A Population Dose–Response Model for Inhaled Technosphere Insulin Administered to Healthy Subjects

D Rüppel1, R Dahmen1, A Boss2, R Jäger1, M Grant3, R Baughman3 and T Klabunde1*

Technosphere insulin (TI), an inhaled insulin with a fast onset of action, provides a novel option for the control of prandial glucose. A euglycemic glucose clamp study was performed to compare the effects of TI and regular human insulin (RHI) on the induced glucose infusion rate (GIR) in healthy volunteers. Generation of a dose–response relationship between insulin dose and effect (expressed as AUC of GIR) was not possible from the clinical data directly. The GIR recording time was too short to capture the full effect and higher doses were not tested. Thus, a pharmacokinetic-GIR model was developed to simulate GIR for a sufficient time window of 20 h and for higher doses. A dose–response model was then generated from the simulated GIR profiles. The resulting model provides an ED50 for TI that is 5-fold higher than for RHI, a ratio that can be used as conversion factor for equivalent doses of RHI and TI.

CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 365–372; doi:10.1002/psp4.12189; published online 16 February 2017.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☒ Technosphere insulin (TI), an inhaled insulin with a fast onset of action, provides a novel option for the control of prandial glucose.

WHAT QUESTION DID THIS STUDY ADDRESS?
☒ The analysis quantifies the dose–response characteristics and pharmacodynamic behavior of TI with respect to onset and duration of action relative to subcutaneously administered regular human insulin (RHI).

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
☒ The work illustrates how modeling and simulation can increase the value of incomplete experimental data. Unexpectedly, a linear dose–response behavior was found in the therapeutically relevant dose range.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☒ The simulations identify a 5:1 dose ratio of TI:RHI that yields equivalent pharmacodynamic effect. The ratio provides additional guidance to clinicians for switching between the two therapies. The faster onset and shorter duration of action also inform clinical use.

Intensive glycemic control often requires basal-bolus insulin treatment. However, hypoglycemia, weight gain, and the burden of multiple injections often lead to poor adherence.1 An inhaled prandial insulin with rapid kinetics may address some of these concerns and could provide important therapeutic options for individualized diabetes management. Technosphere insulin (TI) (Afrezza MannKind, Valencia, CA) is a dry powder formulation of regular human insulin adsorbed onto Technosphere microparticles for oral inhalation.2 Upon inhalation, these microparticles can reach the deep lung, allowing absorption into the systemic circulation with a time to maximum serum insulin concentration of 12–15 min.3,4 TI is administered through the Afrezza inhaler device.5

Given that the pharmacokinetic (PK) profile of TI—with an early and high Cmax—is different from the PK profile of subcutaneously (s.c.) administered regular human insulin (RHI), we wanted to quantify the dose–response relationship of TI and to compare it to the dose–response behavior of RHI:

• Is there a linear or curve-linear dose–response?
• At which dose does the linear relationship turn into curve-linear?
• Are the doses different among TI and RHI? This is important to support dosing recommendations when switching patients from regular human insulin to TI insulin.
• What would be the best starting dose?
• Is this conversion factor dependent on the initial RHI dose?

The PK and pharmacodynamics (PD) of TI was studied in 32 healthy volunteers (NCT01490762) in a hyperinsulinemic euglycemic glucose clamp crossover study.6 Insulin and glucose infusion rates (GIR) were measured to describe the PK profile and PD response. A limitation for a direct analysis from the data is that insulin measurements were taken only up to 3 h after dosing TI and GIR was measured only to 4 h; the full PD response was not covered especially for the higher TI doses (Figure 1). The limitations of the experiment may prevent accurate estimation of the curvature and maximum in a potential Emax dose–response model. Indeed, calculating the GIRAUC as a marker for the PD response for different TI doses directly from the clinical data suggests a nonlinear dose–response relationship for the therapeutically relevant doses (up to 100 TI U).
Here we present the generation and application of a population PK/PD model. The analysis quantifies the dose–response characteristics and pharmacodynamic behavior of TI insulin with respect to onset and duration of action relative to subcutaneously administered RHI. The work also should illustrate how modeling and simulation can increase the value of incomplete experimental data. The main findings from this analysis have been presented as a poster at the ADA2016.

