Selective Inhibition of Tyrosine Kinase 2 With Deucravacitinib Compared With Janus Kinase 1–3 Inhibitors

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Background

- Tyrosine kinase 2 (TYK2), an intracellular kinase involved in the pathogenesis of immune-mediated inflammatory diseases (IMIDs), regulates signaling and functional responses downstream of the interleukin (IL)-12, IL-23, and Type I interferon receptors[1]
- Deucravacitinib is an oral, selective, allosteric TYK2 inhibitor with a unique mode of binding to the less-well-conserved pseudokinase domain rather than to the conserved active site in the catalytic domain[1]
  - This unique mode of binding provides high functional selectivity for TYK2 vs other tyrosine kinases in cellular and other in vitro assays[1]
  - Allosteric inhibition may provide robust efficacy and a differentiated safety profile vs other kinases due to decreased toxicity
- In a 12-week, placebo-controlled, Phase 2 trial in patients with moderate to severe plaque psoriasis, the proportion of patients who achieved a 75% or greater improvement from baseline in the Psoriasis Area and Severity Index (PASI 75) at Week 12 (primary endpoint) was significantly higher with deucravacitinib 3 mg twice daily (BID; 69%), 6 mg BID (67%), and 12 mg once daily (QD; 75%) vs placebo (7%; *P*<0.001).[2] Deucravacitinib also had a favorable safety profile including no significant changes in laboratory parameters[2]
- Deucravacitinib is currently being evaluated in multiple IMIDs including plaque psoriasis, psoriatic arthritis, inflammatory bowel disease, and lupus

Objective

- To compare the selectivity of deucravacitinib vs the approved Janus kinase (JAK) inhibitors baricitinib, tofacitinib, and upadacitinib, at clinically relevant doses and plasma concentrations

Methods

- In vitro whole blood assays that measure activity of TYK2, JAK 1/3, and JAK 2/2 pathways were developed (**Table 1**)
- Half-maximal inhibition concentrations (IC_{50}) of deucravacitinib, baricitinib, tofacitinib, and upadacitinib were determined using these assays, as well as Hill coefficients for inhibition

Table 1. In vitro whole blood assays for JAK 1–3 and TYK2 inhibitors

Signaling kinase	Stimulant	Endpoint
JAK 1/3	IL-2	STAT5 phosphorylation in T cells
JAK 2/2	TPO	STAT3 phosphorylation in platelets
TYK2	IL-12	IFN-γ production in cells

IFN, interferon; IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TYK, tyrosine kinase.

- Pharmacokinetic (PK) profiles were simulated using parameters derived from published population PK models for baricitinib, tofacitinib, and upadacitinib[3-6] and from internal analyses for deucravacitinib
  - PK parameters, including maximum plasma concentration (C_{max}), average plasma concentration (C_{ave}), and minimum plasma concentration (C_{min}), were calculated
- Plasma concentrations of deucravacitinib, baricitinib, tofacitinib, and upadacitinib were plotted relative to their whole blood IC_{50} values
  - If the whole blood IC_{50} value was higher than the C_{max} value, the fold difference between the IC_{50} and C_{max} values was calculated
- Additionally, key exposure parameters (C_{max}, C_{ave}, and C_{min}) of these agents were plotted relative to their individual whole blood IC_{50} values
- Average percent inhibition of JAK 1–3 and TYK2 signaling was calculated using the following equation based on the average drug concentration, whole blood IC_{50}, and the Hill coefficient:
  - Percent inhibition = 100/(1+[(IC_{50}/X)^H]) where X is the average drug concentration and H is the Hill coefficient
- Given that in vitro assays were conducted in whole blood, no adjustments for plasma protein binding differences were considered in this evaluation. Additionally, the blood to plasma concentration ratio of these agents is close to 1 (range, 1.16–1.32).[7] Therefore, no adjustments were considered

Results

In vitro whole blood IC_{50}

- Based on in vitro whole blood IC_{50} values (**Table 2**), deucravacitinib had greater selectivity for TYK2 compared with JAK 1/3 or JAK 2/2
- In contrast, baricitinib, tofacitinib, and upadacitinib demonstrated more potent inhibition of JAK 1/3 and JAK 2/2 compared with TYK2. Whole blood IC_{50} values for baricitinib, tofacitinib, and upadacitinib were within range of values reported in the published literature[8]

