

Insulin Kinetics Unchanged in Albuterol Treated Asthmatics Following Technosphere® Insulin Inhalation Powder Administration

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ABSTRACT

This Phase I, open-label, single-dose, repeat administration study compared the pharmacokinetic (PK) profile of Technosphere® Insulin (TI) in patients with mild to moderate asthma to age, sex and BMI matched healthy volunteers (HV). Pharmacokinetic parameters were evaluated after administration of TI alone (Visit 2), TI administered 5 minutes after pre-treatment with 200 µg albuterol (Visit 3), and TI administered 5 minutes after the treatment of methacholine challenge test (MCT) induced bronchospasm with 200 µg of albuterol inhalation (V4). Asthma medications were withheld 6-48 hours prior to dosing. Single dose of 45 U of TI was administered at V2, V3 and V4 and hyperinsulinemic-euglycemic clamp was used to maintain blood glucose (BG) at 90 ± 10 mg/dL.

PK parameters were calculated from FDKP, the carrier, and baseline corrected insulin concentrations. When TI was administered alone, insulin exposure was reduced by 18% in subjects with asthma compared to HV (geomean AUC₀₋₃₆₀ of 4397 and 5365 µU•min/mL, respectively). Albuterol pre-treatment resulted in comparable insulin exposure in both groups (geomean AUC₀₋₃₆₀ of 4912 in HV and 5500 µU•min/mL, asthma subjects). Following MCT induced bronchospasm and albuterol treatment, insulin exposure in asthmatics (geomean AUC₀₋₃₆₀ of 5835 µU•min/mL) was comparable to that found in HV or asthmatics without MCT. FDKP exposure results were similar to insulin. Three subjects with asthma experienced wheezing following TI only administration (and asthma medication withheld). In all cases wheezing was relieved within 15 minutes following the administration of 200 µg of albuterol. In all subjects, the most common AE was a transient, single cough occurring within 10 minutes of TI administration.

In patients with asthma, when asthma medications were withheld, a decrease in insulin exposure of approximately 18% was observed following TI administration. In subjects with asthma, either with or without induced bronchospasm (MCT), pre-treatment with albuterol 5 minutes prior to TI dosing resulted in comparable insulin exposure to that seen in healthy volunteers.

INTRODUCTION

Since Technosphere® Insulin (TI) Inhalation System is a pulmonary-delivered inhaled insulin using a breath-powered inhaler, altered airway mechanics in diseases like asthma may influence pharmacokinetic and pharmacodynamic response. Asthma is a complex syndrome, characterized by chronic airway inflammation, airway hyper-responsiveness and recurrent, reversible airway obstruction. Distribution and deposition of aerosolized insulin particles in the airways and its subsequent absorption from the lungs may be altered by severity of airflow obstruction, turbulence of air flow, adequacy of peak inspiratory flow rate, degree of airway inflammation, and other patho-physiological factors associated with asthma. On the other hand inhalation of a dry powder may act as trigger for bronchoconstriction of hyperreactive asthmatic airways. Pharmacokinetic and pharmacodynamic studies in subjects with asthma have found approximately 30% to 50% lower insulin exposure as compared to subjects without asthma.^{1,2} Thus, it would be expected that the dose of insulin required to obtain equivalent glycemic control would be higher by ~30% to 40% in subjects with asthma and diabetes (as compared to subjects without asthma but with diabetes).

OBJECTIVES

The primary objective of this Phase 1 study was to compare the rate and extent of insulin exposure (AUC₀₋₃₆₀, PK characterization) in healthy volunteers and subjects with mild to moderate asthma after Afrezza™ (Technosphere® Insulin Inhalation Powder) and also the effects, if any, of administration of a short acting bronchodilator (albuterol) both with and without induced bronchospasm prior to the inhalation of Afrezza (Figure 1). The secondary objectives included the safety parameters of Afrezza.

The study was conducted in the nondiabetic population as finding and enrolling subjects with concurrent diabetes and asthma was unsuccessful in two earlier MannKind sponsored studies.

