original article

*Diabetes, Obesity and Metabolism* 14: 163–173, 2012.


ORIGINAL ARTICLE

# Pulmonary function over 2 years in diabetic patients treated with prandial inhaled Technosphere Insulin or usual antidiabetes treatment: a randomized trial

P. Raskin[1], S. Heller[2], M. Honka[3]*, P.-C. Chang[4], A. H. Boss[4], P. C. Richardson[4] & N. Amin[4]

[1]*University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA*
[2]*Sheffield Teaching Hospitals Foundation Trust, Sheffield, UK*
[3]*University Hospital Ostrava, Ostrava-Poruba, Czech Republic*
[4]*MannKind Corporation, Valencia, CA, USA*

**Aims:** Development of inhaled insulin has increased the need to understand its pulmonary safety. This study evaluated pulmonary function changes in diabetes patients receiving inhaled Technosphere Insulin (TI) or usual antidiabetes treatment (usual care).

**Methods:** This randomized, open-label study was conducted at 220 sites (25 July 2005 to 29 August 2008). Pulmonary function tests [forced expiratory volume in 1 s ($FEV_1$), forced vital capacity (FVC), total lung capacity (TLC) and lung diffusion capacity for carbon monoxide ($DL_{CO}$)] were prospectively followed over 2 years in patients with type 1 or type 2 diabetes receiving TI (n = 730) or usual care (n = 824), along with a cohort without diabetes not receiving any specific therapy (n = 145).

**Results:** Baseline demographics and pulmonary function were similar between diabetes treatment groups. Lung function declined from baseline in all groups. TI was non-inferior to usual care for mean change in $FEV_1$ from baseline to month 24 [mean (s.e.m.) 0.037 (0.0119) l; 95% CI 0.014 to 0.060] using mixed-model repeated-measure with a pre-specified non-inferiority margin of 50 ml/year. After a greater initial decline at month 3 with TI, rate of change (slope) in $FEV_1$, FVC and $DL_{CO}$ (months 3–24) was not statistically different between treatment groups. TI was well tolerated; no serious safety concerns emerged. The most common respiratory event associated with TI was mild, transient cough, occurring within minutes of inhalation.

**Conclusions:** Observed changes in lung function with TI were small, occurred early after therapy initiation, remained non-progressive over 2 years and were unlikely to be clinically meaningful.

**Keywords:** diabetes, inhaled insulin, pulmonary function, Technosphere Insulin, usual antidiabetes treatment

*Date submitted 30 June 2011; date of first decision 2 August 2011; date of final acceptance 20 September 2011*

## Introduction

Lung as a target organ for diabetes-related complications has been recognized in recent years [1–6]. Development of inhaled insulin as a promising alternative to subcutaneous insulin for diabetes treatment has further increased the need to understand its pulmonary safety. Chronic use of inhaled insulin may affect long-term pulmonary function. Small changes in lung function [e.g. forced expiratory volume in 1 s ($FEV_1$), lung diffusion capacity for carbon monoxide ($DL_{CO}$)] have been reported in patients with type 1 and type 2 diabetes treated with other inhaled insulin formulations [7–10]. Observed pulmonary function changes associated with other inhaled insulins were small, noted within weeks of starting therapy, did not progress for up to 2 years [7–10] and were reversible upon discontinuation [7–12]. The mechanism for these pulmonary function changes is unclear.

*Correspondence to:* N. Amin, MannKind Corporation, 61 South Paramus Road, 5th Floor, Paramus, NJ 07562, USA.
E-mail: namin@mannkindcorp.com

*Present address: 2nd Medical School of Charles University, Prague, Czech Republic.

Technosphere Insulin, or TI (MannKind Corporation, Valencia, CA, USA), is a dry powder formulation of recombinant regular human insulin adsorbed onto Technosphere particles for oral inhalation. The primary component of Technosphere particles is fumaryl diketopiperazine (FDKP), a novel excipient. FDKP is highly soluble in water at neutral and basic pH. Under acidic pH, FDKP undergoes intermolecular self-assembly and crystallizes into microparticles (median diameter, approximately 2–2.5 μm) [13]. Technosphere particles demonstrate aerodynamic characteristics well suited for deep lung delivery [13]. Upon inhalation, Technosphere particles carry insulin into the lung where, at the prevailing physiological pH, the particles dissolve readily, allowing rapid absorption of insulin and FDKP into the systemic circulation with a time to maximum serum insulin and FDKP concentration of approximately 15 and 10 min, respectively [14]. Analysis of the bronchoalveolar lavage fluid in healthy individuals after inhalation showed that insulin and FDKP were cleared rapidly from the lungs, with an estimated clearance half-life of approximately 1 h [15]. The absorbed FDKP is not metabolized and is excreted unchanged in the urine [16].

The efficacy of inhaled TI has been demonstrated in patients with diabetes [17,18]. However, long-term effects of inhaled insulin on pulmonary function remain an area of interest. This study compared lung function changes over 2 years in patients with diabetes treated with inhaled TI or usual antidiabetes treatment (usual care) without TI. A cohort of individuals without diabetes was included for comparison.

## Methods

### Patients

In this randomized, open-label study, individuals aged 18–80 years, with type 1 or type 2 diabetes for at least 2 years and HbA1c ≥6.6% and ≤12.0%, participated at investigation sites in Canada (n = 163), Czech Republic (n = 54), Poland (n = 104), Russian Federation (n = 397), Spain (n = 15), Ukraine (n = 251), United Kingdom (n = 45), and United States (n = 1024) between 25 July 2005 and 29 August 2008 (see Supporting information).

Eligible patients had been non-smokers for at least the preceding 6 months, had a body mass index <42 kg/m$^2$, had $FEV_1$ [19] and $DL_{CO}$ [20] ≥70% and had TLC ≥80% of predicted [21]. Exclusion criteria were significant pulmonary, hepatic, renal or cardiac disease (grade III or IV congestive heart failure, myocardial infarction within the past 12 months or unstable angina, severe arrhythmias treated with amiodarone); significant abnormalities on chest X-ray; history of malignancy within the past 5 years; evidence of severe complications of uncontrolled diabetes (e.g. nephropathy, retinopathy); two or more severe hypoglycaemic episodes within the past 6 months; current illicit drug or alcohol use; or past participation in an inhaled insulin trial. Individuals without diabetes had normal glucose tolerance tests.

This study was conducted in accordance with the Declaration of Helsinki, approved by appropriate independent ethics committees or institutional review boards at each participating clinical site, and monitored by an independent Data Safety Monitoring Board. All patients provided written informed consent before study entry.

### Randomization and Masking

The randomization sequence was generated by a centralized independent party (Fisher Clinical Services, Allentown, PA, USA) and stratified by diabetes type and site with a block size of four. A fax-based randomization system was used to conceal treatment allocation. No masking was used because of the study design. Patients with type 1 or type 2 diabetes were randomized 1 : 1 to prandial inhaled TI or a usual care regimen without TI for 24 months. A cohort of individuals without diabetes (approximately 10 : 1 ratio of diabetes : non-diabetes) were enrolled to examine relative changes in pulmonary function over 2 years for comparison.

