

# Population PK model of RPH-104, novel optimized IL-1 beta trap, and assessment of the immunogenicity effect on pharmacokinetics

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## BACKGROUND

RPH-104 (JSC R-Pharm) is a novel heterodimeric fusion protein capable of binding to human IL-1 beta, IL-1 alpha and IL-1 receptor agonist (IL-1RA) for the treatment of autoimmune disorders associated with the overproduction of IL-1 beta cytokine (Behcet disease, FMF). The safety and pharmacokinetics of RPH-104 were assessed in series of studies on cynomolgus monkeys.

The objective of this modeling study was to describe PK data in terms of population PK model. In addition, because anti-drug antibody (ADA) production was observed in studies on monkeys, investigation of immunogenicity impact on pharmacokinetics was performed. Enhancement of elimination due to ADA response on the therapeutic was included in population PK model.

## METHODS

Population PK model of RPH-104 was developed based on PK data from 3 studies of RPH-104 in cynomolgus monkeys.

- JDS1004-00 study of pharmacokinetics: single dosing of RPH-104 of 10 mg/kg, s. c. administration; 6 monkeys; concentration-time profile during 21 days after administration.
- 8305251 study of toxicity and pharmacokinetics: single dosing of RPH-104 of 5, 50 and 200 mg/kg, s. c. or i. v. administration; 20 monkeys; concentration-time profile during 29 days after administration.
- 8305252 study of toxicity and toxicokinetics: multiple weekly dosing of RPH-104 of 5, 50 and 100 mg/kg for 4 weeks, s. c. administration; 22 monkeys; concentration-time profiles during days 1 to 7 (1<sup>st</sup> dose) and days 22 to 28 for 5 and 50 mg/kg dose groups or days 22 to 56 for 100 mg/kg dose group (4<sup>th</sup> dose).

In multiply dosing study ADA immunoassay was conducted. Samples for ADA assessment were collected at pre-dose and days 13, 20, 27, 34, 56. The characterization of ADA response was performed at screening, immunodepletion and titer bioanalytical testing.

PK data are presented in **figure 1**.

