Original Research

Limited Sampling Strategy for Accurate Prediction of Pharmacokinetics of Saroglitazar: A 3-Point Linear Regression Model Development and Successful Prediction of Human Exposure

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ABSTRACT

Purpose: Our aim was to develop and validate the extrapolative performance of a regression model using a limited sampling strategy for accurate estimation of the area under the plasma concentration versus time curve for saroglitazar.

Methods: Healthy subject pharmacokinetic data from a well-powered food-effect study (fasted vs fed treatments; n = 50) was used in this work. The first 25 subjects' serial plasma concentration data up to 72 hours and corresponding AUC_{0-t} (ie, 72 hours) from the fasting group comprised a training dataset to develop the limited sampling model. The internal datasets for prediction included the remaining 25 subjects from the fasting group and all 50 subjects from the fed condition of the same study. The external datasets included pharmacokinetic data for saroglitazar from previous single-dose clinical studies. Limited sampling models were composed of 1-, 2-, and 3-concentration–time points' correlation with AUC_{0-t} of saroglitazar. Only models with regression coefficients (R^2) >0.90 were screened for further evaluation. The best R^2 model was validated for its utility based on mean prediction error, mean absolute prediction error, and root mean square error. Both correlations between predicted and observed AUC_{0-t} of saroglitazar and verification of precision and bias using Bland–Altman plot were carried out.

Findings: None of the evaluated 1- and 2-concentration–time points models achieved $R^2 > 0.90$. Among the various 3-concentration–time points models, only 4 equations passed the predefined criterion of $R^2 > 0.90$. Limited sampling models with time points 0.5, 2, and 8 hours ($R^2 = 0.9323$) and 0.75, 2, and 8 hours ($R^2 = 0.9375$) were validated. Mean prediction error, mean absolute prediction error, and root mean square error were <30% (predefined criterion) and correlation (r) was at least 0.7950 for the consolidated internal and external datasets of 102 healthy subjects for the AUC_{0-t} prediction of saroglitazar. The same models, when applied to the AUC_{0-t} prediction of saroglitazar sulfoxide, showed mean prediction error, mean absolute prediction error, and root mean square error <30% and correlation (r) was at least 0.9339 in the same pool of healthy subjects.

Implications: A 3-concentration–time points limited sampling model predicts the exposure of saroglitazar (ie, AUC_{0-t}) within predefined acceptable bias and imprecision limit. Same model was also used to predict $AUC_{0-\infty}$. The same limited sampling model was found to predict the exposure of saroglitazar sulfoxide within predefined criteria. This model can find utility during late-phase clinical development of saroglitazar in the patient population. (*Clin Ther.* 2018;▮:▮▮▮–▮▮▮)

Key words: bias, BlandAltman, limited sampling, precision, regression, saroglitazar.

INTRODUCTION

Saroglitazar, a dual peroxisome proliferator–activating receptor (PPAR) agonist, has predominantly greater α-receptor activity than γ activity.

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Saroglitazar* has received market approval in India and has been prescribed for treatment in type 2 diabetic mellitus patients for indications such as diabetic dyslipidemia and hypertriglyceridemia.[1–4] The pharmacologic and pharmacodynamic effects of saroglitazar have been studied comprehensively in various animal models comprising genetic and transgenic disease models to characterize the drug-related effects for reduction of triglyceride, glucose, free fatty acids, and serum insulin.[5] The clinical translatability of triglyceride reduction was confirmed in short-term clinical trials of saroglitazar in diabetic–dyslipidemic patients and HIV patients associated with lipodystrophy, where statistically significant reduction of triglyceride was noted.[6–9]

The clinical pharmacokinetic profile of saroglitazar was evaluated in a single ascending-dose (0.125 mg to 128 mg) study in healthy subjects.[10] Saroglitazar was rapidly and consistently absorbed across all of the studied single doses, with T_{max} generally between 0.5 to 1 hours, and T_{max} was found to be independent of dose.[10] The exposure of saroglitazar as measured by C_{max} and AUC over the studied single-dose range was found to be dose-related in this study. Mean $t_{1/2}$ of saroglitazar was approximately 5.6 hours.

Presently, saroglitazar is undergoing global clinical development for various indications to combat ailments such as hypertriglyceridemia, nonalcoholic steatohepatitis, and high triglyceride.[11,12] We were interested in developing a limited sampling strategy to accurately predict the exposure of saroglitazar to minimize blood-sample withdrawal in patient populations during late-phase clinical development. Globally, limited sampling strategy is being used increasingly as a means to accurately obtain exposure values in the various patient population,[13–20] and such exposure values enable dosing decisions or can serve in the correlation of exposure parameters and tolerability-related parameters. Such analysis may be extremely beneficial in understanding the relationship between exposure and tolerability parameters as part of the New Drug Application. Therefore, limited sampling protocols that are developed and validated with rigor may render a prospective determination of exposure values in a large late-phase clinical trial, and would provide a basis for correlation with both efficacy and tolerability parameters, including laboratory values gathered in the clinical trial.

*Trademark: Lipaglyn™ (Cadila Healthcare Ltd, Ahmedabad, Gujarat, India).

Scope

Because saroglitazar is undergoing global clinical development for various indications, we were interested in developing a limited sampling strategy for accurate prediction of the exposure of saroglitazar. Accurate prediction of the exposure would enable correlation of tolerability parameters inclusive of laboratory markers and efficacy parameters with the exposure value of saroglitazar. A strategy was put in place a priori before the initiation of the limited sampling model development.

It was the intent of the present work to develop and validate a simple but effective limited sampling model that would accurately predict the exposure of saroglitazar for consideration in future clinical studies of saroglitazar in a prospective manner. In order to select and validate the developed models, an initial screen of $R^2 > 0.90$ was used and the predicted exposure values from the chosen model were further subjected to statistical evaluation that included Bland–Altman test and assessment of root mean square error (% RMSE) to determine the closeness of the predictions relative to observed exposure values.

METHODS

The individual plasma concentration data and derived exposure data (AUC_{0-t}, ie, 72 hours) or $AUC_{0-\infty}$ of saroglitazar from a food-effect pharmacokinetic study conducted previously,[21] were used in the development and validation of the linear regression model. T_{max} values observed in this study were consistent with the previously published data on saroglitazar. Median T_{max} was approximately 1.00 hour with a range of 0.50 to 4.50 hours across the studies. The food-effect study was a randomized, 2-period, 2-way cross-over design with 2 treatments (fasting and high-fat breakfast) carried out in 54 healthy adult subjects (there were 50 evaluable subjects). There was a 1-week washout period between the 2 successive periods.

Pharmacokinetic samples were collected at 0.00, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 24.00, 36.00, 48.00, and 72.00 hours. Samples were analyzed for saroglitazar and its metabolite, saroglitazar sulfoxide,