

# A Population PK/PD Model of Technosphere® Insulin Administered to Healthy and Type 2 Diabetic Subjects



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## ABSTRACT

Subjects with type 2 diabetes (T2DM) exhibit decreased insulin sensitivity, and the pharmacodynamics (PD) in this population is different from healthy normal volunteers (HNV). The aim of this analysis was to develop a model to better quantify the PD parameter differences between the T2DM and HNV populations following Technosphere® Insulin (TI), an inhaled, regular human insulin with a rapid absorption and systemic clearance and a rapid onset and short duration of action.

A population pharmacokinetic (PK)/PD model was developed using data from 3 euglycemic glucose clamp studies (blood glucose clamp 90 mg/dl in HNV; 110 mg/dL in T2DM) with a pooled population of 16 HNV and 12 T2DM subjects (24 males, 4 females; age [mean±SD] 40±15 years; weight 82±13 kg; BMI 26±4 kg/m<sup>2</sup>) with normal pulmonary function. Insulin was administered via inhalation (25, 50, 100 U to HNV in a crossover fashion; 60 and 90 U to parallel T2DM groups). A total of 621 insulin concentrations and 69 individual profiles were used in the analysis. The data were modeled with NONMEM® (version VI), using the ADVAN6 subroutine and first order (PK) and first order conditional estimation (PD). The PK and PD models were developed sequentially.

A 2-compartment model with first order absorption and elimination described insulin PK well. Typical values were clearance (CL/F), 466 L/h; central volume of distribution (V<sub>d</sub>/F), 38.2 L; intercompartmental clearance (Q/F), 171 L/h; peripheral volume of distribution (V<sub>p</sub>/F), 258 L; and first order absorption rate constant, ka, 2.0 h<sup>-1</sup>. Insulin PD was described by a sigmoidal E<sub>max</sub> model. A hypothetical effect compartment was used to account for the delay in effect. Differences in E<sub>0</sub> (baseline effect) were attributed to different clamp settings.

Almost no difference was observed in the PD parameter estimates between groups, except EC<sub>50</sub>, which was 3-fold higher for subjects with T2DM. This difference is most likely due to the impact of insulin resistance associated with the disease state in human subjects.

Insulin Pharmacodynamic Parameters		
Parameter	HNV	T2DM
E <sub>0</sub> , mg/kg/min	2.5	1.4
E <sub>max</sub> , mg/kg/min	14.4	14.4 fixed
EC <sub>50</sub> , μU/mL	39.9	121.0
K <sub>e0</sub> , h <sup>-1</sup>	1.4	1.8
γ	2.5	2.7

## INTRODUCTION

The glucose clamp procedure has been used extensively to study insulin activity.<sup>1,2</sup> During this procedure, patients are administered a fixed insulin infusion, while at the same time receiving a varying infusion rate of glucose to counteract the test treatment insulin's action and maintain a constant glycemic state. As it is assumed that the exogenous insulin infusion completely suppresses hepatic glucose production as well as appreciable insulin secretion, the glucose infusion rate (GIR) can be used as a measure of the PD response to insulin.

Subjects with type 2 diabetes (T2DM) exhibit decreased insulin sensitivity and it is expected that the pharmacodynamic response in this population will be different from nondiabetics. The aim of this analysis was the development of a PK/PD model for Technosphere® Insulin (TI) Inhalation Powder (AFREZZA™) an inhaled, regular human insulin so as to determine the impact that the disease state has on insulin effect, as determined by the GIR.