METHODS

This was a Phase 1, open-label, nonrandomized, controlled clinical trial in subjects with asthma versus matched subjects with normal lung function. The trial consisted of a screening visit and follow-up visit for all subjects, 3 treatment visits for asthmatic subjects, and 2 treatment visits for healthy subjects as defined in the objectives. During all dosing visits, a hyperinsulinemic (using insulin lispro as the infusate)-euglycemic clamp was initiated at least 180 minutes prior to dosing and continued until the end of that days blood sampling. The clamp was used to suppress endogenous insulin concentrations to facilitate the accurate measurement of the exogenously administered insulin and to ensure the safety of the subjects. For subjects with asthma, their asthma medication was withheld for a period of time to ensure its clearance prior to dosing (short acting bronchodilator for 6 hours and long acting bronchodilators for 24 hours). Serial blood samples were taken from pre-dose until 480 minutes after Afrezza dosing and serum was analyzed for insulin, C-peptide and FDKP concentrations. Pulmonary function was assessed using bedside spirometry and the measurement of forced expiratory volume in 1 second (FEV₁).

FIGURE 1

Dosing Sequences



METHODS (CONTINUED)

The subset that formed the PK population were essentially the same as for the Safety Population.

TABLE 1

| Demographics of Safety Population | | | |
|-----------------------------------|----------------|-----------------------|-------------------|
| | | Non-asthmatics (n=13) | Asthmatics (n=17) |
| Age, years | Mean (range) | 35.4 (23-47) | 39.8 (22-54) |
| Gender | M/F | 12/1 | 14/3 |
| BMI, kg/m ² | Mean (range) | 27.4 (20.5-32.1) | 26.6 (21.5-31.4) |
| FEV ₁ , L | Median (range) | 4.30 (2.7-4.9) | 3.29 (2.1-4.5) |

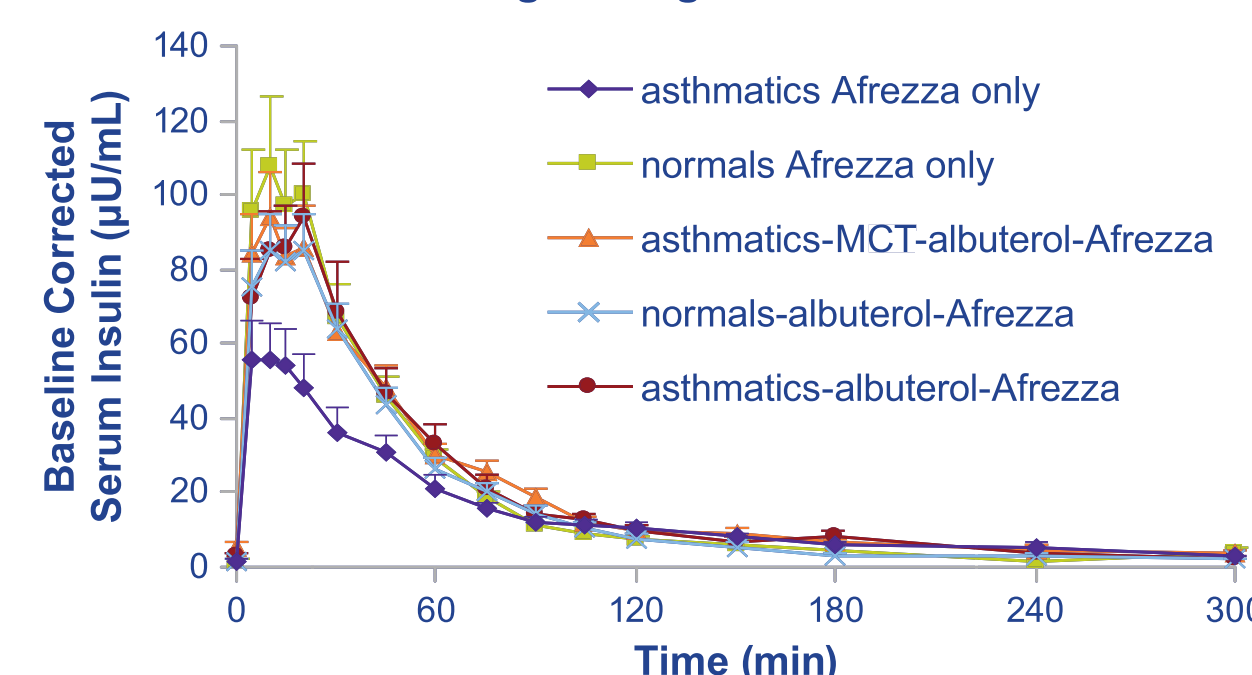
RESULTS

This study used a hyperinsulinemic (using insulin lispro)-euglycemic clamp to suppress endogenous insulin. Approximately 93% of glucose samples were within the defined acceptable range and there was little variation in the individual C-peptide concentrations throughout the course of each treatment period. This permitted data from all clamp procedures to be used and a simple baseline (mean of the 300- to 480-minute insulin concentration/subject/visit) correction to determine the exogenously derived insulin.

