

Population Pharmacokinetics of Rimonabant in Obesity

Jean-Marie Martinez¹, David Fabre¹ & Vanaja Kanamaluru²

Global Pharmacokinetics & Metabolism Department

1: Montpellier, France - 2: Malvern, PA, USA



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L'essentiel c'est la santé.

Science and Medical Affairs

INTRODUCTION

Rimonabant is an orally active selective antagonist for the cannabinoid CB1 receptor which has been developed in the treatment of multiple cardiometabolic risk factors in overweight/obese patients.

OBJECTIVE OF THE ANALYSIS

To develop and qualify a PopPK model for rimonabant and to investigate the influence of several covariates on the PK of rimonabant in the population enrolled in phase III (~3000 patients).

PATIENTS & METHODS

Available Data

Data were obtained from more than 3000 obese patients (BMI ≥ 30) i.e., ~84% of the patients included in the two long term Phase III Studies, RIO Europe and RIO North America. In both studies, rimonabant was given once daily as 5 or 20 mg doses for two years. In RIO North America, patients were re-randomized after 12 months and received either placebo or the active dose (5 or 20 mg) previously administered.

Only the data collected during the first year of treatment for RIO Europe and over the first 15 months for RIO North America were included in this analysis. Peak/trough samples were collected on months 6 & 12, plus one trough on month 3. Three additional trough samples were collected on months 13, 14 & 15 for RIO North America after re-randomization.

The Total Data Set was composed of **3031 patients** and **13695** quantifiable [LOQ=5 ng/mL, LC-MS/MS detection] concentration time points. Patients characteristics are given in Table 1.

PopPK Analysis

The analysis was performed using NONMEM version V coupled with PDX-Pop, running on Xeon bi-processors workstations.

Data handling: once outliers detected (and possibly excluded from the database) from a preliminary pharmacostatistical model obtained with FO estimation method, the Total Data Set was split into a Model Building (70 %) and a Validation (30 %) Data Sets by means of a random procedure which stratified on Study, Sex, Age class and BMI measured at baseline (BMI) class.

Pharmacostatistical model (PSM): one- and two-compartment models with and without lag time and different residual error models (additive, proportional, combined, and power) were evaluated. Log-normal distribution was assumed for interindividual variability (IIV). All runs were performed using the **FOCE with Interaction** method.

Covariates tested: patient's Age, Body Weight (WGT), BMI, Height (HGT), Race, CL_{CR} and Dose. The influence of WGT and BMI was studied as both time-varying and baseline (WGT₀, BMI₀) values. A ΔOFV of at least 10.83 (p<0.001) was required for significance during the stepwise inclusion. The different inclusions were verified by a backward deletion.

Model validation: the PopPK model predictive ability was performed in the Validation Data Set using different approaches (Prediction errors, Bayesian estimation, validation from parameters).

Final model: individual PK parameter estimates were calculated for the Total Data Set using the final model obtained in the Model Building Data Set.

RESULTS

Pharmacostatistical Model

Data were best fitted by a **two-compartment model** with first order absorption (measured by k_a), a central (V2/F) and peripheral (V3/F) volumes of distribution, an elimination (CL/F) and an intercompartmental (Q/F) clearances, an **exponential interindividual** error model and a **power residual** error model.

All the structural PK parameters were estimated (**no parameter fixed**) and the interindividual variability was estimated for all of them, except for Q/F and k_a (no minimization or 95% CIs on ηs or parameters included zero). Details are given in Table 3.

Covariate screening

Covariate inclusion is detailed in Table 2. CL/F was higher in Black patients. V2/F was higher in more obese and younger patients and V3/F was higher in more obese patients.

Sex, Dose, CL_{CR} (classified as normal or impaired renal function) and Study were not retained as covariates.

Δ: Difference in OFV before and after covariate inclusion.
ΔIV: Difference in individual variability (% of decrease of variance).
PSM = Pharmacostatistical model.
99.3 Kg and 46 years are the median values of WGT and AGE.

RESULTS (CONTINUED)

Final model with covariates

The PopPK parameters obtained in the Model Building Data Set before and after inclusion of the covariates are given in Table 3. Some Goodness-of-Fit plots are presented in Figure 1.

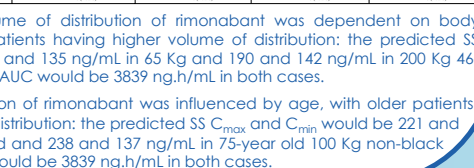
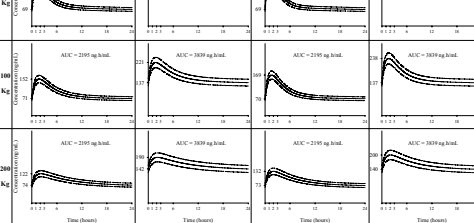
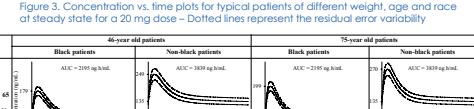
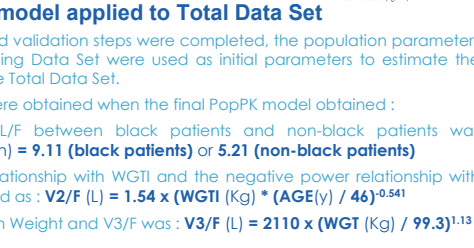
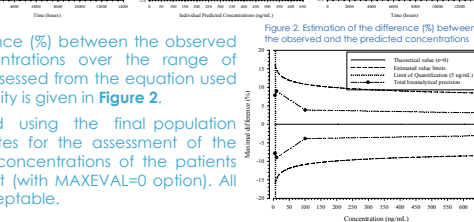
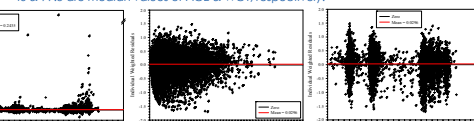
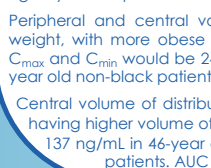
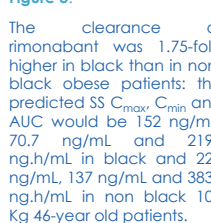
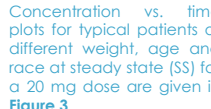
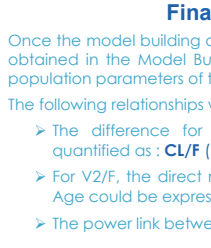
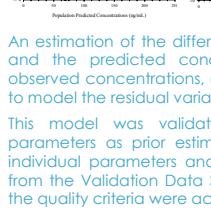
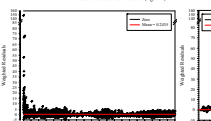
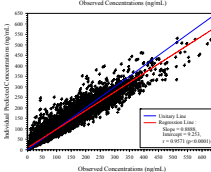
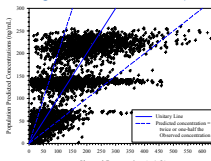
Table 3. Rimonabant structural & final PK models