Table 2. In vitro whole blood IC_{50} values for JAK 1–3 and TYK2 inhibitors

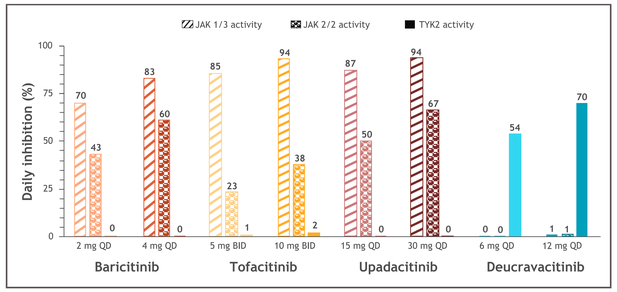
Signaling kinase readout	Whole blood IC_{50} (95% CI), nM			
	Baricitinib	Tofacitinib	Upadacitinib	Deucravacitinib
JAK 1/3 (IL-2–induced pSTAT5)	11 (8.7–13)	17 (15–19)	7.8 (6.5–9.5)	1646 (1446–1872)
JAK 2/2 (TPO–induced pSTAT3)	32 (28–36)	217 (182–258)	41 (36–47)	>10,000 (—)
TYK2 (IL-12–induced IFN-γ release)	2351 (1834–2980)	5059 (3767–7026)	3685 (2346–6208)	40 (29–55)

IC_{50}, half-maximal inhibitory concentration; IFN, interferon; IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TYK, tyrosine kinase.

Daily percent inhibition by JAK 1–3 and TYK2 inhibitors

- At clinically relevant concentrations, deucravacitinib inhibited TYK2 by >50% over 24 hours and exerted minimal effects (<2% inhibition) against JAK 1–3 (**Figure 1**). This indicates that deucravacitinib is a selective TYK2 inhibitor and does not modulate the JAK 1–3 pathways
- Baricitinib, tofacitinib, and upadacitinib exhibited varying degrees of inhibition against JAK 1/3 (daily average inhibition, 70%–94%) and JAK 2/2 (23%–67%) and no meaningful inhibition against TYK2 (<2%)

Figure 1. Daily percent inhibition by JAK 1–3 and TYK2 inhibitors

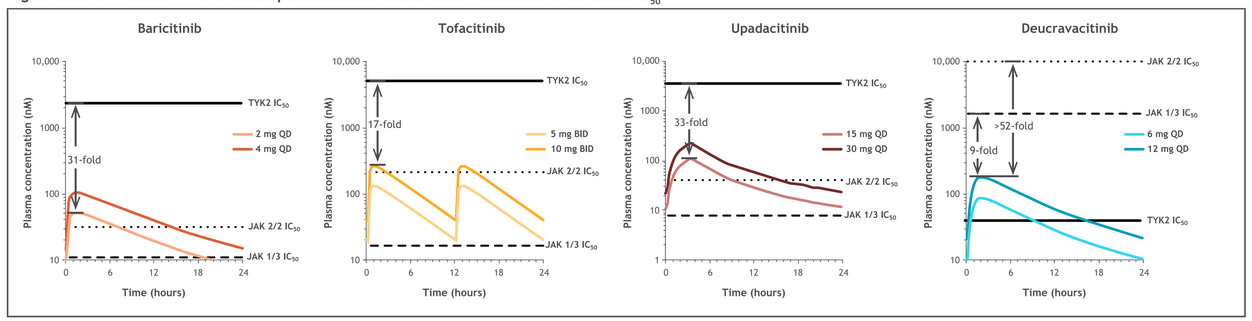


BID, twice daily; JAK, Janus kinase; QD, once daily; TYK, tyrosine kinase.

JAK 1–3 and TYK2 inhibitor plasma concentrations and whole blood IC_{50}

- At clinically relevant doses, deucravacitinib plasma concentrations were higher than the TYK2 whole blood IC_{50} value for a considerable portion (8–16 hours) of the 24-hour dosing interval and considerably lower than the JAK 1–3 IC_{50} values throughout the dosing interval (**Figure 2**)
- Deucravacitinib C_{max} values remained approximately 9- to 18-fold lower than the JAK 1/3 IC_{50} and approximately >52- to 109-fold lower than the JAK 2/2 IC_{50}. In contrast, baricitinib, tofacitinib, and upadacitinib plasma concentrations were higher than JAK 1/3 IC_{50} values over most of the dosing interval but were considerably lower than TYK2 IC_{50} values
- Additionally, baricitinib and upadacitinib plasma concentrations exceeded JAK 2/2 IC_{50} values over part of the dosing interval, especially at higher doses

