Moderated Digital Poster 428

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

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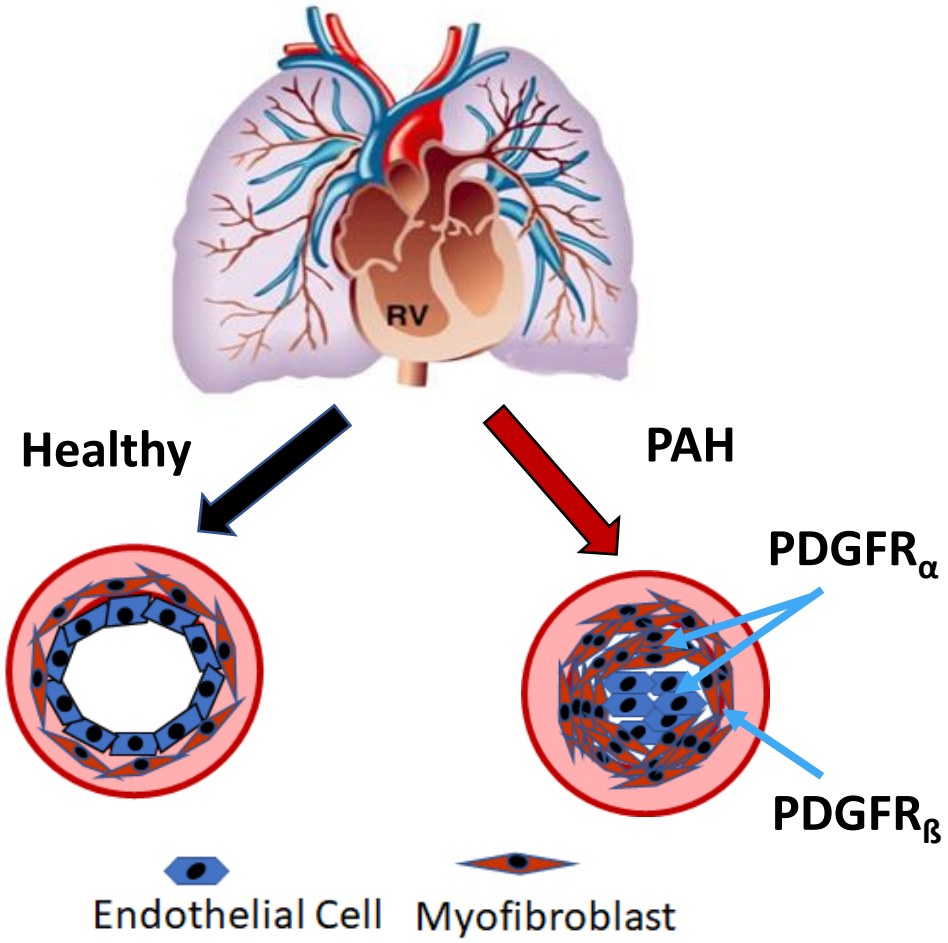
Disclosures

- Gossamer Bio Inc. Employee
- Gossamer Bio Stock Options

Introduction: Platelet-Derived Growth Factor (PDGF) Signaling Contributes to Pulmonary Arterial Remodeling in PAH



Adapted from Pulmonary Hypertension News https://pulmonaryhypertensionnews.com/

- 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

Introduction: GB002, a Novel Inhaled PDGFRα/β Inhibitor, in Clinical Development for PAH