### Procedures

Patients were randomized to prandial inhaled TI or usual care (oral antidiabetes drugs alone or with insulin) without TI. For the TI group, TI was administered at the beginning of each meal or large snack and doses were adjusted based on blood glucose readings in 15-U increments, up to a maximum of 90 U/meal. Patients previously treated with subcutaneous basal-bolus insulin replaced their prandial insulin with a corresponding dose of TI based on the estimated bioavailability of approximately 24–28%. Patients treated with other insulin regimens replaced 50% of the total daily subcutaneous insulin dose with a corresponding dose of TI, divided between meals, while the remaining 50% was given as basal insulin. Oral hypoglycaemic drugs were continued as required. Patients in the usual care group continued their usual pre-enrollment antidiabetes drugs, including insulin. All patients were treated according to established guidelines [22,23], but no target goals for HbA1c were pre-specified. Individuals without diabetes did not receive any study-specific treatment.

Pulmonary function tests [PFTs (spirometry, lung volumes, $DL_{CO}$)] were obtained at baseline and at months 3, 6, 12, 18 and 24 according to American Thoracic Society and European Respiratory Society (ATS/ERS) recommendations [24–26] only at certified PFT laboratories. All certified PFT laboratories received comprehensive on-site training and submitted at least 10 acceptable biological control tests to demonstrate quality standards prior to any patient testing. To ensure test quality throughout the study, each PFT laboratory was required to submit weekly biological and mechanical quality control tests and diffusion simulation tests every 2 months that met the quality standards. All PFTs were reviewed by blinded, independent, central reviewers. Tests not meeting ATS/ERS performance criteria for acceptability or repeatability were repeated within 7 days of notification.

Participants developing a respiratory tract infection had PFTs postponed for a minimum of 15 or 30 days post-symptom resolution for upper or lower respiratory tract infection, respectively.

For safety monitoring during the study, a decrease of ≥15% from baseline in $FEV_1$, FVC, TLC or $DL_{CO}$ was predefined as a PFT finding. The 15% threshold was selected taking into account the expected inherent variability associated with technical and biological factors in such measurements. If there was a PFT finding, investigators were asked to determine its significance based on clinical evaluation.

The primary study objective was to compare the change from baseline in pre-bronchodilator $FEV_1$ at month 24 between the diabetes treatment groups. Secondary objectives were treatment group difference in the incidence of $FEV_1$ findings (≥15% decline) and change from baseline in FVC, TLC, $DL_{CO}$ and HbA1c.

Safety was assessed by monitoring adverse events (AEs), clinical laboratory testing, chest X-rays, 12-lead electrocardiograms and physical examinations.

### Statistical Analysis

Sample size was calculated for the change from baseline in $FEV_1$ and incidence of a ≥15% decrease in $FEV_1$. The null hypothesis for change from baseline in $FEV_1$ was to test that the $FEV_1$ change at month 24 with TI was not >50 ml/year above the change with usual care. Assuming a standard deviation of

100 ml/year, 80% power and a 5% (one-tailed) significance level, 50 patients were required for each diabetes treatment arm. For the incidence of ≥15% decline from baseline in $FEV_1$, the null hypothesis to be tested was that the treatment group difference in incidence was not >5% for TI compared with usual care. Assuming an incidence rate of 15% for $FEV_1$ and a non-inferiority margin of a 5% difference in incidence between treatment groups and 28% dropouts, approximately 860 diabetes patients per group were required for 80% power and an $\alpha$ of 5% (one-tailed). To achieve a 10 : 1 (diabetes : non-diabetes) participant ratio, 170 individuals without diabetes were recruited.

The safety population was defined as all randomized patients with diabetes who received at least one dose of study drug. Primary analyses were performed on the intention-to-treat population, defined as all randomized patients with diabetes who received the study drug and had a baseline and at least one post-baseline $FEV_1$ value. Mixed-model repeated-measure (MMRM) analysis was used to evaluate treatment group differences for change from baseline in $FEV_1$ with treatment, pooled site, visit, diabetes type and baseline $FEV_1$ as fixed terms and patient as random effect fitted in the model. TI was considered non-inferior to usual care if the upper limit of the two-sided 95% confidence interval (CI) for the treatment group difference in the mean change in $FEV_1$ from baseline to month 24 was ≤100 ml (≤50 ml/year).

PFT findings were analysed using logistic regression with treatment, site and diabetes type in the model. TI was considered non-inferior to usual care if the lower limit of 95% CI for the treatment group difference in the incidence of $FEV_1$ finding did not exceed 5%.

Change in FVC, TLC, $DL_{CO}$ and HbA1c from baseline to months 3, 6, 12, 18 and 24 was analysed by MMRM. Adjusted (least squares) mean and mean differences along with the 95% CIs were calculated for the overall change from baseline. Missing data were not imputed.

The treatment group difference in the rate of change (slope) after the first post-baseline assessment visit (month 3) in $FEV_1$, FVC and $DL_{CO}$ and corresponding two-sided 95% CI were calculated via a random coefficient analysis using the PFT data collected from months 3–24. Terms of treatment, site, time (years), baseline PFT value, age, gender and height were fitted in the model. All analyses were performed using SAS, Version 8.2 or higher (SAS Institute, Cary, NC, USA). This trial is registered at ClinicalTrials.gov (NCT00308737).

## Results

Of the 2053 patients who were randomized in the trial, 1699 were included in the intention-to-treat population (figure 1).

Baseline characteristics were similar between diabetes treatment groups (Table 1). Individuals without diabetes were younger, weighed less and had a lower body mass index than the patients with diabetes.

Of the 789 (38.4%) participants who withdrew from the study, 463 (49.4%) received TI, 289 (30.4%) received usual care and 37 (22.6%) did not have diabetes (figure 1). The most common reason for discontinuation in both groups was withdrawal of consent (23.2% with TI, 17.5% with usual care). No association was found between safety parameters, such as cough, hypoglycaemia and PFT findings, among completers and patients who withdrew early.

Baseline PFTs ($FEV_1$, FVC, TLC, $DL_{CO}$) were comparable between treatment groups (Table 2). As expected, individuals without diabetes had better PFTs at study entry than did those with diabetes.

Over 2 years, small declines from baseline in $FEV_1$ were observed in all groups, with the smallest change in those without diabetes (figure 2). The adjusted mean (s.e.m.) treatment group difference in change in $FEV_1$ from baseline to month 24 was 0.037 (0.0119) l (95% CI, 0.014 to 0.060). The upper limit of the 95% CI for the treatment group difference in $FEV_1$ change at month 24 was less than the pre-specified non-inferiority margin of 100 ml (50 ml/year), demonstrating non-inferiority with TI over usual care (Table 3). Results were similar in the per-protocol population (see Supporting information).

At month 24, the adjusted treatment group difference in mean FVC was small [0.034 l (s.e.m. 0.0135)]. TLC and $DL_{CO}$ treatment group differences were not statistically significant (Table 3, figure 2).

After the initial decline at the first post-baseline assessment visit (month 3), annual rates of decline (slope) in $FEV_1$, FVC and $DL_{CO}$ from months 3–24 were not statistically different between groups, indicating that after the early decline, PFT changes associated with TI were non-progressive up to 2 years (Table 4).

Overall, changes from baseline in $FEV_1$, FVC, TLC and $DL_{CO}$ were similar in patients with type 1 and type 2 diabetes. No association was noted in changes in these PFT parameters and the average daily dose of TI (<60 U, >60–120 U, >120–180 U, >180–240 U, >240–300 U and >300 U).