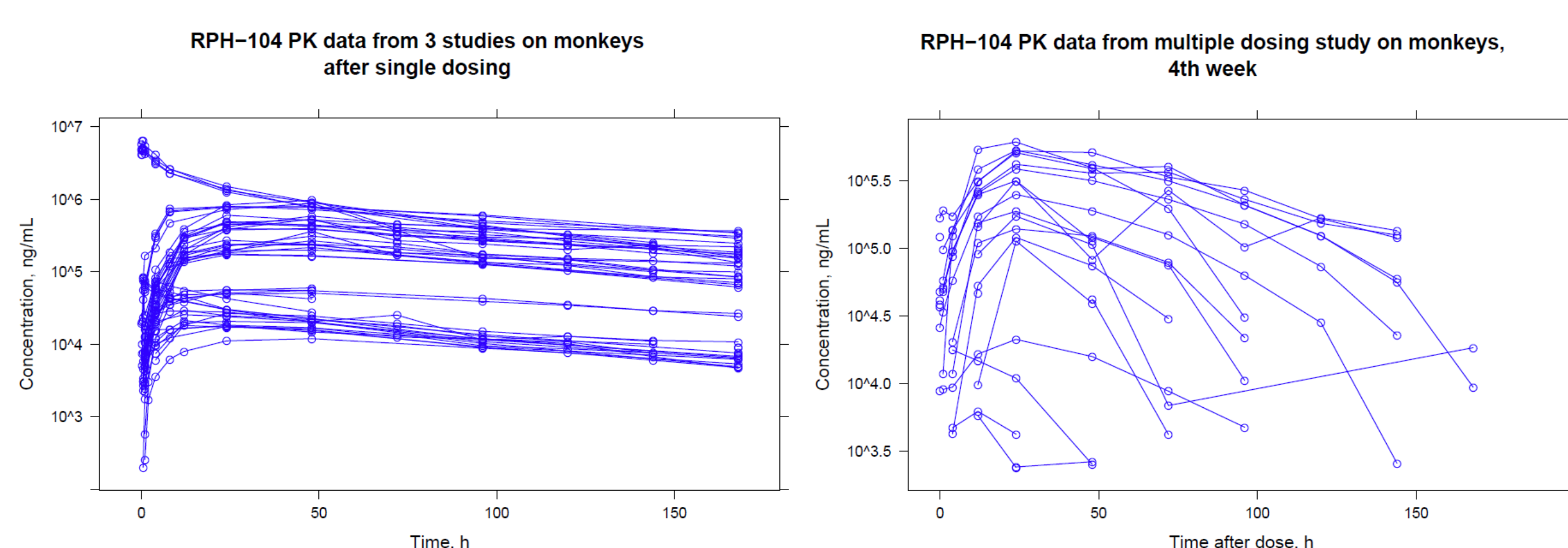


Figure 1. PK profiles for monkeys

As we can see in **figure 1** PK profiles of RPH-104 are changed for 1<sup>st</sup> dose and 4<sup>th</sup> dose and growth of drug clearance can be associated with these PK data. Therefore ADA production impact on PK parameters was supposed.

Additional probability assessment of ADA response was performed based on available data. Results of binomial test of detection ADA response are presented in **figure 2**. Whiskers mean 95% confidence interval for probability and red labels correspond to significant appearance of ADA response in comparison with placebo group ( $\alpha=0.05$ ).

