4534

Population Pharmacokinetics of Ruxolitinib in Patients With aGVHD Who Had an Inadequate Response to Corticosteroids

Presented at the
61st ASH Annual Meeting & Exposition
Orlando, FL, USA • December 7–10, 2019

Xuejun Chen, Xiang Liu, Phillip Wang, Swamy Yeleswaram
Incyte Research Institute, Wilmington, DE

Introduction

- Ruxolitinib is a selective inhibitor of Janus kinase 1/2 and has been approved for treatment of myeloproliferative neoplasms such as myelofibrosis (MF) and polycythemia vera (PV), and steroid-refractory acute graft-versus-host disease (SR-aGVHD)[1]
- REACH-1 is a single-cohort, phase 2 study of ruxolitinib in combination with corticosteroids for the treatment of SR-aGVHD
  - A population pharmacokinetic (PK) analysis based on data from patients with MF was established and demonstrated that ruxolitinib plasma concentrations in patients with MF are adequately described by a 2-compartment model with first-order absorption[2]
- PK data from REACH-1 were combined with data from studies INCB 18424-251 and COMFORT-1 in patients with MF to generate a new modeling dataset **(Table 1)**
  - A covariate was generated to specify different patient populations (MF or SR-aGVHD)
  - The population PK model from the MF population was applied and updated by fitting to the new data to provide dose adjustment suggestions[3]

Objectives

- To characterize the PK profile of ruxolitinib in patients with SR-aGVHD
- To identify predictors of drug exposure in patients with SR-aGVHD using population PK analysis

Methods

Table 1. Studies Included in the PK Analyses

Study	Design	Population	Number of Patients	Treatment Group(s)	Dosing Duration
INCB 18424-271 (REACH-1)	Phase 2; open-label study	Patients with SR-aGVHD	71	• 5 mg BID: dose may be escalated to 10 mg BID after 3 days if hematologic parameters are stable and no treatment-related toxicity is observed • Patients may have dose reductions during the course of treatment based on safety and laboratory assessments	• BID up to 180 days • Tapering can occur after day 180 • Lasting as long as the patient is deriving benefit
INCB 18424-251	Phase 2; open-label study	Patients with PMF, PPV-MF, or PET-MF	154	• Part 1: 25 mg BID and 50 mg BID • Part 2: 10 mg BID, 25 mg BID, 25 mg QD, 50 mg QD, and 100 mg QD • Part 3: 10 mg BID, 15 mg BID, 25 mg BID, 50 mg QD, 100 mg QD, and 200 mg QD	• QD or BID up to 33 cycles • 1 cycle = 28 days
INCB 18424-351 (COMFORT-1)	Phase 3; randomized, double-blind, placebo-controlled study	Patients with PMF, PPV-MF, or PET-MF	309 (154 placebo, 155 active drug)	• Patients with baseline platelet count >200,000/μL began dosing at 20 mg BID (four 5-mg tablets BID) • Patients with baseline platelet count of 100,000–200,000/μL (inclusive) began dosing at 15 mg BID (three 5-mg tablets BID) • A standardized dosing paradigm was used to determine dose adjustments for safety and efficacy	• BID for 24 weeks

BID, twice daily; PET-MF, post-essential thrombocythemia–myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera–myelofibrosis; QD, once daily; SR-aGVHD, steroid-resistant acute graft-versus-host disease.

Bioanalytical Method

- Ruxolitinib in human plasma was analyzed by a validated liquid chromatography–tandem mass spectrometry method
- The calibration range of the method was 1–1000 nM with a 10-fold dilution factor verified, based on a sample volume of 50 μL human plasma

Population PK Analysis

- Data exploration and graphical analysis were performed with SAS version 9.4, SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC)
- Population PK was conducted with NONMEM® (Version 7.4.1, Icon Development Solutions, Ellicott City, MD) and the GFortran Compiler 4.6. NONMEM runs were executed using PDx-Pop for NONMEM (Version 5.2.1, Icon Development Solutions). Bootstraps were performed by Perl-speaks-NONMEM (version 4.7.0, Uppsala, Sweden). Diagnostic graphs and generalized additive model were performed using Xpose4 in R 3.4.0 (Uppsala, Sweden)
- The final PK model for ruxolitinib in patients with MF was applied to the data for patients with MF and SR-aGVHD to assess the validity of the existing MF model in patients with GVHD
  - If significant biases still existed, a new PK model was to be generated based on the pooled data and the forward selection and backward elimination procedures for the covariate analysis
- Final model was validated with a predictive check method