Distribution plots of mean percent change from baseline in $FEV_1$, FVC and $DL_{CO}$ at last measurement (figure 3) showed that the percentage of patients with PFT declines was greater with TI than with usual care, but the declines were driven by a slight shift in population distribution of patients with small changes and not by a few outliers with large declines.

In all, 42 of 730 (5.75%) patients receiving TI and 27 of 824 (3.28%) receiving usual care had protocol-predefined $FEV_1$ findings (≥15% decrease from baseline) at last measurement (Table 5). Treatment group difference (usual care—TI) in the percentage of patients with $FEV_1$ decline of ≥15% from baseline was −2.48% (95% CI, −4.5578 to 0.3956). Lower bound of 95% CI did not exceed −5%, thereby demonstrating that TI was non-inferior to usual care. Only three patients (all receiving TI) discontinued due to ≥15% decline in any PFT parameter from baseline at anytime during the trial ($FEV_1$, 1 of 81 patients; $DL_{CO}$, 2 of 238 patients).

Mean (s.d.) change in HbA1c from baseline to month 24 was comparable between treatment groups: TI −0.59% (1.40%), type 1 diabetes −0.29% (1.31%) and type 2 diabetes −0.70% (1.41%); usual care −0.50% (1.37%), type 1 diabetes −0.31% (1.20%) and type 2 diabetes −0.59% (1.43%).

More treatment-emergent AEs (TEAEs) were reported in patients receiving TI (n = 729 [79.0%]) than in patients receiving usual care (n = 674 [71.0%]; Table 6). Without the

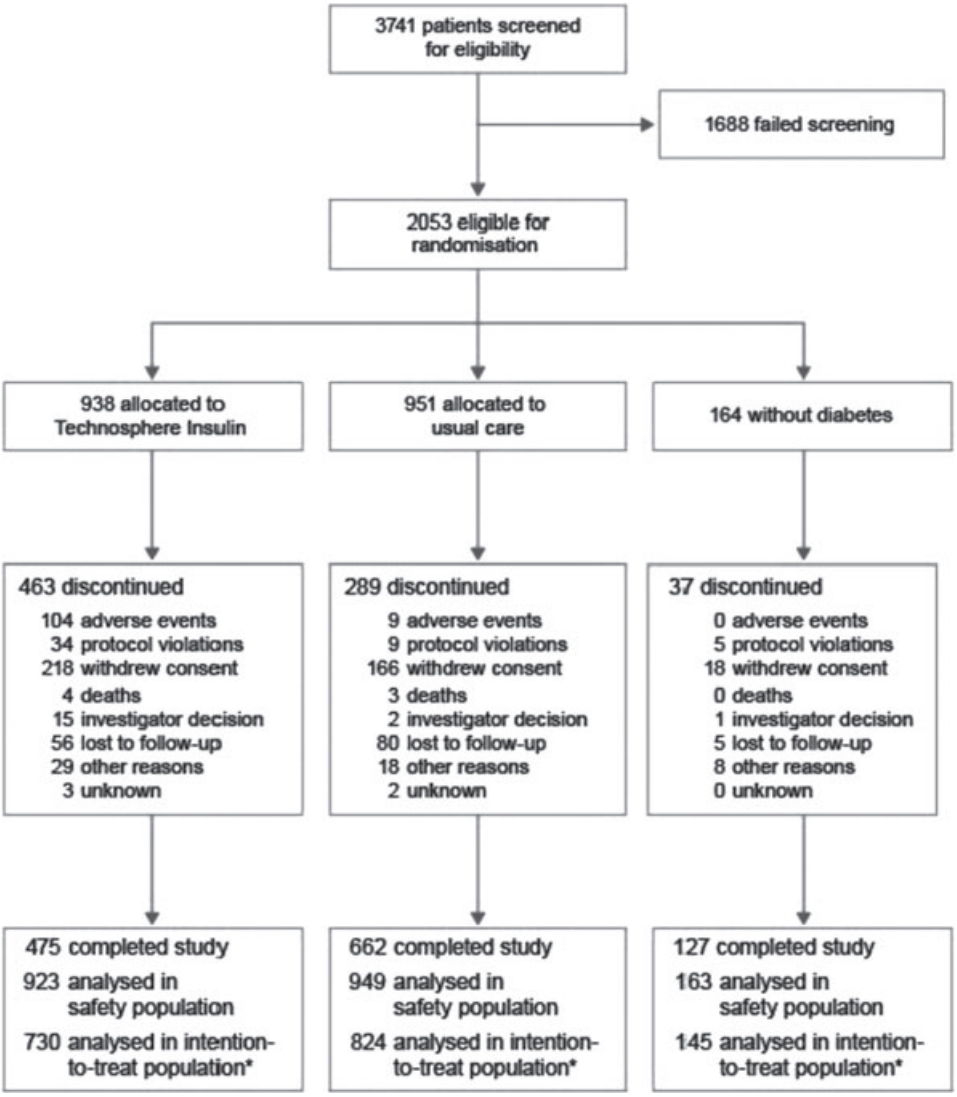


**Figure 1.** Patient enrollment and disposition. *The intention-to-treat population included all patients who were in the safety population and had a baseline value and at least one post-baseline value of the primary variable ($FEV_1$).

cough TEAE, the incidence of TEAEs was 673 (72.9%) with TI and 659 (69.4%) with usual care. The most common TEAE in both treatment groups was hypoglycaemia. Cough, the second most common TEAE, was more frequent with TI than with usual care. Cough was predominantly mild, non-productive, occurred ≤10 min of dry powder inhalation, was reported early (within the first month of treatment initiation) and declined over time (see Supporting information). The mean changes from baseline in PFT variables were similar in patients who did or did not experience cough.

The incidence of serious TEAEs was similar with TI (10.0%) and usual care (9.6%; Table 7). No TEAE of lung malignancy was reported in any group. More neoplasms were reported in the TI group; however, the type and location of tumours were not suggestive of any safety signal. Seven patients died during the trial: four receiving TI (one each due to cardiac arrest, circulatory collapse, cerebrovascular accident and stroke) and three receiving usual care (cardiac arrest, cerebrovascular accident and car accident injuries). None of the deaths were attributed to study drugs.

Study discontinuations due to AEs were more common with TI (n = 104 [11.1%]) than with usual care (n = 6 [0.6%]; see Supporting information). The most common AE leading to discontinuation was cough [n = 43 (4.7%) with TI and n = 0 with usual care]. See the table describing AEs leading to discontinuation in the Supporting information.

## Discussion

Using a highly standardized PFT program, we followed lung function prospectively over 2 years in patients with diabetes and a cohort of individuals without diabetes. The real-world trial design provided a unique opportunity to evaluate the pulmonary safety of inhaled TI in usual clinical practice.