METHODS

The objective of the analysis was to establish a simple mathematical description of the dose–response behavior (expressed as effect on GIR\textsubscript{AUC}) for both insulins. This was not directly possible from the study data due to the “truncation” of the clamp data and due to the fact that higher doses were not tested. A much richer and more flexible PK-GIR model was therefore developed. Figure 2 shows the approach to achieve the desired characterization of TI and RHI with respect to the dose–response and timing of the PD effect. The data from the study were used to develop a dynamic population PK/PD model relating insulin concentrations from an effect compartment to GIR (PK-GIR model). Although the dose–response model is already implicit in the construct of the (dose)-PK-GIR model, integrating the GIR\textsubscript{AUC} analytically to relate dose to GIR\textsubscript{AUC} response seemed to be very complicated, if not impossible. Thus, the model was used to simulate GIR curves beyond the experimentally recorded times up to 20 h to allow GIR values to return to baseline and the full PD effect of TI could be estimated. With this, the GIR\textsubscript{AUC} response vs. dose can be plotted in order to receive a graphical dose–response relationship including higher doses and a 20-h integration time. However, although a figure captures the dose–response relationship graphically for the “dose, simulated GIR-AUC pairs,” it does not provide a simple analytical mathematical relationship. Therefore, in a second step, we fit these pairs with several models, ending up with an E\textsubscript{max}/ED\textsubscript{50} model for both insulins. In other words, the second fitting was used to find an approximate analytical expression for the dose–response relationship in a situation where higher doses were not directly possible from the study data due to the “truncation” of the clamp data and due to the fact that higher doses were not tested. A much richer and more flexible PK-GIR model was therefore developed. Figure 2 shows the approach to achieve the desired characterization of TI and RHI with respect to the dose–response and timing of the PD effect. The data from the study were used to develop a dynamic population PK/PD model relating insulin concentrations from an effect compartment to GIR (PK-GIR model). Although the dose–response model is already implicit in the construct of the (dose)-PK-GIR model, integrating the GIR\textsubscript{AUC} analytically to relate dose to GIR\textsubscript{AUC} response seemed to be very complicated, if not impossible. Thus, the model was used to simulate GIR curves beyond the experimentally recorded times up to 20 h to allow GIR values to return to baseline and the full PD effect of TI could be estimated. With this, the GIR\textsubscript{AUC} response vs. dose can be plotted in order to receive a graphical dose–response relationship including higher doses and a 20-h integration time. However, although a figure captures the dose–response relationship graphically for the “dose, simulated GIR-AUC pairs,” it does not provide a simple analytical mathematical relationship. Therefore, in a second step, we fit these pairs with several models, ending up with an E\textsubscript{max}/ED\textsubscript{50} model for both insulins. In other words, the second fitting was used to find an approximate analytical expression for the dose–response relationship in a situation...
where analytical integration of the full (dose)-PK-GIR model seemed to be impossible.

The dose–response model allowed capturing the relative potency of both insulins by comparison of the ED50 values and to establish a simple relationship for dose pairs of TI and RHI with a matching response in terms of the AUC of GIR (e.g., 8IU dose of RHI and 40U dose of TI). The GIR time curves were simulated for RHI doses and TI doses providing an equivalent overall PD effect (as expressed by GIR\text{AUC}) and could be compared with respect to the onset and duration of action and the time needed to reach half of the overall PD effect.

