GB002, A Novel, Inhaled PDGFR Kinase Inhibitor, Demonstrates Efficacy in the SU5416 Hypoxia Rat Model of Pulmonary Arterial Hypertension

Anna Galkin, Bryan Clemons, Eduardo Garcia, Jennifer Brooks, Debbie Slee, Luisa Salter-Cid, Larry Zisman

Gossamer Bio, Inc.; San Diego, CA
Disclosures

• Gossamer Bio Inc. Employee
• Gossamer Bio Stock Options
Introduction: Platelet-Derived Growth Factor (PDGF) Signaling Contributes to Pulmonary Arterial Remodeling in PAH

• PDGFR signaling drives vascular remodeling in preclinical models of PAH

• Evidence for cross-talk between PDGFR and BMPR2, a key causal gene in hereditary PAH

• PDGFR signaling is activated in human PAH

Adapted from Pulmonary Hypertension News  https://pulmonaryhypertensionnews.com/
Introduction: GB002, a Novel Inhaled PDGFRα/β Inhibitor, in Clinical Development for PAH

- Imatinib, a non-selective PDGFR inhibitor, improved exercise capacity and hemodynamics in patients with advanced PAH in the Phase III IMPRES trial, however, serious adverse events were associated with oral administration\(^1\)

- **Hypothesis**: localized lung delivery of GB002, would reverse vascular remodeling and improve cardiopulmonary hemodynamics, while limiting systemic exposure

<table>
<thead>
<tr>
<th></th>
<th>GB002</th>
<th>Imatinib</th>
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</thead>
<tbody>
<tr>
<td>PDGFRα IC(_{50}) (nM)(^2)</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>PDGFRβ IC(_{50}) (nM)(^2)</td>
<td>6</td>
<td>74</td>
</tr>
<tr>
<td>Lung Exposure</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Systemic Exposure</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>% Rat Phospho-PDGFRα/β Inhibition <em>In Vivo</em>(^3)</td>
<td>77/60</td>
<td>NA</td>
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</tbody>
</table>

\(^1\) Hoeper et al. Imatinib Mesylate as Add-on Therapy for Pulmonary Arterial Hypertension. Circulation 2013.

\(^2\) Biochemical kinase assay activity data

\(^3\) Rat lung phospho-PDGFRα Y849/Y857 and PDGFRβ Y1021 assessed by Western blot. Lung tissues were collected immediately post GB002 inhalation and 5-10 min intra-tracheal stimulation with recombinant rat PDGF-BB; mean % inhibition relative to PDGF-BB stimulated control lungs at efficacious exposure is shown

NA = not available
Materials and Methods: Evaluation of GB002 vs Imatinib in the SU5416 / Hypoxia Induced Rat PAH Model

- **GB002** delivered dose estimated using Guyton's formula (Guyton 1947)
- **Imatinib** in vivo exposures matched to published 400 mg dose clinical exposures (Gschwind et al. Drug Metabolism and Disposition 2005)
Results: GB002 Treatment Restored Rat Lung BMPR2 Expression and Led to Significant Improvement in Hemodynamic Parameters

Arterial blood pressure measured via an intra-arterial fluid-filled catheter (AD Instruments)
Right ventricular and pulmonary blood pressures were recorded via an intra-ventricular fluid-filled catheter (AD Instruments)
Rat BMPR2 (anti-BMPR-II clone 18; BD Bioscience) and β-actin (anti-β-actin clone 8H10D10; Cell Signaling Technology) protein expression assessed by capillary electrophoresis immunoassay on the WES™ platform (ProteinSimple); BMPR2 signal normalized to β-actin; Mean Fold Change vs Healthy Control ± SEM is shown
Mean Values ± SEM are displayed, statistical significance determined via One-Way Anova with Tukey’s multiple comparisons test
Results: 2-Week Treatment with GB002 Reduced Pulmonary Blood Vessel Remodeling in the Rat SU5416/Hypoxia PAH Model

- Development of PAH in the current model led to a 15-fold increase in % of muscular vessels
- GB002 treatment resulted in a significant reduction in % of muscular vessels and restoration of % of non-muscular vessels

Methods: Lung lobes were fixed in 10% formalin, transverse section of middle left lobe was embedded in paraffin, sectioned and stained with H&E. 50 vessels per lobe (n=3 per treatment group) were analyzed by a blinded histopathologist using the NDP.view 2.7.25 Zoomer Digital Pathology (Hamamatsu) software. Mean ± SEM is displayed

Non-Muscular: single elastic lamina for all of circumference
Partially-Muscular: 10-90% smooth muscle layer circumference
Muscular: >90% smooth muscle layer circumference

Statistical significance determined via One-Way Anova with Tukey’s multiple comparisons test
* Significance for GB002 treatment mediated increase in non-muscular vessels vs Vehicle control
** Significance for GB002 treatment mediated decrease in muscular vessels vs Vehicle control
Results: GB002 Treatment Reduced Circulating Plasma NT-proBNP in SU5416/Hypoxia Rat PAH Model

- NT-proBNP plasma levels correlate with functional parameters and patient outcome in PAH\(^1\)
- Rat NT-proBNP plasma levels increased 9-fold in the Vehicle PAH group compared to Healthy Control
- GB002 treatment led to a ~2-fold reduction in circulating NT-proBNP

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NT-proBNP: N-terminal pro-B-type natriuretic peptide; measured with Rat NT-proBNP Kit (MSD)
Statistical significance determined via One-Way Anova with Tukey’s multiple comparisons test

\(^1\) Chin et al. Circulation 2019
Results: GB002 Treatment Modulated Circulating Plasma Levels of TNFα, IL10 and PDGF-BB in SU5416/Hypoxia Rat PAH Model

- GB002 treatment led to a significant 2-fold reduction in circulating plasma levels of TNFα and a 4-fold increase in IL10

- A 30% reduction in PDGF-BB levels was observed with GB002 treatment, although data did not reach statistical significance

Rat TNFα and IL10 were assessed by MSD
Rat PDGF-BB was assessed with Quantikine mouse/rat PDGF-BB ELISA
Mean values ± SEM are displayed, statistical significance determined via One-Way Anova with Dunnett’s multiple comparisons test
Conclusions

• GB002 is a novel inhaled PDGFRα/β inhibitor in clinical development for PAH (Phase Ib, NCT03926793)

• Localized lung delivery of GB002 was efficacious on multiple measures of disease activity in the SU5416/Hypoxia Rat PAH model, in that it
  • Displayed improvement in cardiopulmonary hemodynamic parameters
  • Reduced pathological remodeling
  • Restored BMPR2 protein expression in diseased lung tissue
  • Reduced circulating plasma levels of NT-proBNP, a clinically relevant biomarker associated with disease progression and patient outcome
Acknowledgments

• IPS Therapeutique, Sherbrooke, Canada
Thank you!