Model-Based Development of a PPARγ Agonist, Rivoglitazone, to Aid Dose Selection and Optimize Clinical Trial Designs

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A model-based approach was implemented for the development of the proliferator-activated receptor gamma (PPARγ) agonist rivoglitazone. Population pharmacokinetic and pharmacodynamic models were developed using data collected from 2 phase I and 2 phase II studies in healthy volunteers and participants with type 2 diabetes mellitus. A 2-compartment model with first-order absorption and elimination and an absorption time lag best described rivoglitazone pharmacokinetics. Modified indirect-response models were used to characterize changes in fasting plasma glucose, HbA_{1c}, and hemodilution as a function of rivoglitazone plasma concentrations. In addition, differences in hemodilution among participants correlated with the incidence of edema. Current use of oral antidiabetic medication was a significant covariate for the fasting plasma glucose-HbA_{1c} exposure-response model. Using a learn-and-confirm process, models developed prior to the second phase II study were able to make valid predictions for exposures and response variables in that study. In future studies, seamless designs can be supported by models such as those developed here.

Keywords: *Population pharmacokinetics; rivoglitazone; pharmacodynamics; learn and confirm; exposure response*

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Rivoglitazone (CS-011), a thiazolidinedione (TZD), increases insulin sensitivity by enhancing insulin action in skeletal muscle, liver, and adipose tissue. By binding to and activating the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ), which regulates the expression of genes involved in glucose and lipid metabolism, thiazolidinediones increase glucose utilization, reduce hepatic glucose production, and enhance insulin sensitivity.[1,2] Rivoglitazone has linear pharmacokinetics in the dose range intended for future use, a half-life consistent with once-daily dosing, and very low renal clearance (CL_R).[3,4] In phase II dose-ranging trials of 6 and 26 weeks in duration, rivoglitazone treatment improved glycemic control in participants with type 2 diabetes mellitus (T2DM) and showed a safety profile consistent with the specific side effects (eg, weight gain, edema, and hemodilution) observed in clinical development of the currently marketed thiazolidinediones.[5,6]

Modeling and simulation were implemented for rivoglitazone to enable a more complete and robust understanding of its benefits and risks, thus enabling a more informed and efficient drug development process (Figure 1). In the case of developing a "best-in-class" compound, model-based drug development can use the wealth of knowledge from predecessor drugs with a similar mechanism of

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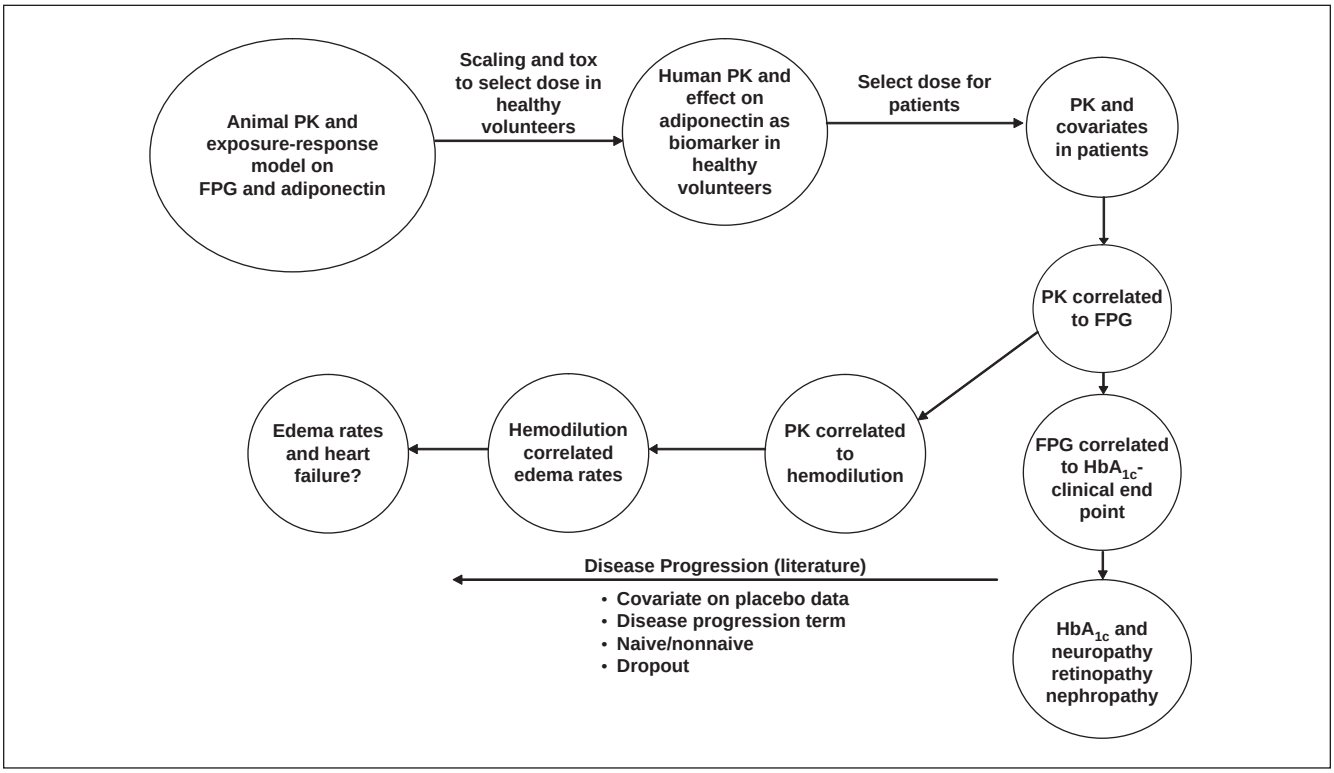

