PIII-87

Development of a Steady-State Exposure-Response Model for Exenatide Once Weekly

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Introduction

- Exenatide is dosed as a subcutaneous (SC) injection of 5 and 10 µg twice daily (BID) before main meals and is indicated for the treatment of type 2 diabetes mellitus in patients failing to achieve adequate glycemic control with metformin (MET), a sulfonylurea (SFU), a thiazolidinedione (TZD), a combination of MET and a SFU, or a combination of MET and a TZD
- Model-based assessments were extensively used to support dose selection in the exenatide clinical development program
- Exenatide once weekly (QW) is being developed as a line extension of exenatide BID administered SC once a week to subjects with type 2 diabetes mellitus
- These analyses describe the empirical relationship between exenatide exposure and glycemic response and constitute an integral part of the dose justification assessment of exenatide 2 mg QW

Objectives

- Develop a model that describes average steady-state plasma exenatide concentrations following exenatide QW administration
- Evaluate the influence of covariates on steady-state plasma exenatide concentrations
- Develop an exposure-response model to describe the relationship between steady-state plasma exenatide concentrations and glycemic response
- Evaluate the influence of covariates on the exenatide exposure–glycemic response relationship

Methods

General Steps of Population PK and PK/PD Analyses

1. Development of a population PK model characterizing average steady-state plasma concentrations
2. Evaluation of the effects of covariates in explaining variability in average steady-state exenatide concentrations
3. Development of a population PK/PD model that characterizes the relationship between average steady-state exenatide concentrations and glycemic response (HbA1c or fasting plasma glucose)
4. Evaluation of the effects of covariates in explaining variability in the exenatide exposure versus glycemic response relationship

Study Design and Data

- Data pooled from two studies that enrolled patients with type 2 diabetes managed with diet and exercise and/or a stable regimen of select antidiabetic agents
  - Phase 2, randomized, placebo-controlled, 15-week comparison of exenatide QW 0.8 or 2 mg SC[1]
  - Phase 3, randomized, multicenter study of exenatide QW 2 mg SC for 52 weeks[2]
- Formal model evaluation evaluated only steady-state data
  - Concentration collected after 8 weeks
  - HbA1c measurements collected after 12 weeks
- Exenatide exposure measures for the PK/PD analyses were estimated using the population PK model
  - The individual predicted average steady-state plasma exenatide concentration (C_{ss_avej}) at the time of each measured glycemic response
  - C_{ss_avej} was assigned a value of zero for placebo subjects
  - Median-predicted average steady-state plasma exenatide concentrations for each individual subject was used for *post hoc* exploratory analyses of the clinical significance of covariate factors

Covariate Assessment

- PK: baseline demographic factors, manufacturing scale, creatinine clearance (capped at 150 mL/min), and anti-exenatide antibody titer level
- PD: baseline demographic factors, baseline HbA1c, fasting plasma glucose, and anti-exenatide antibody titer
- Concomitant medications: MET, SFU, and TZD
- Covariates evaluated using forward selection (α = 0.01) followed by backward elimination (α = 0.001)

Pharmacostatistical Model

- PK and PK/PD analyses were completed using NONMEM software, version VI, level 1.0 with FOCE (GlboMax, Hanover, MD; 2006)

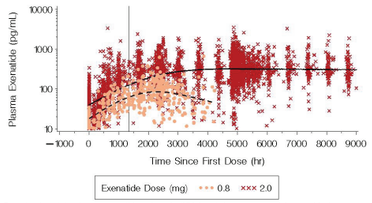
Data and Demographics

- PK: 3188 exenatide concentrations from 165 subjects
- PK/PD: 630 HbA1c measurements from 157 subjects
- Additional covariates evaluated for PD analyses
  - Change in weight from baseline 2.72 (36.8, 10.9) kg, baseline HbA1c 8.35 (6.6, 11.4) %

Demographic	Median (minimum-maximum)
Age (y)	56 (19-80)
Weight (kg)	95.3 (56.5-157.9)
CrCL (mL/min)[3]	84.6 (31.8-150)
Gender, n (%)	
Male	98 (59.4)
Female	67 (40.6)
Dose (mg), n (%)	
0.8	15 (9.1)
2.0	150 (90.9)

Results

Figure 1. Log Plasma Exenatide Versus Time Since First Dose, Stratified by Dose



One steady−state plasma exenatide value of 11052.2 pg/mL was removed for graphical purposes.