### Study design and population

The protocol of study NCT01490762 was approved by the Independent Investigational Review Board on November 8, 2011 and the study-specific informed consent form was approved on November 14, 2011. All subjects provided their written informed consent before initiation of any study-related procedures. The study was conducted at the Profil Institute for Clinical Research (Chula Vista, CA). The study was sponsored by MannKind (Paramus, NJ). In study NCT01490762, 32 healthy volunteers received single doses of 10U, 30U, 60U, 80U TI, and 15IU RHI s.c. in a crossover design. Insulin concentrations were measured predose and serially following administration of study treatments. C-peptide concentrations were measured as a marker for endogenous insulin secretion. For each treatment, total insulin concentration was recorded and the endogenous insulin concentration was estimated from the C-peptide concentration. The exogenous TI or RHI insulin was calculated by subtracting the endogenous insulin from the measured insulin concentration. For each dose a hyperinsulinemic euglycemic clamp experiment was performed: After an overnight fast, insulin (insulin Lispro) is infused intravenously at a constant rate, resulting in a steady-state insulin level that is above the fasting levels. A glucose analyzer was used to frequently monitor blood glucose levels, while 20% dextrose was given intravenously at a variable rate to “clamp” blood glucose concentrations in the normal range. The glucose infusion rate was recorded before and several hours after dosage of RHI or TI. As hepatic glucose production is suppressed due to the hyperinsulinemic insulin levels and since there is no net change in blood glucose concentrations under steady-state clamp conditions, the GIR must be equal to the glucose disposal rate as a response to the exogenous insulin. After administration of the respective investigational drug, GIRs to maintain euglycemia were recorded over 4 h for TI and over 10 h for s.c. RHI. An example of the resulting GIR time course in one subject after receiving an insulin dose is shown in Figure 1.

From the 31 subjects included in the modeling process, 18 were male, 13 female. Their weights ranged from 49–100 kg; their age was between 18 and 53 years.

### Software

Mixed-effects modeling was performed using NONMEM (v. 7.2) with the FOCE INTERACTION approximation. Data management and diagnostics were performed using the statistical language R. PSN (Pearl Speaks NONMEM, Uppsala) was used to generate the visual predictive checks (VPC).

### Mixed-effects models

PK and PD models were developed as mixed-effects models (population models), i.e., deterministic parameters and random parameters (describing the distribution in the population) were fitted together in one step. Random parameters were modeled in exponential form with fixed effect $p_0$ and random effect $\eta$:

$$p = p_0 + e^{\eta i}$$

Nested models were accepted as a better model if the objective function was 3.84 points lower ($P < 0.05$) when including a new parameter or covariate. In the covariate analysis a covariate was accepted if the objective function increased by 6.7 ($P < 0.01$) when the covariate was excluded from the model.

### Population PK model

In order to capture the PK profiles of both insulins, a population PK model previously described by Potocka et al.\(^8\) was used. We adapted the model for the data available from the clinical study. Insulin concentrations corrected by the C-peptide values were fit by NONMEM in the FOCE approximation to a structural model published previously (Figure 3). The model consists of a two-compartment model for distribution with a first-order elimination. Absorption of inhaled insulin was described by a first-order process. Absorption of RHI was modeled with two successive compartments with first-order absorption. A combination of additive and proportional error was used as an error model. Bioavailability of inhalable insulin $F_{TI}$ is relative to subcutaneous application.
PK-GIR model
No smoother was applied and data were fitted directly with NONMEM. Glucose infusion rates as a function of insulin concentrations were modeled as an $E_{\text{max}}$ model already published for this purpose.\textsuperscript{9,10}

$$GIR = GIR_0 + \frac{GIR_{\text{max}} \cdot \text{dose}^\gamma}{ED_{50}^\gamma + \text{dose}^\gamma}. \quad (2)$$

The model was developed in a two-step procedure. Individual PK parameters (post-hoc estimates) were used to predict concentrations at every timepoint necessary for the integration of the PK-GIR model. Random parameters were introduced in exponential form. Data were extremely rich in information, with about 1,800 observations per subject. FOCE INTERACTION was applied with the exception of etas characterizing the interoccasion variability of the baseline (HYBRID). An additive error was used as an error model. An effect compartment was necessary to describe the delay between effect and insulin concentrations.