## MATERIALS AND METHODS

### Study Population

Data from three prospective, single-center, open-label, randomized, euglycemic glucose clamp studies in non-smoking male and female subjects with normal pulmonary function were combined (2 studies in HNV and 1 study in T2DM). The T2DM subjects presented with a diagnosis of type 2 diabetes mellitus for ≥12 months, stable anti-diabetic regimen with insulin for the previous 3 months and HbA1c ≤ 8.5%. All three studies were performed with the Biostat glucose monitoring and infusion system (Biostat, Life Science Instruments, Elkhart, IN, USA), and a continuous insulin infusion. The glucose target was 90 mg/dL for HNV and 110 mg/dL for T2DM. In Study 1, HNV received single dose of 100 U TI (n=5); in Study 2, HNV received single doses of 25, 50, and 100 U TI (n=11); in Study 3, T2DM received 60 U TI (n=6) and 90 U TI (n=6).

### Insulin Sampling and Baseline Correction and GIR smoothing

To account for any incomplete endogenous insulin suppression and the constant insulin infusion, insulin concentrations were baseline corrected. Any resulting negative values were set to zero. For the PD analysis, GIR values were smoothed using a 10-minute running average.

### Insulin and GIR Data for the Pharmacodynamic Analysis

PK model individual predicted parameters were used to simulate the insulin concentrations and were each added to the insulin baseline to establish the relationship between total insulin and GIR. GIR and insulin values every 5 minutes for the first hour and every 10 minutes thereafter were combined for the analysis.

### Population Analysis

NONMEM® (Version VI, Level 1.2, NONMEM Project Group, ICON Development Solutions, USA) was used for the population analysis using both the first order (FO) and the first order conditional estimation method (FOCE) for the Pop PK and PD, respectively. NONMEM describes the model in terms of: fixed effect parameters, θ, typical population values of the base model parameters; ω<sup>2</sup>: the variances of the interindividual variability (η) within the population, and σ<sup>2</sup>: the variances of the residual intraindividual variability (ε). Subject-specific parameters were calculated by NONMEM using the POSTHOC (FO method) option.

## MATERIALS AND METHODS (CONTINUED)

### Pharmacokinetic and Pharmacodynamic Model

Data from all 3 studies were modeled simultaneously. The PK and PD models (Figure 1) were developed sequentially. The PK was described by a two compartment open model with first order absorption and was parameterized in terms of apparent clearance (CL/F), volume of distribution in the central compartment (V<sub>c</sub>/F), the apparent intercompartmental clearance (Q/F), the volume of distribution in the peripheral compartment (V<sub>p</sub>/F) and the first order absorption rate constant (ka). NONMEM library subroutines ADVAN4 and TRANS4 were used. The PD model was described by the following equations:

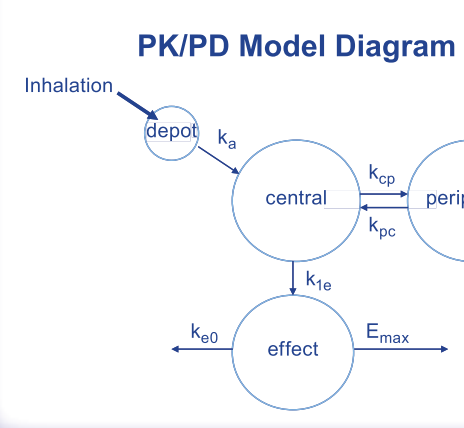
$$(1) \frac{dC_e}{dt} = k_{e0} \cdot (C_p - C_e) \quad (2) \text{GIR} = E_0 + \frac{E_{max} \cdot C_e^\gamma}{EC_{50}^\gamma + C_e^\gamma}$$

(1) describes the relationship between the insulin concentration and the concentration at the effect site; (2) establishes the relationship between the GIR and insulin concentration at the effect site. The PD model was parameterized in terms of E<sub>0</sub>, the baseline GIR value, E<sub>max</sub>, the maximum glucose infusion rate, EC<sub>50</sub>, the effect site concentration eliciting 50% of the maximal response, γ the sigmoidicity factor, and C<sub>p</sub> and C<sub>e</sub> are the plasma and effect site insulin concentrations, respectively.

### Error Model

Interindividual variability was described by an exponential error model. The intraindividual residual variability of insulin plasma concentration was estimated using a proportional and additive error model (PK) and additive error model (PD).

