Clinical Development of Inhaled GB002 for the Treatment of Pulmonary Arterial Hypertension

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Introduction and Overview

• PDGF signaling plays a key role in pulmonary vascular remodeling associated with PAH

• Imatinib provided POC but had limitations due to systemic administration

• GB002 is a unique small molecule PDGFR inhibitor with an improved kinase inhibition profile and is formulated to be administered via dry powder inhaler (DPI)

• GB002 has been evaluated in pre-clinical models of PAH and has demonstrated improvements in hemodynamic parameters, increases in lung BMPR2, reductions in circulating NT-proBNP, and reversal of pulmonary vascular remodeling

• In phase 1 studies, inhaled GB002 has shown a favorable pharmacokinetic profile and was well tolerated

• A phase 2 trial in patients with WHO Group I PAH is being initiated
Components of Vascular Remodeling in PAH: Critical Role of PDGF signaling

Muscularization of pulmonary arterioles: SMC progenitors PDGFR+</sup><sup>1</sup>

Hypertrophy and hyperplasia VSMCs driven by PDGF<sup>2</sup>

PDGFRα highly expressed in VSMCs; PDGFRβ in myofibroblasts<sup>6</sup>

PDGF survival factor for lymphocytes<sup>3</sup>

Neointimal Proliferation: myofibroblasts and endothelial cells PDGF-PDGFR paracrine signaling<sup>2</sup>

Perivascular infiltrates secrete PDGF; PDGFB gene expression most increased CV gene by single cell RNA seq in PAH<sup>3</sup>,<sup>4</sup>

Genetic Dissection Studies show importance of targeting both PDGFRα and PDGFRβ<sup>5</sup>

Targeting the PDGF Pathway in PAH is Supported by Strong Scientific and Clinical Rationale

- PDGF pathway is upregulated in PAH\(^1\)
- Ablation of PDGFR\(\beta\) signaling prevented hypoxia induced PAH\(^3\)
- PDGFR inhibition is effective in animal models of PAH\(^2\)
- Clinical studies of imatinib in PAH demonstrate efficacy\(^4-7\)

Photomicrograph shows increased phosphorylated PDGFR\(\beta\) in PAH lesions\(^1\)

Phase 3 IMPRES Trial Provides Clinical Proof of Principle for Targeting the PDGF Pathway in PAH with Imatinib

- Improvements in 6MWD and PVR were demonstrated at 24 weeks
- Systemic side effects of imatinib were observed
- GB002 developed as a novel molecule with improved kinase specificity and inhaled route of administration to optimize the therapeutic index of a PDGF inhibitor for PAH

GB002 Overview

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<thead>
<tr>
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<th>GB002</th>
<th>Imatinib</th>
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<tbody>
<tr>
<td>PDGFRα IC_{50} (nM)</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>PDGFRβ IC_{50} (nM)</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>
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- GB002 is a novel chemical entity; small molecule platelet-derived growth factor receptor (PDGFR) kinase inhibitor
- Equipotent against PDGFRα and β; 10-fold more potent than imatinib against PDGFRβ in vitro; GB002 more potent in fibroblast assay
- In preclinical models, inhaled administration results in greater lung to systemic exposure
- GB002 formulation and administration via dry powder inhaler (DPI) designed to reach areas of the deep lung

GB002 Treatment Demonstrates Efficacy in SU5416/Hypoxia and MCT/PN models

**SU5416/H telemetry study**

- PASP (mmHg)
  - Vehicle (n = 3)
  - GB002 (n = 9)
  - *P < 0.0001

**MCT/PN study**

- RVESP (mmHg)
- Fulton’s Index (RV/(LV+IVS))
- Lumen/ Media

Vehicle (n = 6)  
GB002 (n = 11)  
*P < 0.001

*Manuscript in preparation*  
Rat AAV-PDGF SU5416/Hypoxia Model: GB002 Provides Additive Benefit Combined with Tadalafil and Ambrisentan

V-V, vehicle gavage + vehicle inhalation; TA-V, tadalafil + ambrisentan gavage + vehicle inhalation; V-GB, vehicle gavage + GB inhalation; TA-GB, tadalafil + ambrisentan gavage + GB inhalation

[p<0.01 vs V-V; ¶ p<0.01 vs TA-V and V-GB]
Inhaled GB002 Outperformed Gavage Imatinib in Head-to-Head Preclinical SuHx PAH Study

- GB002 treatment led to a significant improvement in RVSP
- GB002 reduced circulating levels of NT-proBNP and increased lung BMPR2 protein expression

Data presented as mean ± SEM. Statistical analysis was performed using one-way ANOVA with Dunnett’s multiple comparisons test. (Healthy n = 8, Vehicle n = 7, GB002 n = 9, Imatinib n = 7)

GB002 Increases BMPR2: Potential for Crosstalk Between PDGF, BMPR2, and Activin Pathways

Adapted from: Chen, et al. BMC Genomics 2016
GB002 Clinical Development Program Overview

**Phase 1a**
- **COMPLETE**
  - SAD/MAD in Healthy Volunteers
  - ATS 2020 Abstract/Poster

**Phase 1b**
- **ONGOING**
  - Objectives:
    - Examine safety and tolerability in PAH subjects
    - Examine early PK/PD relationships
    - Identify potential biomarkers for Phase 2
  - (NCT03926793)

**Phase 2**
- **PLANNED**
  - Study start 2H 2020
  - Study population: WHO Group 1 PH (PAH)

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GB002-2101 Study Design

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Clinical Study to Evaluate the Efficacy and Safety of Oral Inhalation of GB002 for the Treatment of WHO Group 1 Pulmonary Arterial Hypertension (PAH)\(^1\)

**Primary Endpoint**
- PVR at week 24

**Secondary Endpoint**
- 6MWD at week 24

Summary and Conclusions

• GB002 is a unique small molecule PDGFR kinase inhibitor delivered by DPI

• Efficacy has been demonstrated in preclinical animal models of severe PAH including reversing pulmonary arteriolar remodeling and decreasing NT-proBNP

• GB002 increased lung BMPR2 levels highlighting the intersection of the PDGF, BMPR2 and activin pathways

• Phase 1 studies support the favorable pharmacokinetics and safety profiles of GB002

• A phase 2 trial in patients with WHO Group I pulmonary arterial hypertension (PAH) is being initiated
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