Over 2 years, patients receiving TI or usual care and individuals without diabetes experienced a decline from

**Table 1.** Patient demographic and baseline characteristics (safety population).

| Baseline characteristics | TI (n = 923) | Usual care (n = 949) | Non-diabetes (n = 163) |
|---|---|---|---|
| Type 1 diabetes [n (%)] | 267 (28.9) | 271 (28.6) | NA |
| Type 2 diabetes [n (%)] | 656 (71.1) | 678 (71.4) | NA |
| Age (years) | 50.8 ± 11.55 | 50.4 ± 11.62 | 38.2 ± 12.59 |
| Age group (years) [n (%)] | | | |
| 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) |
| Sex [n (%)] | | | |
| Male | 557 (60.3) | 578 (60.9) | 71 (43.6) |
| Female | 366 (39.7) | 371 (39.1) | 92 (56.4) |
| Race [n (%)] | | | |
| White | 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 |
| Weight (kg) [mean (s.d.)] | 87.69 (18.628) | 87.53 (17.638) | 74.35 (16.204) |
| BMI (kg/m$^2$) [mean (s.d.)] | 29.87 (5.366) | 29.76 (5.035) | 25.27 (4.494) |
| Baseline HbA1c (%) [mean (s.d.)] | 8.7 (1.39) | 8.7 (1.38) | NA |
| Duration of diabetes (years) [mean (s.d.)] | 11.9 (8.47) | 11.8 (8.04) | NA |
| Past smoker [n (%)] | 277 (30.0) | 285 (30.0) | 29 (17.8) |

BMI, body mass index; s.d., standard deviation; TI, Technosphere Insulin; usual care, usual antidiabetes treatment.

**Table 2.** Baseline pulmonary function tests by randomized groups (intention-to-treat population).

| | TI | Usual care | Non-diabetes |
|---|---|---|---|
| $FEV_1$ (l) | | | |
| n | 730 | 824 | 145 |
| Mean (s.d.) | 3.213 (0.711) | 3.299 (0.804) | 3.666 (0.912) |
| % predicted | 96.69 | 97.28 | 100.89 |
| FVC (l) | | | |
| n | 730 | 824 | 145 |
| Mean (s.d.) | 4.084 (0.926) | 4.205 (1.030) | 4.608 (1.079) |
| % predicted | 96.06 | 97.20 | 103.29 |
| TLC (l) | | | |
| n | 726 | 821 | 145 |
| Mean (s.d.) | 5.928 (1.129) | 6.043 (1.238) | 6.218 (1.216) |
| % predicted | 97.52 | 98.59 | 104.25 |
| $DL_{CO}$ (ml/min/mm Hg) | | | |
| n | 728 | 821 | 145 |
| Mean (s.d.) | 26.73 (5.902) | 27.23 (6.349) | 28.70 (7.372) |
| % predicted | 98.72 | 99.41 | 99.68 |

$DL_{CO}$, lung diffusion capacity for carbon monoxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; s.d., standard deviation; TI, Technosphere Insulin; TLC, total lung capacity; usual care, usual antidiabetes treatment.

baseline in lung function. At 24 months, TI was non-inferior to usual care for mean $FEV_1$ change from baseline, with a pre-specified non-inferiority margin of 100 ml/2 year (50 ml/year). The CI around the mean $FEV_1$ change at month 24 does not encompass zero, as the sample size greatly exceeded the necessary sample size for this endpoint ($\alpha$ error). Overall, observed treatment group differences in mean change from baseline in PFTs were small, were noted early (3 months) and remained non-progressive for up to 2 years of continuous therapy.

The pattern and magnitude of observed PFT changes with TI were generally comparable to other long-term studies of inhaled insulin formulations in patients with diabetes [8–12]. With Exubera inhaled insulin, declines in $FEV_1$ and $DL_{CO}$ were reversible and restored to the same level as subcutaneous insulin within 1 week of treatment cessation [11,12]. Similarly, in a follow-on study evaluating PFTs in patients with type 1 or type 2 diabetes after treatment duration of up to 2 years, differences in $FEV_1$, FVC and $DL_{CO}$ between TI and the comparator resolved by 1 month after TI discontinuation [27].

The rate of pulmonary function decline (slope) observed in patients in both diabetes treatment groups was similar but exceeded the rate of decline in the non-diabetes cohort and the expected age-related decline in non-smoking healthy individuals without underlying lung disease [28]. This finding adds to the growing literature showing an accelerated rate of lung function decline in patients with diabetes [2,6,9]. Although the exact underlying mechanism for pulmonary dysfunction in diabetes remains unclear, changes are ostensibly related to complex interactions among diabetes-induced chronic hyperglycaemia, oxidative stress, microangiopathy, accumulation of glycosylated collagen in lung connective tissue and systemic inflammation [3,29].

We do not consider the observed small, non-progressive lung function changes to be clinically significant. Declines from baseline in PFT of ≥15% were pre-specified solely for safety monitoring. Investigators were instructed to correlate each PFT decline with the patient's clinical condition and determine