Figure 1. Overview of rivoglitazone model-based drug development. PK, pharmacokinetic; FPB, fasting plasma glucose; Tox, toxicology.

action. Beginning with first-in-human trials for the new drug, efficacy and safety models can be constructed based on both the compound's preclinical data and the predecessor's clinical experience. As data are generated at each stage of clinical development, the models (and future projections) are updated, with the new drug's properties becoming more definitive as the process matures. At all stages, the model-based process allows for the entire basis of relevant knowledge to be incorporated into decision-focused recommendations, following the learn-and-confirm paradigm promoted by Sheiner.[7]

As part of the model-based process, initial doses for rivoglitazone in diabetics were chosen using adiponectin as a biomarker for PPARγ activity. Adiponectin, a hormone secreted by adipocytes, has been observed to reduce glucose levels in different animal models of obesity and diabetic mellitus by increasing insulin sensitivity. Circulating levels of adiponectin are lower in the obese and in patients with type 2 diabetes with respect to healthy controls and negatively correlate with the plasma levels of glucose, insulin, triglycerides, and insulin resistance.[8,9] Members of the TZD class are known to increase the circulating plasma levels of the active form of adiponectin in both healthy volunteers and diabetic participants.[2] Based on the phase I data, up to 2 weeks of daily dosing with 1 to 5 mg produced increases from baseline in adiponectin of 66% to 527% with no additional effect at the 10-mg dose (see Supplemental Figure 1).[10] Hence, the first phase IIa study in diabetic participants was conducted with doses of placebo or 0.5, 1, or 5 mg, administered once daily for 6 weeks.[5]

The specific objectives of the present analysis were to model the population pharmacokinetics (PK) of orally administered rivoglitazone using data collected from 2 phase I studies and 2 phase II studies. A pharmacodynamic (PD) model based on rosiglitazone[11] was applied to characterize effects on fasting plasma glucose (FPG), hemoglobin A_{1c} (HbA_{1c}), and hemodilution as a function of rivoglitazone plasma concentrations (C_p). The effects of covariates on the oral clearance (CL) of rivoglitazone and on the parameters of the exposure-response models were characterized and quantified. For the exposure-response analyses, models were applied for the initial phase II study, confirmed by the second phase II study, and then updated based on the full data set.

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METHODS

Trial Design and Participants

The pharmacokinetic data and population analysis were derived from 60 healthy volunteers (58 men, 2 women) enrolled in 2 phase I studies (CS0011-A-U103 and CS0011-A-U104) with full-profile sampling and 461 diabetic participants (265 men, 196 women) enrolled in 2 phase II studies (CS0011-A-U202 and CS0011-A–U203). Only data from the phase II studies were used to conduct the pharmacodynamic analysis (n = 461 on active treatment and n = 184 on placebo). Phase I studies were conducted at MDS Pharma Services (Neptune, New Jersey), and the phase II studies were conducted at multiple clinical sites in the United States. An investigational review board approved each study protocol. Written informed consent was obtained from each study participant before any study-specific procedures or assessments. Studies were conducted under the principles of the World Medical Assembly Declaration of Helsinki and its most recent amendments, the US Code of Federal Regulations, and good clinical practice.

All participants received either oral rivoglitazone or a matching placebo. Trial design, population, treatment regimens, duration, and sampling schedules are available online in Supplemental Table 1.

