CT243

Presented at the
American Association for Cancer Research
Orlando, FL, USA • April 14-19, 2023

Modeling and Simulation to Inform Dose Escalation of Zilurgisertib, an ALK2 Inhibitor, in Patients With Anemia Due to Myelofibrosis

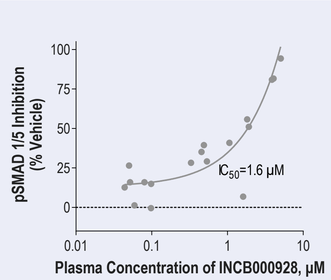
Yan-ou Yang, Hong Yang, Betty Lamothe, Matthew Stubbs, Amanda McBride, Francis Seguy, Kevin Rockich, Jay Getsy, Phillip Wang, Xiang Liu, Jeff Jackson, Ekaterine Asatiani, Xuejun Chen

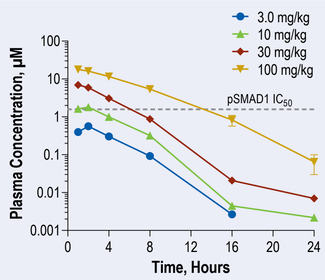
Incyte Corporation, Wilmington, DE

Introduction

- Disease-associated anemia is reported in over one-third of patients at myelofibrosis (MF) diagnosis and can be exacerbated by currently available MF therapies.[1,2] Furthermore, anemia is associated with poor prognosis in MF[2,3] and reductions in health-related quality of life[4]
- Activation of activin receptor-like kinase (ALK)-2 (also known as ACVR1) may contribute to MF-associated anemia via upregulated levels of hepcidin[2,5]
- Zilurgisertib (INCB000928) is a potent and selective ALK2 inhibitor that has demonstrated generally dose-dependent improvement in hemoglobin levels in a cancer-induced anemia mouse model. Three clinical studies in healthy volunteers, including a single ascending dose study, a multiple ascending dose study, and a CYP3A4 drug-drug interaction study, have been completed
- Zilurgisertib is being evaluated as monotherapy or in combination with ruxolitinib in a phase 1/2 dose-escalation and dose-expansion study in patients with anemia due to MF (NCT04455841), with initial data from dose escalation showing favorable safety and on-target pharmacodynamic activity[6]
- The objective of the current study is to use modeling and simulation, which integrate both preclinical and clinical data, to predict the dose needed to achieve maximum efficacy, which informs the dose-escalation decision for the ongoing phase 1/2 trial in patients with MF

Zilurgisertib Target Coverage in a Mouse Efficacy Model



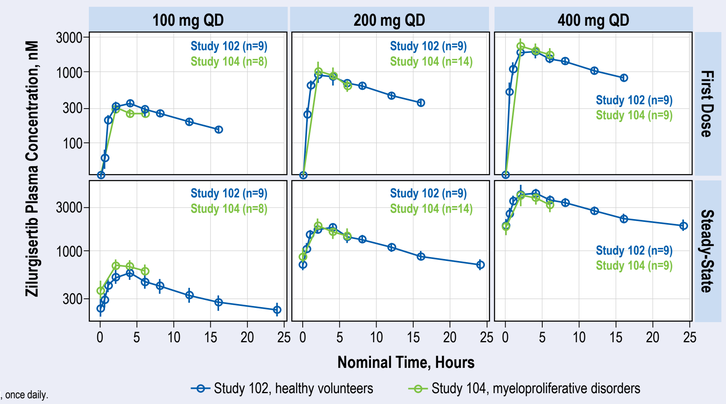


Dose	Approx. pSMAD IC_{50} Coverage, h	Hemoglobin Level Increase (vs Vehicle) in Cancer-Anemia Model, g/dL
3 mg/kg QD	0	−0.04
10 mg/kg QD	2	1.64
3 mg/kg BID	0	1.73
30 mg/kg QD	6	1.65
10 mg/kg BID	4	2.15
30 mg/kg BID/100 mg/kg QD	12	3.01

BID, twice daily; IC_{50}, half maximal inhibitory concentration; QD, once daily.

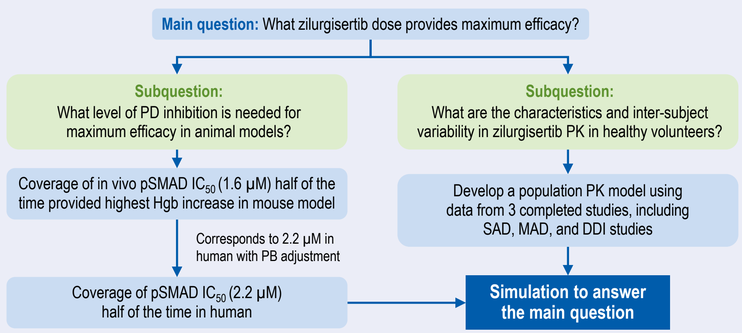
- The hemoglobin increase in a cancer-induced anemia mouse model treated with zilurgisertib was generally dose-dependent
- In a cancer-induced anemia mouse model, the maximum hemoglobin increase was observed at 100 mg/kg once daily (QD). An additional study dosing >100 mg/kg QD did not lead to higher hemoglobin increase (data not shown)
- The observed concentrations of zilurgisertib at 100 mg/kg QD are above 1.6 μM (roughly estimated in vivo pSMAD half maximal inhibitory concentration [IC_{50}] in mouse) for 12 hours out of 24 hours
- The protein binding–adjusted pSMAD IC_{50} in humans is 2.2 μM

Zilurgisertib Pharmacokinetic Profiles From 0-6 Hours Are Similar Between Healthy Individuals and Patients With MF



QD, once daily.