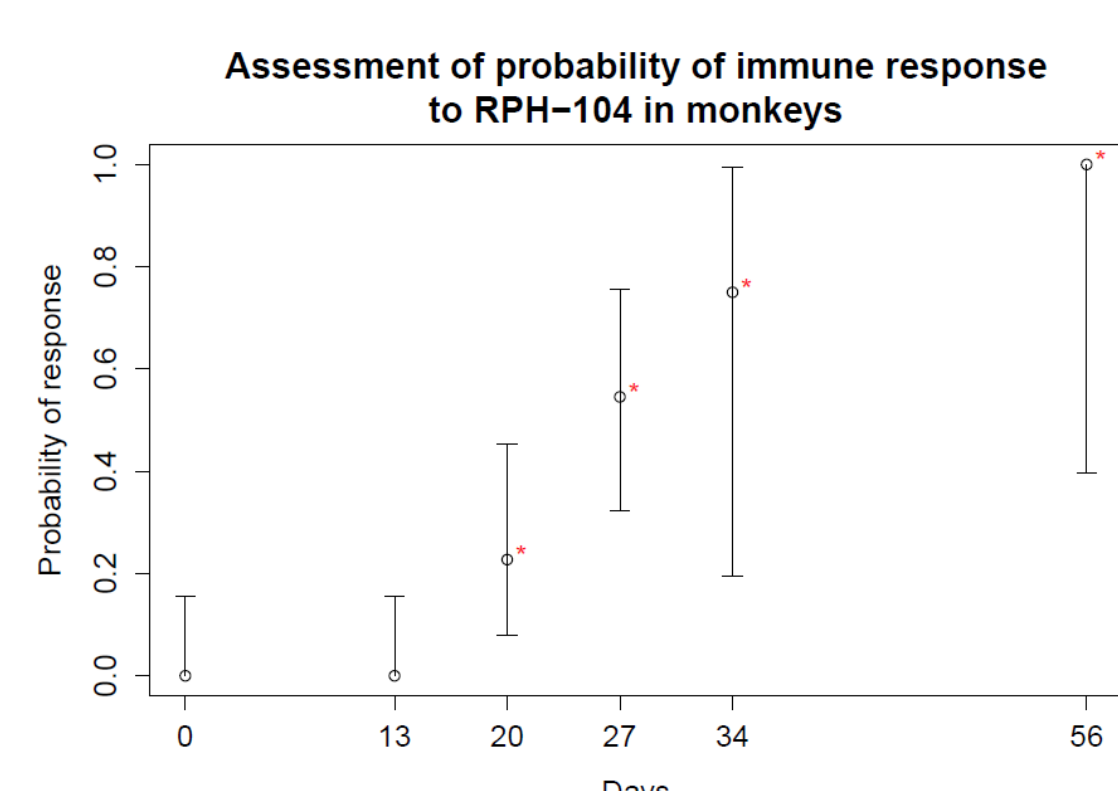


Figure 2. Probability of immune response by days

ADA response was included as categorical covariate in clearance parameter:

$CL = popCL * (1 + Response * THETA)$ , where  $CL$  and  $popCL$  are individual and population values of clearance,  $Response$  is ADA response factor and is 0 or 1.

Modeling and estimation PK parameters were performed using non-linear mixed-effects (NLME) approach implemented in NONMEM V.7.3.0. FOCE method was used to estimation.

## RESULTS

Pharmacokinetics of RPH-104 in monkeys was described by 2-compartment model with linear elimination. Parameters of this model and their estimates with 95% confidence intervals from bootstrap are shown in **table 1**. Bioavailability of RPH-104 was defined as 100% via modeling. Unexplained inter-individual variability was evaluated for parameters of central compartment volume and clearance. Individual weight values were used as covariate in parameters of volumes and clearances. Residual error combines proportional and additive components.

Table 1. PK parameters and 95% confidence interval from the optimal population model of RPH-104

| Parameter                                  | Notation          | Final model point estimates (95% CI) |
|--------------------------------------------|-------------------|--------------------------------------|
| Volume of central compartment, mL          | $V_2$             | 254 (182.15, 327.96)                 |
| Clearance, mL/h                            | $CL_2$            | 5.58 (5.016, 6.224)                  |
| Absorption rate constant, $h^{-1}$         | $K_a$             | 0.0286 (0.0209, 0.0384)              |
| Intercompartmental clearance, mL/h         | $Q$               | 9.37 (5.498, 15.204)                 |
| Volume of peripheral compartment, mL       | $V_3$             | 179 (134.30, 215.08)                 |
| Anti-drug antibodies factor                | ADA_factor        | 4.54 (1.99, 174.5)                   |
| Proportional residual error, %             | $\epsilon_{prop}$ | 40.5 (33.7, 47.6)                    |
| Additive residual error, ng/mL             | $\epsilon_{add}$  | 1540 (491, 2842)                     |
| Inter-individual variability on $V_2$ , %  | $\eta_{V2}$       | 51.1                                 |
| Inter-individual variability on $CL_2$ , % | $\eta_{CL2}$      | 25.2                                 |
| OFV = 13289.739; AIC = 13309.739           |                   |                                      |

Goodness-of-fit plots are presented in **figure 3**.

ADA factor parameter estimation is 4.54, that means an increase of clearance by 5.54 times ( $1+4.54$ ) if ADA response was detected at according time. Found value is closed to some published data [1], although built model is not sufficiently stable and it needs further development. There are established methods to describe immunogenicity in PK [2], but available studies data of RPH-104 are sparse and do not allow to apply more complex models.