The baseline corrected insulin (i.e., exogenously administered insulin following Afrezza administration) concentration-time curves are shown in Figure 2 and the resultant PK parameters are found in Table 2. Except for subjects with asthma who had their asthma medication withheld prior to dosing with Afrezza, the results were similar across treatment groups for insulin AUC₀₋₃₆₀ and C_{max}. The median t_{max} of insulin was from 10 to 20 minutes for all treatments and was not dependent upon asthma status.

FIGURE 2

Mean (SE) Serum Baseline Corrected Insulin Concentrations Following Dosing with Afrezza



RESULTS (CONTINUED)

Table 2 is a summary of the statistical comparisons. Although the maximum and total exposure to exogenous insulin in asthmatics who have had their asthma medication withheld is about 20% less than that seen in normal healthy subjects, this did not show statistical significance within this small study population.

TABLE 2

| Statistical Comparison of Insulin Pharmacokinetic Parameters (ANOVA Results; Per Protocol Population) | | | | | |
|---|------------------------|----------------|---------------------|-----------------------------------|---------|
| Treatment Regimen Comparison ^c | Parameter ^a | Geometric Mean | | Geometric Mean Ratio (%) (90% CI) | p Value |
| | | Test (n=13) | Reference (n=12) | | |
| Visit 2 asthmatic: Visit 2 nonasthmatic | AUC ₀₋₃₆₀ | 4397 | 5365 | 81.96 (63.02, 106.59) | 0.2090 |
| | C _{max} | 73.482 | 98.494 | 74.61 (53.85, 103.37) | 0.1378 |
| Visit 3 asthmatic: Visit 3 nonasthmatic | AUC ₀₋₃₆₀ | 5500 | 4912 | 111.97 (86.10, 145.62) | 0.4717 |
| | C _{max} | 84.909 | 82.726 | 102.64 (74.08, 142.21) | 0.8931 |
| Visit 3 asthmatic: Visit 2 asthmatic | AUC ₀₋₃₆₀ | 5500 | 4397 ^b | 125.08 (108.3, 144.54) | 0.0131 |
| | C _{max} | 84.909 | 73.482 ^b | 115.55 (99.27, 134.50) | 0.1169 |
| Visit 4 asthmatic: Visit 3 asthmatic | AUC ₀₋₃₆₀ | 5835 | 5500 ^b | 106.10 (91.82, 122.60) | 0.4936 |
| | C _{max} | 93.685 | 84.909 ^b | 110.34 (94.79, 128.43) | 0.2814 |
| Visit 4 asthmatic: Visit 2 asthmatic | AUC ₀₋₃₆₀ | 5835 | 4397 | 132.71 (114.9, 153.35) | 0.0022 |
| | C _{max} | 93.685 | 73.482 | 127.49 (109.5, 148.41) | 0.0106 |

^aUnits: AUC (mU•min/L); C_{max} (mU/L); t_{max} (min)

