

# THE IMPACT OF BASELINE LUNG FUNCTION ON OUTCOMES WITH INHALED TECHNOOSPHERE INSULIN (TI)

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## Abstract

TI is a novel inhaled rapid-acting insulin (RAI) approved for use in the US. This analysis explored the impact of baseline lung function on clinical outcomes and lung function changes in patients with T1D or T2D initiating inhaled TI therapy. This pooled analysis of 7 studies (duration 6-24 months) included 949 patients with T1D and 1,132 with T2D using TI. Patients were stratified based on baseline percent predicted forced expiratory volume in 1 second (FEV<sub>1</sub>PP): 70% to < 80%, 80% to < 90%, 90% to < 100%, and ≥ 100%. Differences among strata were assessed with one-way ANOVA analysis for demographics and regression modeling (MMRM) for FEV<sub>1</sub> change. Patients in the lowest stratum were older and more had T2D than in the higher strata; they also had the lowest baseline FEV<sub>1</sub> for T1D. Baseline FEV<sub>1</sub> did not differ across strata for T2D (Table 1). There were no significant differences among the baseline FEV<sub>1</sub>PP groups for the proportion of patients experiencing hypoglycemia, reporting cough, or reaching A1C < 7.0%, or in A1C at the end of the study (Table 2). The decline in lung function from baseline to 3 months was small and not significantly different among the groups. The results show that patients with lower baseline lung function (70-80% of predicted normal at baseline) experienced similar glycemic efficacy, hypoglycemia, and lung function changes after 3 months when compared to those with better baseline lung function.

## Introduction

- Technosphere<sup>®</sup> insulin inhalation powder (TI) is a novel inhaled human insulin approved in the US for use as a rapid-acting insulin (RAI) to improve glycemic control in adult patients with diabetes.
- In people with type 1 or 2 diabetes (T1D and T2D, respectively), TI has been shown to provide a comparable degree of glycemic control with that achieved using premixed insulin or an RAI in combination with basal insulin.<sup>1-4</sup>
- Small declines in pulmonary function have been seen in people treated with TI;<sup>1,3,5,6</sup> these declines have also been observed with other inhaled insulins.<sup>7</sup>
- Forced expiratory volume in 1 second (FEV<sub>1</sub>) is one measure of pulmonary function. FEV<sub>1</sub> can, however, be influenced by many patient characteristics.
  - Predicted values based upon reference ranges from healthy people can be used to generate percent predicted values.
  - Lower percent predicted FEV<sub>1</sub> may indicate impairment of pulmonary function;<sup>8</sup> patients with a percent predicted FEV<sub>1</sub> down to 70% were included in the TI studies.

## Objective

To determine the impact of baseline pulmonary function on clinical outcomes and pulmonary function changes in patients with T1D or T2D initiating inhaled TI therapy.

## Methodology

### Study Selection

- Patient-level data were pooled from 7 prospective Phase 3 randomized controlled trials with a duration of > 6 months that were conducted in adults with T1D or T2D who initiated TI.<sup>1,4,9</sup>
- All patients who were randomized, treated, and had pulmonary function testing (PFT) data at baseline and at least 1 follow-up timepoint were considered eligible for inclusion.
- Only patients in the TI arms of the studies were assessed.
- For inclusion in this analysis, PFT in these trials had to be conducted following 2005 American Thoracic Society/European Respiratory Society guidelines.

### Endpoints and Statistical Analyses

- Patients were stratified into 4 groups by their percent predicted FEV<sub>1</sub> at baseline: 70 to < 80%, 80 to < 90%, 90 to < 100%, ≥ 100%.
- Outcomes included percentage of patients experiencing hypoglycemia during the study, percentage of patients achieving glycated hemoglobin A<sub>1c</sub> (A1C) < 7.0% by study end, A1C value at study end, patients reporting adverse events or cough over the duration of the study, and FEV<sub>1</sub> over the duration of the study.
- Differences between strata were assessed using one-way analysis of variance (ANOVA) for demographics and clinical outcomes.
- Mixed-model repeated-measures (MMRM) with baseline FEV<sub>1</sub>, height, age, gender, and visit by treatment as covariates were used to assess change in FEV<sub>1</sub> from baseline.

## Results

### Patients and Baseline Demographics

- 2,081 patients were included (T1D = 949, T2D = 1,132); baseline characteristics are shown in Table 1.

### Clinical Outcomes

- FEV<sub>1</sub> from baseline over 24 months and analyzed by MMRM is shown in the Figure.
- The greatest change in FEV<sub>1</sub> occurred over the first 3 months; the magnitude did not differ between the strata of percent predicted FEV<sub>1</sub>.
  - In patients with T1D, there were reductions of 22.9, 36.9, 48.0, and 43.2 mL from baseline to 3 months in those with percent predicted FEV<sub>1</sub> of 70 to < 80%, 80 to < 90%, 90 to < 100%, and ≥ 100%, respectively (p = 0.779, comparison of all 4 percent predicted levels analyzed by MMRM).
  - In patients with T2D, there were reductions of 59.1, 55.8, 78.2, and 55.2 mL from baseline to 3 months in those with percent predicted FEV<sub>1</sub> of 70 to < 80%, 80 to < 90%, 90 to < 100%, and ≥ 100%, respectively (p = 0.224, comparison of all 4 percent predicted levels analyzed by MMRM).