Dose–response model (dose-GIRAUC model)
The PK-GIR model described above was used to simulate GIR curves beyond the experimentally recorded times up to 20 h to allow the simulation of higher doses and the return of GIR values to baseline. Doses of up to 240U for TI and up to 80IU for RHI were simulated to fully capture the dose–response behavior by using the individual post-hoc parameter estimates from the PK-GIR model. From the resulting GIR(t) curves the AUC was calculated for the time window between 0 and 20 h for each dose/patient. Population dose–response models (dose-GIRAUC) were developed relating insulin doses with the AUC of GIR. GIR-AUCs were modeled as a function of dose:

$$GIRAUC = \frac{GIRAUC_{\text{max}} \cdot \text{dose}^\gamma}{ED_{50}^\gamma + \text{dose}^\gamma}. \quad (3)$$

$ED_{50}$ and $GIRAUC_{\text{max}}$ are not independent in $E_{\text{max}}$ models. Fitting is problematic without sufficient observations near $E_{\text{max}}$ and can be significantly improved by using prior information. The maximal GIR for each patient $GIRAUC_{\text{max}}$ is known from the PK-GIR model. With an integration time of 20 h the maximal area under the GIR time course can easily be calculated as the product of the maximal GIR for each patient (value at saturation) and the integration time:

$$GIRAUC_{\text{max}} = GIR_{\text{max}} \cdot 20 \text{h}. \quad (4)$$

The central value for $GIRAUC_{\text{max}}$ was found to be 11.9 mg/kg/min *1200min = 14.3g/kg (g refers to glucose, kg to body weight).

$GIRAUC_{\text{max}}$ was therefore not fitted but calculated individually and introduced as a covariate.

Random parameters were introduced in exponential form. A proportional error was used as error model. Fits were performed with the FOCE INTERACTION approximation.

RESULTS
Pharmacokinetics
In order to capture the PK profiles of both insulins a population PK model previously described by Potocka et al.\textsuperscript{8} was used (Figure 3). All five dosing occasions were fitted together. One subject was excluded from the analysis, showing occasionally very high exposure impeding proper regression analysis. The VPC plot for all four doses of TI and one dose of RHI are shown as Supplementary Figure S1. The VPC indicates that the model correctly describes the central tendency. Variability in some cases tends to be either over or under observations. As the data did not include i.v. measurements, the elimination rate of insulin could not be fitted, but was taken from Ref. 8.

The resulting PK parameters of insulin are listed in Supplementary Table S1 and are within the 95% confidence interval with the previously reported values in Ref. 8, with the exception of $K_{\text{out}}$.TI. This difference could be most likely attributed to different inhaler versions used in both studies.

Please also note that the bioavailability of TI insulin of 25% (21%-28%) identified in this study is relative to RHI, as no absolute bioavailability could be quantified in the absence of insulin i.v. data. With a bioavailability of RHI determined to 53%\textsuperscript{8} the absolute bioavailability of TI found in this study can be estimated to 12–13%. This is in good agreement with the bioavailability of TI of 11% found in Ref. 8. Individual pharmacokinetic parameters were used in the PK-PD development.

PK-GIR model
The GIR curves show a significant noise with a high interoccasion variability for the baseline GIR. In Figure 1 the GIR curves of one example subject are given, each showing the GIR curves from the five different occasions (four doses TI, one dose RHI). As data were not baseline-corrected, the baseline was part of the fit. The population $GIRAUC_{\text{max}}$ was determined by profiling, starting with a value from Ref. 10. The result of the profiling is shown in Supplementary Material Figure S2. Individual $GIRAUC_{\text{max}}$ and their distribution were fit. Results for the fit parameters are documented in Table 1. The additive error of the fit seems to be comparable to the baseline. The results from

| Parameters | Estimate (95% CI) |
|------------|------------------|
| $GIRAUC_{\text{max}}$ (mg/kg/min) | 2.7 (2.3–3.1) |
| $GIRAUC_{\text{max}}$ (mg/kg/min) | 11.9 (--): |
| $EC_{50}$ (mU/L) | 152 (130–174) |
| $EC_{50}$ (%) | 38 (23–49) |
| $IOV_{GIRAUC}$ (%) | 61 (51–70) |
| $a_1$ (mg/kg/min) | 2.1 (1.9–2.4) |

