

Population pharmacokinetic modelling of oral ruxolitinib: a real-world prospective observational study

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Background

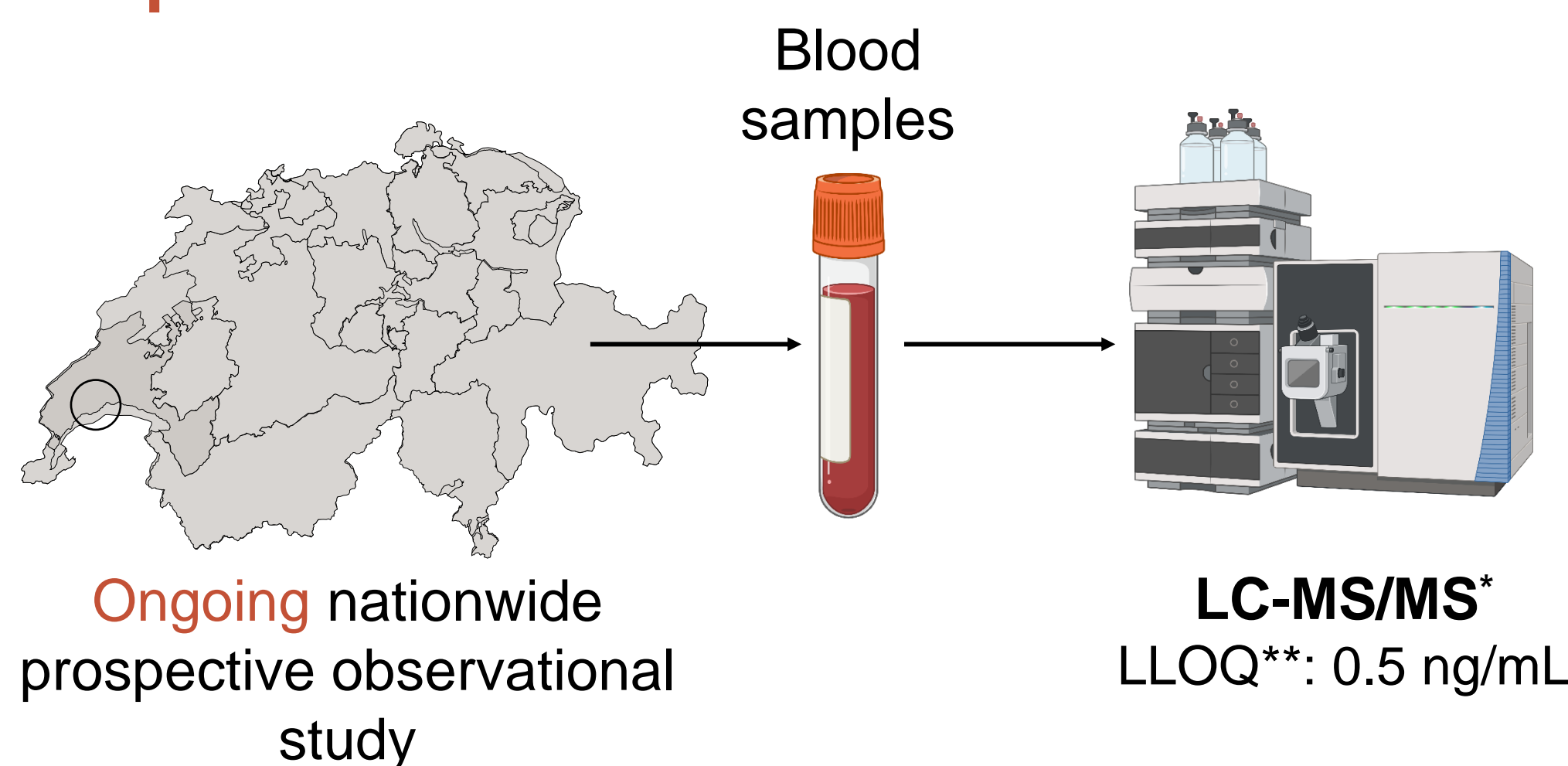
- **Ruxolitinib** is a small immunosuppressant molecule targeting JAK1 and JAK2 proteins and used orally for the treatment of myeloproliferative neoplasms (**myelofibrosis, polycythemia vera**), **graft-versus-host disease**, and in some cases of myelodysplastic syndromes.
- Dose-response relationship and exposition-dependent tolerability issues have been reported.^{1,2} Efficacy and safety, including adverse events with special interest, could be improved by determining ruxolitinib plasma concentrations for **drug exposure optimization**.
- A previous published study reported that patients with a C_{min} exceeding the threshold of **21 ng/mL** are at an increased risk of experiencing adverse events (AE) of any grade.³

Objectives

- To develop a population pharmacokinetic (popPK) model of ruxolitinib and to analyze patient-related factors influencing exposition.