Results

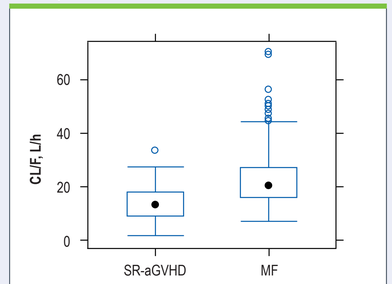
Data Description

- A total of 646 plasma ruxolitinib concentration records from 71 patients with SR-aGVHD enrolled in REACH-1 and a total of 2193 plasma ruxolitinib concentration records from 272 patients enrolled in MF studies were used for the final population PK model

Model Validation of the Existing PK Model in MF

- The existing PK model in patients with MF could be applied to pooled MF and SR-aGVHD data with re-estimation of some population parameters and addition of effect of SR-aGVHD–related covariates on PK parameters
- A slower rate of absorption and lower apparent oral clearance (CL/F) **(Figure 1)** were observed in patients with GVHD compared with patients with MF

Figure 1. Apparent Oral Clearance Versus Populations for the Base Population PK Model



CL/F, apparent oral clearance; MF, myelofibrosis; SR-aGVHD, steroid-resistant acute graft-versus-host disease.

Final PK Parameter Estimations

- In addition to the effects of body weight on apparent central volume of distribution and sex on clearance previously identified in the existing MF model **(Table 2)**, the other predictors of ruxolitinib PK in patients with SR-aGVHD included grades II–IV disease (per Mount Sinai Acute GVHD International Consortium [MAGIC] guidelines) on first-order absorption rate constant, grade IV disease (per MAGIC guidelines) on CL/F, liver involvement stage on CL/F, and moderate or potent CYP3A4 inhibitors on CL/F **(Table 3)**
- Coadministration of moderate or potent CYP3A4 inhibitors resulted in 15.4% decrease in CL/F **(Table 3)**
- Limited data demonstrated that concomitant administration of CYP3A4 inducers lacked influence on ruxolitinib PK
- Coadministration with antifungal therapy, anti-cytomegalovirus (CMV) therapy, or corticosteroids as a group shows an insignificant impact on ruxolitinib exposures

Table 2. Parameter Estimates and Standard Errors From the Ruxolitinib Final Population PK Model

	Final Parameter Estimate			Magnitude of Interindividual Variability (%CV)		
Parameter	Population Mean	%SEM	95% CI	Final Estimate	%SEM	95% CI
K_a, h^{-1}	4.06	13.3	3.08 to 5.34	115	14.2	97.2 to 131
$ALAG_1$, h	0.0753	4.25	0.068 to 0.168	NE	NE	
CL/F for male, L/h	23.5	3.45	22.0 to 25.2	43.1*	9.68	38.5 to 47.0
CL/F for female, L/h	18.4	3.60	17.2 to 19.7			
$V_c/F^{\dagger}$ for patients with body weight of 72.9 kg, L	59.3	2.63	55.7 to 62.4	26.2	17.7	20.9 to 31.2
V_p/F, L	12.1	13.2	9.25 to 17.0	88.2	44.5	50.0 to 131
Q/F, L/h	2.02	15.4	1.57 to 2.91	NE	NE	

*Cov (IIV CL/F, IIV V_c/F) = 0.0864; r = 0.764.

† $V_{c_j}/F_j = 59.4 \times \left(\frac{WTKG_j}{72.9}\right)$, where j represents the jth subject.

$ALAG_1$, absorption lag time; CI, estimated 95% confidence interval by bootstrap; CL/F, apparent oral clearance; Cov, covariance; %CV, percent coefficient of variation; IIV, interindividual variability; K_a, first-order absorption rate constant; NE, not estimated; Q/F, apparent intercompartmental clearance; r, correlation coefficient; %SEM, percent standard error of the mean; V_c/F, apparent volume of distribution for the central compartment; V_p/F, apparent volume of distribution for the tissue (peripheral) compartment; WTKG, weight in kilograms.