- Time to achieve steady-state trough levels is illustrated to be approximately 10 weeks (1344 hours) of therapy

Table 1. Parameter Estimates for Final Pharmacokinetic Model

Parameter	Final Parameter Estimate: Population Mean	%SEM	Magnitude of Interindividual Variability: Final Estimate	%SEM
Steady-state exenatide concentration for 0.8-mg dose for a subject with a CrCL value of 84.6 (pg/mL)	65.9	17.0		
Additive shift for 2-mg dose (pg/mL)	200.0	12.4		
Power for baseline CrCL capped at 150 mL/min	1.84	27.0	0.195*	13.8
Additive shift for antibody titer of 25 (pg/mL)	21.1	40.8		
Additive shift for antibody titer of 125 (pg/mL)	82.6	36.1		
Additive shift for 1 kg manufacturing scale (pg/mL)	98.7	51.9		
Residual variability† (%CV)	34.77	10.1		

Minimum value of the objective function = 35265.561

* The estimate provided in the table (0.195) is a variance term. The corresponding %CV = 44.18%.

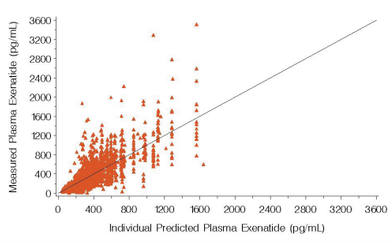
† Residual variability was modeled using a proportional error model.

$$C_{ss\_avej} = \left[65.9 \cdot \left(\frac{CrCL_j}{84.6}\right)^{1.84} + 200 \cdot Dose_j + 21.1 \cdot T2D_j + 82.6 \cdot T12D_j + 98.7 \cdot Scale_j\right] \cdot \exp(\eta_j)$$

Where:

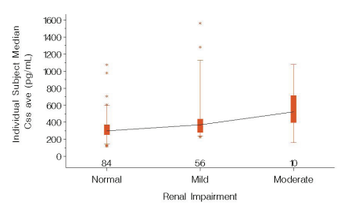
- C_{ss_avej} = Individual predicted steady-state exenatide concentration (pg/mL) for the j^{th} subject at the j^{th} measurement
- $CrCL_j$ = Observed baseline creatinine clearance (mL/min) in the j^{th} subject
- $Dose_j$ = Indicator variable for the exenatide dose (mg) observed in the j^{th} subject (1 = 2 mg and 0 = 0.8 mg)
- $T2D_j$ = Indicator variable for the presence of anti-exenatide antibody titer of 25 observed in the j^{th} subject at the j^{th} measurement (1 = titer of 25 else 0)
- $T12D_j$ = Indicator variable for the presence of anti-exenatide antibody titer of 125 observed in the j^{th} subject at the j^{th} measurement (1 = titer of 125 else 0)
- $Scale_j$ = Indicator variable for the presence of 1 kg manufacturing scale observed in the j^{th} subject (1 = 1 kg and 0 = 105 g)
- η_j = Interindividual variability random effect estimate for the j^{th} subject

Figure 2. Goodness-of-Fit Plot From Final Pharmacokinetic Model



- Final PK model predicts a C_{ss_avej} average of 365 pg/mL for the 2 mg dose, and 165 pg/mL for the 0.8 mg dose, for antibody-negative subjects with a normal renal function (CrCL = 84.6 mL/min) receiving the 1 kg material

Figure 3. Influence of Renal Impairment



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles.
Asterisks show data points outside this range.
The number below each box represents the number of subjects in each box.

Renal Function	Population Mean Predicted C_{ss}	Mean Change in Exposure
Normal	365	
Mild	472	107
Moderate	743	271

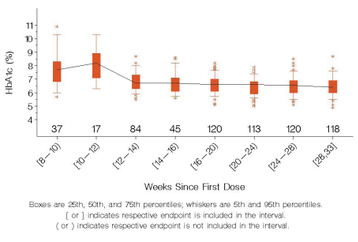
Population mean-predicted C_{ss} for the 2-mg dose for an antibody-negative subject receiving the 1-kg material.