Analytical Methods for Rivoglitazone Measurement in Plasma Samples

A validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method was used for measuring rivoglitazone in plasma for the 2 phase II studies (CS0011-A-U202 and CS0011-A-U203) and 2 phase I studies (CS0011-A-103 and CS0011-A-U104). An aliquot of human plasma (EDTA) containing the analyte and internal standard was extracted using an automated TOMTEC solid-phase extraction procedure. The extracted samples were analyzed by a high-performance liquid chromatography (HPLC; Polaris 50 × 2-mm, 5-µm column, 60/40 methanol/10 mM ammonium acetate [pH 4.0] mobile phase, isocratic mode) system equipped with an ABI/MDS Sciex API 3000 mass spectrometer. Positive ions were monitored in the multiple-reaction monitoring (MRM) mode. The lower limit of quantification (LLOQ) of the validated method was set at 0.5 ng/mL, whereas the dynamic ranges were 0.5 to 1000 ng/mL (for the CS0011-A-U103 study) and 0.5 to 500 ng/mL (for the CS011-A-U104, CS011-A-U202, and CS011-A-U203 studies). The MRM transition was 398.3/176.1 for rivoglitazone and 404.3/182.1 for the internal standard ($^2H_6$-Rivoglitazone). Human plasma (EDTA), free of significant interference, was used to prepare calibration standard and quality control (QC) samples. A $^1/_x^2$ weighted linear regression model was then used to calculate slope, intercept, and correlation coefficient. Back-calculated results of QCs and study samples were then obtained by fitting the peak area ratio to the $^1/_x^2$ weighted regression equation for the relevant standards. For QC samples, between-batch precision (% coefficient of variation [CV]) ranged from 2.1 to 8.2, and accuracy (%Bias) ranged from –4.2 to 8.7. For calibration standards, between-batch precision (%CV) ranged from 1.4 to 7.0, and accuracy (%Bias) ranged from –4.0 to 6.0.

Pharmacokinetic Sampling

Intensive pharmacokinetic sampling was conducted after both single and multiple oral doses in the phase I trials, up to 72 hours postdose. In the phase II trials, pharmacokinetic and biomarker samples were drawn at the time of trough steady-state concentration—that is, at predose; at weeks 0, 2, 4, and 6 in the CS0011-A-U202 study; and at weeks 0, 4, 8, 12, 16, 20, and 26 in the CS0011-A-U203 study. In study CS0011-A-U203, intensive PK sampling was performed after the last dose in the study in a subset of subjects who volunteered for intensive sampling.

Pharmacokinetic Data Analysis and Model Development

All data preparation and graphic representations were performed using S-PLUS software, Version 6.2. All pharmacokinetic and pharmacodynamic analyses were implemented within the NONMEM software program, Version V, Level 1.1. The development of the population pharmacokinetic model was based on the Food and Drug Administration's (FDA's) *Guidance for Industry Population Pharmacokinetics*.[12] Further details are provided online in supplemental materials.

Change in FPG concentrations was modeled as a function of C_p via an indirect-effect model on the assumption that rivoglitazone reduces glucose by increasing the removal rate of glucose from the plasma compartment (Figure 2) as developed by Benincosa and Jusko[11]:

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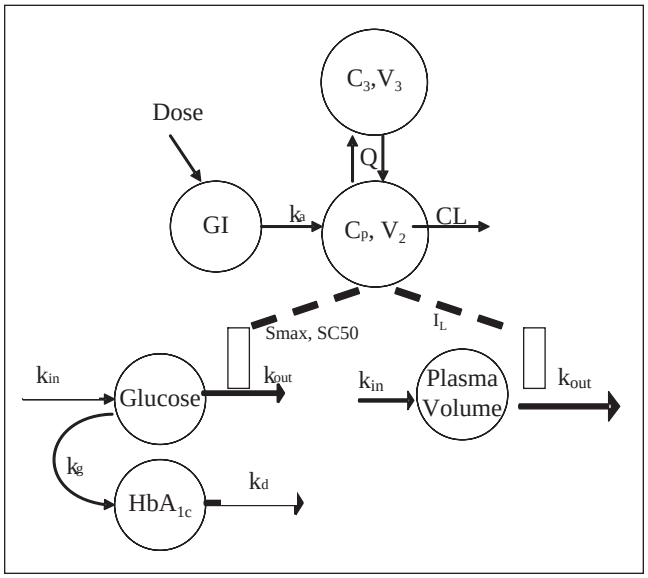

Figure 2. Depiction of FPG-HbA$_{1c}$ and hemodilution exposure-response models. FPG, fasting plasma glucose; GI, gastrointestinal tract.

$$dFPG/dt = k_{in} - k_{out}*S(C_p)*FPG(t)\ FPG(0) = FPG_0, \quad (1)$$

where k_{in} is the zero-order glucose production rate, k_{out} is the first-order glucose removal rate from plasma, $S(C_p)$ is the function for the stimulation of k_{out} by C_p, and FPG is the fasting plasma glucose concentration. Changes in HbA_{1c} were modeled as secondary to changes in FPG in a first-order process:

$$dHbA_{1c}/dt = k_g*FPG(t) - k_d*HbA_{1c}(t)$$
$$HbA_{1c}(0) = HbA_{1c0}, \quad (2)$$

where k_g is the pseudo first-order HbA_{1c} production rate constant, and k_d is the first-order HbA_{1c} degradation rate constant.

For hemodilution, the inverse of hemoglobin concentration, denoted PV for *plasma volume*, was modeled as a function of the plasma concentration of rivoglitazone via an indirect-effect model on the assumption that rivoglitazone increases plasma volume by a linear inhibition of the loss of plasma volume:

$$dPV/dt = k_{inp} - k_{outp}*I(C_p)*PV(t)\ PV(0) = PV_0, \quad (3)$$

where k_{inp} is the zero-order plasma volume production rate, k_{outp} is the first-order removal rate, $I(C_p)$ is the function for the inhibition of k_{outp} by C_p, and PV is the plasma volume. Pretreatment baseline values were set as the initial conditions. The potential relationship between edema and hemodilution was explored first through exploratory graphical analysis and subsequently through logistic regression models.