Table 3. Covariate Analysis Result for the Final Model

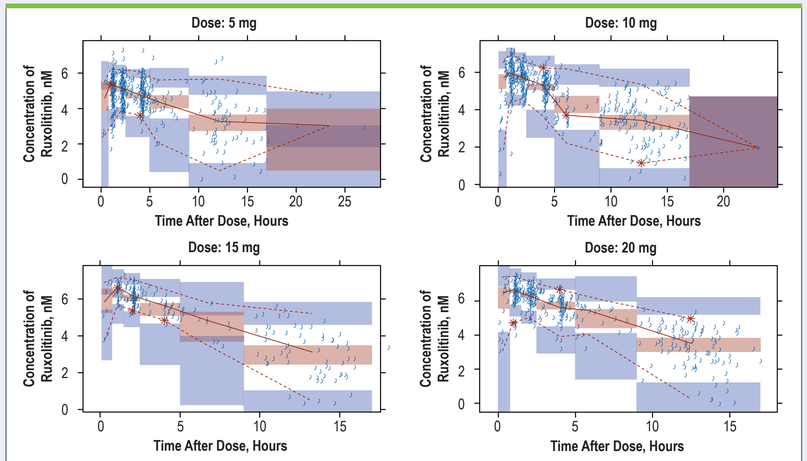
	Final Parameter Estimate		
Parameter	Population Mean	%SEM	95% CI
aGVHD on CL/F	−0.333	16.7	−0.43 to −0.23
Moderate and potent CYP3A4 inhibitor on CL/F	−0.154	41.3	−0.26 to −0.023
GVHD grade per MAGIC guidance (≤I vs >I) on K_a	−0.718	8.09	−0.81 to −0.53
GVHD grade per MAGIC guidance (<IV vs IV) on CL/F	−0.272	34.4	−0.45 to −0.06
Liver involvement stages 1–3 on CL/F	−0.326	30.6	−0.51 to −0.09
Liver involvement stage 4 on CL/F	−0.815	3.99	−0.86 to 0.91*
RV	0.193	8.08	0.163 to 0.226

*The 95% CI by the model is −0.879 to −0.751.
aGVHD, acute graft-versus-host disease; CI, confidence interval; CL/F, apparent oral clearance; K_a, first-order absorption rate constant; MAGIC, Mount Sinai Acute GVHD International Consortium; RV, residual variability; %SEM, percent standard error of the mean.

Model Evaluation

- Visual predictive check (VPC) was performed to further evaluate the accuracy and predictive performance
- A total of 1000 replicate simulations were performed and the 50th (estimated population median), 5th, and 95th percentiles of the generated concentrations plotted against time were compared with observed concentrations
- VPC results showed that most of the observed data points were overlaid between the 5th and 95th percentiles of the simulated data **(Figure 2)**

Figure 2. Quantiles of Simulated Data From the Visual Predictive Check of the Final Population PK Model Overlaid on the Dose-Normalized Observed Ruxolitinib Concentration Data, by Study and Dose



Solid line: median value of predicted concentrations; dotted lines: 5th and 95th of the predicted concentrations; curves: observed concentration values; red shaded area: observed median value with 90% confidence interval; blue shaded area: observed 5th and 95th value with 90% confidence interval.

Discussion and Conclusion

- **Overall, the population PK analysis supports the proposed dose regimen in patients with GVHD**
  - **No dose adjustment needed when coadministered with CYP2C9 inhibitors or dual CYP3A4 and CYP2C9 inhibitors (eg, fluconazole) in patients with aGVHD**
  - **No dose adjustment needed when coadministered with CYP3A4 inducers (including coadministration of a corticosteroid), although this is based on limited data and caution should be exercised when CYP3A4 inducers are used**
  - **No dose adjustment needed when coadministered with antifungal therapy, anti-CMV therapy, or corticosteroids unless the concomitant medication is ketoconazole, where a 5-mg once-daily (QD) starting dose should be considered**
  - **No dose adjustment needed for patients with mild renal impairment; 5 mg QD for moderate or severe renal impairment patients; 5-mg single dose after dialysis session for patients with end-stage renal disease**
  - **No dose adjustment needed for patients with any hepatic impairment; for patients with SR-aGVHD with stage 3 or 4 liver involvement, a starting dose of 5 mg QD should be considered**
- **In general, the exposures of ruxolitinib 5 mg twice daily (BID) in patients with SR-aGVHD is expected to be similar to that of ruxolitinib 10 mg BID in patients with MF based on the population PK analysis. In addition, patients with SR-aGVHD tend to have low platelet counts at baseline (median 74 × 10^9/L)**
- **Therefore, a starting dose of ruxolitinib 5 mg BID in patients with SR-aGVHD is consistent with the recommended starting dose of ruxolitinib in patients with MF with baseline platelet count of 50 × 10^9/L to <100 × 10^9/L**

Disclosures

All authors: Employment and stock ownership – *Incyte Corporation*.

Acknowledgments

The authors wish to thank the patients, investigators, and site personnel who participated in this study. The authors wish to thank Jia Li for assistance with the poster development. This study was sponsored by Incyte Corporation (Wilmington, DE). Editorial, graphics, and printing support was provided by Envision Pharma Group (Philadelphia, PA), funded by Incyte Corporation.

References

1. Jakafi (ruxolitinib) [prescribing information]. Wilmington, DE: Incyte Corporation; May 2019.
2. Chen X, et al. *J Clin Pharmacol*. 2013;53:721–730.
3. US Food and Drug Administration. Guidance for industry: population pharmacokinetics. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf. Published February 1999. Accessed August 20, 2018.

Scan code to download a copy of this poster