# Pharmacologic Characterization of GB002, a Novel Inhaled PDGFR Kinase Inhibitor in Development for Pulmonary Arterial Hypertension (PAH)

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## INTRODUCTION

- PAH is characterized by vascular remodeling, increased pulmonary arterial pressure (PAP) and right ventricular hypertrophy
- Dysregulation of BMPR2 signaling is linked to hereditary and idiopathic forms of PAH[1]
- PDGF signaling plays an important role in BMPR2 regulation and is activated in human PAH[1]
- Here we studied effects of GB002, a novel inhaled PDGFRα/β inhibitor, on PDGFR pathway inhibition and BMPR2 modulation

## METHODS

- *In vitro* GB002 potency was evaluated in biochemical and cell-based assays
- *In vivo* dose- and time- dependent modulation of PDGFR phosphorylation and BMPR2 expression was assessed in healthy male Sprague Dawley rats
- Impact of GB002 on disease progression was evaluated in the SU5416 Hypoxia rat PAH model
- Statistical analysis was performed with one-way ANOVA with Dunnett's Test for Multiple Comparisons ($p < 0.05$)

### Table 1. Overview of in Vitro Pharmacology

| | Biochemical $IC_{50}$ (nM) | | Cell-Based Proliferation Assays $IC_{50}$ (nM) | | Cell-Based Phosphorylation Assays $IC_{50}$ (nM) | | | |
|---|---|---|---|---|---|---|---|---|
| Compound | PDGFRα[a] | PDGFRβ[a] | PDGFRα[b] | PDGFRβ[c] | PDGFRα[d] | PDGFRβ[d] | pERK[e] | pERK[f] |
| GB002 | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ |
| Imatinib | +++ | ++ | +++ | + | + | ++ | - | + |

[a]Carna Biosciences Inc, Biochemical Assay

[b]H1703 proliferation assay (PDGFRα dependent)

[c]PDGF-BB induced human lung fibroblast (HLF) proliferation assay (predominantly PDGFRβ dependent)

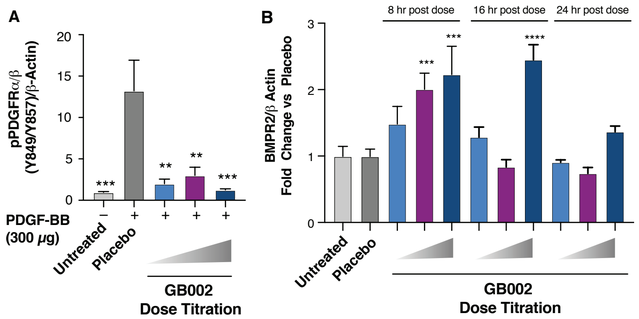
[d]PDGF-BB induced phosphorylation of PDGFRα or PDGFRβ in HLF cells

[e]PDGF-BB induced phosphorylation of pERK in HLF cells (predominantly PDGFRβ dependent signaling)

[f]PDGF-BB induced phosphorylation of pERK in H1703 cells (PDGFRα dependent signaling)

## RESULTS

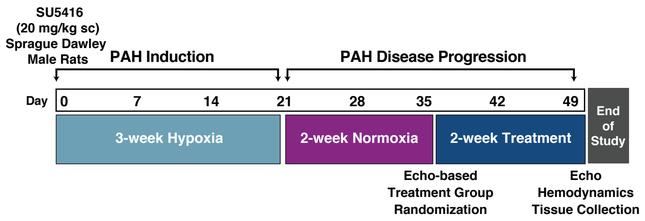
### Figure 1. Lung pharmacodynamic effects of inhaled GB002 in vivo




**A.** GB002-mediated inhibition of lung PDGFRα/β phosphorylation in healthy Sprague Dawley rats immediately post inhalation. PDGF-BB was delivered via intratracheal insufflation 5 minutes prior to lung extraction. Data shown as mean phospho-PDGFR / β-Actin Ratio ± SEM (n = 4). *$p < 0.05$, **$p < 0.005$, ***$p < 0.001$ as compared to PDGF-BB-stimulated placebo.