Source: Fit119360. PK, pharmacokinetic; Glucose infusion rate; $GIRAUC_{\text{max}}$, maximum GIR; $EC_{50}$, concentration of half maximum effect; $IOV_{GIRAUC}$, interoccasion variability of fixed effects parameters; $a_1$, Intrasubject variability.
A VPC stratified by dose are shown in Supplemental Figure S3A–E. The 15IU dose in Figure S3B corresponds to RHI, all other doses refer to TI. The VPC indicates that the model correctly describes the central tendency, but slightly overpredicts the variability for higher doses. The variability of the baseline in the beginning is overpredicted. The baseline is fitted over the whole time of the experiment. The contribution before the experiment is certainly higher than during the period under exogenous insulin. However, a positive or negative drift of the baseline during the experiment will influence the fitted baseline, which may become higher or lower than in the beginning. Our interpretation is that the variability in addition to what was observed in the beginning is influenced by drifting baselines.

Dose–response model (dose-GIRAUC model)
The objective of the analysis was to establish a simple mathematical description of the relative dose–response behavior for both insulins. Due to the limitations of the experimental data, which were 1) limited to testing lower doses of TI insulin and 2) not allowing GIR curves to return to baseline, thus truncating parts of the effect, the PK-GIR model was used to simulate GIR curves beyond the experimentally recorded times up to 20 h to allow the simulation of higher doses and the return of GIR values to baseline. GIR curves were simulated for all 31 healthy subjects using the individual post-hoc estimates from the PK-GIR model for doses up to 240U for TI and up to 80IU for RHI and times up to 20 h. The AUC of the GIR was integrated up to 20 h and fit with the dose-GIRAUC model described above (Table 2). GIRAUC,max is not a fit parameter but calculated individually according to Eq. 4. Results from a visual predictive check for RHI and TI are shown in Supplemental Figure S4. Mean GIRAUC as a function of dose for TI and RHI is shown in Figure 4a. TI reached its half-maximal effect ED50 at a dose of 249U and RHI at a dose of 43IU. The higher ED50 of TI reflects its lower bioavailability and its higher, sharper peak resulting in a reduced PD action at a given dose.

From our work it is evident that the time window used for integration of the GIR time profiles is important and that short integration times (e.g., 4 h) not allowing to capture the full pharmacodynamic effect lead to an apparent saturation as part of the effect is truncated for high doses. This is reflected in Figure 4b. Here the dose-GIRAUC relationship is shown for RHI and TI based on simulated GIR time curves using an integration time of 4 h. The ED50s are much lower (RHI: 20IU, TI: 35IU), indicating an artificial apparent saturation of the response at much lower doses. Doses of TI and RHI producing the same GIRAUC are considered equivalent. Due to the fact that the Hill coefficients for TI and RHI dose–response model are almost the same, a simple conversion rule for equivalent TI and RHI doses can be derived from Eq. 3:

$$\text{dose}_{\text{TI}} = \frac{\text{ED}_{50,\text{TI}}}{\text{ED}_{50,\text{RHI}}} \times \text{dose}_{\text{RHI}}$$