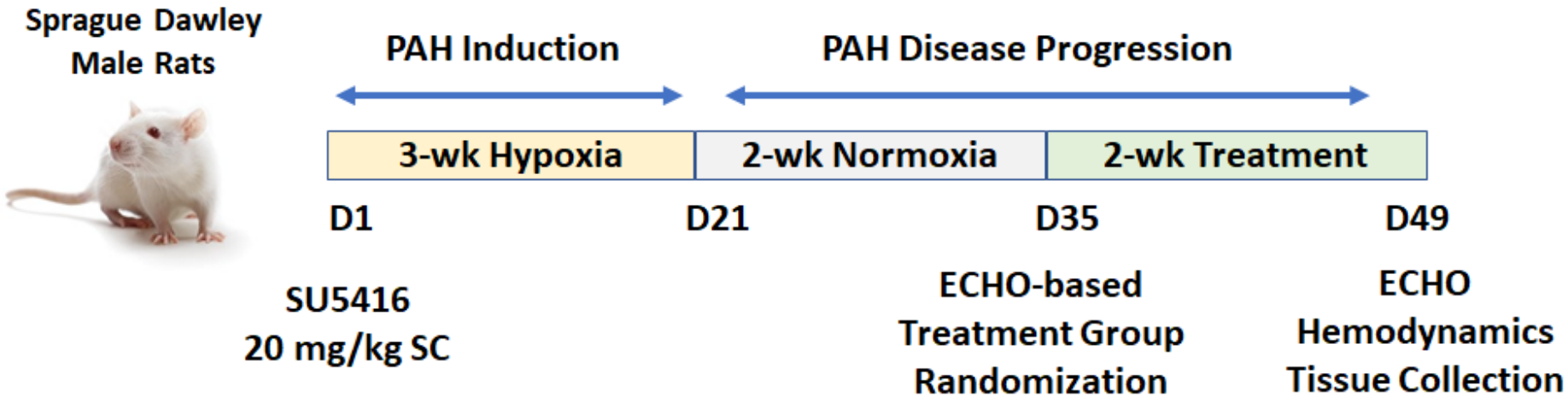
	GB002	Imatinib
PDGFRα IC_{50} (nM) [2]	7	12
PDGFRβ IC_{50} (nM) [2]	6	74
Lung Exposure	++++	+++
Systemic Exposure	+	++
% Rat Phospho-PDGFRα/β Inhibition *In Vivo* [3]	77/60	NA

- 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

[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-trachael 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