FIGURE 1



## RESULTS

### Patient Population

A total of 621 insulin concentrations from 28 subjects and 50 profiles were included (Table 1). When the mean insulin concentration-time and GIR-time profiles (Figure 2) were combined, a hysteresis in the insulin effect became apparent. (Figure 3)

FIGURE 2

Insulin and GIR-Time Profiles  
 A) Mean Baseline-corrected Insulin Concentrations by Dose Group and B) Mean Observed GIR by Dose Group

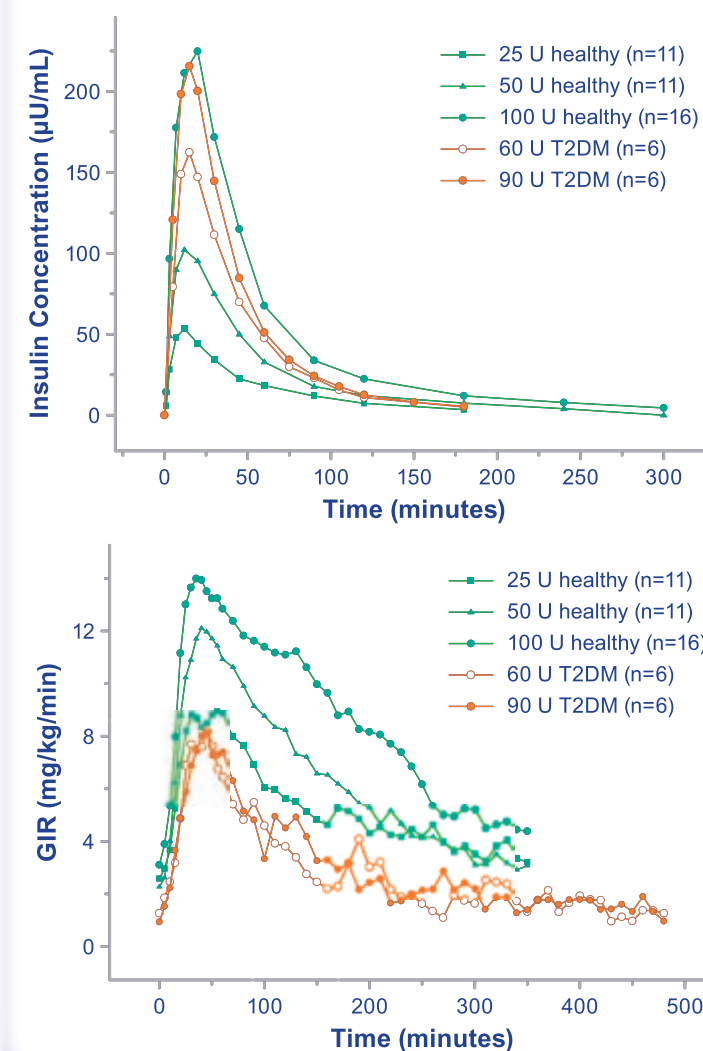
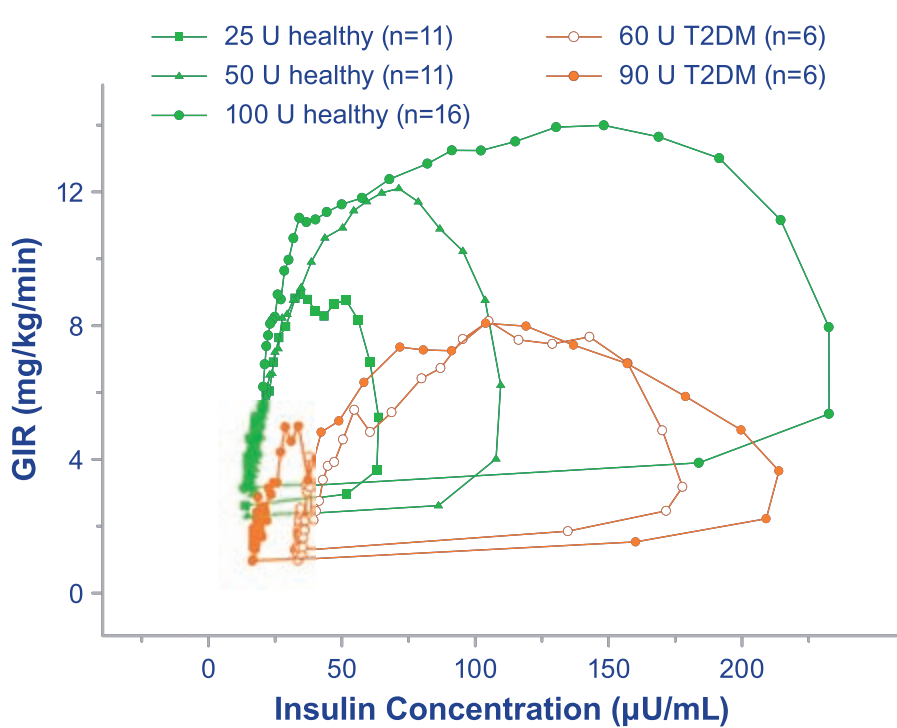


