BACKGROUND

• Pulmonary arterial hypertension (PAH) is an orphan disease associated with high morbidity and mortality with high unmet medical needs.
• Increased platelet-derived growth factor receptor (PDGFR) signaling plays a role in the pathophysiology of PAH; inhibition of this pathway may improve cardio-pulmonary hemodynamics in patients with PAH.

GB002 (formerly PK10571) is a potent, small molecule, PDGFR kinase inhibitor in development as a novel non-systemic therapy for patients with PAH.

Preclinical efficacy of GB002 has been demonstrated in two animal models of PAH, the rat monocrotaline plus pneumectomy model and the SUGEN4146 hypoxia model, supported by significant reductions in pulmonary arterial pressure compared to vehicle.

OBJECTIVES

• Primary: Determine safety and tolerability of single and multiple doses of GB002 by oral inhalation in healthy adult subjects.
• Secondary: Evaluate the pharmacokinetics (PK) of GB002 following single- and multiple-dose regimens.

METHODS

• Two phase 1a, randomized, double-blind, placebo-controlled studies (Figure 1):
  - Part A: Single ascending dose and multiple dose administrations
  - Part B: Multiple dose administration

• Subjects were healthy, non-smoking adults, 18-50 years of age, body mass index 18-32 kg/m²

RESULTS

GB002 was administered to 62 healthy adult subjects in single doses of 3.75 mg to 90 mg and multiple doses of 18 to 30 mg twice daily (BID) for 7 days.

Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>GB002 3.75 mg</th>
<th>GB002 7.5 mg</th>
<th>GB002 15 mg</th>
<th>GB002 30 mg</th>
<th>GB002 48 mg</th>
<th>GB002 90 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.0 (3.0)</td>
<td>39.0 (7.5)</td>
<td>38.6 (10.3)</td>
<td>38.5 (8.9)</td>
<td>39.5 (6.3)</td>
<td>35.4 (9.5)</td>
<td>44.2 (9.7)</td>
</tr>
<tr>
<td>Male</td>
<td>8 (66.7)</td>
<td>5 (62.5)</td>
<td>3 (50.0)</td>
<td>3 (50.0)</td>
<td>4 (66.7)</td>
<td>4 (57.1)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Race</td>
<td>10 (83.3)</td>
<td>8 (100)</td>
<td>7 (77.8)</td>
<td>7 (77.8)</td>
<td>5 (83.3)</td>
<td>4 (66.7)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>26.9 (3.0)</td>
<td>28.1 (3.4)</td>
<td>23.9 (2.4)</td>
<td>26.6 (1.5)</td>
<td>30.2 (1.5)</td>
<td>25.9 (3.6)</td>
<td>25.7 (4.1)</td>
</tr>
</tbody>
</table>

GB002 plasma concentrations declined rapidly after Tmax:

GB002 plasma concentrations declined rapidly after Tmax: Mean terminal elimination half-life ranged from 3.1 to 5.8 hours.

GB002 peak plasma concentrations (Cmax) and area under the concentration-time curves (AUC) increased in an approximately dose-proportional manner following single and multiple dose administrations.

Steady-state plasma levels were reached by Day 3 following multiple doses, with minimal accumulation in plasma after multiple dose administrations.

GB002 exposure increased in an approximately dose-proportional manner following single and multiple dose administrations. Minimal accumulation in plasma was observed after multiple days of BID or TID dosing.

No serious adverse events were reported.

Safety

• The most common adverse events were respiratory-related, primarily throat irritation and cough, which were mild in severity and similar to placebo.

CONCLUSIONS

GB002 is an orally inhaled PDGFR kinase inhibitor designed for targeted delivery to the lungs that is in clinical development for patients with PAH.

Following single and multiple doses, GB002 was rapidly absorbed into and cleared from the systemic circulation.

GB002 exposure increased in an approximately dose-proportional manner following single and multiple dose administration. Minimal accumulation in plasma was observed after multiple days of BID or TID dosing.

In healthy volunteers, inhalation of GB002 was well tolerated.

These results are consistent with your data from preclinical models and support the hypothesis that inhaled GB002 will result in effective local lung concentrations while limiting systemic exposure.

REFERENCES


ACKNOWLEDGEMENTS

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DISCLOSURES

JL, MY, MC, RM, RA, and LZ are employees of Gossamer Bio, Inc.