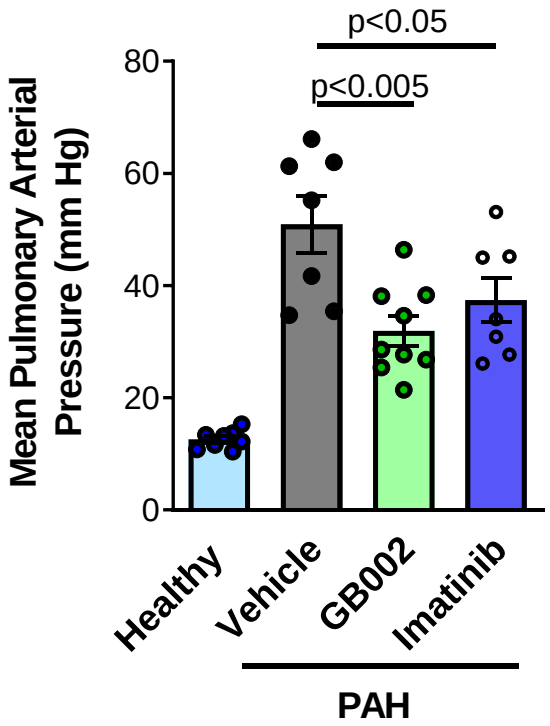


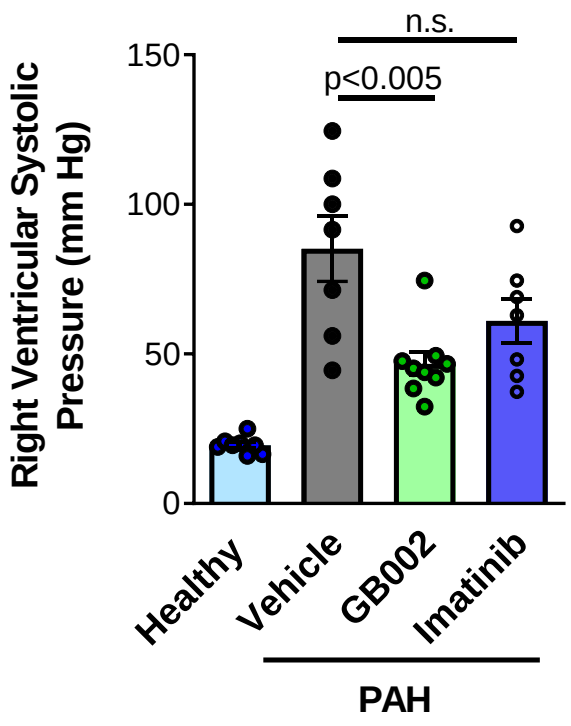
Group	Treatment	N	Dose mg/kg	Route/ Regimen
Healthy	-	8	-	-
PAH	Vehicle	8	-	Oral Gavage QD
	GB002*	8	12.8	Passive Inhalation BID
	Imatinib**	8	15.0	Oral Gavage QD

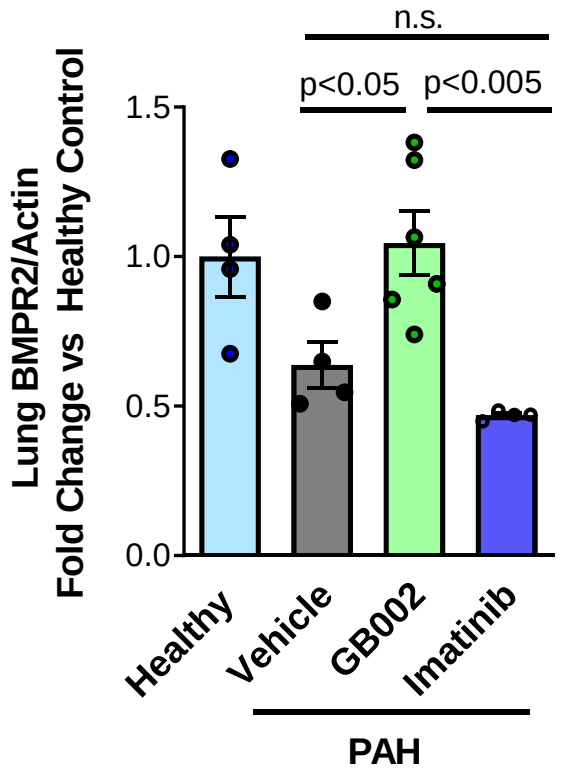
* GB002 delivered dose estimated using Guyton's formula (*Guyton 1947*)