TABLE 1

Summary of Demographics and Baseline Characteristics		
Demographic Variable		Value
Diabetes Status		
Healthy	N (number of profiles)	16 (38)
Type 2 diabetic	N (number of profiles)	12 (12)
Gender		
Male	N	24
Female	N	4
Race		
Caucasian		27
Asian		1
Age (years)	Mean ± SD	40 ± 15
Weight (kg)	Mean ± SD	82 ± 13
BMI (kg/m <sup>2</sup> )	Mean ± SD	26 ± 4
Height (cm)	Mean ± SD	178 ± 8
FEV <sub>1</sub> (L)	Mean ± SD	4 ± 1
Percent of predicted FEV <sub>1</sub> (%)	Mean ± SD	99 ± 13

FIGURE 3

Hysteresis in the Insulin-GIR Relationship for HNV and T2DM



## RESULTS (CONTINUED)

### Pharmacokinetic Model

A two compartment open model with first order absorption and first order elimination described the insulin concentration data well (Table 2, Figure 4).

### Pharmacodynamic model

To account for the different blood glucose clamp settings, the E<sub>0</sub> was estimated separately for the two groups. E<sub>max</sub> was fixed to the value estimated for the HNV alone, due to the limited range of values and small N associated with the data from T2DM. Previous work suggests that insulin E<sub>max</sub> would not be affected by the disease state.<sup>3</sup> All other parameters were estimated separately for HNV and T2DM (Table 3). The E<sub>max</sub> model described the GIR data well. (Figure 5 and Figure 6)

TABLE 2

Insulin Population PK Parameters			
Pharmacokinetic Parameters	Parameter Values	Interindividual and Residual Variability	
Parameter	Estimate (%RSE)	Parameter	CV
CL (L/hr)	466 (9.7)	ω <sub>CL</sub>	33.6
V <sub>c</sub> (L)	38.2 (19.3)	ω <sub>Vc</sub>	72.9
Q (L/hr)	171 (13.9)	ω <sub>Q</sub>	64.0
V <sub>p</sub> (L)	258 (21.8)	ω <sub>Vp</sub>	67.3
ka <sub>T1</sub> (hr <sup>-1</sup> )	2.0 (7.4)	ω <sub>ka</sub>	22.2
		ω <sub>IOV FT1</sub>	35.4
		σ <sub>1</sub>	24.6
		σ <sub>2</sub>	1.42*

Note: \*σ<sub>2</sub> (additive residual error) is expressed in μU/mL. The magnitude of interindividual and residual variability was expressed as CV%, approximated by the square root of the variance estimate.

