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

Shashank Rohatagi, PhD, Timothy J. Carrothers, ScD, JinYan Jin, PhD, William J. Jusko, PhD, Tatiana Khariton, PhD, Joseph Walker, PharmD, Kenneth Truitt, MD, and Daniel E. Salazar, PhD

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

From Daiichi Sankyo Pharma Development, Edison, New Jersey (Dr Rohatagi, Dr Walker, Dr Truitt, Dr Salazar); Pharsight Corporation, Mountain View, California (Dr Carrothers, Dr Khariton); and Department of Pharmaceutical Sciences, SUNY/Buffalo, Buffalo, New York (Dr Jin, Dr Jusko). Supplemental figures and the appendix are available online at http://jcp.sagepub.com/supplemental/. Submitted for publication March 28, 2008; revised version accepted July 6, 2008. Address for correspondence: Shashank Rohatagi, PhD, MBA, Fellow FCP, Daiichi Sankyo Pharma Development, 399 Thornall St, Edison, NJ 08837; e-mail: Srohatagi@dsus.com.
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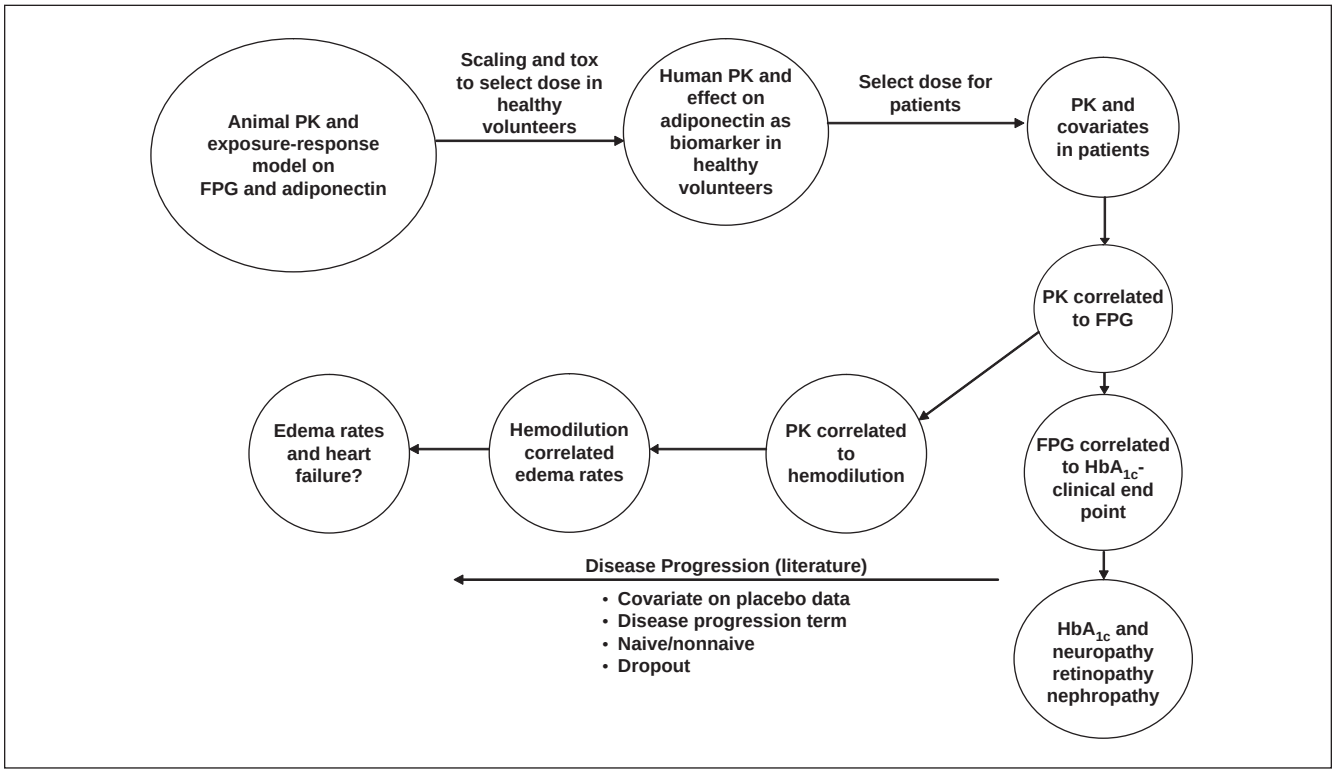

Figure 1. Overview of rivoglitazone model-based drug development. PK, pharmacokinetic; FPB, fasting plasma glucose; Tox, toxicology.

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.

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]:

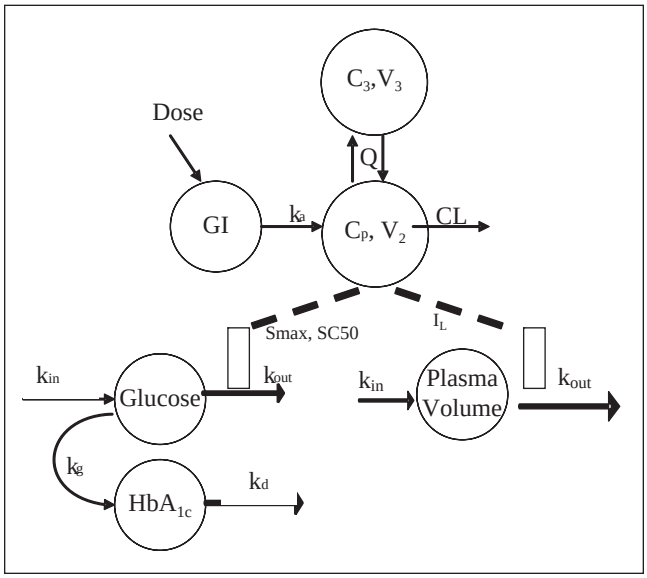

Figure 2. Depiction of FPG-HbA$_{1c}$ and hemodilution exposure-response models. FPG, fasting plasma glucose; GI, gastrointestinal tract.

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

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

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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