In order to establish this relationship we also fit the dose–response of TI and RHI using a common Hill coefficient (Table 2, right column). Here we obtained ED50 values of

| Parameters | Ti | Rhi | Ti/Rhi* |
|------------|----|-----|---------|
| Fixed effects | | | |
| ED50,TI (U) | 249 (202–296) | 245 (201–290) |
| ED50,RHI (IU) | 43 (36–51) | 48 (39–57) |
| $\gamma$ (1) | 1.07 (0.98–1.15) | 1.15 (1.08–1.23) |
| Random effects | | | |
| $\sigma_{\text{ED50,TI}}$ (%) | 40 (24–52) | 40 (25–51) |
| $\sigma_{\text{ED50,RHI}}$ (%) | 49 (40–56) | 45 (35–54) |
| $\sigma_{\text{c}}$ (%) | 17 (9–23) | 17 (12–21) |
| $\sigma_{\text{r}}$ (%) | 22 (20–25) | 21 (18–23) |
| Source | Fit 626954 | Fit 629531 | Fit 47694 |

ED50, dose of half maximum effect; $\gamma$, Hill coefficient; $\sigma_{\text{ED50}}$, $\sigma_{\text{c}}$, intersubject variability of fixed effects; $\sigma_{\text{r}}$, intra-subject variability, proportional error; CI, confidence interval.

*Common fit of TI and RHI with same Hill coefficient.
245U for TI and 48IU for RHI. The ratio $ED_{50, TI}/ED_{50, RHI}$ was calculated to 5.1 and Eq. 5 with this factor applies for all doses.

Cumulative GIR_{AUC} and comparison of onset of action

In order to evaluate the onset of action for equivalent TI and RHI doses (same GIR_{AUC}), cumulative AUCs of simulated GIR profiles were calculated and normalized to GIR integrated over 20 h.

Cumulative GIR_{AUC} is given by:

$$GIR_{AUC,cum}(t) = \int_0^t GIR(t) dt$$

(Cumulative GIR_{AUC} is normalized to GIR integrated over 20 h.)

Curves for the equivalent doses 8IU RHI and 40U TI are shown in Figure 5. TI has a steeper increase of GIR_{AUC,cum} than RHI in each individual time course. Times to reach 10%, 50%, and 90% of the individual total PD effect, measures of both onset and duration, are shorter for TI than for RHI are given in Supplemental Table 2. The steeper cumulative GIR_{AUC} time curves reflect a faster onset of action ($T_{10\%}$-GIR_{AUC,0-20 h; RHI, 122 ± 23 min; TI, 35 ± 5 min) and a shorter duration of action ($T_{90\%}$-GIR_{AUC,0-20 h; RHI, 621 ± 152; TI, 386 ± 136 min). Time to reach half of the overall effect was shorter for TI ($T_{50\%}$-GIR_{AUC,0-20 h; RHI, 296 ± 64 min vs. TI, 124 ± 25 min).

DISCUSSION

TI, an inhaled human insulin with a fast onset of action, provides a novel option for postprandial glucose control. However, the sharp and high insulin peaks after TI dosing have raised concerns that its PD effects (e.g., glucose disposal) might be saturated at doses within the therapeutic range. This would contrast with regular human insulin or prandial insulin analogs administered via the s.c. route, where saturation is only seen beyond the therapeutic range. Differences in the dose–response behavior, in bioavailability, and in the time-action profiles between RHI and TI might lead to complex dose conversion rules for patients switching from TI to RHI or vice versa. Thus, it is of utmost importance to compare the dose–response relationships of TI and RHI.

