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 AND METHODS
Data
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. In both studies, rimonabant was given once daily as 5 or 20 mg doses for two years. In the 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 [LOG5ng/mL, LC-MS/MS detection] concentration time points. Patient characteristics are given in Table 1.

PopPK Analysis
The analysis was performed using NONMEM version V coupled with P-DAPOP, 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 (BMIclass).

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, CLC1, and Dose. The influence of WGT and BMI was studied as both time-varying and fixed effects. Individual Weighted Residuals plots for typical patients of different weight, age and race of steady state (SS) for a 20 mg dose are given in Figure 3.

Results
Pharmacostatistical Model Data were best fitted by a two-compartment model with fi rst order absorption measured by k1, a central (V2/F) and peripheral (V3/F) volumes of distribution, an elimination (CL/F) and an intercompartmental (Q/F) clearance, 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 k1 (no minimization or 95%CI’s on an or parameter included). Details are given in Table 3.

Covariate screening
Covariate inclusion is detailed in Table 2. CL/F was higher in Blacks patients. V2/F was higher in more obese young patient and V3/F was higher in more obese patients.

Final model: Individual PK parameter estimates were calculated for the Total Data Set using different approaches (Prediction errors, Bayesian estimation, validation from parameters).

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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 (h-1) = 0.89 (2.06%) for 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 [WGT (Kg)] (4) (AGE/45) (0.4).
- The power link between Weight and V3/F was: V3/F (L) = 4110 x [WGT (Kg)] (0.97).3

Concentration vs. time plots for typical patients of different weight, age and race of steady state (SS) for a 20 mg dose are given in Figure 3.

Figure 3: Observation of the difference (%) between the observed and the predicted concentrations across the range of observed concentrations, assessed from the equation used to model the residual variability is given in Figure 2.

The model was validated using the final population parameters as prior estimates for the assessment of the individual parameters and concentrations of the patients from the Validation Data Set (with MAXEVAL=0 option). All the quality criteria were acceptable.

Final model applied to Total Data Set
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