Predicted subject-specific plasma concentrations of rivoglitazone, available from the population pharmacokinetic model, were used for pharmacodynamic model-fitting purposes. Stimulation and inhibition functions in the indirect-response models were investigated with saturable (ie, $S_{max}*C_p/(C_p + SC_{50})$) and linear models (ie, $1 + slope*C_p$). If the relationship showed linearity without saturation, or if the saturable model parameters could not be estimated, the linear model was used.

RESULTS

Participant Demographics

Data were available for 518 unique participants for the pharmacokinetic analysis and 461 unique participants for the pharmacodynamic analyses. A summary of the demographic characteristics of the data sets is presented online in Supplemental Table 2.

Pharmacokinetic Model

Population Pharmacokinetic Analysis

Explorations of 1- and 2-compartment models determined that the pharmacokinetics of rivoglitazone were best described by a 2-compartment linear model (CL, V_2, V_3, Q) with first-order absorption/elimination (k_a) and an absorption time lag (t_{lag}).

The parameters for the final covariate model for the compartmental pharmacokinetics of rivoglitazone are shown in Table I. Clearance was significantly affected by sex, body weight, renal function (as measured by SCr), and subject/healthy volunteer status ($P < .05$) as follows:

$$CL_i\,(L/h) = 1.15 \times (SCr_i/1)^{-0.246} \times (WT_i/191)^{0.347}$$
$$- (0.163*SEX_i) + (0.17*Healthy_i). \quad (4)$$

The model indicates that a male patient with baseline SCr and body weight equivalent to the median of the study population, 1 mg/dL and 191 lb, would have a CL estimated to be 1.15 L/h. A healthy male volunteer with similar SCr and body weight had a CL of 1.32 L/h. Female patients had approximately

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Table I Rivoglitazone Population Pharmacokinetic Parameter Estimates, Standard Errors of Estimates, and Variability Estimates Before and After Inclusion of CS0011-A-U203 Data Set

	Population Mean		Intersubject Variability	
Parameter	**Estimate**	**SE[a]**	**Estimate[b]**	**SE[c]**
Before CS0011-A-U203				
Fixed effects				
CL_{TYP}, L/h	1.10	3.0	22	44
V2, L	19.1	9.0	42	64
V3, L	3.02	13	65	57
k_a, per h	1.93	12	35	66
t_{lag}, h	0.295	10	42	61
Q, L/h	0.323	19	—	—
Effect of covariates on CL				
Gender, CL_{SEX}	–0.159	26	—	—
Renal function, CL_{SCR}	–0.210	41	—	—
Weight, CL_{WT}	0.288	21	—	—
Health status, CL_{HV}	0.121	44	—	—
Residual variability[d]	0.046	7.6	—	—
After CS0011-A-U203				
Fixed effects				
CL_{TYP}, L/h	1.15	3.2	36	56
V2, L	22.1	8.4	76	68
V3, L	2.92	15	79	62
k_a, per h	1.87	10	74	96
t_{lag}, h	0.273	8.7	55	70
Q, L/h	0.280	31	—	—
Effect of covariates on CL				
Gender, CL_{SEX}	–0.163	23	—	—
Renal function, CL_{SCR}	–0.246	31	—	—
Weight, CL_{WT}	0.347	15	—	—
Patient status, CL_{PS}	0.172	16	—	—
Residual variability[d]	0.067	8.2	—	—

a. Coefficient of variation of the estimates (100 × SE estimate/estimate).
b. Estimates of variability expressed as appropriate percent coefficient of variation (%CV) $100\sqrt{\Omega}$.
c. Percent square root of the relative standard error of the coefficient of variation $100\sqrt{SE_{ETAestimate}}$ / ETA estimate.
d. Residual intrasubject variability.

14% lower CL rates than men. Each 10% decrease in body weight from the data set median of 86 kg translated to a 3.4% decrease in CL, and each 10% increase in SCr translated to a 2.5% decrease in CL.

Goodness-of-fit plots for the final 2-compartment model showed the model to be appropriate (Supplemental Figure 2). The individual- and population-predicted plasma concentrations matched the observed plasma concentrations, demonstrating that the model adequately described the data. Supplemental Figure 2 also shows the residuals and weighted residuals versus the population predictions. Covariate plots for the final model showed no remaining patterns between the covariates and rivoglitazone clearance.

Prediction of CS0011-A-U203 results from the best model developed prior to inclusion of that study's data was robust and validated the learn-and-confirm process. Supplemental Figure 3 depicts model prediction plots for rivoglitazone trough concentrations in each of the 3 CS0011-A-U203 dose arms, overlaid with observed concentrations. Across the plots, 82% to 94% of the data were within the 95% confidence interval (CI) of the model predictions, supporting the validity of the model. Supplemental Figure 4 depicts the observed concentration versus time profiles data and prediction intervals for the 8 intensively sampled participants, indicating the appropriateness of the predictions.

