Development of a Pharmacokinetic-Pharmacodynamic Model to Describe Blood Hepcidin Levels in Patients With Myelofibrosis and Assess Target Engagement of Zilurgisertib, an ALK2 Inhibitor

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Introduction

- Zilurgisertib is a novel and selective activin receptor-like kinase 2 (ALK2) inhibitor under clinical development for the treatment of anaemia due to myelofibrosis (MF)
- The study objective was to develop a pharmacokinetic-pharmacodynamic (PK-PD) model to describe plasma zilurgisertib and blood hepcidin concentration levels to assess zilurgisertib target engagement

Methods

Data

- Population PK-PD model development used PK and PD data from 3 clinical trials: 2 phase 1 studies (00928-101, 00928-102; healthy individuals), and 1 phase 1/2 study (00928-104; patients with MF)
- Data related to zilurgisertib at doses ranging from 10 mg to 600 mg administered once daily were studied

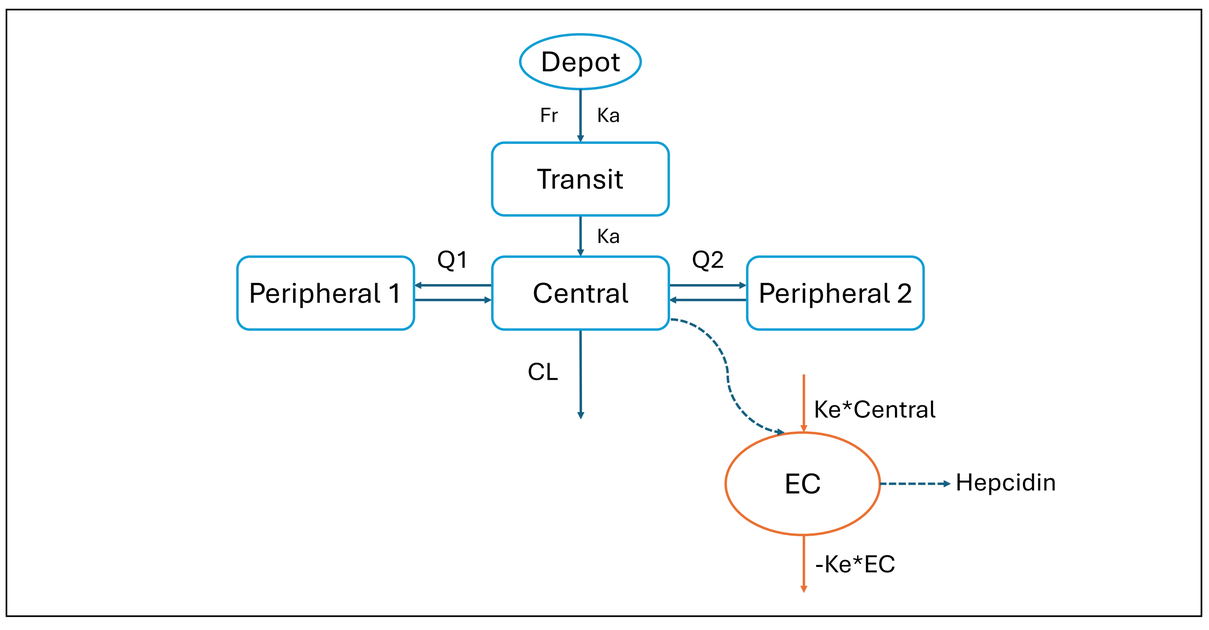
Model Development

- A population PK-PD model was developed sequentially to describe the zilurgisertib plasma concentration: blood hepcidin concentration relationship
- Non-linear mixed effect modelling was used, implemented in Pumas software (version 2.4.1; Pumas-AI, Inc., DE, USA)
- Model selection was based on the objective function value (OFV), precision and plausibility of parameter estimates and goodness-of-fit diagnostic plots

Results

- The final combined analysis dataset included 3033 PK samples from 177 study participants and 3501 hepcidin measurements from 196 study participants, including placebo cohorts
- A schematic representation of the final PK-PD model is shown in **Figure 1**
- Dose-dependent bioavailability was included in the model to capture the lack of dose proportionality following oral administration of increasing doses of zilurgisertib **(Equation 1)**
- PD response, represented by hepcidin blood concentration levels over time, was described using an empirical model that incorporated hepcidin's circadian rhythm using a cosine function **(Equation 2)**
- Zilurgisertib concentrations were linked to hepcidin concentrations by means of a power function, with an effect compartment (EC) added to capture the delay observed between zilurgisertib administration and subsequent decrease in hepcidin concentrations **(Equation 3)**

Figure 1. Schematic Representation of the Final PK-PD Model



CL, clearance; EC, effect compartment; Fr, relative bioavailability; Ka, absorption rate constant; Ke, equilibrium rate constant for effect compartment; Q1, intercompartmental clearance 1; Q2, intercompartmental clearance 2.

