MPI-96

Population Modeling to Guide Phase 3 Dose Selection for AC2993 (Synthetic Exendin-4)

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ABSTRACT

Introduction. AC2993 is a novel glucose lowering agent for the treatment of patients with type 2 diabetes.

Methods. Population PK and PK/PD models were developed for AC2993 using subject data from four Phase 2 trials evaluating subcutaneous injections of 0.02-0.4 µg/kg administered QD, BID, or QID. The models simulated the relationship between plasma glucose and drug exposure ($AUC_{0\text{-}5hr}$) to select a fixed dose (not normalized to bodyweight) that balances efficacy and dose-related nausea.

Results. The resultant PK model was a one-compartment model with dose-dependent first-order absorption. Clearance was related to weight and bilirubin, although the latter relationship was based on few subjects. Weight explained 5.5% of the inter-individual variability of clearance. The PK/PD model was an inhibitory Emax model, with the maximum reduction in glucose AUC expressed as % of the placebo glucose AUC. For the simulations, the target range for AC2993 exposure was 600-950 pg*hr/mL, to balance glucose-lowering effects with dose-related nausea. The glucose response target was at least a 20% reduction in glucose $AUC_{0\text{-}5hr}$. Simulations of 10 clinical trials (100 subjects; 50-120kg bodyweight) using 5, 9, 10, and 12 µg doses predicted the % of subjects above the target exposure range (associated with increased nausea) to be 0, 15, 23, and 51, respectively. The % of subjects under/above 20% glucose reduction were predicted to be 39/61, 24/76, 23/77, and 20/80, respectively.

Conclusion. Overall, these results support the selection of a 5 µg and 10 µg dose for Phase 3 evaluation. (Revised)

INTRODUCTION

- AC2993 (synthetic exendin-4) is a 39 amino acid soluble peptide that has several anti-diabetic (glucose lowering) actions. These include:
  - stimulation of insulin secretion in a glucose-dependent manner;
  - inhibition of glucagon secretion; and
  - modulation of gastric emptying to slow the entry of ingested glucose into the bloodstream.
- AC2993 has been shown to activate the GLP-1 receptor in vitro[1] and in diabetic mice, lowers plasma glucose with one thousand fold greater potency than GLP-1.[2]
- Single and multiple subcutaneous doses of 0.05-0.4 µg/kg lead to significant reductions in plasma glucose in patients with type 2 diabetes.
- AC2993 (0.08 µg/kg) administered BID for 28 days resulted in HbA_{1c} reductions of 0.8% compared to placebo.
- The most common adverse event reported was dose-dependent, transient nausea.

OBJECTIVES

- To develop a population pharmacokinetic (PK) model that describes the disposition of AC2993 following subcutaneous administration
- To develop a model for the relationship between glucose $AUC_{0\text{-}5hr}$ and AC2993 $AUC_{0\text{-}5hr}$ following subcutaneous AC2993 administration at 0 hr
- To evaluate fixed dosing regimens via simulation with the pharmacokinetic and pharmacokinetic/pharmacodynamic (PK/PD) models for future application in long-term controlled trials

METHODS

Study Design/Data

- Data pooled from four Phase 2 studies (crossover design)
- Subjects: N=51; people with type 2 diabetes mellitus, controlled by diet or oral anti-diabetic agents (discontinued during study), 6 subjects continued insulin therapy, baseline HbA_{1c}: 7-12%
- Single/multiple AC2993 doses with QD, BID, and QID dosing regimens
- Doses were: QD: 0.02, 0.05, 0.1, 0.2, 0.3, and 0.4 µg/kg
  BID: 0.01 µg/kg
  QID: 0.05 µg/kg
- Sampling design: full profiles ranging in duration from 5-23 hours

Subject Covariates

- PK: gender, race, height, weight, age, serum creatinine, albumin, alkaline phosphatase, total bilirubin, ideal body weight, body surface area, and creatinine clearance
- PK/PD: glucose concentrations were collected for 5 hours following breakfast and the glucose $AUC_{0\text{-}5hr}$ was calculated using the trapezoidal rule; AC2993 concentrations were obtained simultaneously and AC2993 $AUC_{0\text{-}5hr}$ was calculated

