# A Phase 1, Open-Label, Randomized Dose Proportionality Study of Technosphere Insulin Inhalation Powder (TI) Doses up to 80 U Administered with the Gen2 Inhaler in Healthy Subjects

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## Abstract

A Phase 1, Open-Label, Randomized Dose Proportionality Study of Technosphere Insulin Inhalation Powder (TI) Doses up to 80 U Administered with the Gen2 Inhaler in Healthy Subjects.

This study incorporated a 4-way crossover of TI doses (10, 30, 60 and 80 U) with a 5th treatment of sc insulin in subjects maintained via hyperinsulinemic, euglycemic clamp. Clinical experience has that > 95% of patient doses are 60 U TI or less. Thirty-two of the 35 randomized subjects (57.1% male, 42.9% female; mean age 34.3 ± 9.7 yrs) completed all study treatments and visits.

Primary PK parameters (area under the curve [AUC], maximum serum concentration [Cmax]) were calculated from C-peptide corrected. Dose proportionality was evaluated by comparing the proportionality slope and associated 90% CIs for each PK parameter against predefined 90% CIs. Relative bioavailability (Frel) was determined by dose-normalized AUC comparisons of the various TI doses to sc insulin. The PD effect was assessed by the GIR required to maintain euglycemia (90 ± 10 mg/dL) for 4 hrs post-dosing.

The insulin exposure over 3 hrs post-dosing (AUC0-180) of C-peptide corrected data was the primary parameter, and was shown to be dose proportional (slope = 1.00 (90% CI - 0.939, 1.061) from 10 to 80 U. Evaluation of exposure extrapolated to infinity (AUC0-inf) provided a slope = 0.949 (90% CI – 0.880, 1.019). The median bioavailability of TI using the Gen2 inhaler was approximately 24% relative to sc injection of 15 IU insulin. The glucose infusion rate (GIR) during the clamp after TI dosing reached a maximum within 30 – 50 mins, whereas after sc insulin the GIR peaked at 170 – 234 minutes.

The most frequent adverse event was mild, asymptomatic hypoglycemia, reported for 85% of subjects after TI dosing and 12.5% following sc insulin, which was classified as related to study procedure (ie, inability of glucose infusion to respond at a rate to maintain euglycemia post-dosing).

Insulin exposure following administration of TI doses from 10 to 80 U via the Gen2 inhaler was shown to be dose-proportional.

## Objective

The objective of the study was to determine the dose proportionality and linearity, relative bioavailability, pharmacodynamic response, and safety of TI Inhalation Powder administered using the Gen 2C inhaler at the following dose levels:

- 10 U (one 10 U cartridge)
- 30 U (one 10 U and one 20 U cartridge)
- 60 U (three 20 U cartridges)
- 80 U (four 20 U cartridges)

TI Inhalation Powder was compared to 15 IU SC RHI.

TI Inhalation Powder treatments were administered in random order while SC RHI was administered as the last treatment for all subjects.

A blood glucose (BG) target of 90 ± 10 mg/dL was established and maintained by a variable rate glucose infusion. The glucose clamp procedure and dosing occurred at Visits 3 through 7.

The study consisted of 7 clinic visits, and 1 or more telephone contacts before admission, at the discretion of the principal investigator (PI) or a designee, and an optional eighth visit, if necessary: 1 screening (Visit 1); 1 inhalation training and insulin/C-peptide evaluation (Visit 2); 5 treatment visits (Visits 3, 4, 5, 6, and 7); and 1 follow-up visit (Visit 8) if required to follow ongoing AEs.

## Study Design

Subjects received treatment based on the following crossover design:

| | TI | | | | SC RHI |
|---|---|---|---|---|---|
| **Sequence** | Visit 3 | Visit 4 | Visit 5 | Visit 6 | **Visit 7** |
| 1 | 10U | 10U + 20U | 3 × 20U | 4 × 20U | 15 IU |
| 2 | 3 × 20U | 10U | 4 × 20U | 10U + 20U | 15 IU |
| 3 | 4 × 20U | 3 × 20U | 10U + 20U | 10 U | 15 IU |
| 4 | 10U + 20U | 4 × 20U | 10U | 3 × 20U | 15 IU |

Each training and dosing visit lasted 1 day. There were at least 3 days between visits. A subject was in the study approximately 12 weeks from screening to the last dosing visit.

## Methodology

Approximately 72 HNVs were to be screened to achieve up to 32 randomized HNVs to complete all treatments. Subjects who dropped out were to be replaced.

The **key inclusion criteria** were:

- Men and women aged 18 to 55 years who were considered healthy based on screening physical examination, medical history, clinical chemistry, and urinalysis
- No previous smoking in the past 6 months (including cigarettes, cigars, pipes) and negative urine cotinine testing (< 100 ng/mL)
- Body mass index (BMI) < 32 kg/m2
- FEV1 ≥ 80% of the Third National Health and Nutrition Examination Survey (NHANES III) predicted and FVC ≥ 80% of the Third National Health and Nutrition Examination Survey (NHANES III) predicted

The **key exclusion criterion** was blood donation of 500 mL within the previous 56 days.