$$Fr = Fr0 + (1 - Fr0) \cdot (1 - e^{-k \cdot dose}) \quad \text{(Equation 1)}$$

$$Hepcidin = E_{base} \cdot \exp\left(Amplitude \cdot \cos\left(2\pi \frac{time - acrophase}{24}\right)\right) \cdot E_{drug} \quad \text{(Equation 2)}$$

$$E_{drug} = \exp(-slope \cdot EC^{power}) \quad \text{(Equation 3)}$$

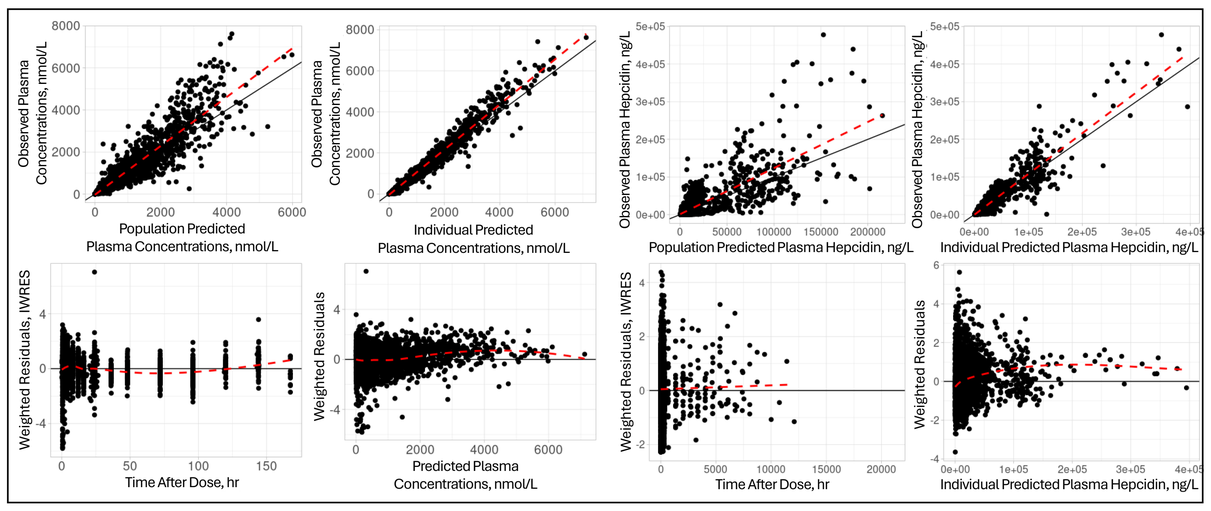
Ebase, baseline hepcidin concentration; EC, effect compartment; Fr, relative bioavailability, FR0, relative bioavailability for dose 0; k, constant governing the exponential increase in relative bioavailability per mg of dose.

Table 1. Parameter Estimates of the Final PK-PD Model

Parameter	Estimates	RSE %	IIV (CV%)/ Shrinkage, %
Clearance, L/hr	10.63	5.7	31/3
Volume of distribution central compartment, L	204.8	6.6	39/5
Absorption rate constant, 1/hr	1.678	3.7	33/15
Intercompartmental clearance 1, L/hr	16.77	9.1	
Volume of distribution peripheral compartment 1, L	104.2	7.5	19/45
Intercompartmental clearance 2, L/hr	1.196	13.5	
Volume of distribution peripheral compartment 2, L	56.68	8.3	
Constant governing the exponential increase in relative bioavailability per mg of dose	0.0056	25.3	
Relative bioavailability for dose	0.523	7.0	
Baseline hepcidin concentration in healthy individuals, ng/L	10,389	6.4	77/10
Baseline hepcidin concentration in patients with MF, ng/L	39,749	36.3	38/71
Amplitude	0.275	10.4	42/29
Acrophase, hr	7.327	8.5	62/14
Ferritin effect on Ebase	0.385	35.2	
Equilibrium rate constant for effect compartment, 1/hr	0.010	23.6	
Slope, healthy individuals	0.019	57.9	85/28
Slope, patients with MF	0.018	90.1	85/28
Power, healthy individuals	0.629	13.5	
Power, patients with MF	0.412	34.6	
Residual Variability (CV%)/Shrinkage, %			
σ_prop_zilurgisertib	16.7/8		
σ_prop_hepcidin	44/6		

σ_prop, proportional residual error; CV, coefficient of variation; Ebase, baseline hepcidin concentration; IIV, interindividual variability; MF, myelofibrosis; PK-PD, pharmacokinetic-pharmacodynamic; RSE, relative standard errors.

Figure 2. Goodness-of-Fit Plots of the Final PK-PD Model



Conclusions

- **The developed PK-PD model adequately described the relationship between plasma zilurgisertib and blood hepcidin concentration levels, in both healthy individuals and patients with MF**
- **The addition of the circadian rhythm component helped capture the natural fluctuations of hepcidin blood levels**
- **The PK-PD model was used to inform decision-making during dose-escalation studies of zilurgisertib in patients with MF**

Disclosures

Guermi, Guglieri-Lopez: Employment – *Pumas-AI*. **Wang, Lamothe, McBride, Sheng, Chen, Yang:** Employment and stock ownership – *Incyte Corporation*.

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