- The biggest change in concentration is predicted for the moderate renal impairment group, but the number of subjects in this group is small (n = 10)
- As shown by the exposure-response analysis (Figure 5), concentrations are on the plateau of the curve. This trend for an increase in C_{ss_avej} with increasing renal impairment was not clinically relevant given that no difference in adverse event profiles were observed for patients with renal impairment compared to those with normal renal function[4]

Exposure Glycemic Response Analysis

- The individual predicted C_{ss_avej} from the population model were combined with the observed HbA1c measurements for the exposure-response modeling

Figure 4. HbA1c Versus Weeks Since First Dose



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles.
[or] indicates respective endpoint is included in the interval.
(or) indicates respective endpoint is not included in the interval.

- The exposure-response relationship was best described by an inhibitory E_{max} model with interindividual variability on maximum response
- IIV on EC_{50} could not be estimated

Table 2. Parameter Estimates for the Final Pharmacokinetic/Pharmacodynamic Model

Parameter	Final Parameter Estimate: Population Mean	%SEM	Magnitude of Interindividual Variability: Final Estimate	%SEM
T_{max} (%)	1.45	8.9		
Change in log HbA1c per unit change in log baseline HbA1c on E_{max} (%)	0.393	8.4		
Slope for change in weight on E_{max} (%/kg)	-0.0533	16.7	0.101*	24.5
Additive shift on E_{max} for titer = 0 (%)	0.227	29.9		
Additive shift on E_{max} for titer = 25 (%)	0.209	30.6		
EC_{50} (pg/mL)	83.1	42.2		
Residual Variability† (%CV)	3.62	11.1		

Minimum value of the objective function = -644.837

* The estimate provided in the table (0.101) is a variance term. The corresponding %CV = 31.79%.

† Residual variability was modeled using a proportional error model.

$$HbA_{1c_{ij}} = BHbA_{1c_j} \cdot \left(\frac{E\max_j \cdot Css_{ave_{ij}}}{ED_{50_j} + Css_{ave_{ij}}}\right)$$

$$E\max_j = \left[1.45 \cdot \left(\frac{wt_{ij}}{84.6}\right)^{-0.0533} \cdot \left(0.393^{BHbA_{1c_j} - 8.83}\right) + 0.227 \cdot TI_{25_{ij}} + 0.209 \cdot TI_{125_{ij}}\right] \cdot \exp(\eta_{2j})$$

Where:

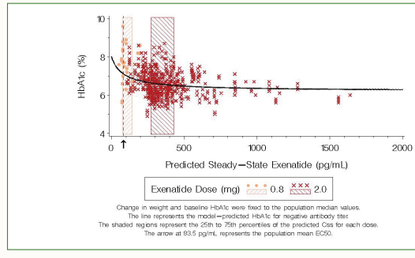
- $HbA_{1c_{ij}}$ = Individual predicted HbA1c (%) in the i^{th} subject at the j^{th} measurement
- $BHbA_j$ = Observed baseline HbA1c (%) in the i^{th} subject
- $Css_{ave_{ij}}$ = Individual predicted steady-state exenatide concentration (pg/mL) for the i^{th} subject at the j^{th} measurement
- $CHGWT_{ij}$ = Observed change in weight from baseline (kg) in the i^{th} subject at the j^{th} measurement
- $TI_{25_{ij}}$ = Indicator variable for the antibody-negative observed in the i^{th} subject at the j^{th} measurement
- $TI25_{ij}$ = Indicator variable for the presence of anti-exenatide antibody titer of 25 observed in the i^{th} subject at the j^{th} measurement
- η_{2j} = Interindividual variability random-effect estimate for the i^{th} subject

Table 3. Population-Predicted HbA1c Reductions (%) From Baseline: Final Pharmacokinetic/ Pharmacodynamic Model

Antibody Titer	Baseline HbA1c (%): 7	8	10
Negative	1.03	1.39	2.71
Titer 25	0.95	1.31	2.63
Titer 125	0.77	1.13	2.45