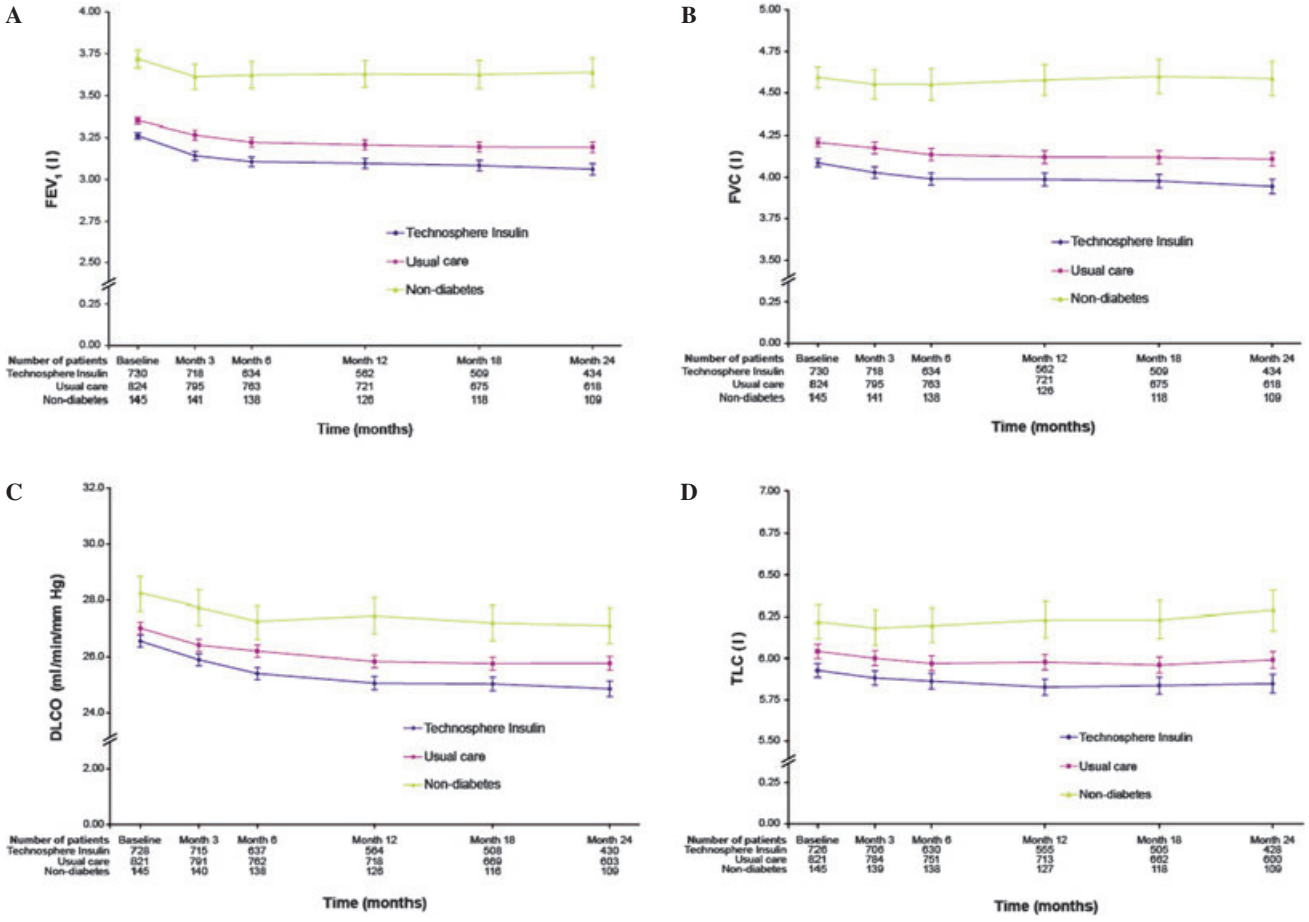


**Figure 2.** Changes in pulmonary function over time in (A) $FEV_1$, (B) FVC, (C) $DL_{CO}$ and (D) TLC (intention-to-treat population). Data are mean (s.e.).

its significance. However, in all but three patients with PFT declines of ≥15%, physicians at the bedside considered the finding clinically not meaningful and opted to continue TI.

When interpreting changes in lung function over time, examination of the quality of PFT measurements is critical. PFT measurements have inherent biological and technical/mechanical variability. Additional variability can be introduced by using different testing centres in a longitudinal, large-scale, multicentre, global trial. To minimize inter- and intra-laboratory variability, and ensure reliability in measurements, a comprehensive, standardized PFT and quality control program was implemented. PFTs were obtained only at certified PFT laboratories by trained personnel according to ATS/ERS recommendations. Individuals were tested at the same PFT laboratory throughout the study. Adherence to the quality standards throughout the study was monitored by on-going centralized review of weekly biological and mechanical quality control tests submitted by each laboratory. In our experience, intersession coefficient of variation of biological control tests for $FEV_1$ (mean 3.4%) and $DL_{CO}$ (mean 6.6%) is smaller or comparable to published values [25,26,30–33].

The exact mechanism of observed lung function changes is unclear. In clinical trials of TI, non-progressive changes in PFTs disappearing upon discontinuation suggest that such changes are unlikely due to permanent structural alterations in the lungs. Preclinical chronic inhalation studies of both TI and Technosphere powder (FDKP) in Sprague Dawley rats and beagle dogs showed no degenerative, cytotoxic, neoplastic or proliferative changes in the lungs [34]. A trial examining bronchoalveolar lavage fluid in patients with type 1 or type 2 diabetes after 12 weeks of Exubera showed no evidence of pulmonary inflammation to explain the observed small, non-progressive, reversible treatment effect on pulmonary function [35]. One of the speculations was that mannitol, an osmotic, in the Exubera® (Pfizer Inc, New York, NY, USA) excipient caused subtle physiological fluid shifts within the lungs, resulting in the observed pulmonary function changes [35]. However, such a mechanism is unlikely for TI because the excipient FDKP is metabolically inert.

This study demonstrated that glycaemic control was sustained and comparable between treatment groups over 2 years. Inhaled TI was well tolerated and no serious safety concerns emerged. The most common TEAEs were hypoglycaemia and transient, mild, dry cough. The pattern and characteristics of cough associated with TI are similar to the cough reported with other inhaled insulin dry powder formulations and probably represents transient airway irritation during dry powder inhalation.

**Table 3.** Change from baseline to month 24 in $FEV_1$, FVC, TLC and $DL_{CO}$ for all patients and by type 1 and type 2 diabetes (intention-to-treat populations).

| Parameter (unit) | Difference between treatment groups [LS mean (s.e.)]* | 95% CI* |
|---|---|---|
| All patients, usual care—TI | | |
| $FEV_1$ (l) | 0.037 (0.0119) | 0.014 to 0.060 |
| FVC (l) | 0.034 (0.0135) | 0.008 to 0.061 |
| TLC (l) | 0.005 (0.0185) | −0.042 to 0.031 |
| $DL_{CO}$ (ml/min/mm Hg) | 0.269 (0.1560) | −0.037 to 0.574 |
| Patients with type 1 diabetes, usual care—TI | | |
| $FEV_1$ (l) | 0.045 (0.0220) | 0.002 to 0.088 |
| FVC (l) | 0.008 (0.0235) | −0.038 to 0.054 |
| TLC (l) | 0.000 (0.0342) | −0.067 to 0.067 |
| $DL_{CO}$ (ml/min/mm Hg) | 0.398 (0.3026) | −0.195 to 0.992 |
| Patients with type 2 diabetes, usual care—TI | | |
| $FEV_1$ (l) | 0.037 (0.0142) | 0.009 to 0.064 |
| FVC (l) | 0.047 (0.0165) | 0.015 to 0.079 |
| TLC (l) | −0.006 (0.0222) | −0.050 to 0.037 |
| $DL_{CO}$ (ml/min/mm Hg) | 0.188 (0.1826) | −0.170 to 0.546 |

CI, confidence interval; $DL_{CO}$, lung diffusion capacity for carbon monoxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; LS, least squares; s.e., standard error; TI, Technosphere Insulin; TLC, total lung capacity; usual care, usual antidiabetes treatment.
*The LS mean (s.e.) and 95% CI are based on MMRM analysis with trial group, visit, baseline PFT value, pooled site and diabetes type (for analysis of combined type 1 and type 2 populations) as fixed effect and patient as random effect.

More patients receiving TI than usual care discontinued early, with more of these discontinuations due to AEs. The higher number of discontinuations due to AEs may have been influenced by the unique design of this open-label study. Unlike the TI group, where prandial TI was either added or substituted for a prandial subcutaneous insulin, patients in the usual care group continued their usual pre-enrollment antidiabetes regimen and were allowed to adjust the regimen at the investigator's discretion. This may have obviated the need for discontinuation. TI, with its inhaled mode of administration, may have created bias as patients with respiratory AEs would be more likely to discontinue treatment if they were receiving inhaled therapy than subcutaneous insulin or an oral agent. Indeed, respiratory AEs, such as cough, were the most common AEs leading to discontinuation. Cough after inhalation of a dry powder was not unexpected, and mean change from baseline in lung function was similar in patients who did or did not experience cough.

Importantly, differential dropouts between the treatment groups had no influence on the results and primary non-inferiority conclusions. Patients dropping out early were noted to have smaller decreases in $FEV_1$, FVC and $DL_{CO}$ than those who completed the study. More TI patients with the largest drops in lung function completed the study than usual care patients, suggesting that patients did not drop out due to decreases in lung function. Additional examination of the data using various populations, models and imputation techniques showed that the dropouts did not influence the results. In all cases, the primary objective of non-inferiority at the 100-ml margin was met (see Supporting information).