Parameter	PSM Estimates (RSE %)	Final model Estimates (RSE %)
θ ₁₁ (L/h), CL/F for non-black patients	5.40 [1.61 %]	5.12 [1.49 %]
θ ₁₁ (L/h), CL/F for black patients	N/A	9.02 (4.93 %)
θ ₂₁ (L/Kg) in [V2/F = θ ₂₁ * WGT]	171 [7.78 %]	1.69 (8.58 %)
θ ₁₁ in [V2/F = θ ₂₁ * WGT * (AGE / 46) ** θ ₁₁]	N/A	-0.494 [20.4 %]
θ ₃₁ (L/h), Q/F	29.6 [13.4 %]	28.0 (13.3 %)
θ ₃₁ (L), V3/F	1950 [3.42 %]	2060 (2.97 %)
θ ₃₁ in [V3/F = θ ₃₁ * (WGT / 99.3) ** θ ₃₁]	N/A	1.17 (6.09 %)
θ ₃₁ (h ⁻¹), k ₁₂	1.17 [15.0 %]	1.17 (16.2 %)
Interindividual variability (CV%)		
CL/F	48.7 % (4.68 %)	46.0 % (4.64 %)
V2/F	63.0 % (16.5 %)	56.4 % (16.0 %)
ω-Block V2/F - V3/F (r=0.988)	0.133 [16.7 %]	0.0947 (20.3 %)
V3/F	32.2 % (16.0 %)	17.0 % (32.6 %)
Residual variability Y = C _{pred} * C _{pred} ** θ ₄₁ * ε		
σ (SE[σ])	0.197 (16.9 %)	0.199 (15.9 %)
θ ₄₁	0.869 (2.19 %)	0.868 (2.06 %)

N/A: Not Applicable

46 & 99.3 are median values of AGE & WGT, respectively.

Figure 1. Goodness of Fit plots



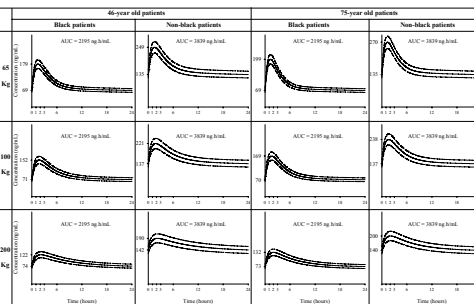
Final model applied to Total Data Set

Once the model building and validation steps were completed, the population parameters obtained in the Model Building Data Set were used as initial parameters to estimate the population parameters of the Total Data Set.

The following relationships were obtained when the final PopPK model obtained :

- The difference for CL/F between black patients and non-black patients was quantified as : **CL/F (L/h) = 9.11 (black patients) or 5.21 (non-black patients)**
- For V2/F, the direct relationship with WGT and the negative power relationship with Age could be expressed as : **V2/F (L) = 1.54 x (WGT₀ (Kg) * (AGE(y) / 46)^{-0.541}**
- The power link between Weight and V3/F was : **V3/F (L) = 2110 x (WGT (Kg) / 99.3)^{1.13}**

Concentration vs. time plots for typical patients of different weight, age and race at steady state for a 20 mg dose - Dotted lines represent the residual error variability



The clearance of rimonabant was 1.75-fold higher in black than in non-black obese patients: the predicted SS C_{max}, C_{min} and AUC would be 152 ng/mL, 70.7 ng/mL and 2195 ng.h/mL in black and 221 ng/mL, 137 ng/mL and 3839 ng.h/mL in non black 100 Kg 46-year old patients.

Peripheral and central volume of distribution of rimonabant was dependent on body weight, with more obese patients having higher volume of distribution: the predicted SS C_{max} and C_{min} would be 249 and 135 ng/mL in 65 Kg and 190 and 142 ng/mL in 200 Kg 46-year old non-black patients. AUC would be 3839 ng.h/mL in both cases.

Central volume of distribution of rimonabant was influenced by age, with older patients having higher volume of distribution: the predicted SS C_{max} and C_{min} would be 221 and 137 ng/mL in 46-year old and 238 and 137 ng/mL in 75-year old 100 Kg non-black patients. AUC would be 3839 ng.h/mL in both cases.

CONCLUSIONS

A PopPK model was developed and validated for rimonabant data obtained from more than 3000 obese patients. It showed good agreement with observed plasma concentrations and was used to assess exposure parameters (AUC_{0-24h}, C_{max} and C_{min} at steady state) for each patient.