Pharmacostatistical Model

- NONMEM® V, Level 1.1, using first-order conditional with interaction estimation
- PK: one-compartment model, with first-order absorption and elimination
- PK/PD: inhibitory Emax – for glucose $AUC_{0\text{-}5hr}$ vs. AC2993 $AUC_{0\text{-}5hr}$ relationship
- Interindividual variability models: exponential error for PK and exponential or additive error for PK/PD
- Residual variability models: proportional error for PK and additive error for PK/PD

Subject Covariate Analysis

- Continuous covariates modeled using linear, exponential, and/or power models
- Dichotomous and categorical covariates modeled using proportional or additive shift models
- Univariate analyses performed followed by stepwise backward elimination to determine significant subject covariates

Statistical Analyses

- Statistical significance: univariate analyses: α = 0.05; backward elimination: α = 0.001
- Goodness-of-fit of each NONMEM® analysis assessed by examination of:
  - scatterplots of predicted versus measured concentrations and versus weighted residuals
  - % SEM of the parameter estimates
  - changes in the estimates of the interindividual and residual variability

Simulation Study

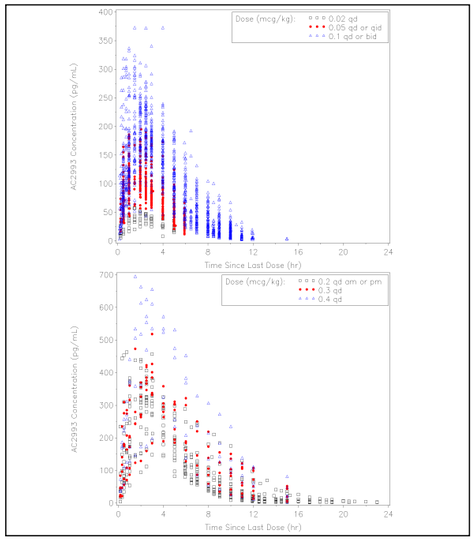
- Dose selection: four fixed doses between 5-12 µg
- Data: 10 trials, 100 subjects each were simulated at each dose
- Subject characteristics:
  - 50 ≤ weight (kg) ≤ 120
  - 0.1 ≤ total bilirubin (mg/dL) ≤ 1.0
  - 480 ≤ placebo glucose $AUC_{0\text{-}5hr}$ (mg*hr/dL) ≤ 730
- Blood sampling: every 15 minutes after a single dose
- Simulation:
  - Different sets of random numbers were used to generate the data for each of the 10 trials
  - Simulations at each dose level used the same set of random numbers

RESULTS

Population Demographics

- Total of 2,341 AC2993 concentrations from 51 subjects
- Subject demographics: gender: 73% male; mean age was 55 yrs (range 29-68); mean weight was 83 kg (range 50-118); mean creatinine clearance was 89 mL/min (range 44-297)

Figure 1: Scatterplot of Concentration Versus Time Since Last Dose Stratified by Treatment Regimen



Pharmacokinetic Model

- One-compartment PK model with dose-dependent Ka and first-order elimination

Table 1: Final Parameter Estimates and Standard Errors for the Final Pharmacokinetic Model

Parameter[1,2]	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
Baseline Ka (1/hr)	0.490	7.0		
Maximum Fractional Reduction of Ka	0.847	14.8		
$Dose_{5hr}$ (µg)	28.0	46.1	115.33	59.0
CL Intercept (L/hr)	8.16	3.0	19.90	22.6
CL Slope for Weight	0.0966	17.3		
CL Slope for Bilirubin	2.98	31.4		
Vc (L)	10.6	8.3	47.33	24.5
Residual Variability (%CV)				
No Assay Correction	25.10	9.2		
Assay Correction < 20 (pg/mL)	27.62	12.2		
Assay Correction ≥ 20 (pg/mL)	29.27	17.7		