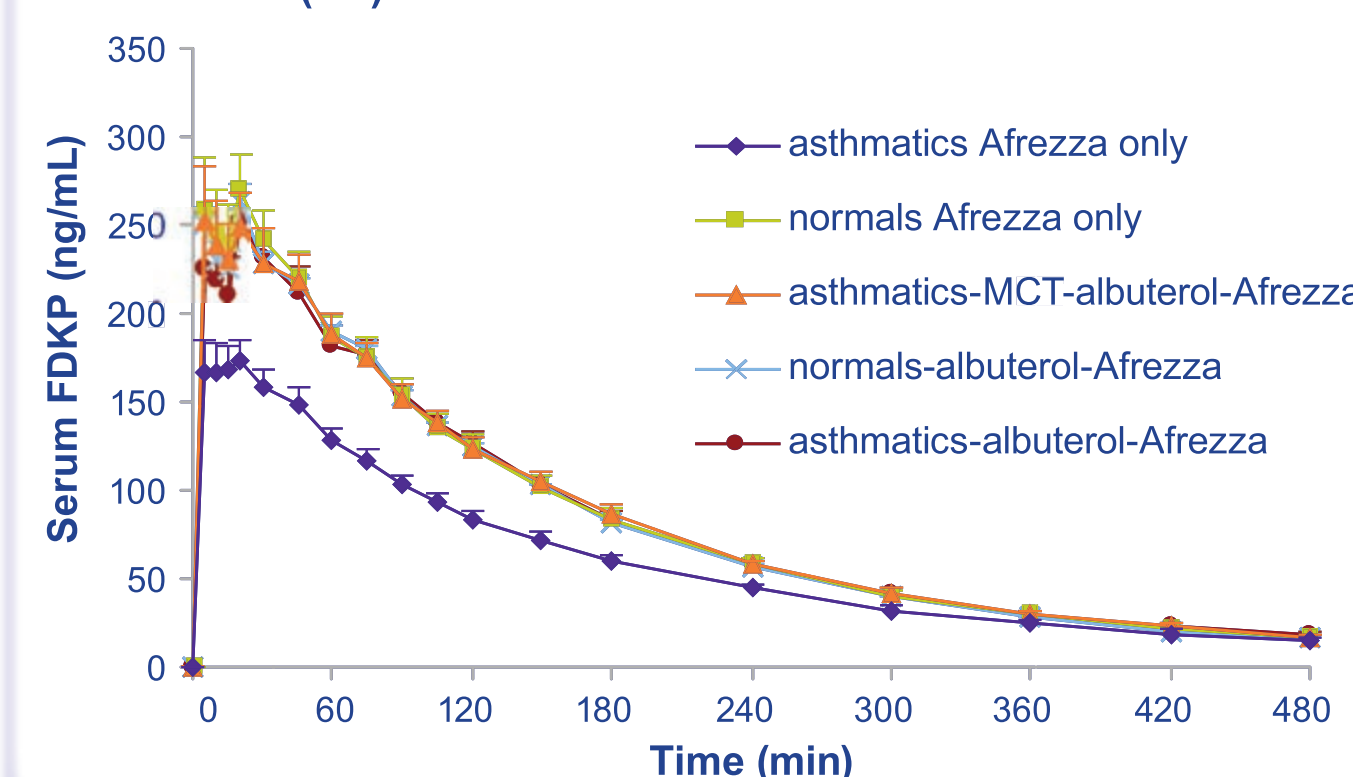
^bn=13

^cTreatments administered: Visit 2: Afrezza alone
 Visit 3: Afrezza after salbutamol
 Visit 4: Afrezza after MCT after salbutamol

The concentration-time profile of the carrier molecule, FDKP (fumaryl diketopiperazine), is shown in Figure 3. The kinetics characterized by a fast rise in serum concentration is shown by the median t_{max} being observed within 8.5 to 20 minutes of administration with no obvious effect of asthma; and a t_{1/2} of approximately 120 minutes was similar across all treatment groups. The FDKP AUC₀₋₄₈₀ after Afrezza was approximately 25% to 32% lower in subjects with asthma and no bronchodilator versus all other groups (subjects with and without asthma), and the differences were statistically significant. However, when Afrezza followed the administration of a bronchodilator (at Visits 3 and 4), subjects with asthma demonstrated an FDKP exposure (AUC₀₋₄₈₀ and C_{max}) approximately equal to the exposure seen in subjects without asthma (normals).