In conclusion, pulmonary function changes associated with TI were small, noted early at treatment initiation and remained non-progressive over 2 years of continuous therapy. The magnitude and pattern of PFT changes are reassuring in that the observed changes are unlikely due to permanent structural changes in lungs.

**Table 5.** Percentage of patients with a decrease of ≥15% in $FEV_1$, FVC, TLC and $DL_{CO}$ from baseline (intention-to-treat population).

| | Pulmonary function test finding at the last measurement | |
|---|---|---|
| | TI [n/N (%)] | Usual care [n/N (%)] |
| $FEV_1$ | 42/730 (5.75) | 27/824 (3.28) |
| FVC | 23/730 (3.15) | 17/824 (2.06) |
| TLC | 7/717 (0.98) | 6/817 (0.73) |
| $DL_{CO}$ | 105/723 (14.52) | 108/818 (13.2) |

$DL_{CO}$, lung diffusion capacity for carbon monoxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; TI, Technosphere Insulin; TLC, total lung capacity; usual care, usual antidiabetes treatment.

**Table 4.** Annual rate of change from months 3–24 (type 1 and type 2 diabetes mellitus analysis*).

| Treatment group | $FEV_1$ (l/year) | FVC (l/year) | $DL_{CO}$ (ml/min/mm Hg/year) |
|---|---|---|---|
| Non-diabetes | n = 141 | n = 141 | n = 140 |
| [mean (s.e.m.)] | −0.024 (0.010) | −0.021 (0.013) | −0.466 (0.139) |
| TI | n = 718 | n = 718 | n = 715 |
| [mean (s.e.m.)] | −0.047 (0.005) | −0.045 (0.006) | −0.507 (0.067) |
| Usual care | n = 795 | n = 795 | n = 791 |
| [mean (s.e.m.)] | −0.036 (0.004) | −0.033 (0.005) | −0.455 (0.055) |
| Difference between usual care and TI | 0.010 | 0.014 | 0.117 |
| [mean (95% CI)] | (−0.003 to 0.022) | (−0.002 to 0.029) | (−0.058 to 0.292) |

CI, confidence interval; $DL_{CO}$, lung diffusion capacity for carbon monoxide; $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; s.e.m., standard error of the mean; TI, Technosphere Insulin; usual care, usual antidiabetes treatment.
*Random coefficient analysis. The model included treatment, region, time (in years), baseline, age, height and sex fitted to the observed data to estimate annual change.

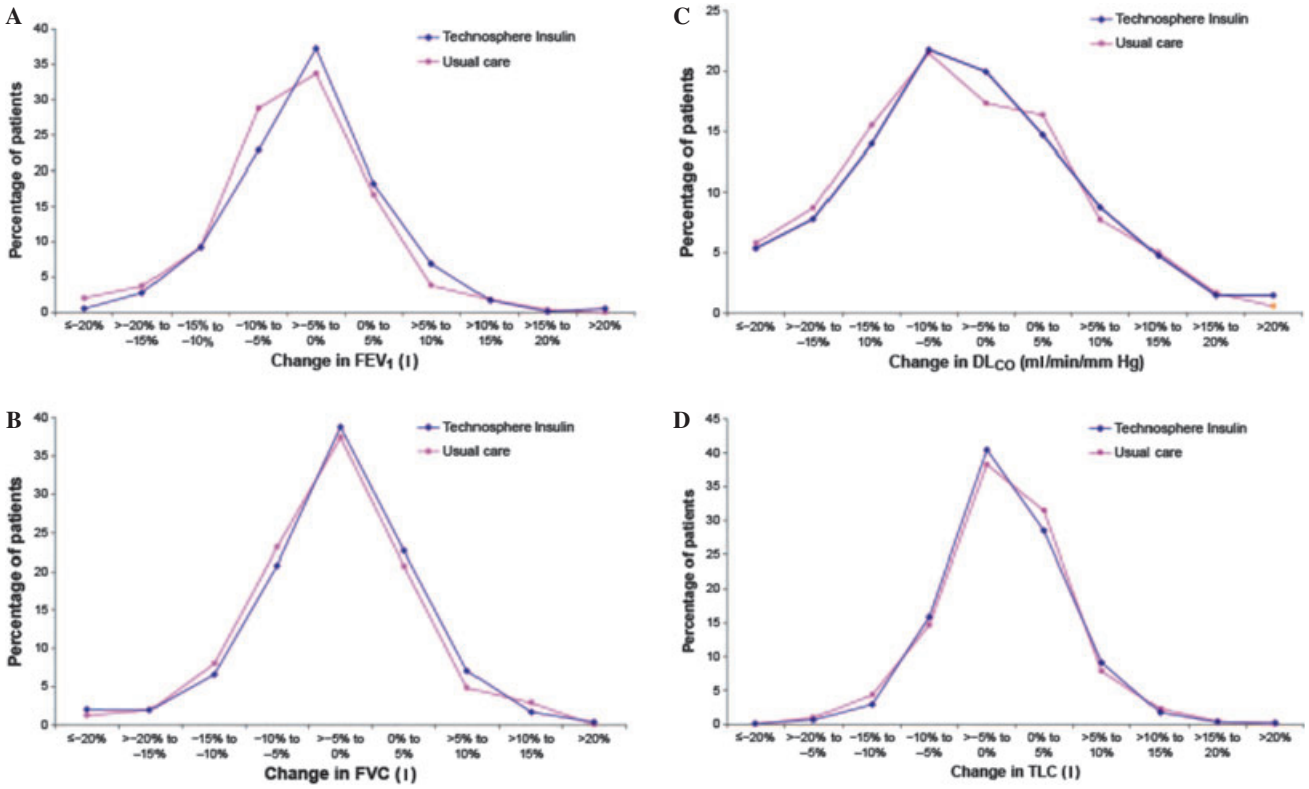


**Figure 3.** Percentage of patients with change in (A) $FEV_1$, (B) FVC, (C) $DL_{CO}$ and (D) TLC from baseline at the last measurement (intention-to-treat population).

**Table 6.** Treatment-emergent adverse events (TEAEs) of any severity reported in ≥5% of patients by preferred term in any treatment group (safety population).

| | All patients | | Type 1 diabetes | | Type 2 diabetes | | Non-diabetes |
|---|---|---|---|---|---|---|---|
| Adverse events | TI (n = 923) [n (%)] | Usual care (n = 949) [n (%)] | TI (n = 267) [n (%)] | Usual care (n = 271) [n (%)] | TI (n = 656) [n (%)] | Usual care (n = 678) [n (%)] | (n = 163) [n (%)] |
| Any TEAE | 729 (79.0) | 674 (71.0) | 217 (81.3) | 223 (82.3) | 512 (78.0) | 451 (66.5) | 86 (52.8) |
| Hypoglycaemia | 365 (39.5) | 371 (39.1) | 165 (61.8) | 179 (66.1) | 200 (30.5) | 192 (28.3) | 0 |
| Cough | 257 (27.8) | 42 (4.4) | 67 (25.1) | 13 (4.8) | 190 (29.0) | 29 (4.3) | 5 (3.1) |
| Upper respiratory tract infection | 119 (12.9) | 143 (15.1) | 36 (13.5) | 47 (17.3) | 83 (12.7) | 96 (14.2) | 35 (21.5) |
| Nasopharyngitis | 67 (7.3) | 69 (7.3) | 19 (7.1) | 28 (10.3) | 48 (7.3) | 41 (6.0) | 14 (8.6) |
| Influenza | 38 (4.1) | 41 (4.3) | 11 (4.1) | 18 (6.6) | 27 (4.1) | 23 (3.4) | 2 (1.2) |
| Hypertension | 39 (4.2) | 45 (4.7) | 8 (3.0) | 9 (3.3) | 31 (4.7) | 36 (5.3) | 3 (1.8) |

TI, Technosphere Insulin; usual care, usual antidiabetes treatment.