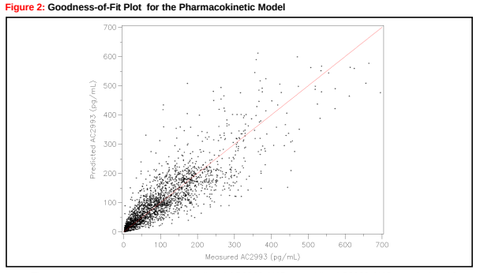
Min. value of Objective Function = 16069.620

1. $$\mathrm{Ka}(1/\mathrm{hr}) = 0.49 \bullet \left(1 - \frac{0.847 \bullet \mathrm{Dose}}{28 + \mathrm{Dose}}\right)$$

2. $$CL(L/hr) = 8.16 + 0.0966 \bullet (Weight - 82) + 2.98 \bullet (TotalBilirubin - 0.49)$$

- The relationship between bilirubin and AC2993 clearance was statistically significant, however the database included only 4 subjects with elevated bilirubin levels (> 1.0 mg/dL). As more data become available from subjects with elevated total bilirubin, this relationship may become insignificant.

Figure 2: Goodness-of-Fit Plot for the Pharmacokinetic Model



- The relationship between the model-predicted AC2993 $AUC_{0\text{-}5hr}$ and the AC2993 $AUC_{0\text{-}5hr}$ calculated from the observed concentrations exhibited a high degree of correlation (r^2 = 0.90).

Pharmacokinetic/Pharmacodynamic Model

- Dataset: 195 pairs of measured AC2993 $AUC_{0\text{-}5hr}$ and glucose $AUC_{0\text{-}5hr}$ from 50 subjects (one subject from PK dataset excluded because placebo glucose $AUC_{0\text{-}5hr}$ was missing)

Figure 3: Glucose $AUC_{0\text{-}5hr}$ versus AC2993 $AUC_{0\text{-}5hr}$ Stratified by Baseline Glucose $AUC_{0\text{-}5hr}$ (bl glucose)

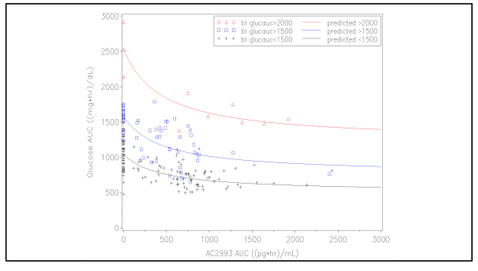


Table 2: Final Parameter Estimates and Standard Errors for the Pharmacokinetic/Pharmacodynamic Model

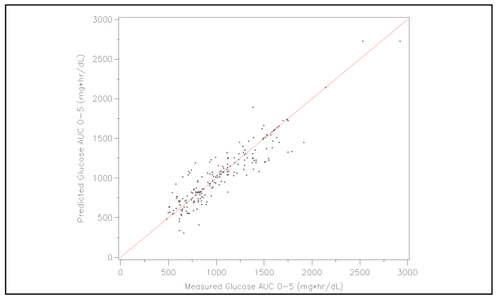
Parameter[1]	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
AUC_{50} (pg*hr/mL)	444	29.3	108.63	39.6
Emax (Fraction of Glucose $AUC_{0\text{-}5hr}$ prior to treatment)	0.515	6.6		
Residual Variability (SD)	100.0	19.6		

Min. value of Objective Function = 2072.545

1. $$\mathrm{Glucose}AUC_{0\text{-}5} = PlaceboAUC_{0\text{-}5} \bullet \left(1 - \frac{E\max \bullet AC2993AUC_{0\text{-}5}}{AUC_{50} + AC2993AUC_{0\text{-}5}}\right)$$

- AUC_{50} is the AC2993 $AUC_{0\text{-}5hr}$ that elicits 50% of the maximum reduction in glucose $AUC_{0\text{-}5hr}$

Figure 4: Goodness-of-Fit Plot for the Pharmacokinetic/Pharmacodynamic Model



- None of the covariates evaluated were significant predictors of the AUC_{50}.