**Insulin concentrations** were measured pre-dose and serially following administration of study treatments. For each treatment, for each patient, 4 sets of insulin concentration values were produced: 1) uncorrected values, 2) C-peptide corrected values, 3) baseline corrected values, and 4) C-peptide, baseline corrected values, combined.

The primary pharmacokinetic (PK) variables, based on C-peptide corrected insulin values, were:

- Area under the insulin concentration-time curve from time 0 to 180 minutes (AUC(0-180)) for each dose of TI Inhalation Powder
- Area under the insulin concentration-time curve from time 0 to 600 minutes (AUC(0-600)) for SC RHI
- Cmax for both study treatments

FDKP concentrations were also measured pre-dose and serially post-dose to assess delivery of TI Inhalation Powder.

The pharmacodynamic variable was: Evaluation of the glucose infusion rate (GIR) necessary to maintain euglycemia in normal subjects maintained on a glucose clamp.

**Statistical Methods & Analysis**

The AUC(0-180) and Cmax of the C-peptide corrected insulin concentration data analysis was based on a power model of the log-transformed AUC(0-180) and Cmax parameters with subject as a random effect, period, and dose as fixed effects. Dose proportionality was evaluated by comparing the proportionality slope and associated 90% CIs against predefined 90% CIs. Further, a sensitivity analysis, which applied a combination of a C-peptide correction and a baseline correction, was conducted to evaluate the potential impact of cross-reactivity from lispro insulin in the RIA assay.

The relative bioavailability was evaluated as dose-normalized, pair-wise comparisons between each TI Inhalation Powder dose level and 15 IU SC RHI. The ratios of TI Inhalation Powder to SC RHI and the 90% CIs for the ratios were derived from an ANOVA using subject as a random effect and treatment sequence and study treatment as fixed effects.

Pharmacodynamic effect was measured by baseline corrected glucose infusion rates. These parameters were summarized and analyzed as described for the pharmacokinetic parameters. Dose effect response was analyzed using the power model and relative effect was analyzed

**Patient Disposition**

Thirty-five subjects were randomized into the study and 32 subjects completed all study treatments and visits. Most subjects were Caucasian (26/35; 74.6%) and there were 5 more males (20/35; 57.1%) than females (15/35; 42.9%) in the study. The mean age of subjects was 34.3 years (SD 9.67; range 18 to 53 years).

**Safety**

- TI Inhalation Powder was well tolerated by the subjects in this study. There were no serious or significant AEs. Most AEs that occurred during the study overall, and for either treatment group, were events of mild hypoglycemia assessed as related to the study procedure.
- All AEs were mild except for moderate dyspnea in 1 subject, and all except 2 AEs were assessed as unrelated or unlikely related to treatment with TI Inhalation Powder; 1 subject experienced mild treatment related chest discomfort (80 U dose level) and was subsequently withdrawn from the study, and the other subject experienced mild treatment related cough (30 U dose level).
- Cough was an infrequent AE during the study, only occurring following TI Inhalation Powder dosing in 2 subjects. Both events of cough were mild and assessed as related to treatment in only 1 of the subjects.

## Results

PK analyses were performed on a complete and evaluable set of serum assay data for 32 subjects in the PK population.

In HNVs, there was increasing insulin exposure at each successive dose level (from 10 U to 80 U) of TI Inhalation Powder as reflected in Cmax and in the total insulin concentration-time data (AUC(0-inf)) when using the Gen2C inhaler. This increase in insulin exposure with each increasing dose level of TI Inhalation Powder occurred regardless of whether the resulting insulin concentration data were uncorrected, baseline corrected, or C-peptide corrected.

**Figure 1. Mean (SE) of C-Peptide Corrected Serum Insulin Concentration (µIU/mL), 0 to 600 Minutes, RIA Assay (PK Population)**

**Figure 2. Mean of Baseline Corrected Glucose Infusion Rate (mg/kg/min), Moving Averages of 5-Minute Window (PK Population)**

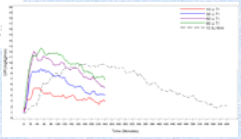

**Table 1. Bioavailability of Technosphere Insulin Relative to RHI, C-Peptide Corrected, RIA Assay (PK Population)**

| Parameter | 15IU RHI (N=32) Reference | 10U TI (N=32) | 30U TI (N=32) | 60U TI (N=32) | 80U TI (N=32) |
|---|---|---|---|---|---|
| **$AUC_{(0-180)}$ (min*µIU/mL)** | | | | | |
| **N** | 32 | 32 | 32 | 32 | 32 |
| **LS Mean** | 515.07 | 341.65 | 272.04 | 316.93 | 345.10 |
| **Ratio** | | 0.66 | 0.53 | 0.62 | 0.67 |
| **(90% CI)** | | (0.57,0.77) | (0.46,0.61) | (0.53,0.71) | (0.58,0.77) |
| **$AUC_{(0-inf)}$ (min*µIU/mL)** | | | | | |
| **N** | 29 | 27 | 29 | 28 | 29 |
| **LS Mean** | 1531.43 | 416.04 | 302.87 | 350.91 | 379.94 |
| **Ratio** | | 0.27 | 0.20 | 0.23 | 0.25 |
| **(90% CI)** | | (0.23,0.32) | (0.17,0.23) | (0.19,0.27) | (0.21,0.29) |
| **$C_{max}$ (µIU/mL)** | | | | | |
| **N** | 32 | 32 | 32 | 32 | 32 |
| **LS Mean** | 4.03 | 5.38 | 4.99 | 5.84 | 6.18 |
| **Ratio** | | 1.34 | 1.24 | 1.45 | 1.53 |
| **(90% CI)** | | (1.16,1.54) | (1.08,1.43) | (1.26,1.67) | (1.33,1.76) |