Pharmacodynamic Analyses

The proposed structural model for the PK/PD models fit the data well for both study CS-011-202 alone and together with study CS-011-203.

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Table II Rivoglitazone FPG-HbA1c Pharmacodynamic Parameter Estimates, Standard Errors of Estimates, and Variability Estimates Before and After Inclusion of CS0011-A-U203 Data Set

	Population Mean		Intersubject Variability	
Parameter	**Estimate**	**SE[a]**	**Estimate[b]**	**SE[c]**
CS0011-A-U202 Model				
Fixed effects				
k_{out}, 1/h	0.00235	8.9	—	—
FPG_{ss}, mg/dL	160	2.6	20	34
SC_{50}, ng/mL	91.8	30	193	54
S_{max} (-)	0.81	13	—	—
k_d, 1/h	0.000525	6.1	—	—
$HbA_{1c,ss}$, %	7.66	2.2	21	33
Effect of covariates				
Nonnaive on FPG_{ss}, mg/dL	48	Fixed	—	—
Nonnaive on $HbA_{1c,ss}$, %	2.3	Fixed	—	—
Residual variability[d]				
FPG, mg/dL^2	9.6	10.5	—	—
HbA_{1c}, $\%^2$	2	8.5	—	—
CS0011-A-U202 + CS0011-A-U203 Model				
Fixed effects				
k_{out}, 1/h	0.00259	12	—	—
FPG_{ss}, mg/dL	160	3	16	19
SC_{50}, ng/mL	126	25	316	80
S_{max} (-)	0.43	36	—	—
k_d, 1/h	0.000664	8	—	—
$HbA_{1c,ss}$, %	7.57	3	15	35
Effect of covariates				
Nonnaive on FPG_{ss}, mg/dL	48	Fixed	—	—
Nonnaive on $HbA_{1c,ss}$, %	2.3	Fixed	—	—
Residual variability[d]				
FPG, mg/dL^2	12	12	—	—
HbA_{1c}, $\%^2$	3	20	—	—

FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}.
a. Coefficient of variation of the estimates (100 × SE estimate/estimate).
b. Estimates of variability expressed as appropriate percent coefficient of variation (%CV) $100\sqrt{\Omega}$.
c. Percent square root of the relative standard error of the coefficient of variation $100\sqrt{SE_{ETAestimate}}$ / ETA estimate.
d. Residual intrasubject variability.

Population parameters for the FPG-HbA_{1c} and hemodilution models are listed in Tables II and III.

The FPG decrease depended on drug concentration. For this relationship, a saturable pharmacologic model for stimulation of k_{out} gave a better fit than a similar linear model. One covariate relationship on model parameters was found, that of prior medication status on steady-state FPG and steady-state HbA_{1c}. This difference, representing the impact of prior medications on nonnaive patients, was 48 mg/dL and 2.3%. To achieve model convergence, we estimated this effect through model iterations wherein one or more model parameters were fixed.

For hemodilution, a linear function for inhibition of k_{outp} was preferable to a saturable model, and gender had a significant influence on baseline plasma volume, with women having a higher baseline plasma volume. No other covariate relationships on model parameters were observed.

As seen in Figure 3, individual predictions plotted against observed values in residual plots for the final PK/PD models showed the models to be appropriate. Simulations of CS0011-A-U203 based on the CS0011-A-U202 data generally showed the actual data to fall within the 90% prediction interval for each of the 3 response variables (Figure 4).

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Table III Rivoglitazone Hemodilution Pharmacodynamic Parameter Estimates, Standard Errors of Estimates, and Variability Estimates Before and After Inclusion of CS0011-A-U203 Data Set

	Population Mean		Intersubject Variability	
Parameter	**Estimate**	**SE[a]**	**Estimate[b]**	**SE[c]**
CS0011-A-U202 Model				
Fixed effects				
k_{outp}, 1/h	0.00293	11	26	103
PV^0, dL/mg	0.0671	5.5	7.1	32
Slope, mL/ng	0.000809	6.2	45	53
Effect of covariates on CL				
Gender on PV^0	0.00579	12	—	—
Residual variability[d]	2.9	6.3	—	—
CS0011-A-U202 + CS011-A-U203 Model				
Fixed effects				
k_{outp}, 1/h	0.00220	11	94	73
PV^0, dL/mg	0.0669	0.4	7.3	28
Slope, mL/ng	0.000786	4.6	58	47
Effect of covariates on CL				
Gender on PV^0	0.00663	7.7	—	—
Residual variability[d]	3.1	5.2	—	—

a. Coefficient of variation of the estimates (100 × SE estimate/estimate).
b. Estimates of variability expressed as appropriate percent coefficient of variation (%CV) $100\sqrt{\Omega}$.
c. Percent square root of the relative standard error of the coefficient of variation $100\sqrt{SE_{ETAestimate}}$ / ETA estimate.
d. Residual intrasubject variability.