- Assumes C_{ss_avej} of 300 pg/mL and change in weight from baseline of -2.8 kg
- For a given exenatide concentration, the decrease in HbA1c from baseline is predicted to be greatest for subjects with high baseline HbA1c and greatest weight loss
- Controlling for other influential factors, the magnitude of the reduction in HbA1c is greater for subjects who have a negative anti-exenatide antibody titer than for those who are antibody positive

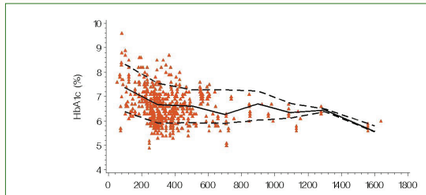
Figure 5. HbA1c Versus C_{ss_avej} Stratified by Dose



Change in weight and baseline HbA1c were fixed to the population median values.
The line represents the model−predicted HbA1c for negative antibody titer.
The shaded regions represent the 25th to 75th percentiles of the predicted Css for each dose.
The arrow at 83.5 pg/mL represents the population mean EC50.

- Overlay is the population mean-predicted line for negative anti-exenatide antibody titer
- All subjects who received the 2-mg dose of exenatide QW had median-predicted steady-state plasma exenatide concentrations that exceeded the model-predicted EC_{50} (83.5 pg/mL); of subjects who received the 0.8-mg dose of exenatide once weekly, 50% had median-predicted steady-state plasma exenatide concentrations that exceeded the EC_{50}

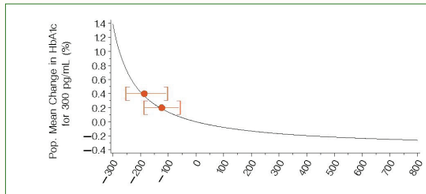
Figure 6. HbA1c Versus C_{ss_avej} With 90% Prediction Interval Overlaid



The solid line represents the median−simulated HbA1c.
The dashed lines represent the 90% prediction interval.

- A visual predictive check and model diagnostics indicated that the PK/PD model generally described the data well

Figure 7. Population Mean Change in HbA1c by Change in C_{ss_avej}



The dot represents the median change in Css ave.
The [,] represent 90% prediction intervals.

- Simulations were performed to evaluate the reduction in exenatide concentration required to modify the HbA1c response to a clinically relevant degree (-0.2%, -0.4%) from a starting level of 300 pg/mL
  - An average decrease of approximately 186 pg/mL (90% prediction interval of required reduction in concentrations = 96.9 pg/mL, 259.1 pg/mL) will be required to cause a clinically relevant change of -0.4% in HbA1c response
  - An average decrease of approximately 122.9 pg/mL (90% prediction interval of required reduction in concentrations = 63.4 pg/mL, 184.9 pg/mL)

Conclusions

PK

- The final population PK model describes average steady-state exenatide concentrations, incorporating the influence of baseline creatinine clearance, anti-exenatide antibody titer, and manufacturing scale (105-g versus 1-kg)
- The covariate effects of age, race, gender, IBW, BMI, body weight, and concomitant MET, SFU, and TZD were not statistically significant predictors of the variability in steady-state plasma exenatide concentrations
- Based on the known clearance mechanisms of exenatide, the effects of creatinine clearance and anti-exenatide antibody on exenatide pharmacokinetics were expected and are in accordance with pharmacokinetic evaluations of the immediate-release formulation of exenatide

PK/PD

- The exposure-glycemic response model was an inhibitory E_{max} model describing the relationship between steady-state HbA1c and average steady-state plasma exenatide concentrations, incorporating the influence of baseline HbA1c, anti-exenatide antibody titer, and change from baseline in body weight on maximum response
- The covariate effects of age, race, gender, and concomitant MET, SFU, and TZD were not statistically significant predictors of the variability in HbA1c
- The 2-mg dose of exenatide once weekly results in a robust clinical response. The majority of the data associated with a 2-mg dose lies within the plateau of the exposure-response curve
- Simulations concluded that large decreases in exenatide exposure would be required before a clinically relevant change in HbA1c response is elicited

References

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