

Optimizing ruxolitinib therapy using a population approach: insights from a real-world prospective observational study

Jérémie Tachet¹, Paul Thoueille¹, Francesco Grandoni², Monika Nagy-Hulliger³, Jörg Halter⁴, Jakob Passweg⁴, Nhu-Nam Tran-Thang⁵, Carine Bardinet¹, Laurent A. Decosterd¹, François Girardin¹, Monia Guidi^{1,6,7}

¹Service and laboratory of Clinical Pharmacology, University Hospital and University of Lausanne, Lausanne, Switzerland; ²Service and Central Laboratory of Hematology, University Hospital of Lausanne, Lausanne, Switzerland; ³Service of hematology, Hospital of Morges, Morges, Switzerland; ⁴Service of hematology, University Hospital and University of Basel, Basel, Switzerland; ⁵Service of medical oncology, Clinique La Source, Lausanne, Switzerland; ⁶Center for Research and Innovation in Clinical Pharmaceutical Sciences, Department of Education and Research, University Hospital and University of Lausanne, Lausanne, Switzerland; ⁷Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Geneva, Lausanne, Switzerland

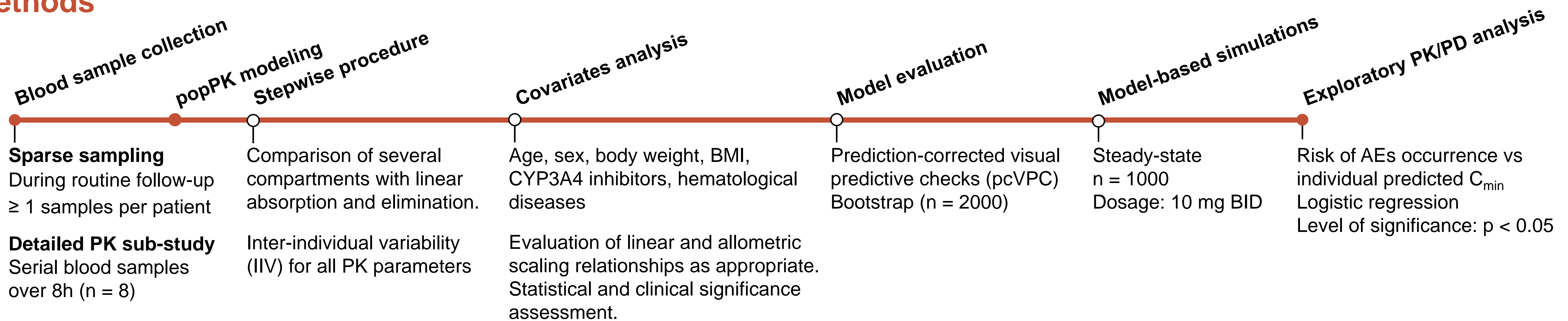
Background

- Ruxolitinib is an **orally administered small-molecule** that inhibits the isoforms Janus kinase (JAK) 1 and JAK2 for treatment of primary and secondary myelofibrosis, graft-versus-host disease (GvHD), and polycythaemia vera.
- It is **primarily metabolized by CYP3A4** and susceptible to drug-drug interactions¹.
- Ruxolitinib has **efficacy- and toxicity-exposure relationships**^{1-3,5}. Trough concentration (C_{min}) > **21 ng/mL** was associated with a higher risk of adverse events (AEs)¹.

Objectives

- To develop a population pharmacokinetic (popPK) model for ruxolitinib within a prospective observational study and to analyze patient-related factors influencing exposition, outside the clinical trial stringent settings.

Methods



Study population : adult patients (≥ 18-year-old) receiving ruxolitinib.
Population modeling and simulations were performed with NONMEM®.
The first-order absorption rate (k_a) was fixed at 3.8 h⁻¹ based on the initial model results.

Results

PopPK model

Patients: n = 50

Blood samples: n = 160

- Eleven patients included in the detailed PK sub-study (88 samples)

Table 1: Final population PK parameters estimates with bootstrap evaluations

Parameters	Final model		Bootstrap (n = 2000)	
	Estimate	(RSE, %)	Median	[CI _{95%}]
k_a [h ⁻¹]	3.8	FIX	3.8	FIX
TVV [L]	71	(6.1)	71	[63 – 78]
TVCL [L/h]	16	(5.9)	16	[14 – 17]
ω_{CL} [CV, %]	37	(16)	35	[20 – 47]
$\theta_{Potent\ CYP3A4\ inhibitor}$	-0.419	(24)	-0.418	[-0.660 to -0.174]
σ_{prop} [CV, %]	34	(8.3)	34	[29 – 41]

$$V_i = TVV \times \left(\frac{BW_i}{70}\right) \times e^{\eta_i}$$

$$CL_i = TVCL \times (1 + \theta_{Potent\ CYP3A4\ inhibitors}) \times e^{\eta_i}$$

BW_i : individual body weight, $CI_{95\%}$: 95% confidence interval, CL_i : individual value of clearance, k_a : absorption rate, RSE: relative standard error, TVCL: typical clearance in the population, TVV: typical volume of distribution in the population, V_i : individual value of the volume of distribution, η_i : individual random effect of the inter-individual variability (IIV), $\theta_{Potent\ CYP3A4\ inhibitor}$: estimated parameter for the covariate effect of potent CYP3A4 inhibitors, σ_{prop} : proportional residual error, ω_{CL} : IIV on clearance.