** 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

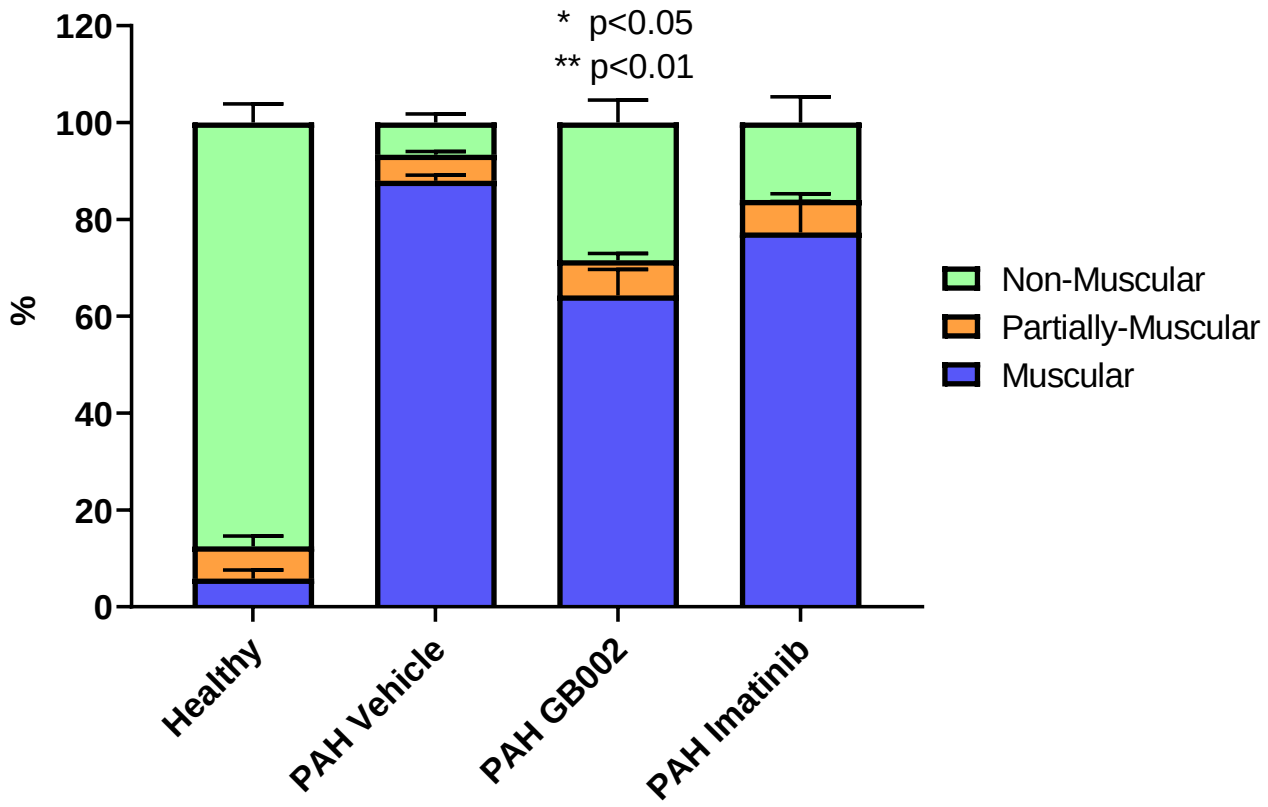






Arterial blood pressure measured via an intra-arterial fluid-filled catheter (AD Instruments)
Right ventricular and pulmonary blood pressures were recorded via an intra-ventricular fluid-filled catheter (AD Instruments)
Rat BMPR2 (anti-BMPR-II clone 18; BD Bioscience) and ß-actin (anti-ß-actin clone 8H10D10; Cell Signaling Technology) protein expression assessed by capillary electrophoresis immunoassay on the WES™ platform (ProteinSimple); BMPR2 signal normalized to ß-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



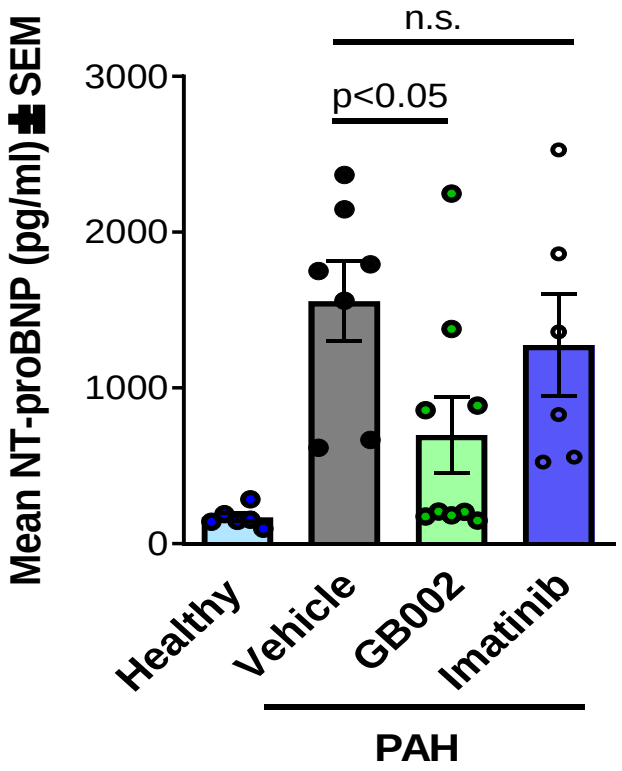
- Development of PAH in the current model led to a 15-fold increase in % of muscular vessels
- GB002 treatment resulted in a significant reduction in % of muscular vessels and restoration of % of non-muscular vessels