Simulation Strategy



DDI, drug-drug interaction; Hgb, hemoglobin; IC_{50}, half maximal inhibitory concentration; MAD, multiple ascending dose; PB, protein-binding; PD, pharmacodynamics; PK, pharmacokinetics; SAD, single ascending dose.

Population PK Model Development

POPPK Model (POPPK_22)

- Pharmacokinetic (PK) data from 00928-101, 00928-102, and 00928-103 (fasted, monotherapy) were used to develop the population PK (POPPK) model
- PK models with different distribution (1-3 compartments), clearance (linear and nonlinear), and absorption models were tested and compared, and a 3-compartment model with nonlinear clearance and inter-occasion variability on absorption rate constant (Ka) and bioavailability (F) best described PK data

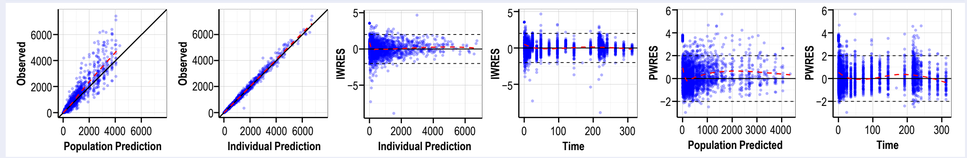
Simulation Condition

- Dose: 200-600 mg QD for 28 days
- Population: 1000, repeat once
- Steady-state on days 14-15 is shown

Major Metrics

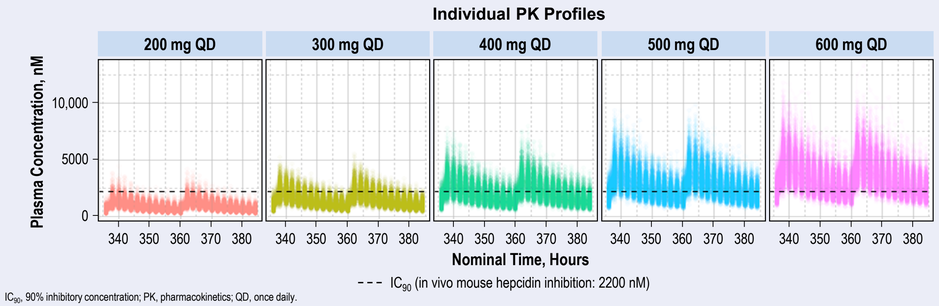
- Percentage of simulated population with PK coverage (>2200 nM) equal or more than half of the time post-treatment

Goodness-of-Fit Plots



IWRES, individual weighted residuals; PWRES, population weighted residuals.

Simulation Results



IC_{90}, 90% inhibitory concentration; PK, pharmacokinetics; QD, once daily.

Percentage of Simulated Population With PK (Concentration) Coverage Equal or More Than Half of the Time Post-treatment

Metric (>2200 nM)	200 mg QD (n=1000)	300 mg QD (n=1000)	400 mg QD (n=1000)	500 mg QD (n=1000)	600 mg QD (n=1000)
No, n (%)	989 (98.9)	832 (83.2)	539 (53.9)	259 (25.9)	98 (9.8)
Yes, n (%)	11 (1.1)	168 (16.8)	461 (46.1)	741 (74.1)	902 (90.2)

QD, once daily.

- It is predicted that desired target coverage is achieved in approximately 90% of patients at the 600-mg dose

Conclusions

- **Simulation results showed that daily doses of ≥600 mg would be needed in order for >90% of patients with MF to achieve sustained exposure similar to the observed exposure associated with maximum efficacy in the mouse model**
- **The results from this clinical trial simulation support the decision to continue dose escalation to ≥600 mg in patients with MF receiving monotherapy**

Disclosures

Y. Yang, H. Yang, Lamothe, Stubbs, McBride, Seguy, Rockich, Getsy, Wang, Liu, Jackson, Asatiani, Chen: Employment and stock ownership – *Incyte Corporation*.

Acknowledgments

The clinical studies are sponsored by Incyte Corporation (Wilmington, DE). Editorial and graphics support was provided by Envision Pharma Group (Philadelphia, PA), and funded by Incyte Corporation.

References

1. Tefferi A, et al. *Mayo Clin Proc.* 2012;87:25-33. **2.** Naymagon L, Mascarenhas J. *Hemasphere.* 2017;1:e1. **3.** Passamonti F, et al. *Blood.* 2010;115:1703-1708. **4.** Tefferi A, et al. *Clin Ther.* 2014;36:560-566. **5.** Zhou A, et al. *Br J Haematol.* 2022;197:e49-e52. **6.** Mohan SR, et al. *Blood.* 2022;140(Suppl 1):3943-3944.

Scan code to download a copy of the poster