FIGURE 4

A) Model Individual Predicted vs. Observed Insulin Concentrations on a Linear Scale and B) Log Scale  
 C) Weighted Residuals vs. Model Predicted Insulin Concentrations (orange=T2DM, green=HNV)

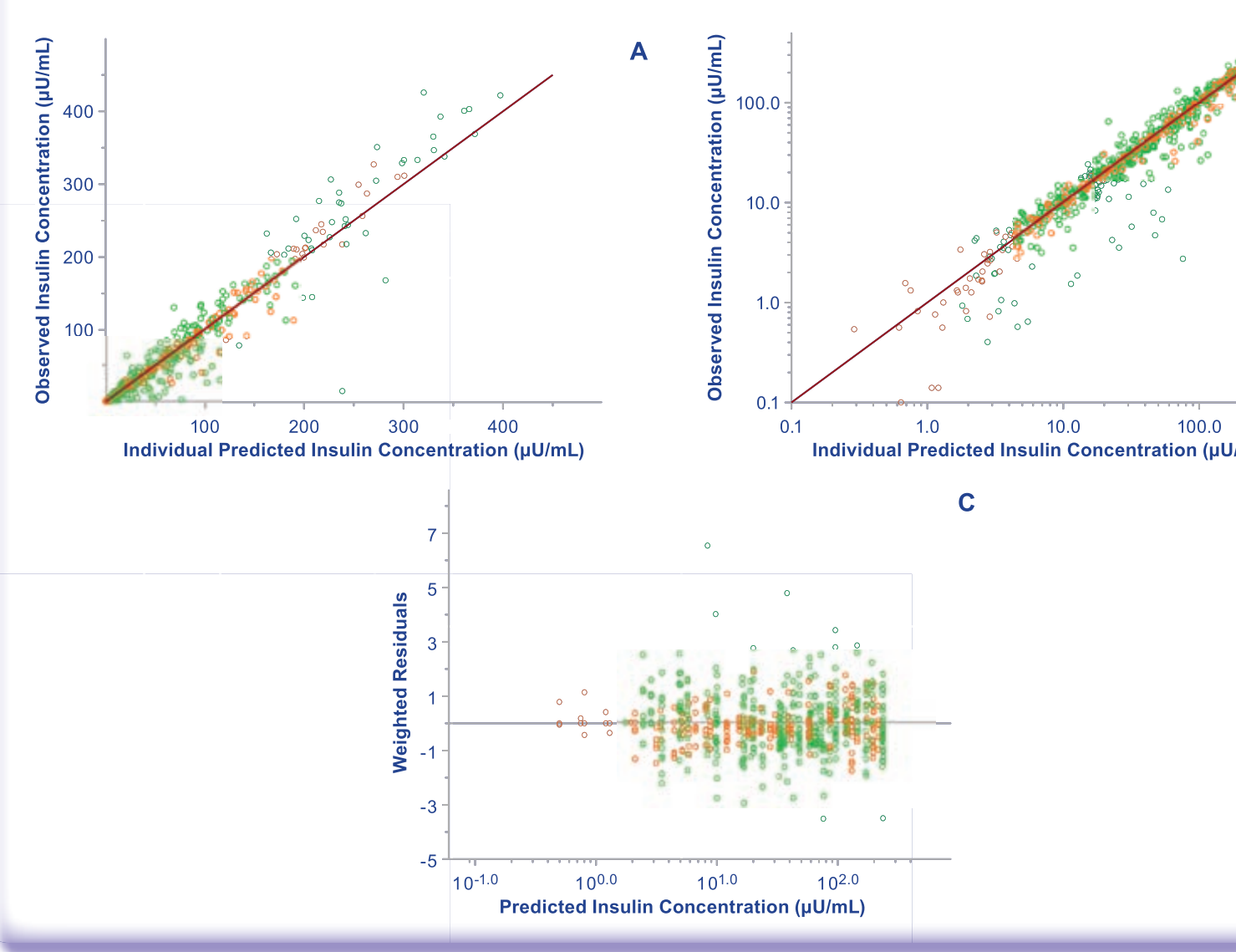


TABLE 3

Insulin PD Parameters in HNV and T2DM		
Parameter	HNV Parameter Estimate (%RSE)	T2DM Parameter Estimate (%RSE)
E <sub>0</sub> (mg/kg/min)	2.5 (17.1)	1.4 (15.2)
E <sub>max</sub> (mg/kg/min)	14.4 (14.5)	14.4 fixed
EC <sub>50</sub>	39.9 (15.2)	121.0 (6.5)
K <sub>e0</sub> (hr <sup>-1</sup> )	1.4 (14.9)	1.8 (16.4)
γ	2.5 (16.0)	2.7 (16.7)
Interindividual and Residual Variability	%	%
ω <sub>E0</sub>	49.5	39.9
ω <sub>Emax</sub>	37.0	58.8
ω <sub>EC50</sub>	39.0	—
ω <sub>Ke0</sub>	49.5	53.0
ω <sub>γ</sub>	44.6	49.3
σ <sub>1</sub>	1.80	1.16

Note: \*σ<sub>1</sub> (additive residual error) is expressed in mg/kg/min. The magnitude of interindividual and residual variability was expressed as CV%, approximated by the square root of the variance estimate.

## RESULTS (CONTINUED)

FIGURE 5

A) Individual Predicted GIR vs. Observed GIR and B) Weighted Residuals vs. Population Predicted GIR (orange=T2DM, green=HNV)