Methods

Sample collection



* LC-MS/MS: liquid chromatography coupled to tandem mass spectrometry
** LLOQ: lower limit of quantification

Data analysis

Stepwise procedure

- Several compartment models with first-order absorption

Inter-individual variability assessment on all PK parameters

- Log-normal distribution

Covariates analysis

- Age, sex, bodyweight, body mass index (BMI)
- Linear and allometric scaling equations
- Statistical and clinical significance assessment

Model evaluation

- Visual predictive checks
- Bootstrap

Model-based simulations

- Monte-Carlo simulations at steady-state
- 1,000 virtual subjects
- Dosage: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg b.i.d.

Due to limited absorption phase data, the first-order absorption rate (k_a) was fixed at 4 h^{-1} based on previous work.⁴

Results

- Patients: N = 26 (♂ 60% ♀ 40%)
- Blood samples: N = 79
- Six patients included in a detailed PK study (48 samples)

PopPK model of ruxolitinib

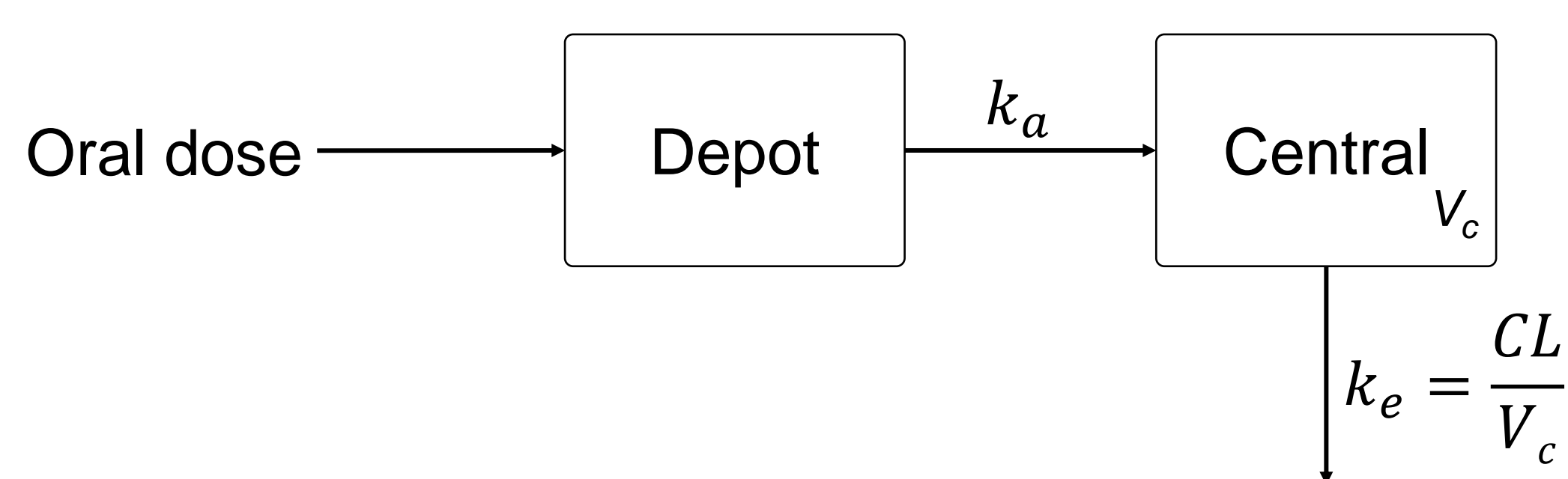


Figure 1: Schematic representation of the popPK model of ruxolitinib.

k_a : first-order absorption rate; k_e : linear elimination rate; BW: bodyweight; BW_M : median bodyweight; θ_{BW} : allometric power coefficient; V_i : typical value of V.

Allometric scaling function of body weight on V was included a priori with a fixed power of 1.

Table 1: Preliminary results. RSE: relative standard error

| Parameters | Final model | |
|---------------------------|-------------|----------|
| | Estimate | (RSE, %) |
| k_a (h^{-1}) | 4 | FIX |
| V_c (L) | 62.8 | (7) |
| CL (L/h) | 10.7 | (19) |
| ω_{CL} (%) | 49.9 | (26) |
| θ_{male} | 0.381 | (79) |

$$V_i = V_c \times \left(\frac{BW}{BW_M} \right)$$

$$CL_i = CL \times (1 + \theta_{male}) \times e^{\eta_{cl}}$$

Covariate analyses revealed an **effect of sex on CL**: males showed a 38% higher clearance than females, consistent with literature.^{3,4}