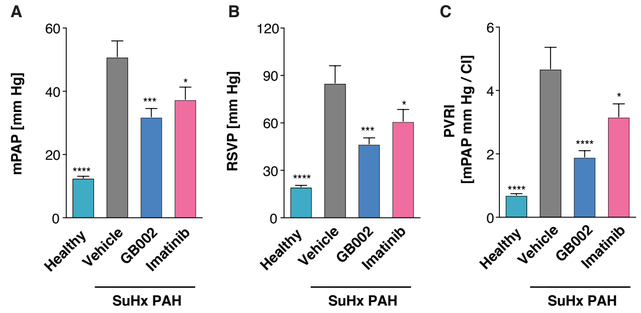
**B**. GB002 dose- and time-dependent induction of lung BMPR2 protein expression. Data shown as mean fold change vs placebo treatment group ± SEM (n = 4 to 8). **$p < 0.005$, ***$p < 0.0005$, ****$p < 0.0001$ as compared to placebo.

### Figure 2. SU5416/hypoxia rat PAH model efficacy study schematic



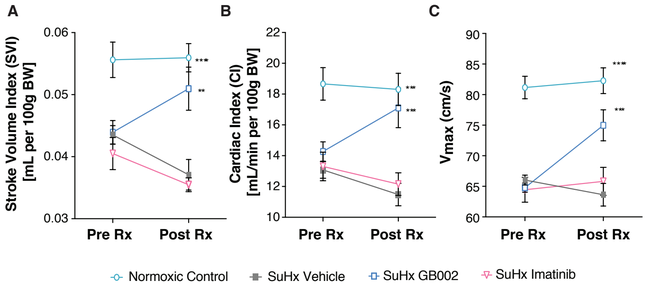

- GB002 and imatinib doses were selected to match clinical exposures at an efficacious dose

### Figure 3. Impact of inhaled GB002 vs. imatinib on hemodynamic parameters in the SU5416/hypoxia rat PAH model




GB002 treatment led to significant reduction in **A.** Pulmonary arterial pressure (mPAP), **B.** Right ventricular systolic pressure (RVSP), **C.** Pulmonary vascular resistance index (PVRI). Vehicle (n = 7), GB002 (n = 8), imatinib (n = 7). Data presented as mean ± SEM. *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$, ****$p < 0.0001$ vs. vehicle.

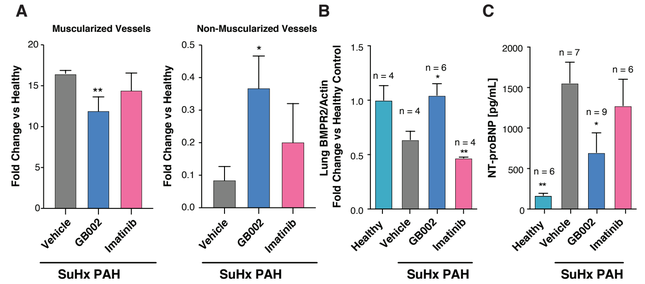
### Figure 4. GB002 improves Echo parameters in the SU5416/hypoxia rat model




Echocardiograms were recorded on day 35 (at start of treatment) to verify disease induction and randomize animals into treatment groups and at the end of treatment.

GB002 treatment led to significant improvements in **A.** Stroke volume, **B.** Cardiac index and **C.** $V_{max}$. Data is presented as mean ± SEM (n = 7-8 per treatment group). *$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$, ****$p < 0.0001$ vs. vehicle

### Figure 5. GB002 significantly decreased pulmonary arteriolar muscularization and improved disease biomarkers in the SU5416 hypoxia rat model




**A.** Impact of GB002 on vascular remodeling. Vessels were defined as non-muscular or muscular (> 90% smooth muscle layer circumference). 50 vessels per lobe (n = 3 per group) were analyzed by a blinded histopathologist. Data shown as mean ± SD, *$p < 0.05$, **$p < 0.005$, **** $p<0.0001$ vs vehicle.

**B.** Effects on lung BMPR2 protein expression on day 49. Data shown as fold change ± SEM. *$p < 0.05$ vs vehicle.

**C.** Circulating plasma levels of NT-proBNP on Day 49. Data shown as mean ± SEM. *$p < 0.05$, **$p < 0.005$ vs vehicle.

## CONCLUSION

- Localized lung delivery of GB002 inhibits PDGFR signaling and restores BMPR2 expression in vivo, translating to improved cardiopulmonary hemodynamics and disease reverse remodeling in the SU5416/H rat PAH model.
- GB002 is in clinical development for PAH (NCT03926793).

## ACKNOWLEDGEMENTS

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## DISCLOSURES

All authors are employed by Gossamer Bio, Inc.

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