From ANOVA model: log(parameter) = sequence + treatment + subject; where subject is a random effect.
Source: Section 14.2, Table 14.2.4.1

## Results

**Table 2. Dose Response Analysis of Pharmacokinetic Parameters, C-Peptide Corrected, RIA Assay (PK Population)**

| Parameter | 10U TI (N = 32) | 30U TI (N = 32) | 60U TI (N = 32) | 80U TI (N = 32) | Slope (90% CI) |
|---|---|---|---|---|---|
| **$AUC_{(0-180)}$ (min*µIU/mL)** | | | | | |
| **n** | 32 | 32 | 32 | 32 | |
| **Mean** | 3863.2 | 9325.4 | 22424.3 | 34893.6 | |
| **Geometric Mean** | 3416.52 | 8161.34 | 19015.68 | 27608.14 | 1.000 (0.939, 1.061)[a] |
| **SD** | 1634.31 | 5693.38 | 16294.82 | 31258.28 | |
| **Median** | 3869.4 | 8333.4 | 16433.5 | 29353.3 | |
| **%CV** | 42.3 | 61.1 | 72.7 | 89.6 | |
| **Min** | 600.4 | 3236.4 | 7044.9 | 9022.6 | |
| **Max** | 9139.8 | 33135.2 | 93548.5 | 175579.1 | |
| **$AUC_{(0-inf)}$ (min*µIU/mL)** | | | | | |
| **n** | 29 | 32 | 31 | 32 | |
| **Mean** | 4760.5 | 10231.1 | 24242.0 | 36661.3 | |
| **Geometric Mean** | 4151.07 | 9087.54 | 20951.49 | 29608.04 | 0.949 (0.880, 1.019) |
| **SD** | 1903.21 | 5679.94 | 16423.00 | 31438.66 | |
| **Median** | 5111.8 | 9361.0 | 18758.7 | 31091.6 | |
| **%CV** | 40.0 | 55.5 | 67.7 | 85.8 | |
| **Min** | 658.4 | 3424.6 | 8293.5 | 10076.2 | |
| **Max** | 9677.4 | 33722.5 | 95079.2 | 178408.0 | |
| **$C_{max}$ (µIU/mL)** | | | | | |
| **n** | 32 | 32 | 32 | 32 | |
| **Mean** | 63.3 | 187.8 | 444.3 | 681.5 | |
| **Geometric Mean** | 53.82 | 149.80 | 350.23 | 494.38 | 1.067 (1.013, 1.120) |
| **SD** | 44.24 | 156.40 | 361.79 | 704.66 | |
| **Median** | 50.0 | 129.9 | 308.5 | 481.1 | |
| **%CV** | 69.9 | 83.3 | 81.4 | 103.4 | |
| **Min** | 15.6 | 56.1 | 88.0 | 131.4 | |
| **Max** | 233.6 | 840.1 | 1827.1 | 3704.5 | |

[a]From power model: log(parameter) = period + log(dose) + subject; where subject is a random effect and dose is a continuous effect with compound symmetry variance/covariance matrix. Dose proportionality is achieved if the confidence limits are between 0.885 and 1.107.

## Discussion

In HNVs, systemic insulin exposure increased at each successive dose (from 10 U to 80 U) of TI Inhalation Powder as reflected in Cmax and in the total insulin concentration-time data (AUC(0-inf)) when using the Gen2C inhaler. This increase in insulin exposure with each increasing dose of TI Inhalation Powder occurred regardless of whether the resulting insulin concentration data were uncorrected, baseline corrected, or C-peptide corrected. Insulin exposure over 3 hours following TI Inhalation Powder dosing, reflected by the AUC(0-180) of C-peptide corrected insulin concentration-time data, was shown to be dose proportional.

The median percent (%) bioavailability of TI Inhalation Powder based on analysis of the ratio of the log-transformed AUC(0-inf) of C-peptide corrected, RIA insulin concentration data was approximately 24% relative to 15 IU SC RHI.

In HNVs, there was an increasing but non-linear glucodynamic effect from increasing doses of TI Inhalation Powder administered using the Gen2C inhaler (ie, the incremental changes in glucodynamic effect decreased with increasing TI Inhalation Powder dose). This is in agreement with the Emax model7,8 for insulin concentration and insulin effect. The data also show that insulin effect from the inhaled dose of TI Inhalation Powder continues at 4 hours post-dose.

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