Simulation Study

- Definitions
  - PK target range: AC2993 $AUC_{0\text{-}5hr}$ 600-950 pg*hr/mL. This target range was identified as it is high enough to result in at least an average 30% reduction in glucose $AUC_{0\text{-}5hr}$ yet is low enough to have no associated increase in gastrointestinal side effects (nausea/vomiting).
  - PD target response: ≥ 20% reduction in glucose $AUC_{0\text{-}5hr}$
- Fixed doses: 5, 9, 10, 12 µg
- Simulated subject covariates: median weight range: 78.3 - 84.0 kg; median total bilirubin: 0.4 - 0.5 mg/dL

Figure 5: Weight Distribution of Simulated Population (All Trials)

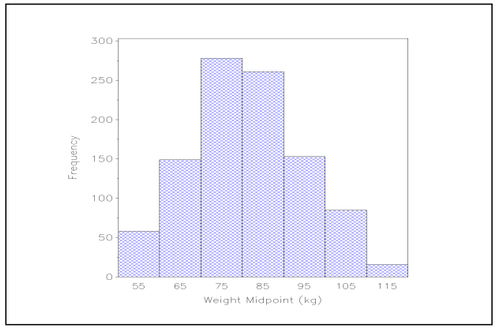


Figure 6: Percent of Subjects Categorized by AC2993 $AUC_{0\text{-}5hr}$ and Percent Decrease in Glucose $AUC_{0\text{-}5hr}$ Range Stratified by Weight Category (All Trials)

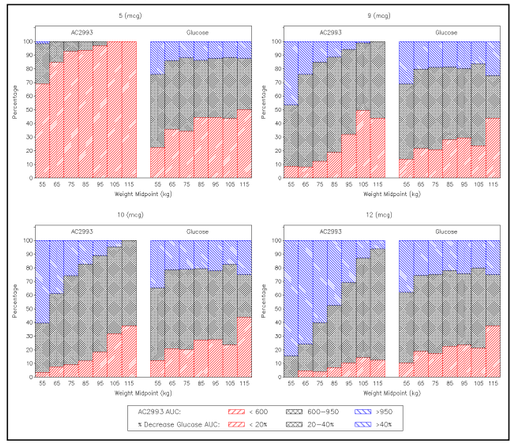


Table 3: Mean Percentage of Subjects Categorized by Response and Dose Level

Response	Dose (µg)			
	5	9	10	12
AC2993 $AUC_{0\text{-}5hr}$ Target Range, pg*hr/mL (% of subjects)				
< 600	91.7	19.8	13	6.6
600-950	8.2	65.7	63.9	42.2
>950	0.1	14.5	23.1	51.2
Percent Decrease in Glucose $AUC_{0\text{-}5hr}$, mg*hr/dL (% of subjects)				
< 20	39	24.3	23.4	20.1
20-40	47.5	55.9	54.8	55.5
>40	13.5	19.8	21.8	24.4

CONCLUSIONS

- AC2993 clearance was related to weight (5.5% of the intersubject variability), with an average increase of 6.8 L/hr for subjects weighing 120 kg compared to subjects weighing 50 kg.
- PK was the only independent predictor of PD.
- None of the covariates evaluated were significant predictors of the AC2993 $AUC_{0\text{-}5hr}$ at which 50% of the maximum reduction in glucose $AUC_{0\text{-}5hr}$ occurs (AUC_{50}).
- From the simulations, the 10 µg dose best balances effectiveness and tolerability: 77% of subjects are predicted to have AC2993 $AUC_{0\text{-}5hr}$ levels less than that associated with an increased risk of nausea and vomiting, and approximately 77% of subjects are expected to achieve ≥ 20% decrease in glucose $AUC_{0\text{-}5hr}$.
- The 5 µg dose may be a beneficial alternative as 99% of subjects are predicted to tolerate the dose without nausea and vomiting, yet approximately 61% of subjects are expected to achieve ≥ 20% decrease in glucose $AUC_{0\text{-}5hr}$.

REFERENCES

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2. Young AA, Gedulin BR, Bhavsar S, et al. Glucose-lowering and insulin-sensitizing actions of exendin-4: studies in obese diabetic (ob/ob, db/db) mice, diabetic Fatty Zucker rats and diabetic rhesus monkeys (Macaca mulatta). Diabetes 48 (5):1026-1034, 1999.