An additional analysis was performed to look at the correlation of hemodilution with edema. In study CS-011-203, 50 participants developed edema. As shown by the histograms of percent change in hemoglobin concentrations in Figure 5, patients with edema had, on average, a greater drop in their hemoglobin concentrations. A logistic relationship (Figure 5) fit this relationship well:

$$\text{logit(probability of edema)} = -2.47 - 0.117 * (\%\ \Delta \text{ baseline of Hb}). \quad (5)$$

Finally, the performance of adiponectin as a biomarker for PPARγ activity was confirmed by its correlation with the respective changes from baseline of each response variable (Supplemental Figure 5).

DISCUSSION

The broader objectives achieved by this pharmacometric analysis for rivoglitazone included (1) establishing a quantitative understanding of key dose-exposure-biomarker-endpoint relationships (both safety and efficacy), (2) understanding the impact of intrinsic and extrinsic factors on the pharmacokinetics and exposure-response relationships to determine whether there was a need for dose adjustment in special populations, and (3) having a fuller understanding of the impacts of trial design (eg, length of washout period for participants on prior antidiabetic medications, inclusion/exclusion criteria, participant baseline characteristics, and discontinuation criteria), for both better explanation of results within the rivoglitazone trial sequence as well as to enable a more direct comparison to historical trials with different designs and/or participant characteristics.

For the pharmacokinetics of rivoglitazone, a 2-compartment model with log residual error and a lag time for absorption was found to be the best structural PK model. Clearance was found to be affected by gender, serum creatinine, weight, and patient status, with lower clearance (and higher exposure) for women, diabetic patients, and those with higher serum creatinine and/or lower weight. As rivoglitazone has very low renal clearance, the relationship with serum creatinine may reflect changes in protein concentrations and subsequent changes in free (unbound) rivoglitazone. Correlated reductions in renal and hepatic clearance have been seen in patients with lower renal function.[13] This relationship will need to be clarified further in future studies because fraction bound/unbound was not assessed during the 2 phase II studies comprising this analysis.

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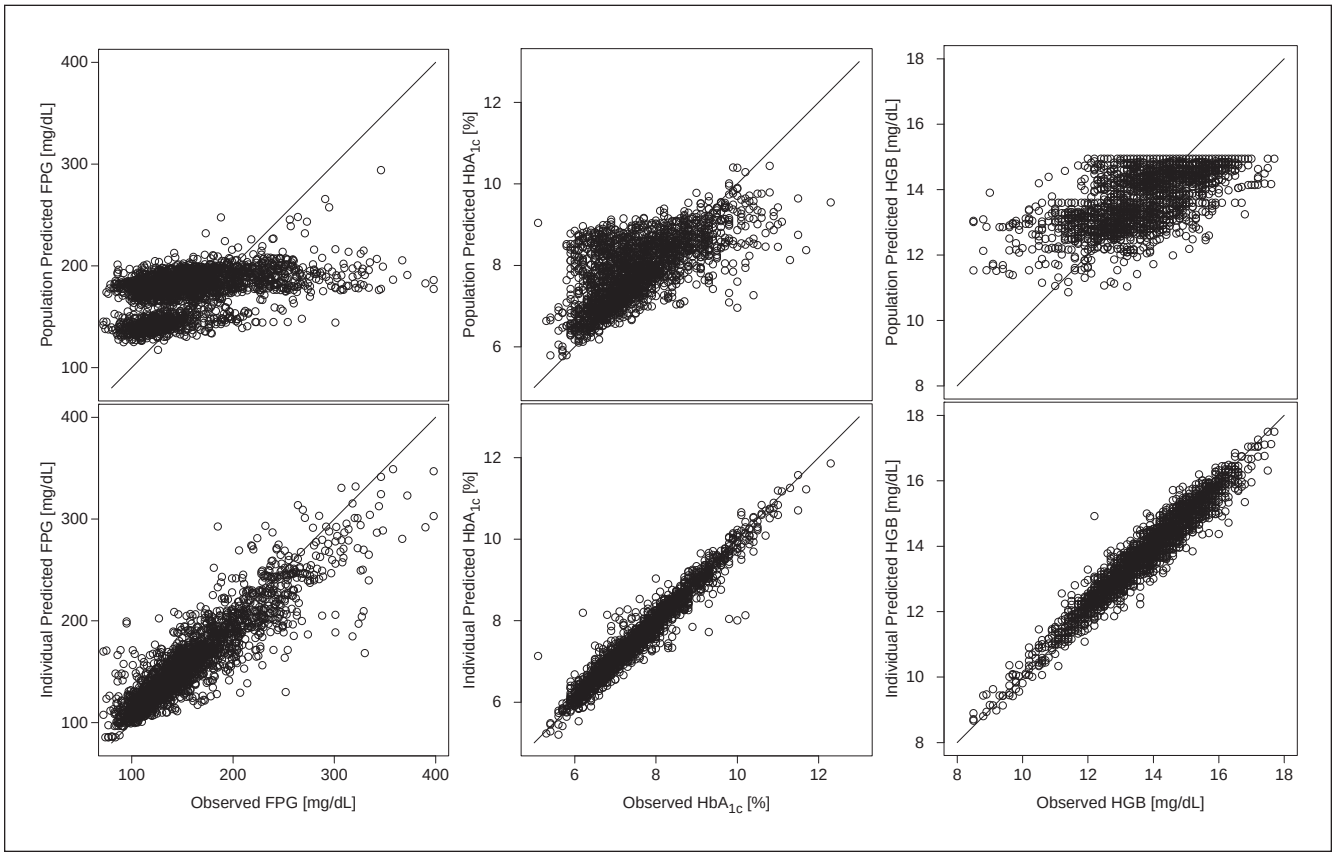