## Acknowledgements

This study was funded by MannKind Corporation. We thank the MKC-TI-030 investigators, their staff and the clinical trial personnel; the patients for their participation in this trial; and Marjorie Pestel Zimmerman and Jane Moore of Peloton Advantage for writing and editorial assistance (supported by MannKind Corporation). Technosphere is a registered trademark of MannKind Corporation. Exubera is a registered trademark of Pfizer Inc.

## Conflict of Interest

P. R.'s institution has received research support from and P. R. has served as a consultant for MannKind. S. H. has received payment for lecture fees, consultancy and research support from Amylin, Astra Zeneca, Eli Lilly, Johnson & Johnson, MannKind, Novo Nordisk, sanofi-aventis and Takeda. M. H. has received honoraria or consulting fees and travel reimbursement related to this study from MannKind, is a board member for MSD and has served as a speaker for Novo

**Table 7.** Serious treatment-emergent adverse events (TEAEs) reported by patients and by type 1 and type 2 diabetes (safety population).

| | All patients | | Type 1 diabetes | | Type 2 diabetes | | Non-diabetes |
|---|---|---|---|---|---|---|---|
| Serious TEAEs | TI (n = 923) [n (%)] | Usual care (n = 949) [n (%)] | TI (n = 267) [n (%)] | Usual care (n = 271) [n (%)] | TI (n = 656) [n (%)] | Usual care (n = 678) [n (%)] | (n = 163) [n (%)] |
| Overall | 92 (10.0) | 91 (9.6) | 27 (10.1) | 27 (10.0) | 65 (9.9) | 64 (9.4) | 5 (3.1) |
| Blood and lymphatic system disorders | 2 (0.2) | 1 (0.1) | 0 | 1 (0.4) | 2 (0.3) | 0 | 0 |
| Cardiac disorders | 17 (1.8) | 19 (2.0) | 2 (0.7) | 3 (1.1) | 15 (2.3) | 16 (2.4) | 0 |
| Ear and labyrinth disorders | 0 | 1 (0.1) | 0 | 0 | 0 | 1 (0.1) | 0 |
| Endocrine disorders | 0 | 1 (0.1) | 0 | 0 | 0 | 1 (0.1) | 0 |
| Eye disorders | 2 (0.2) | 2 (0.2) | 0 | 1 (0.4) | 2 (0.3) | 1 (0.4) | 0 |
| Gastrointestinal disorders | 9 (1.0) | 6 (0.6) | 3 (1.1) | 1 (0.4) | 6 (0.9) | 5 (0.7) | 0 |
| General disorders and administration site conditions | 4 (0.4) | 1 (0.1) | 0 | 0 | 4 (0.6) | 1 (0.1) | 0 |
| Hepatobiliary disorders | 6 (0.7) | 4 (0.4) | 3 (1.1) | 1 (0.4) | 3 (0.5) | 3 (0.4) | 0 |
| Infections and infestations | 19 (2.1) | 14 (1.5) | 1 (0.4) | 3 (1.1) | 18 (2.7) | 11 (1.6) | 3 (1.8) |
| Injury, poisoning and procedural complications | 7 (0.8) | 6 (0.6) | 4 (1.5) | 1 (0.4) | 3 (0.5) | 5 (0.7) | 0 |
| Investigations | 0 | 1 (0.1) | 0 | 1 (0.4) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | 18 (2.0) | 23 (2.4) | 15 (5.6) | 11 (4.1) | 3 (0.5) | 12 (1.8) | 0 |
| Musculoskeletal and connective tissue disorders | 6 (0.7) | 8 (0.8) | 1 (0.4) | 2 (0.7) | 5 (0.8) | 6 (0.9) | 1 (0.6) |
| Neoplasms: benign, malignant and unspecified (including cysts and polyps) | 10 (1.1) | 3 (0.3) | 1 (0.4) | 0 | 9 (1.4) | 3 (0.4) | 1 (0.6) |
| Prostate cancer | 2 (0.2) | 1 (0.1) | 1 (0.4) | 0 | 1 (0.2) | 1 (0.2) | 0 |
| Breast cancer | 2 (0.2) | 0 | 0 | 0 | 2 (0.3) | 0 | 0 |
| Uterine leiomyoma | 1 (0.1) | 1 (0.1) | 0 | 0 | 1 (0.2) | 1 (0.2) | 0 |
| Basal cell carcinoma | 1 (0.1) | 0 | 0 | 0 | 1 (0.2) | 0 | 0 |
| Benign salivary gland neoplasm | 1 (0.1) | 0 | 0 | 0 | 1 (0.2) | 0 | 0 |
| Bile duct cancer | 1 (0.1) | 0 | 0 | 0 | 1 (0.2) | 0 | 0 |
| Ovarian epithelial cancer | 1 (0.1) | 0 | 0 | 0 | 1 (0.2) | 0 | 0 |
| Benign pituitary tumour | 1 (0.1) | 0 | 0 | 0 | 1 (0.2) | 0 | 0 |
| Cervix carcinoma | 0 | 1 (0.1) | 0 | 0 | 0 | 1 (0.2) | 0 |
| Benign ovarian tumour | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.6) |
| Nervous system disorders | 11 (1.2) | 10 (1.1) | 4 (1.5) | 2 (0.7) | 7 (1.1) | 8 (1.2) | 1 (0.6) |
| Psychiatric disorder | 1 (0.1) | 1 (0.1) | 0 | 1 (0.4) | 1 (0.2) | 0 | 0 |
| Renal and urinary disorders | 2 (0.2) | 4 (0.4) | 0 | 0 | 2 (0.3) | 4 (0.6) | 0 |
| Reproductive system and breast disorders | 3 (0.3) | 0 | 1 (0.4) | 0 | 2 (0.3) | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | 4 (0.4) | 1 (0.1) | 0 | 0 | 4 (0.4) | 1 (0.1) | 0 |
| Skin and subcutaneous tissue disorders | 0 | 2 (0.2) | 0 | 0 | 0 | 2 (0.3) | 0 |
| Vascular diseases | 2 (0.2) | 2 (0.2) | 1 (0.4) | 1 (0.4) | 1 (0.2) | 1 (0.1) | 0 |

TI, Technosphere Insulin; usual care, usual antidiabetes treatment.


doi:10.1111/j.1463-1326.2011.01500.x

Nordisk and Eli Lilly and Company. P.-C. C., A. H. B., P. C. R. and N. A. are employees of and have shares or stocks in MannKind. No author received an honorarium related to the development of this paper.

P. R., S. H. and M. H. were study investigators and participated in the data collection, study analysis, interpretation of data and development of the report. A. H. B., P. C. R. and N. A. participated in the study analysis, interpretation of the data and development of the manuscript. P.-C. C. was the study statistician. The final version was reviewed and approved by all authors. P. R. was the lead author during the review process.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Study site listing.