Covariate analysis revealed that **strong CYP3A4 inhibitors (e.g. posaconazole)** significantly reduced CL by 42% compared to patients on weak or without inhibitors, consistent with previous findings³⁻⁵.

Model-based simulations and PK/PD analysis

Model-based simulations showed that median C_{min} of ruxolitinib was >3x higher in patients receiving strong CYP3A4 inhibitors.

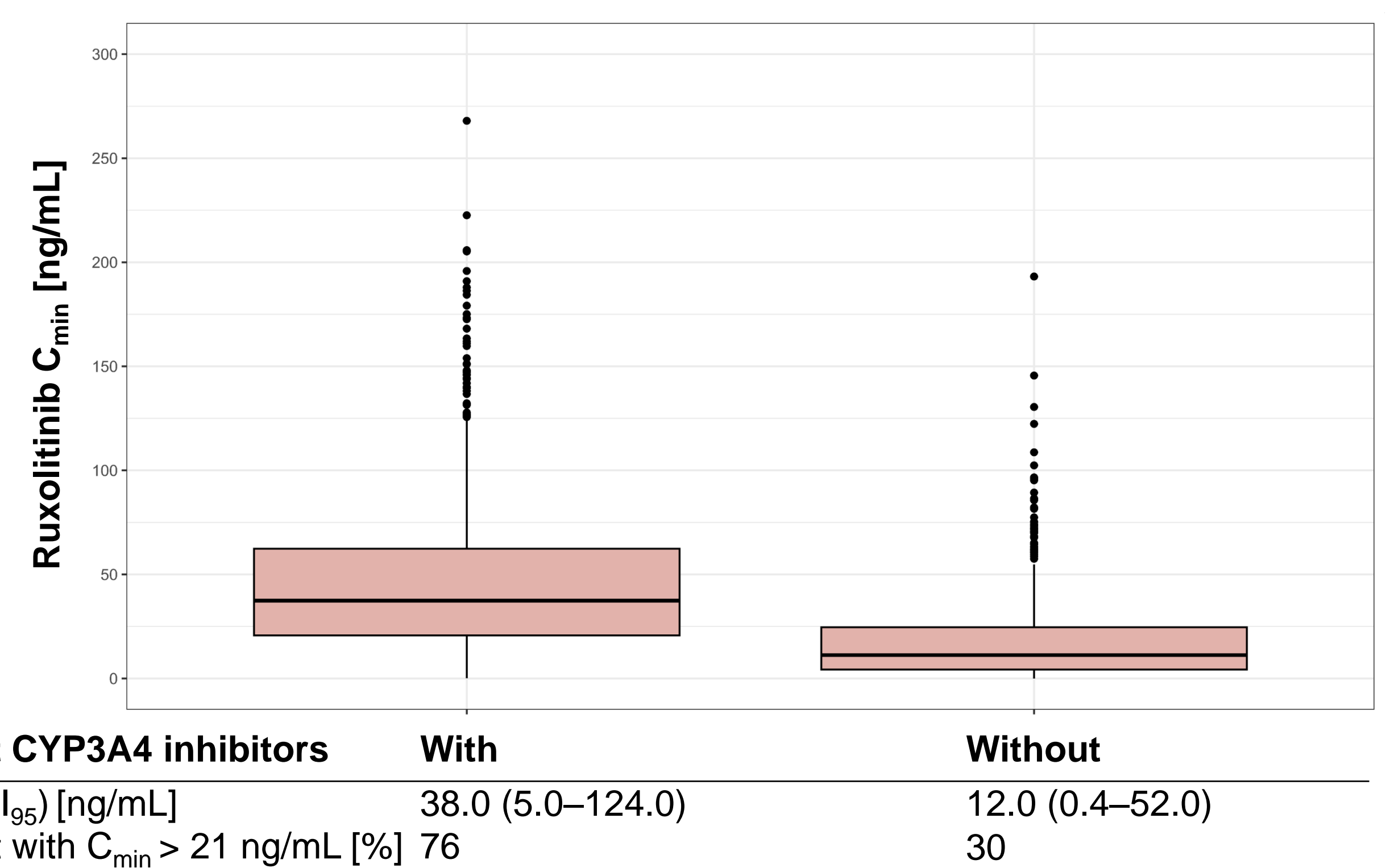


Figure 1: Simulated steady-state C_{min} of ruxolitinib (10 mg BID) with or without strong CYP3A4 inhibitors.

Exploratory PK/PD analysis: no significant association between C_{min} and the probability of experiencing at least one AE was observed ($p > 0.05$).

Conclusions

Our findings are consistent with previous clinical studies showing significant variability in ruxolitinib exposure.

CYP3A4 inhibitors, often prescribed concomitantly, significantly increased ruxolitinib C_{min} , while exploratory PK/PD analysis did not identify any relationship between C_{min} and toxicity in our population. Next step will be to define therapeutic ranges for ruxolitinib dose optimization, along with improved AEs reporting to better explore PK/PD-safety relationships.

References

¹Isberner N, Kraus S, Grigoleit GU, Aghai F, Kurlbaum M, Zimmermann S, et al. Cancer Chemother Pharmacol. 2021; ²Le RQ, Wang X, Zhang H, Li H, Przepiora D, Vallejo J, et al. The Oncologist. 2022; ³Plosker GL. Drugs. 2015; ⁴Chen X, Williams WV, Sandor V, Yeleswaram S. The Journal of Clinical Pharmacology. 2013; ⁵Incyte Corp. Jakafi. Clinical Pharmacology and Biopharmaceutics review(s). U.S. Food and Drug Administration (FDA) website.