Selective Inhibition of Tyrosine Kinase 2 With Deucravacitinib (BMS-986165) Compared With Janus Kinase 1–3 Inhibitors

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Background
- Tyrosine kinase 2 (TYK2), an intracellular kinase involved in the pathways of immune-related inflammatory diseases (IRDs), regulates signaling and functional responses downstream of the cytokine receptor (IL-12, IL-23, and IFN-γ) receptor 1 interfaces.
- Deucravacitinib (BMS-986165) is an oral, selective, and allosteric TYK2 inhibitor with a unique mode of binding to two shared, well-conserved residues domain rather than to the conserved active site in the catalytic domain.
- This unique mode of binding provides high functional selectivity for TYK2 vs other tyrosine kinases.

Methods
- In vitro whole blood assays that measure activity of TYK2, JAK 1/3, and JAK2 pathways were conducted to compare deucravacitinib vs the approved Janus kinase (JAK) inhibitors: tofacitinib, upadacitinib, and baricitinib, at clinically relevant doses and plasma concentrations.
- The selectivity of deucravacitinib vs the approved Janus kinase (JAK) inhibitors was assessed using whole blood IC50 values, half-maximal inhibitory concentration (IC50), fold-increase values, and percent inhibition.
- Pharmacodynamic (PD) profiles were simulated using parameters derived from published population PK models for tofacitinib, upadacitinib, and baricitinib.

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

Results

In vitro whole blood IC50
- As seen in Table 2, deucravacitinib had greater selectivity for TYK2 compared with JAK1 and JAK2.
- In contrast, tofacitinib, upadacitinib, and baricitinib demonstrate no more potent inhibition of JAK1 and JAK2 compared with TYK2.
- Whole blood IC50 values for tofacitinib, upadacitinib, and baricitinib are within the range of values reported in the published literature.

Table 1. In vitro whole blood IC50 values for JAK1–3 and TYK2 inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>JAK1 IC50 (nM)</th>
<th>JAK2 IC50 (nM)</th>
<th>TYK2 IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>3767–7026</td>
<td>2346–6208</td>
<td>10,000</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>8.7–13</td>
<td>28–36</td>
<td>10,000</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>&gt;10,000</td>
<td>&gt;10,000</td>
<td>10,000</td>
</tr>
</tbody>
</table>

Daily percent inhibition by JAK1–3 and TYK2 inhibitors
- Daily average inhibition SR (min–max) was higher than JAK1–3 IC50 values at each dose level and time point.

Table 2. JAK1–3 and TYK2 inhibitor plasma concentrations over time and whole blood IC50

<table>
<thead>
<tr>
<th>Inhibitor</th>
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<tbody>
<tr>
<td>Tofacitinib</td>
<td>10,000</td>
<td>10,000</td>
<td>10,000</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>10,000</td>
<td>10,000</td>
<td>10,000</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>10,000</td>
<td>10,000</td>
<td>10,000</td>
</tr>
</tbody>
</table>

Conclusions
- This analysis confirms that deucravacitinib is a highly selective, allosteric TYK2 inhibitor with minimal or no activity against JAK1–3.
- Selective TYK2 inhibition was consistent with the reduced potential for treatment-related toxicities (eg, laboratory parameter abnormalities, gut perforation, thrombosis) in deucravacitinib-treated patients, effects generally associated with JAK1–3 inhibition.
- Conversely, the JAK1–3 inhibitors included in this analysis (tofacitinib, upadacitinib, and baricitinib) did not inhibit TYK2.
- Therefore, the undesirable adverse effects associated with these agents as noted above are unlikely to be related to TYK2 inhibition.

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

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