Figure 3. Goodness-of-fit plots for the final exposure-response models based on CS0011-A-U202 and CS0011-A-U203. FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; and HGB, hemoglobin.

The mixed-effects indirect-response model of FPG and HbA_{1c} fit the data adequately for both studies, with excellent fits at the individual level. For nonnaive patients, the removal of their prior medications was evident in the model parameters of FPG_{ss} and $HbA_{1c,ss}$ as their glucose concentrations returned to their nonmedicated equilibrium. Rivoglitazone counteracted this rebound, especially at higher doses. This impact of prior medications identified in the model is roughly in line with the effects of metformin and sulfonylureas on FPG and HbA_{1c}. The exact impact would have been easier to quantify more precisely had there not have been such frequent discontinuations in the study, especially in the placebo arm.

A drawback of this model is that the population predictions showed a bias when plotted against the observed data. Fortunately, the individual predictions were generally able to achieve a much closer fit. However, this was accomplished by an unusually large degree of interindividual variability in model parameters. Here again, the frequent dropouts in the placebo and lower dose arms made parameter estimation difficult, as many patients did not remain in the study long enough to achieve a new equilibrium for FPG, much less HbA_{1c}. Data from future studies may be needed to further evaluate the stability of exposure-response parameters as well as the potential effects of covariates.

The indirect-response model of changes in hemoglobin concentrations fit the data quite well for both studies, with a clear PK/PD relationship identified. In addition, the CS011-A-U202 model predicted the CS011-A-U203 results well. As women have lower baseline hemoglobin levels, the model accounts for this difference. Changes in hemoglobin were also shown to correlate with the incidence of edema.

The exposure-response data set from CS0011-A-U202 and CS0011-A-U203, plus corresponding fasting serum insulin (FSI) values from the sample points, was used to extend a disease progression model of pioglitazone[14] to rivoglitazone. (Details on the

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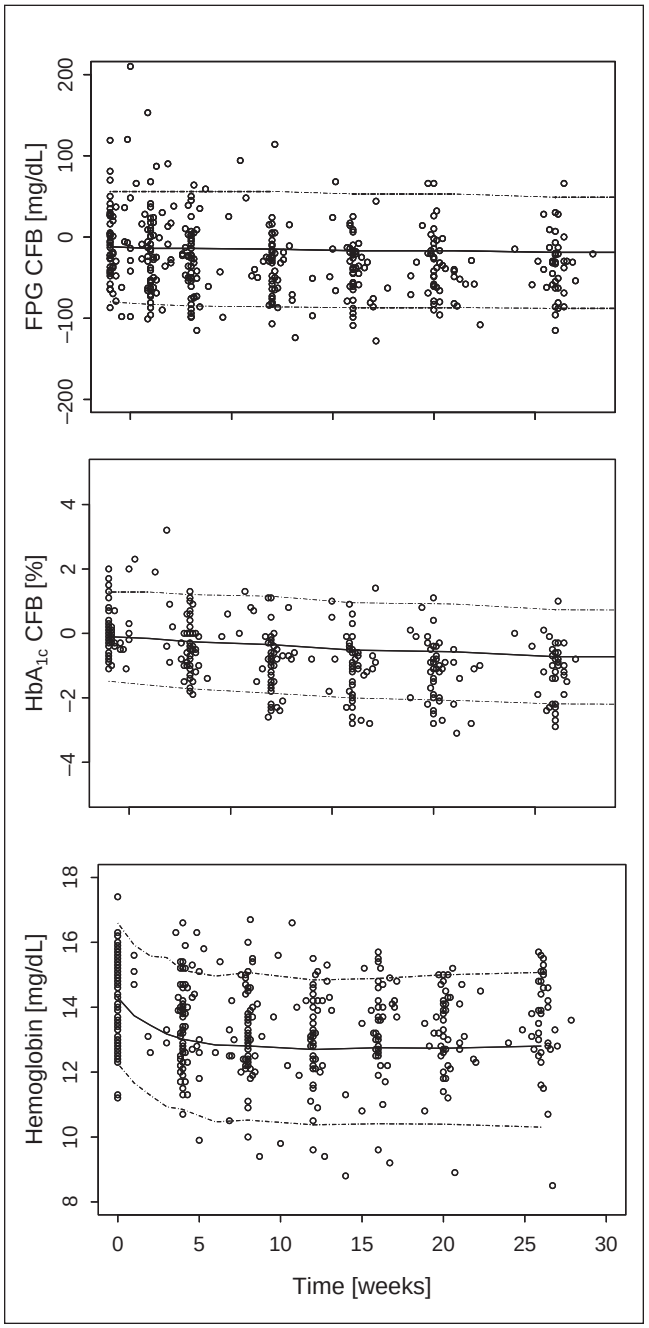