FIGURE 3

Mean (SE) Serum FDKP Concentrations vs. Time

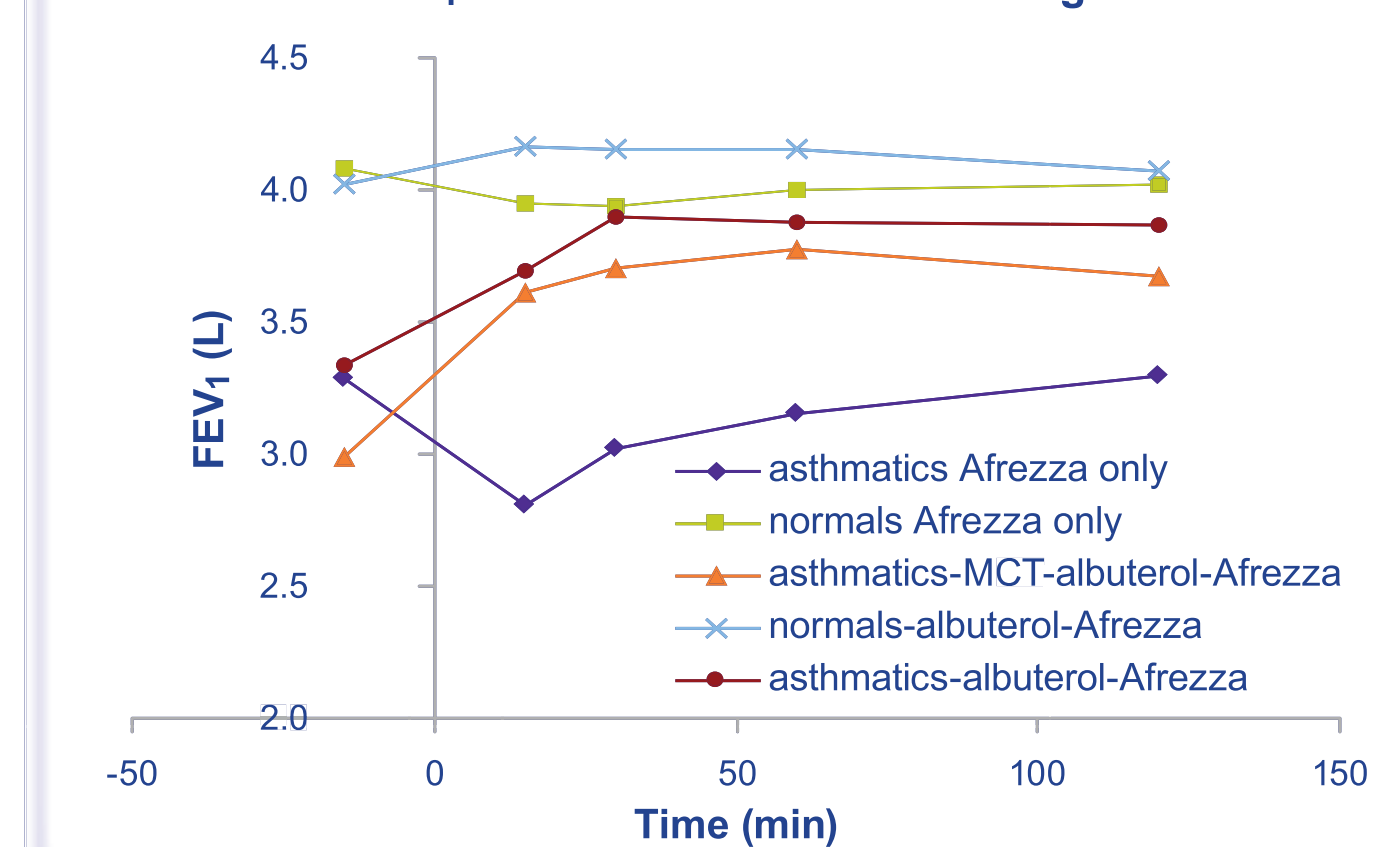


RESULTS (CONTINUED)

Figure 4 displays acute changes in FEV₁ before and 15, 30, 60, and 120 minutes after administration of Afrezza. In patients with asthma when asthma medications were withheld, there was acute decline in FEV₁ of approximately 12% from baseline at 15 minutes post-Afrezza inhalation, which returned to baseline values spontaneously by 120 minutes. This may account the observed reduction in insulin exposure in patients with asthma. However, when asthmatics were pre-treated with a short acting bronchodilator 5 minutes prior to Afrezza inhalation at Visit 3, no acute decline in FEV₁ was observed and insulin and FDKP exposure was similar to healthy volunteers. At Visit 4, in subjects with asthma, bronchodilator administration immediately after induction of bronchospasm with MCT then Inhalation of Afrezza 5 minutes later resulted in insulin exposure similar to asthmatic subjects pre-treated with Albuterol or healthy volunteers.

FIGURE 4

Mean FEV₁ Pre- and Post-Afrezza Dosing at t=0



Safety Results

Single doses of 45 U of Afrezza administered alone and after albuterol were well tolerated by the subjects without asthma in this study.

Three of the asthmatic subjects who were off of their asthma medication had SAEs of wheezing or moderate bronchospasm at Visit 2 following administration of Afrezza that was reversed within 15 minutes following a single treatment of albuterol. These subjects discontinued the study.

The most common TEAE was cough which was reported by at least 71 % and 85% of subjects with and without asthma, respectively. Cough after administration of Afrezza generally occurred within 10 minutes after inhalation and was nonproductive. This is typical across all clinical studies using Afrezza.

No clinically relevant findings were observed for vital signs, laboratory parameters, physical examination findings, or ECGs.

CONCLUSIONS

- In patients with mild to moderate asthma, slight/nonsignificant decrease in exogenous insulin exposure of approximately 18% was observed following administration of Afrezza.
- In patients with mild to moderate asthma, pre-treatment with a short acting bronchodilator as little as 5 minutes prior to Afrezza administration resulted in exogenous insulin exposure to that seen in healthy volunteers.

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