 mL for 2 years). SE = standard error. CI = confidence interval. LSM = least squares mean.

Parameter	Treatment Group	LSM (SE) Difference UC - TI	95% CI
All subjects			
FVC (L)	Usual Care - TI	0.034 (0.0135)	(0.008, 0.061)
TLC (L)	Usual Care - TI	0.005 (0.0185)	(-0.042, 0.031)
DL _{CO} (mL/min/mm Hg)	Usual Care - TI	0.269 (0.1560)	(-0.037, 0.574)
Subjects with type 1 diabetes			
FVC (L)	Usual Care - TI	0.008 (0.0235)	(-0.038, 0.054)
TLC (L)	Usual Care - TI	0.000 (0.0342)	(-0.067, 0.067)
DL _{CO} (mL/min/mm Hg)	Usual Care - TI	0.398 (0.3026)	(-0.195, 0.992)
Subjects with type 2 diabetes			
FVC (L)	Usual Care - TI	0.047 (0.0165)	(0.015, 0.079)
TLC (L)	Usual Care - TI	-0.006 (0.0222)	(-0.050, 0.037)
DL _{CO} (mL/min/mm Hg)	Usual Care - TI	0.188 (0.1826)	(-0.170, 0.546)

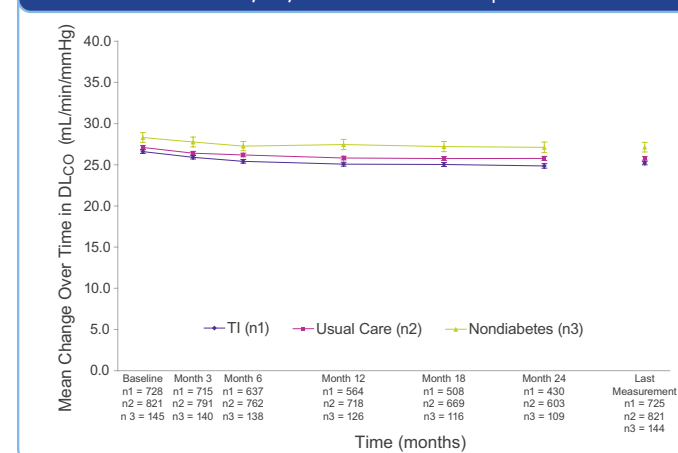
Changes from Baseline to Month 24 in other key lung functions in TI-treated and UC-treated subjects are compared in Table 4.

The changes in PFTs were greatest from Baseline to Month 3 (at the first assessment time point) in both the TI and UC groups, as well as in subjects without diabetes, followed by small fluctuations over time (Figure 1 and Figure 2).



RESULTS (CONT'D)

Figure 2. Change Over Time in DL_{CO} in TI, UC, and Nondiabetes Groups



After the initial slightly greater decline in the first 3 months of treatment, the annual rate of change (slope) in FEV₁ and DL_{CO} in the TI and UC groups between month 3 (first post-Baseline assessment) and month 24 (final study assessment) was not statistically different, indicating that the effects associated with TI on FEV₁ and DL_{CO} are nonprogressive (Table 5).

Table 5. Mean Annual Rate of Change Between Month 3 and Month 24 (ITT Population)*

Parameter	TI	UC	Non-diabetes	UC - TI	95% CI
FEV ₁ (L/year)	-0.047 ± 0.005	-0.036 ± 0.004	-0.024 ± 0.010	0.010 ± 0.006	-0.003, 0.022
DL _{CO} (mL/min/mm Hg)	-0.507 ± 0.067	-0.455 ± 0.055	-0.466 ± 0.139	0.117 ± 0.089	-0.058, 0.292

* A random coefficient model that included terms for treatment, site, time (in years), Baseline FEV₁, and the interaction term of treatment and time was fitted to the observed data to estimate the annual rate of decline for each treatment group, the treatment group differences in annual rate of decline, and corresponding two-sided 95% CI.

CONCLUSIONS

- TI was noninferior to UC for mean change in FEV₁ from Baseline to 24 months using Mixed Model Repeated Measure analysis with a prespecified noninferiority margin of 50 mL/year.
- Over 2 years, small declines from baseline in PFTs were observed in all groups, including the nondiabetic group. Decline was greater in TI group.
- Observed differences between TI and UC groups in the change from Baseline in lung functions were small, noted at the first post-Baseline assessment visit (3 months), and thereafter remained nonprogressive over 2 years of continuous therapy.
- Overall, rate of change in lung functions associated with the continued use of TI was similar to the rate of decline reported in subjects with diabetes in general.

REFERENCES

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