Figure 2. JAK 1–3 and TYK2 inhibitor plasma concentrations over time and whole blood IC_{50}

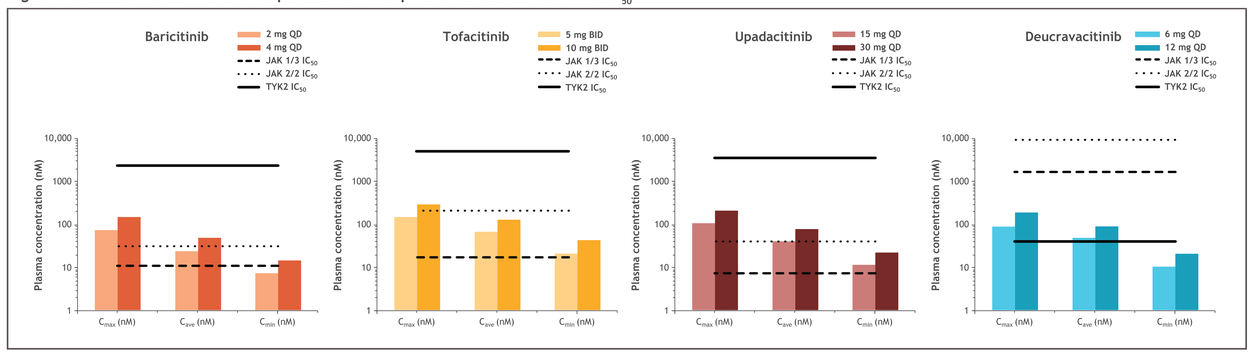


Arrows and fold-increase values pertain to the highest approved dose for each agent.
Tofacitinib 10 mg BID is approved for treating ulcerative colitis but not for rheumatoid arthritis.[a] Baricitinib, tofacitinib, and upadacitinib: margins to TYK2 inhibitor IC_{50} are provided for the highest approved dose.
BID, twice daily; IC_{50}, half-maximal inhibitory concentration; JAK, Janus kinase; QD, once daily; TYK, tyrosine kinase.

JAK 1–3 and TYK2 inhibitor pharmacokinetic parameters and whole blood IC_{50}

- At clinically relevant doses, deucravacitinib C_{max}, C_{ave}, and C_{min} were higher than or close to the TYK2 IC_{50} value, but were considerably lower than JAK 1/3 and JAK 2/2 IC_{50} values (**Figure 3**)
- C_{max}, C_{ave}, and C_{min} values for baricitinib, tofacitinib, and upadacitinib were many-fold lower than TYK2 IC_{50} values, but were above or within range of JAK 1/3 and JAK 2/2 IC_{50} values

Figure 3. JAK 1–3 and TYK2 inhibitor pharmacokinetic parameters and whole blood IC_{50}



BID, twice daily; C_{ave}, average plasma concentration; C_{max}, maximum plasma concentration; C_{min}, minimum or trough plasma concentration; IC_{50}, half-maximal inhibitory concentration; JAK, Janus kinase; QD, once daily; TYK, tyrosine kinase.

Conclusions

- This analysis confirms that deucravacitinib is a highly selective, allosteric TYK2 inhibitor with minimal or no activity against JAK 1–3
- Selective TYK2 inhibition is consistent with the reduced potential for treatment-related toxicities (eg, laboratory parameter abnormalities, gut perforation, thrombosis) in deucravacitinib-treated patients, effects generally associated with JAK 1–3 inhibitors[2,10,11]
- Conversely, the JAK 1–3 inhibitors included in this analysis (baricitinib, tofacitinib, and upadacitinib) did not exhibit TYK2 inhibition. Hence, the undesirable adverse effects associated with these agents as noted above are unlikely to be related to TYK2 inhibition
- These results suggest that deucravacitinib is in a distinct therapeutic class compared with inhibitors of the closely related intracellular signaling kinases, JAKs 1–3
- Ongoing trials in plaque psoriasis (NCT03624127, NCT03611751, NCT04167462, NCT03924427, and NCT04036435) and other IMIDs will provide additional safety information about deucravacitinib

References

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Relationships and Activities

- AC, LC, JS, IC, AP, IGG, SB, and JT are employees and shareholders of Bristol Myers Squibb; JB was an employee and shareholder of Bristol Myers Squibb at the time the analysis was conducted

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