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MODEL-INFORMED COMPARATIVE PHARMACOKINETIC AND PHARMACOLOGIC PROFILING HIGHLIGHT JAK1 SELECTIVITY OF POVORCITINIB

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Introduction

The Janus kinase/signal transducer and activator of transcription (JAK–STAT) pathway mediates signaling from cytokines and growth factors central to inflammation and immune regulation. Among the four JAK isoforms (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]), JAK1 is a key therapeutic target in inflammatory diseases [1]. However, off-target inhibitions of the first-generation JAK inhibitors, particularly JAK2 inhibition, has been associated with cytopenias due to effects on nonmalignant hematopoietic stem and progenitor cells [2].

In vivo selectivity is determined not only by in vitro potency but also by pharmacokinetics (PK). Povorcitinib is a highly selective oral JAK1 inhibitor with a long half-life and sustained systemic exposure with a low peak to trough ratio, under Phase 3 clinical development across several inflammatory conditions. This analysis uses model-informed PK/PD approaches to quantify its functional selectivity in vivo relative to other JAK inhibitors.

Objective

- Quantitatively characterize the in vivo functional selectivity of povorcitinib vs. marketed JAK inhibitors using model-informed PK approaches
- Compare steady-state exposure profiles across compounds and indications
- Evaluate JAK1/JAK2 target coverage (time above IC_{50}, daily inhibition, IC_{50}/Cmax)
- Assess the impact of half-life and peak-to-trough fluctuation on sustained vs. intermittent inhibition
- Establish a framework linking PK to functional selectivity

Methods

PopPK Simulations

Population PK (popPK) simulations were performed for povorcitinib using an internally developed model and marketed JAK inhibitors (upadacitinib [2-5], abrocitinib [6], baricitinib [7,8], tofacitinib [9-12]) using published models, across selected disease indications and healthy volunteers. For each compound–population–dose scenario, 1,000 virtual participants representing the reference population were simulated under steady-state conditions.

Functional Selectivity

Daily inhibition was calculated using a sigmoidal E_{max} model:

$$Daily\ Inhibition\ (\%) = \frac{100}{1 + \left(\frac{IC_{50}}{C_{ave}}\right)^{HILL}}$$

where HILL is the Hill parameter derived in-house.

Reference populations

Atopic dermatitis (AD) and rheumatoid arthritis (RA) were selected as reference indications to allow cross-compound comparison. Hidradenitis suppurativa (HS) is the most advanced indication under development for Povorcitinib (**Table 1**).

JAK1/JAK2 in Vitro Selectivity

Povorcitinib demonstrates high JAK1 over JAK2 selectivity (>16-fold), whereas comparator compounds exhibit lower JAK1/JAK2 selectivity, as shown below. All compounds were evaluated under the same experimental conditions utilizing in vitro whole-blood assays (**Table 2**).

Table 1. JAK inhibitors and respective doses selected for comparison

Compound	Selectivity	Dose	Indications
Povorcitinib (INCB054707)	JAK1	75 mg QD	HS
Upadacitinib (ABT-494)	JAK1	30 mg QD	AD
Abrocitinib (PF-04965842)	JAK1	200 mg QD	AD
Baricitinib (INCB028050; LY-3009104)	Nonselective	4 mg QD	AD
Tofacitinib (CP-690550)	Nonselective	10 mg BID*	RA (not evaluated in AD)

*Tofacitinib 10mg BID was explored in RA and UC patients.

Table 2. Potency and Selectivity of Povorcitinib compared to Marketed JAK inhibitors

	Povorcitinib	Upadacitinib	Abrocitinib	Baricitinib	Tofacitinib
			IL-6 (JAK1) IC_{50} (nM)		
Geo. Mean (STD)	623 (1.8)	57(1.8)	1213 (2.3)	43(2)	266(1.8)
			TPO (JAK2) IC_{50} (nM)		
Geo. Mean (STD)	> 10,000	92	> 10,000	16	250
			JAK1/JAK2 selectivity (Fold)		
Geo. Mean Ratio JAK1 selectivity	>16.1	1.6	>8.2	0.4	0.9

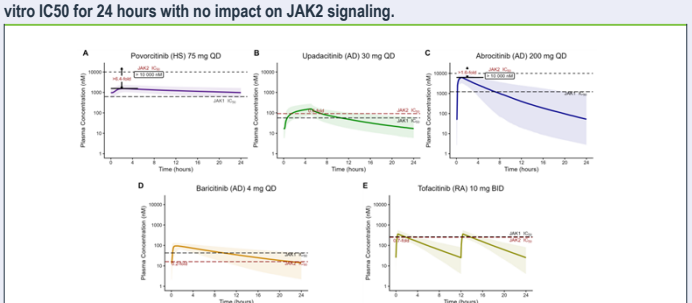
JAK1 (IL-6-mediated pSTAT3) and JAK2 (TPO-mediated pSTAT3) inhibition IC50 values.