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

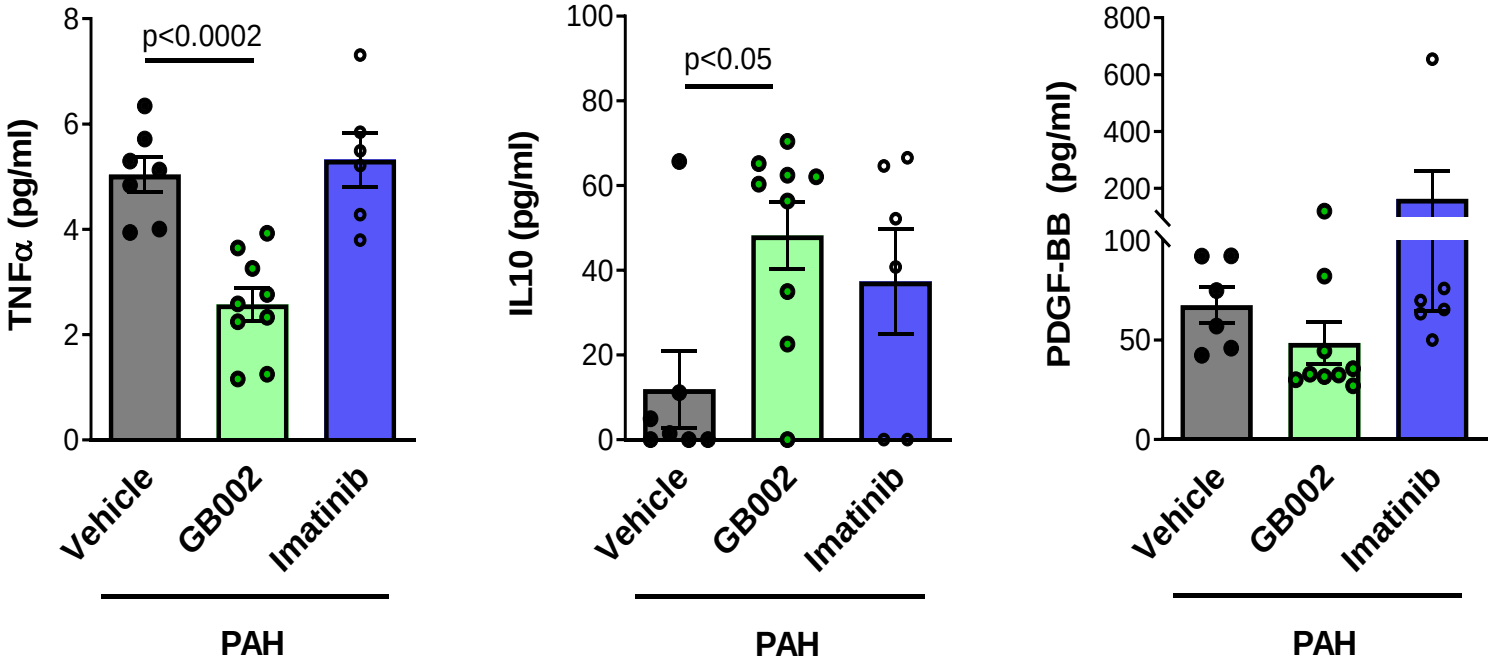


- NT-proBNP plasma levels correlate with functional parameters and patient outcome in PAH[1]
- Rat NT-proBNP plasma levels increased 9-fold in the Vehicle PAH group compared to Healthy Control
- GB002 treatment led to a ~2-fold reduction in circulating NT-proBNP

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!

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