Here the results from an euglycemic clamp study in healthy volunteers were used to compare the effects of TI and RHI on the induced GIR time curves at various doses. Since the study examined only a single dose of RHI and up to only 80U for TI, a population PK/PD model (PK-GIR model) was generated and applied to simulate GIR curves for an extended range of doses and to capture the full PD effects over 20 h (instead of 4 h for TI and up to 10 h for RHI, as in the clamp study apparently truncating parts of the PD effect; Figure 1). We are confident that our concentration-effect model (PK-GIR model) is sufficiently
robust for extrapolation to higher doses and times. It is relatively simple and based on thousands of observations covering a concentration range that generates glucose infusion rates from zero to GIR$_{\text{max}}$, thus also describing the saturation of the effect on the GIR. In addition, the model is not time-dependent and assumes quick equilibration of the insulin/glucose relationship (steady state, as assumed in GIR experiments, measurements up to 24 h reported). Concentrations and their time courses are described by the PK models for the TI and s.c. formulations. The disposition part is identical for both formulations; differences for the absorption process (s.c. vs. inhaled) are covered. As TI and s.c. formulations both show dose-proportional exposure of clinically relevant doses, the model appears to be robust enough to extrapolate in time and dose within the therapeutic dose range. The PK of TI was tested up to 80U in this study, but recently up to 120U in a recent clamp study performed in type-1 patients (NCT02470637). The results have been shown at ADA2016 and describe the C$_{\text{max}}$ and AUC of TI as dose-proportional. Subcutaneously applied human insulin was tested up to 30U and found to be dose-proportional. Beyond these limits, deviation from dose-linearity may occur and the model should be considered a hypothesis. Extrapolation to higher doses was nevertheless necessary to fit the dose effect relationship, especially the ED$_{50}$. The relationship is therefore valid in the limits of the known PK dose linearity, which is approximately the therapeutically relevant dose range.

The objective of the analysis was to establish a simple mathematical description of the dose-GIR$_{\text{AUC}}$ response behavior for both insulins. GIR curves were simulated for all 31 healthy subjects using the PK-GIR model for doses up to 240U for TI and up to 80IU for RHI and times up to 20 h. The resulting AUC of the GIR curves were used to fit a dose-GIR$_{\text{AUC}}$ model. Not surprisingly, an ED$_{50}$/E$_{\text{max}}$ model was best able to describe the observed dose–response for TI and RHI covering a wider dose range, indicating saturation of the overall PD effect at very high doses. Unexpectedly, the dose-GIR$_{\text{AUC}}$ for TI appeared to be almost linear for lower doses of TI (10–120U), indicating that in the therapeutically relevant dose range the dose–response of TI and RHI is dose linear (Figure 4a).

The dose needed to achieve the half-maximal effect was 245U for TI compared to 48IU for RHI. The factors reducing the PD effect of TI are its lower bioavailability, higher C$_{\text{max}}$, and shorter absorption half-life. A simple dose conversion rule could be generated from the ratio of these ED$_{50}$, suggesting that a 5.1-fold higher dose of TI matches the PD effect of a given RHI dose. A similar effect factor is evident in a clinical phase III study in type-1 patients comparing the treatment effects on HbA1c for TI and insulin aspart. After 24 weeks of treatment the average daily dose of insulin aspart 25.8U and the average daily dose of TI was 115.4U (factor 4.5).

In spite of limitations of the present population PK/PD and simulation approach—extrapolating in time and dose—to characterize the dose–response relationship of inhaled TI insulin and RHI, it needs to be mentioned that our findings are in line with the analysis of a very recent PK/PD clamp study of inhaled TI insulin in type-1 patients (NCT02470637). In the recent study, inhaled TI doses of up to 120U and up to 90U insulin Lispro were tested in type-1 patients with a GIR recording time of 12 h. In this study a dose-proportional response was found for TI doses of up to 120U and a dose–response ratio of TI:Lispro of ~6.5 was found (ED$_{50}$ of 51U for insulin lispro and 325.2 TIU for inhaled TI).

One might argue that for a prandial insulin like TI, a shorter PD window (e.g., 4 or 6 h) is physiologically more meaningful. To define the full dose-GIR$_{\text{AUC}}$ curve, however, supratherapeutic doses were required and shortening the integration time truncated the GIR curves and introduced an artifact into the results: an apparent saturation of the PD effect within the therapeutic range. Using a 4 h integration time the ED$_{50}$ become smaller and the response relationship turns from linear to curve-linear at therapeutically relevant doses (ED$_{50}$ ratio of 1.75).