## Results

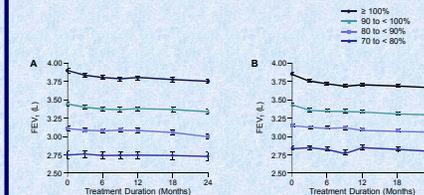
- Comparable proportions of patients in each stratum achieved A1C < 7.0% in both T1D and T2D (Table 2).
  - Those with T2D and the highest percent predicted FEV<sub>1</sub> had lower A1C by study end.
- The proportion of patients experiencing hypoglycemia was comparable across percent predicted FEV<sub>1</sub> stratum (Table 2) for both T1D and T2D.
- The proportion of patients reporting adverse events or episodes of cough was comparable across percent predicted FEV<sub>1</sub> strata for both T1D and T2D (Table 2).

Table 1. Baseline Characteristics

Characteristic	Percent Predicted FEV <sub>1</sub>				p value*
	70 to < 80%	80 to < 90%	90 to < 100%	≥ 100%	
<b>T1D</b>					
Patients, n	54	206	350	339	
Mean age, years (SD)	39 (12.7)	41 (13.2)	39 (12.3)	38 (12.5)	0.589
Female, n (%)	30 (55.6)	104 (50.5)	175 (50.0)	165 (48.7)	0.820
Baseline mean FEV <sub>1</sub> , L (SD)	2.73 (0.54)	3.11 (0.62)	3.44 (0.63)	3.83 (0.82)	
<b>T2D</b>					
Patients, n	91	250	346	445	
Mean age, years (SD)	57 (7.7)	55 (9.0)	55 (8.7)	57 (9.3)	0.002
Female, n (%)	30 (33.0)	92 (36.8)	157 (45.4)	219 (49.2)	0.002
Baseline mean FEV <sub>1</sub> , L (SD)	2.47 (0.48)	2.79 (0.55)	2.98 (0.62)	3.20 (0.74)	

\*Differences between strata were assessed using one-way ANOVA. SD, standard deviation.

Figure. FEV<sub>1</sub> in Patients Treated With TI Stratified by Baseline Percent Predicted FEV<sub>1</sub> Over 24 Months: T1D (A) and T2D (B)



Data represent least squares means ± SE. MMRM analyses were used; FEV<sub>1</sub>, age, height, and gender as covariates. SE, standard error.

## Results

Table 2. Clinical Outcomes at End of Study

Outcome	Percent Predicted FEV <sub>1</sub>				p value*
	70 to < 80%	80 to < 90%	90 to < 100%	≥ 100%	
<b>T1D</b>					
n	54	206	350	339	
Mean A1C, % (SD)	8.1 (0.82)	8.2 (1.21)	8.1 (1.30)	8.2 (1.17)	0.720
A1C < 7.0%, n (%)	2 (4)	25 (13)	43 (13)	32 (10)	0.217
Incidence of hypoglycemia, n (%)	25 (46)	110 (53)	171 (49)	159 (47)	0.503
Incidence of cough, n (%)	17 (32)	59 (29)	114 (33)	85 (25)	0.181
Adverse events, n (%)	41 (76)	175 (85)	281 (80)	258 (76)	0.082
<b>T2D</b>					
n	91	250	346	445	
Mean A1C, % (SD)	8.4 (1.38)	8.2 (1.30)	8.2 (1.40)	8.0 (1.31)	0.029
A1C < 7.0%, n (%)	12 (15)	39 (17)	54 (17)	89 (22)	0.279
Incidence of hypoglycemia, n (%)	26 (29)	74 (30)	113 (33)	143 (32)	0.783
Incidence of cough, n (%)	21 (23)	78 (31)	107 (31)	134 (30)	0.496
Adverse events, n (%)	71 (78)	211 (84)	282 (82)	343 (77)	0.108

\*Differences between strata were assessed using one-way ANOVA. SD, standard deviation.

## DISCUSSION

- Patients with T1D and T2D within the same percent predicted FEV<sub>1</sub> category demonstrated comparable FEV<sub>1</sub> across the assessed timepoints (from baseline up to 24 months).
- Moreover, patients with lower baseline pulmonary function demonstrated comparable glycemic efficacy and safety (hypoglycemia, adverse events) when compared with those with greater baseline pulmonary function.
  - Patients with T2D and the lowest percent predicted FEV<sub>1</sub> (70 to < 80%) had higher A1C at the endpoint, but were also older and more likely to be male compared with those in the highest percent predicted FEV<sub>1</sub> categories.

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