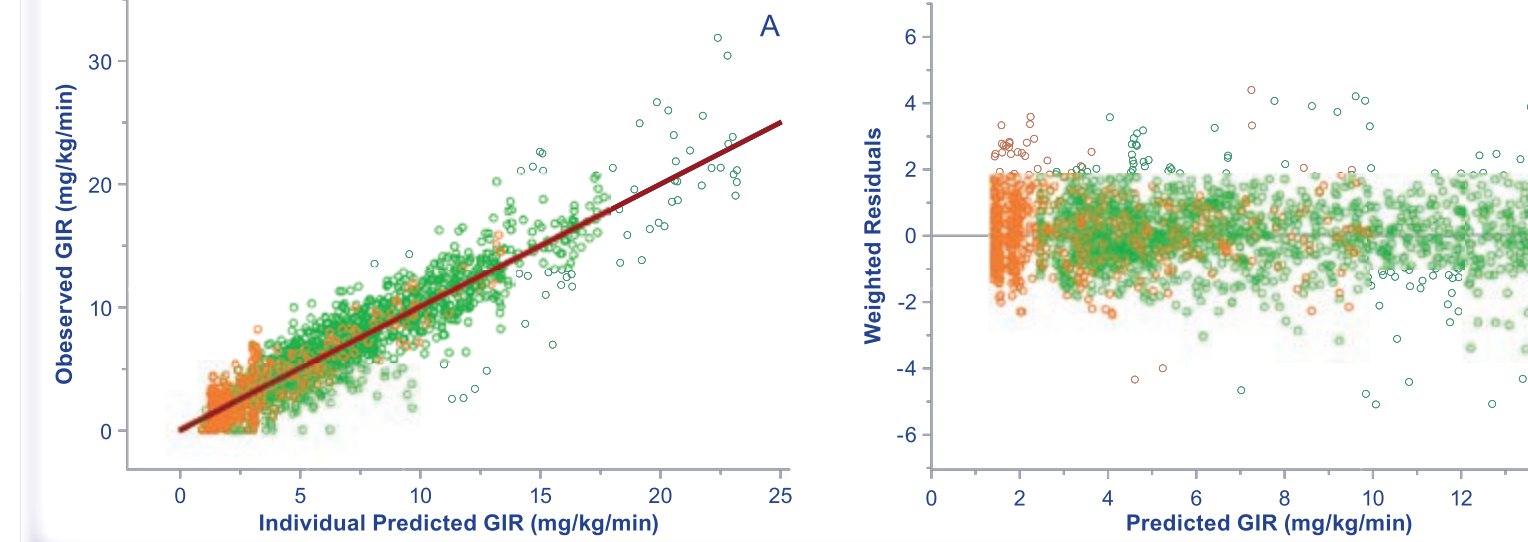
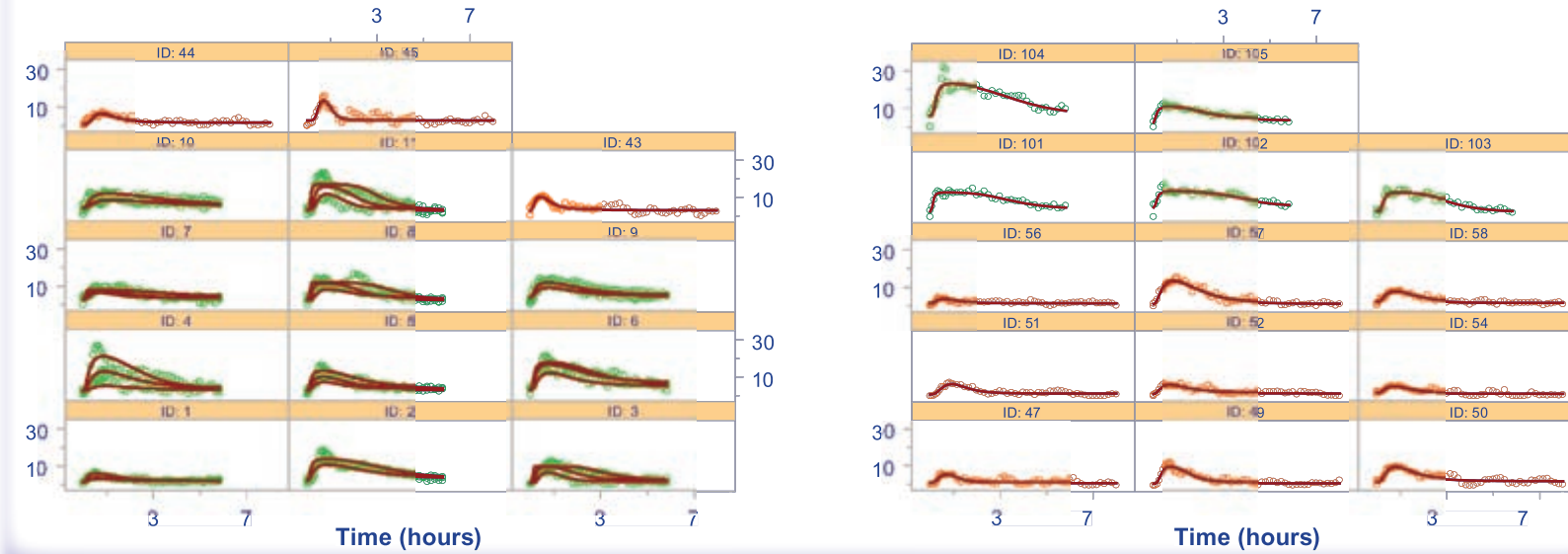


FIGURE 6

Individual Predicted and Observed GIR by Subject (green symbols=HNV, orange symbols=T2DM)



## CONCLUSIONS

- Insulin pharmacodynamics were found to be well described by an E<sub>max</sub> model, after a hypothetical effect compartment was used to collapse the hysteresis in insulin effect observed during clamp procedures in HNV and T2DM subjects
- The EC<sub>50</sub> parameter estimate was approximately three-fold higher for subjects with T2DM, most likely due to the insulin resistance that is associated with this disease state.

## REFERENCES

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