**Appendix S2.** MKC-TI-030 primary investigators.

**Figure S1.** Cough incidence by month quartiles (safety population).

**Table S1.** Treatment-emergent adverse events (TEAEs) leading to discontinuation (safety population).

**Table S2.** Impact of clinical trial dropouts on treatment group differences for change from baseline in $FEV_1$ at month 24: intention-to-treat, intention-to-treat last-observation-carried-forward, per-protocol and imputed analyses.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

## References

1. Litonjua AA, Lazarus R, Sparrow D, Demolles D, Weiss ST. Lung function in type 2 diabetes: the Normative Aging Study. Respir Med 2005; **99:** 1583–1590.
2. Davis WA, Knuiman M, Kendall P, Grange V, Davis TM. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care 2004; **27**: 752–757.
3. Hsia CC, Raskin P. Lung function changes related to diabetes mellitus. Diabetes Technol Ther 2007; **9**(Suppl. 1): S73–82.
4. Klein OL, Krishnan JA, Glick S, Smith LJ. Systematic review of the association between lung function and Type 2 diabetes mellitus. Diabet Med 2010; **27**: 977–987.
5. van den Borst B, Gosker HR, Zeegers MP, Schols AM. Pulmonary function in diabetes: a metaanalysis. Chest 2010; **138**: 393–406.
6. Yeh HC, Punjabi NM, Wang NY et al. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2008; **31**: 741–746.
7. Ceglia L, Lau J, Pittas AG. Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. Ann Intern Med 2006; **145**: 665–675.
8. Garg SK, Mathieu C, Rais N et al. Two-year efficacy and safety of AIR inhaled insulin in patients with type 1 diabetes: an open-label randomized controlled trial. Diabetes Technol Ther 2009; **11**(Suppl. 2): S5–16.
9. Rosenstock J, Cefalu WT, Hollander PA et al. Two-year pulmonary safety and efficacy of inhaled human insulin (Exubera) in adult patients with type 2 diabetes. Diabetes Care 2008; **31**: 1723–1728.
10. Skyler JS, Jovanovic L, Klioze S, Reis J, Duggan W. Two-year safety and efficacy of inhaled human insulin (Exubera) in adult patients with type 1 diabetes. Diabetes Care 2007; **30**: 579–585.
11. Rosenstock J, Cefalu WT, Hollander PA, Klioze SS, Reis J, Duggan WT. Safety and efficacy of inhaled human insulin (Exubera) during discontinuation and readministration of therapy in adults with type 2 diabetes: a 3-year randomized controlled trial. Diabetes Technol Ther 2009; **11**: 697–705.
12. Skyler JS, Hollander PA, Jovanovic L et al. Safety and efficacy of inhaled human insulin (Exubera) during discontinuation and readministration of therapy in adults with type 1 diabetes: a 3-year randomized controlled trial. Diabetes Res Clin Pract 2008; **82**: 238–246.
13. Leone-Bay A, Grant M. Technosphere®/Insulin: mimicking endogenous insulin release. In: Rathbone M, Hadgraft J, Roberts M, Lane M eds. Modified Release Drug Delivery Technology, 2nd edn, Vol **2.** New York: Informa Healthcare USA, Inc.; 2008: 673–679.
14. Richardson PC, Boss AH. Technosphere® Insulin technology. Diabetes Technol Ther 2007; **9**(Suppl. 1): S65–72.
15. Cassidy JP, Amin N, Marino M et al. Insulin lung deposition and clearance following Technosphere® Insulin inhalation powder administration. Pharm Res 2011; **28**: 2157–2164.
16. Potocka E, Cassidy JP, Haworth P, Heuman D, van Marle S, Baughman RA. Pharmacokinetic characterization of the novel pulmonary delivery excipient fumaryl diketopiperazine. J Diabetes Sci Technol 2010: **4**: 1164–1173.
17. Rosenstock J, Lorber DL, Gnudi L et al. Prandial inhaled insulin plus basal insulin glargine versus twice daily biaspart insulin for type 2 diabetes: a multicentre randomised trial. Lancet 2010; **375**: 2244–2253.
18. Tack CJ, Christov V, de Galan BE et al. Randomized forced titration to different doses of Technosphere® Insulin demonstrates reduction in postprandial glucose excursions and hemoglobin A1c in patients with type 2 diabetes. J Diabetes Sci Technol 2008; **2**: 47–57.
19. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999; **159**: 179–187.
20. Miller A, Thornton JC, Warshaw R, Anderson H, Teirstein AS, Selikoff IJ. Single breath diffusing capacity in a representative sample of the population of Michigan, a large industrial state. Predicted values, lower limits of normal, and frequencies of abnormality by smoking history. Am Rev Respir Dis 1983; **127**: 270–277.
21. Morris AH, Kanner RE, Crapo RO, Gardner RM. Clinical pulmonary function testing: a manual of uniform laboratory procedures, 2nd edn. Salt Lake City, UT: Intermountain Thoracic Society; 1984.
22. American Diabetes Association. Standards of medical care in diabetes-2007. Diabetes Care 2007; **30**(Suppl. 1): S4–41.
23. Rodbard HW, Blonde L, Braithwaite SS et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007; **13**(Suppl. 1): 1–68.
24. Miller MR, Hankinson J, Brusasco V et al. Standardisation of spirometry. Eur Respir J 2005; **26**: 319–338.
25. Wanger J, Clausen JL, Coates A et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005; **26**: 511–522.
26. MacIntyre N, Crapo RO, Viegi G et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; **26**: 720–735.
27. Petrucci R, Amin N, Lovertin P, Boss A, Richardson P. Pulmonary function tests remain similar in patients who received Technosphere insulin and in patients currently receiving standard antidiabetic therapy (Abstract 919). Diabetologia 2009; **52**(Suppl. 1): S361.
28. James AL, Palmer LJ, Kicic E et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. Am J Respir Crit Care Med 2005; **171**: 109–114.

29. Duncan BB, Schmidt MI, Pankow JS et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2003; **52**: 1799–1805.

30. Jensen RL, Teeter JG, England RD et al. Sources of long-term variability in measurements of lung function: implications for interpretation and clinical trial design. Chest 2007; **132**: 396–402.

31. Wise RA, Teeter JG, Jensen RL et al. Standardization of the single-breath diffusing capacity in a multicenter clinical trial. Chest 2007; **132**: 1191–1197.

32. Blonshine S, Harris R, Snow M. Evaluation of biologic quality control variance in a multi-center clinical trial for inhaled insulin (e-poster 229). Presented at Annual Congress of the European Respiratory Society; September 15–19, 2007; Stockholm, Sweden.

33. Wanger J, Irvin C. Comparability of pulmonary function results from 13 laboratories in a metropolitan area. Respir Care 1991; **36**: 1375–1382.

34. Greene S, Nikula K, Reynolds J et al. Long-term pulmonary safety assessment of Afrezza™ in rats and dogs (Abstract PS 811). The Toxicologist 2011; **120**(Suppl. 2): 175.

35. Liu MC, Riese RJ, Van Gundy K et al. Effects of inhaled human insulin on airway lining fluid composition in adults with diabetes. Eur Respir J 2008; **32**: 180–188.