To compare the timing of the pharmacodynamic activity of RHI and TI, we compared simulated GIR-time curves for doses that produced the same GIR$_{\text{AUC}}$. Specifically, we compared an RHI dose of 8IU and a TI dose of 40U with a dose ratio of 5. For these doses the onset of action of TI was found to be faster, indicated by a 3.5-fold shorter time to reach 10% of the total effect. Also, the duration of action of TI was shorter, as reflected by a 1.6-fold shorter time to reach 90% of the total effect. This faster PD profile would be expected to translate into an immediate postprandial glucose control after a meal.

Conflict of Interest. The clinical study was sponsored by MannKind Corporation. MG and RB are employees of MannKind. DR, TK, RD, RJ, and AB are employees of Sanofi. Technosphere and Afrezza are registered trademarks of MannKind Corporation.

Author Contributions. D.R., R.D., A.B., R.J., and T.K. wrote the article; M.G. and R.B. designed the research; D.R. and T.K. analyzed the data.

1. Morris, A., Boyle, D., McMahon, A., Greene, S., MacDonald, T. & Newton, R. Adherence to insulin treatment, glycaemic control, and ketoadiposis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. Lancet 350, 1505–1510 (1997).
2. Leone-Bay, A. & Grant, M. Technosphere/insulin: mimicking endogenous insulin release. In Modified-Release Drug Delivery Technology (eds. Rathbone M., et al.) 673–679. New York: Informa Healthcare USA (2008).
3. Boss, A., Petrucci, R. & Lorber, D. Coverage of prandial insulin requirements by means of a rapidly-acting inhaled insulin. J. Diabetes Sci. Technol. 6, 773–779 (2012).
4. Richardson, P. & Boss, A. Technosphere insulin technology. Diabetes Technol. Ther. 2(suppl. 1), S65–S72 (2007).
5. Marino, M.T., Cassidy, J.P., Smutney, C.C., Zupon, M. & Kocinski, J. Bioequivalence and dose proportionality of AFREZZA® inhalation powder administered using a Gen2 inhaler compared to the MedTone® inhaler. J. Diabetes Sci. Technol. 5, 457–468 (2011).
6. Baughman, R.A., Amin, A., Atkins, E., Chung, P.-C., Nezamis J. & Boss, A.H. Phase 1, open-label, randomized dose proportionality study of technosphere insulin inhalation powder (TI) doses up to 80U administered with the Gen2 inhaler in healthy subjects. Diabetes 62(suppl. 1), A251, 982-P (2013).
7. Rüppel, D. et al. A population PK/PD model of technosphere insulin administered to healthy subjects. Diabetes 65(suppl. 1), A525, 975-P (2016).
8. Potocka, E., Baughman, R.A. & Derendorf, H. Population pharmacokinetic model of human insulin following different routes of administration. J. Clin. Pharmacol. 51, 1015–1024 (2011).
9. Landersdorfer, C. & Juusko, W. Pharmacokinetic/pharmacodynamic modelling of glucose clamp effects of inhaled and subcutaneous insulin in healthy volunteers and diabetic patients. Drug Metab. Pharmacokin. 25, 418–429 (2010).
10. Potocka, E., Baughman, R., Derendorf H. A population PK/PD model of technosphere insulin administered to healthy and type 2 diabetic subjects. Diabetes 59(suppl. 1), 624–P (2010).

11. Bode, B.W., McGill, J.B., Gross, J.L., Chang, P.C., Bregman, D.B.; Affinity 1 Study Group. Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. Diabetes Care 38, 2266–2273 (2015).

12. Baughman, R. et al. Technosphere insulin powder (TI) displays earlier onset and shorter duration than insulin Lispro (Lispro). Diabetes 65(suppl. 1 A), 105–LB (2016).

13. Becker, R.H., Frick, A.D., Nosek, L., Heinemann, L. & Rave, K. Dose-response relationship of insulin glulisine in subjects with type 1 diabetes. Diabetes Care 30, 2506–2507 (2007).

Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (http://psp-journal.com)