Model-based simulations

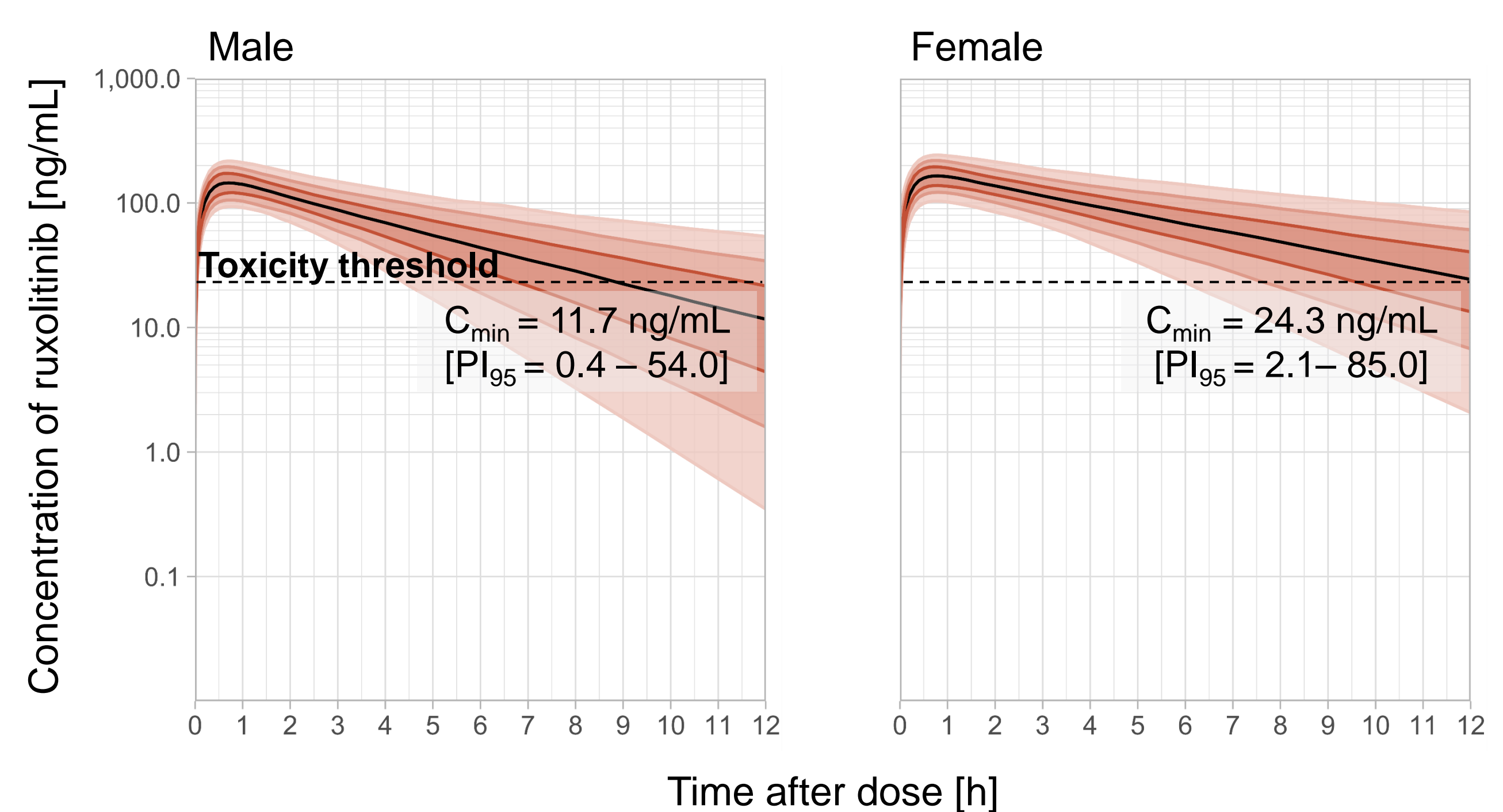


Figure 2: Individual predicted concentrations of ruxolitinib for males and females taking 10 mg twice daily. Light grey areas: 95% prediction intervals and 80% prediction intervals. Dark grey area: 50% prediction interval. Black solid line: 50% percentile (median).

Simulations showed that 57% of females and 26% of males are expected to reach trough concentration above the reported toxicity threshold of 21 ng/mL.

Conclusions

- Our findings confirm a **large inter-individual variability** among patients.
- Simulations predict an important number of subjects above the previously reported toxicity threshold: **females exhibiting higher trough concentrations** across all dosages, thus likely to increase their susceptibility to AE.
- Therapeutic drug monitoring for ruxolitinib could be clinically relevant to predict dose-dependent efficacy and safety issues.

References

¹Le RO, Wang X, Zhang H, Li H, Przepiora D, Vallejo J, et al. The Oncologist. 2022; ²Plosker GL. Drugs. 2015; ³Isberner N, Kraus S, Grigoleit GU, Aghai F, Kurlbaum M, Zimmermann S, et al., Cancer Chemother Pharmacol. 2021; ⁴Chen X, Williams WV, Sandor V, Yeleswaram S., The Journal of Clinical Pharmacology. 2013