BLU-808, a Potent and Selective Small Molecule Inhibitor of Wild-Type KIT for Mast Cell Disorders

Alexandra Grassian,1 Andrew Haidle,1 Sophia AuDuong,1 James Baker,1 Guangyan Du,1 Megan Hatten,1 Melissa Hiki,1 Karen Ho,1 Wei Hu,1 Kevin Keane,1 Thiwanka Samarakoon Mudiyanselage,1 Emanuele Perola,1 Christine Pien,1 Priyanka Sawant,1 Doug Wilson,1 Rob Meissner,1 Jason Brubaker,1 Scott Ribich,1 Joseph Kim1

1Blueprint Medicines Corporation, Cambridge, MA, USA

Background

KIT is a transmembrane tyrosine kinase receptor tyrosine kinase that is the primary drug target for mast cell disorders including chronic urticaria, asthma, and mast cell activation syndrome. KIT is activated by its ligand stem cell factor (SCF), binds to KIT and induces the formation of homodimers/oligomers, trans phosphorylation, and activation of downstream intracellular signaling cascades.

Inhibition of asthma-like symptom was assessed in a rodent ovalbumin-induced asthma model

Table 1. BLU-808 is an investigational potent and selective inhibitor of WT KIT

<table>
<thead>
<tr>
<th>IC50 (nM)</th>
<th>BLU-808</th>
<th>CSF1R</th>
<th>PDGFRA/B/FLT3</th>
<th>PDGFB</th>
<th>PDGFRA</th>
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<tr>
<td>WT KIT</td>
<td>0.8</td>
<td>&gt;800x</td>
<td>&gt;9600x</td>
<td>&gt;300x</td>
<td>&gt;400x</td>
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<tr>
<td>PDGFB</td>
<td>0.8</td>
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<td>&gt;9600x</td>
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<tr>
<td>FLT3</td>
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<td>&gt;800x</td>
<td>&gt;9600x</td>
<td>&gt;300x</td>
<td>&gt;400x</td>
</tr>
</tbody>
</table>

Figure 1. BLU-808 inhibits WT KIT-dependent proliferation and SCF-mediated KIT phosphorylation were used to

Figure 5. BLU-808 inhibits degranulation of human-derived CD34+ mast cells

Figure 6. In an exposure-dependent manner, BLU-808 can decrease mast cell number after 7 days

Conclusions

BLU-808 is an investigational novel mast cell modulator that shows promising activity in vitro and in vivo in model systems of mast cell disorders. BLU-808 offers a potential best in class mast cell modulator that has shown dose-dependent inhibition of mast cell degranulation and reduction of mast cell number after 7 days of treatment in vivo.

Poster Number: 189

Poster available for download at: https://blueprintmedicines.com/BLU-808/MastCellPoster

References