Figure 4. Results from study CS0011-A-U203 were well predicted by prior exposure-response models. CFB, change from baseline; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}.

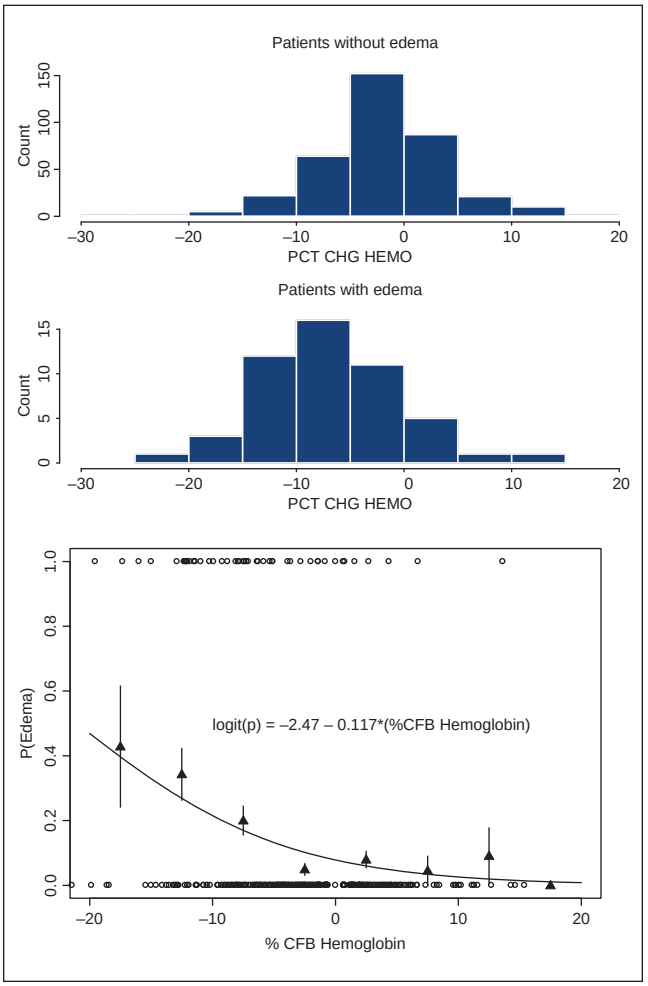

Figure 5. Edema was shown to be related to hemodilution in both the graphical analysis (top) and subsequent logistic regression model (bottom). CFB, change from baseline.

modeling steps are included as an online appendix.) Figure A1 in the online appendix shows that the model was successfully adapted from its previous dose-response form to an exposure-response form for rivoglitazone. As the literature model used studies up to 2 years in length versus the 6 months of data in CS0011-A-U203, some model parameters in the rivoglitazone analysis were fixed to the literature values. The disease progression model separated the short- and long-term effects of oral antidiabetic therapy on beta-cell function and insulin sensitivity, enabling simulations (Figure A2) of the predicted long-term effectiveness of rivoglitazone and distinguishing it from older therapies such as metformin and the sulfonylureas.

The results of these modeling analyses were communicated regularly at all phases of the program, thus enabling the continuous improvements of the models and testing of a variety of "what-if" scenarios for study populations and study designs. Pharmacometric knowledge informed phase III design decisions for

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selection of doses, timing of samples, inclusion/exclusion criteria, length of washout, and definition of discontinuation criteria. Future development of similar compounds can use models such as these to enable seamless phase II designs, with the promise of faster, cheaper, and more informative trials.

CONCLUSIONS

An iterative learn-and-confirm, model-based process for development of a "best-in-class" compound was successfully implemented during the development of rivoglitazone to support development decision making. Successful use of adiponectin as a biomarker for phase IIa dose selection was verified by the subsequent activity of the drug in the selected dose range and by the correlation of changes in adiponectin with changes in clinical response variables. Models of rivoglitazone population PK/PD based on the phase I and initial phase IIa studies were able to make valid predictions for the second, longer term phase IIb study. In an example of sharing and adopting common disease progression models, the exposure-response model developed for rivoglitazone was successfully linked to a published disease progression model for a similar compound, enabling predictions of long-term clinical response and differentiation from other classes of oral antidiabetic compounds. The rivoglitazone modeling experience provides an example of both the challenges and promise of model-based drug development.

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