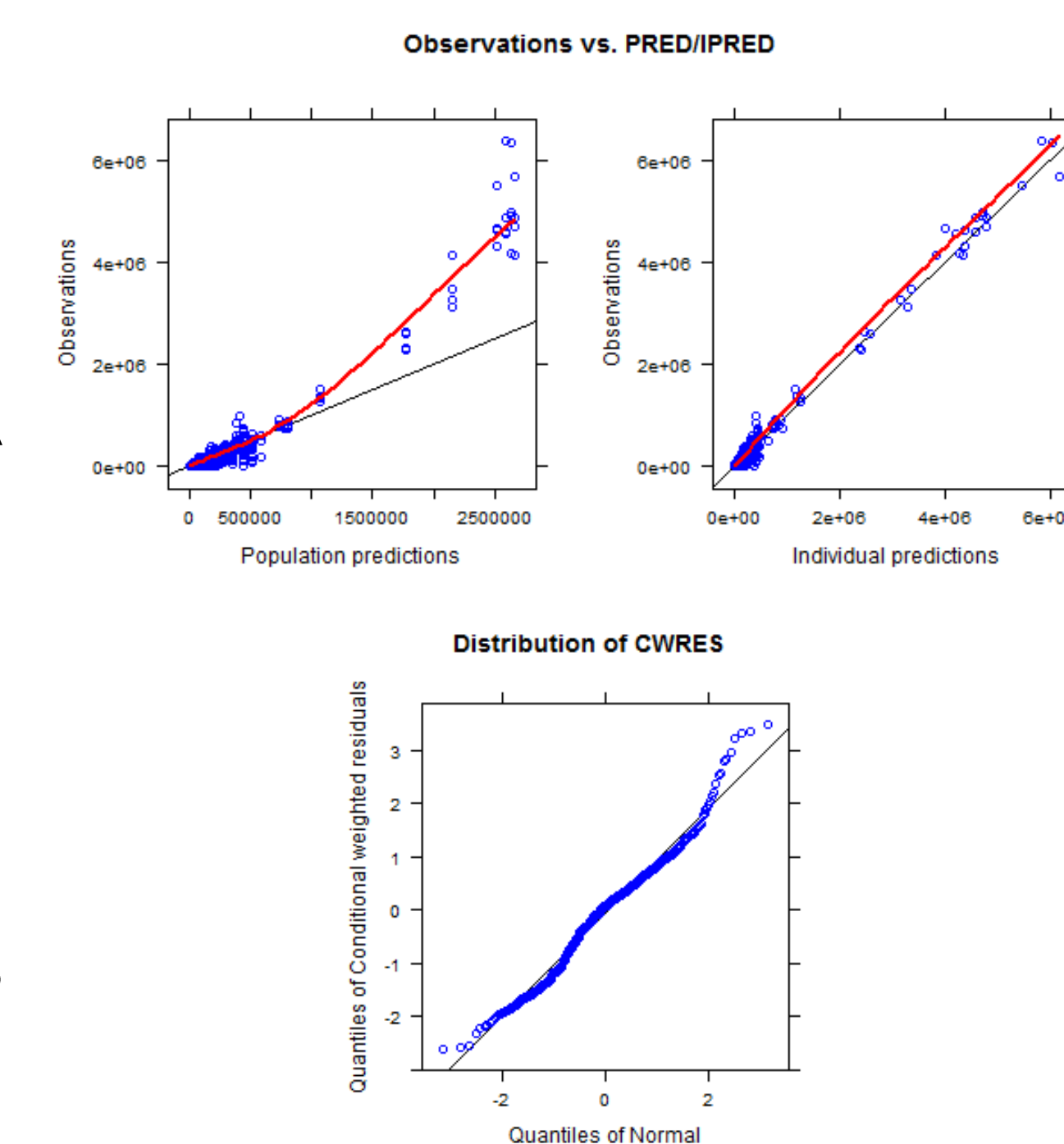


Figure 3. Goodness-of-fit plots

## CONCLUSIONS

Population PK model of RPH-104 was developed based on studies data in monkeys. Anti-drug antibody response was included in PK model. According to a simple model ADA production resulted in 5.5 fold increase of drug clearance.

## REFERENCES

- Leonid Gibiansky, Ekaterina Gibiansky, Immunogenicity in PK of monoclonal antibodies: detection and unbiased estimation of model parameters, PAGE 22 (2013) Abstr 2703
- Steven Kathman Jr., Theigi M. Thway, Lei Zhou, Stephanie Lee, et al. Utility of a Bayesian mathematical model to predict the impact of immunogenicity on pharmacokinetics of therapeutic proteins. AAPS J. 2015;18(2):424–431.

## CONTACTS

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