Phase 1 Drug-Drug Interaction Studies of Inhaled Seralutinib in Healthy Subjects

Jack Li, Ed Parsley, Matt Cravets, Anita Mathias
Gossamer Bio, Inc., San Diego, CA, USA

BACKGROUND

• Pulmonary arterial hypertension (PAH) treatment requires co-administration of multiple therapies, some of which are metabolized by cytochrome P450 (CYP) enzymes and/or cleared by drug transporters
• Seralutinib is a potent, small molecule kinase inhibitor cleared by drug transporters
• Seralutinib targets key pathways involved in PAH pathogenesis, namely PDGFR α, β, CSF1R, e-KIT, and BMPR2 deficiency (Figure 1)1

STUDY 1

STUDY 2

• Seralutinib is administered by dry powder inhalation and was specifically designed to maximize the therapeutic index by directly targeting diseased pulmonary arteries and reducing systemic exposure
• In vitro experiments suggest that seralutinib may impact CYP enzymes and drug transporters and is primarily metabolized by CYP3A; however, the clinical impact on co-administration with CYP substrates and transporters is unclear

• We conducted two studies in healthy volunteers to assess for potential drug-drug interactions with seralutinib

OBJECTIVE

• Study 1: Evaluate potential effects of inhaled seralutinib on the PK of a cocktail of CYP enzyme and transporter substrates2
• Study 2: Examine the effect of CYP3A inhibition on the PK of seralutinib

METHODS

• The potential drug interaction liability of seralutinib was evaluated in two healthy volunteer studies

STUDY 1 – Seralutinib as a perpetrator (drug interaction)

• Open-label, single-group, single-sequence, ODI study to simultaneously assess 6 different potential interactions (Figure 2)
• 24 healthy adult subjects received a cocktail of 6 probe substrates (Dig + Treatment A) with or without seralutinib

STUDY 2 – Seralutinib as a victim (drug interaction)

• Open-label, single-group, single-sequence, ODI study of inhaled seralutinib plus fosaprepitant (weak CYP3A inhibitor) or itraconazole (strong CYP3A inhibitor) (Figure 3)

METHODS (continued)

• Plasma concentrations were determined using validated assays: PK parameters were estimated using noncompartmental methods
• Point estimates of geometric mean ratios (GMRs) and associated 2-sided 90% CIs for Cmax and AUC for CYP substrates (Study 1) and probe substrates (95% CI) were calculated using nonparametric bootstrap with 1000 samples

RESULTS

Demographics and Baseline Characteristics

Baseline Characteristics

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>44.5 (7.37)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Female</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Black</td>
</tr>
<tr>
<td></td>
<td>White</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²), mean (SD)</td>
<td>26.90 (2.85)</td>
</tr>
</tbody>
</table>

Pharmacokinetics

STUDY 1 (Figure 4)

• Seralutinib co-administration increased midazolam Cmax 2-fold and AUC 3-fold, indicating that seralutinib is a moderate inhibitor of CYP3A
  - caffeine AUC by 33%, indicating that seralutinib is a weak inhibitor of CYP1A2

• Seralutinib
  - is neither an inhibitor nor an inducer of CYP2C9, CYP2D6 and OATP1B1/1B3
  - slightly inhibits P-gp (CYP3A4 substrate) with caution for co-dosing with P-gp inhibitors

STUDY 2 (Figure 5)

• Fosaprepitant and itraconazole increased seralutinib AUC by 8% and 84%, respectively
  - digoxin AUC by 0.8576 (0.6956, 1.0575)

• Ethromycin was predicted to increase seralutinib AUC by 25-39%

• No effect on CYP2D6 was observed or predicted for these CYP3A inhibitors

SUMMARY AND CONCLUSIONS

• Seralutinib demonstrated a favorable DDI profile and can be co-administered with most medications, including PAH background therapies
• Seralutinib was generally well tolerated
• Treatment emergent AEs of constipation and a fall in a single subject were reported, both of which were considered mild in severity and considered related to seralutinib by the investigator
• No SAEs or AEs leading to drug withdrawal or early termination from the studies were reported

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Brian Freedy for editorial support.

REFERENCES


ABBREVIATIONS