Results

JAK1/JAK2 in vivo Selectivity

- Atopic dermatitis (AD) and rheumatoid arthritis (RA) were selected as reference indications (**Table 1**)
- Analyses were conducted at the highest approved maintenance doses to provide clinically relevant benchmarking of exposure and JAK1/JAK2 target coverage within the JAK inhibitor class.
- Simulated PK profiles and corresponding JAK1/JAK2 inhibitory outcomes are shown in **Figure 1, Figure 2** and **Table 3**.

Figure 1. Highest clinical dose of povorcitinib maintains plasma concentrations over the JAK1 in vitro IC50 for 24 hours with no impact on JAK2 signaling.



Data were simulated at clinically relevant doses using published population pharmacokinetic models and are presented for median plasma concentrations for the 5th and 95th percentiles indicated by the shaded bands. Fold changes between the relevant JAK1 or JAK2 IC50 and Cmax were calculated and presented. Cmax, maximum plasma concentration; IC50, half-maximal inhibitory concentration; pSTAT, phosphorylated signal transducer and activator of transcription; TPO, thrombopoietin.

Figure 2. Highest clinical dose of povorcitinib results in plasma concentrations above the JAK1 IC50 threshold for 23 hours and over 66% inhibition of JAK1 signaling, with no impact on JAK2 signaling

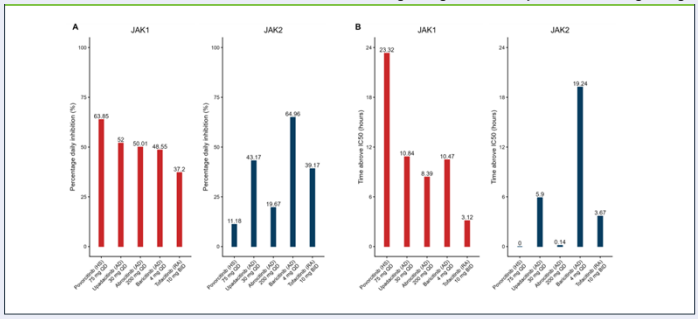


Table 3. Peak-to-Trough Ratio and Half-Life of Povorcitinib compared to JAK inhibitors

	Povorcitinib HS 75 mg QD	Upadacitinib AD 30 mg QD	Abrocitinib AD 200 mg QD	Baricitinib AD 4 mg QD	Tofacitinib RA 10 mg BID*
Peak/Trough Ratio					
Geo. Mean (Geo. CV%)	1.62 (13.3%)	8.63 (106.6%)	126 (417.5%)	8.56 (103.1%)	16.3 (131.9%)
Half-life (hr)					
Geo. Mean (Geo. CV%)	42.1 (28.0%)	4.36 (85.0%)	5.87 (18.5%)	20.8 (84.1%)	3.05 (35.0%)

*Tofacitinib 10mg BID was explored in RA and UC patients.

Discussion

- **Povorcitinib (JAK1, 75 mg QD):** ~23.3 h above JAK1 IC_{50} (97% of dosing interval) with **0 h above JAK2 IC_{50},** Maintains strong separation from JAK2 (IC_{50}/Cmax = 6.4) with **low JAK2 percentage daily inhibition (~11%)**
- **Upadacitinib (JAK1, 30 mg QD):** shorter JAK1 coverage (10.8 h) with meaningful JAK2 engagement (5.9 h; ~43% inhibition)
- **Abrocitinib (JAK1, 200 mg QD):** partial JAK1 coverage (8.4 h) with intermittent JAK2 engagement*
- **Baricitinib (nonselective, 4 mg QD) and tofacitinib (nonselective, 10 mg BID):** prolonged JAK2 engagement (19.2 h and 3.7 h, respectively)
- PK differentiation: Povorcitinib displayed **the longest half-life (~42 hours) and lowest peak-to-trough ratio (1.62)**, whereas the other JAK inhibitors showed shorter half-lives (3 – 21 hours) and substantially greater exposure fluctuation (peak-to-trough ratios 9 – 126). Additionally, povorcitinib demonstrated the most consistent and specific JAK1 inhibition, which is expected to yield sustained modulation of immunoinflammatory pathways associated with disease.

* JAK1/JAK2 coverage for abrocitinib may be underestimated due to exclusion of active metabolites

Conclusions

- **The PK/pharmacologic contextualization modeling highlights povorcitinib as a best-in-class JAK1 inhibitor considering its differentiated PK properties, as well as the high JAK1-over-JAK2 selectivity, yielding sustained and clinically relevant pathway modulation.**
- **These data support functional selectivity in vivo and illustrate how exposure dynamics and in vitro selectivity determine class differentiation among JAK inhibitors. This integrated PK profile can be used to assess therapeutic potential across immune-mediated inflammatory diseases requiring sustained selective inhibition of JAK1 pathway.**

Disclosures

KS., YW, VP, JW, and LLS are employees and shareholders of Incyte Corporation.

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