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

Hossein-Ardeschir Ghofrani

University Hospital Giessen und Marburg GmbH
Kerckhoff Klinik Bad Nauheim
Department of Medicine, Imperial College London

Disclosures: Dr. Ghofrani

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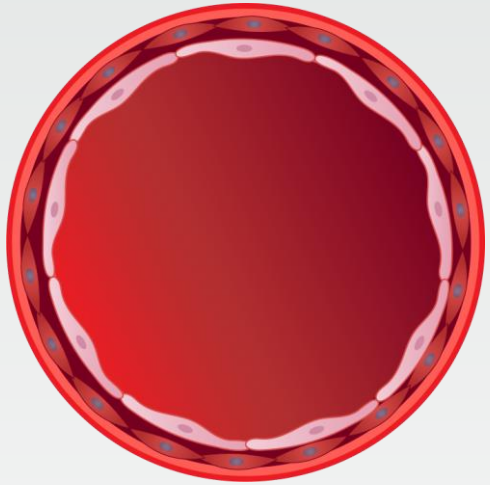
Introduction and Overview

- 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

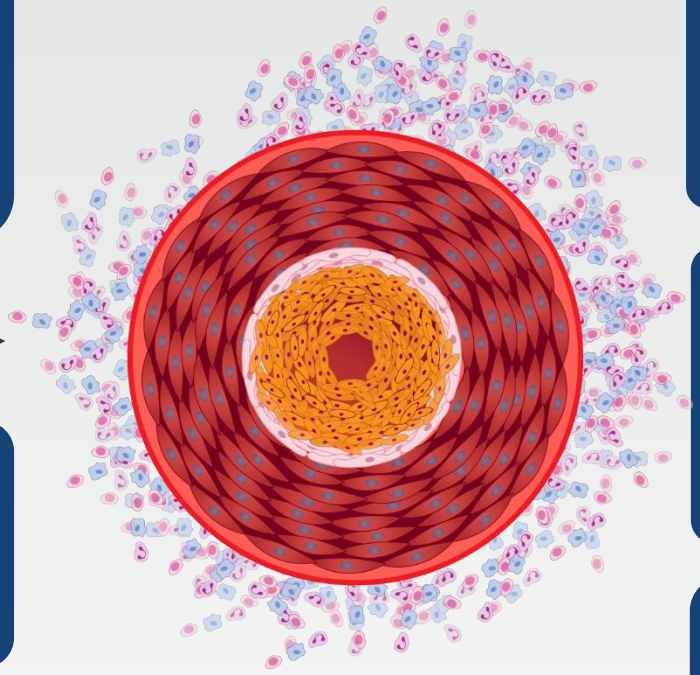
Components of Vascular Remodeling in PAH: Critical Role of PDGF signaling



Muscularization of pulmonary arterioles: SMC progenitors PDGFR+[1]

Hypertrophy and hyperplasia VSMCs driven by PDGF[2]

PDGFRα highly expressed in VSMCs; PDGFRβ in myofibroblasts[6]

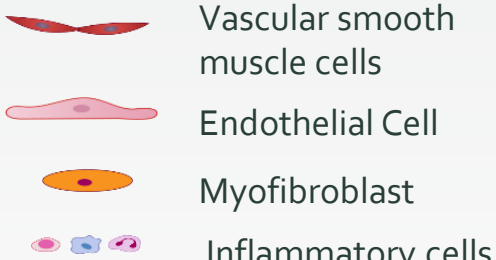


PDGF survival factor for lymphocytes[3]

Neointimal Proliferation: myofibroblasts and endothelial cells PDGF-PDGFR paracrine signaling[2]

Perivascular infiltrates secrete PDGF; PDGFB gene expression most increased CV gene by single cell RNA seq in PAH[3,4]

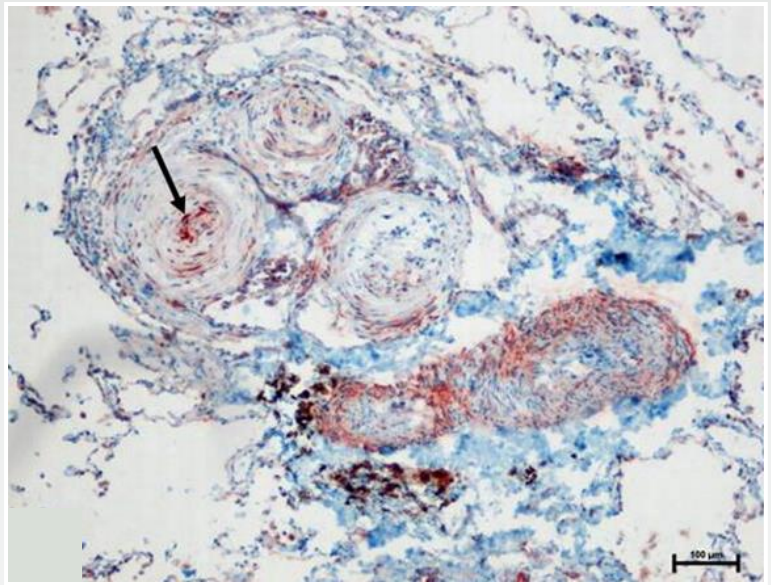
Genetic Dissection Studies show importance of targeting both PDGFRα and PDGFRβ[5]



1. Sheikh et al Sci Trans Med 2015 **2.** Adv Exp Med Biol 2010; JCI 2005 **3.** Perros et al AJRCCM 2012
4. Saygin et al Pulm Circ 2020 **5.** Wu et al. PLoS One 2008 **6.** Medarametla et al Pulm Circ 2013

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

- PDGF pathway is upregulated in PAH[1]



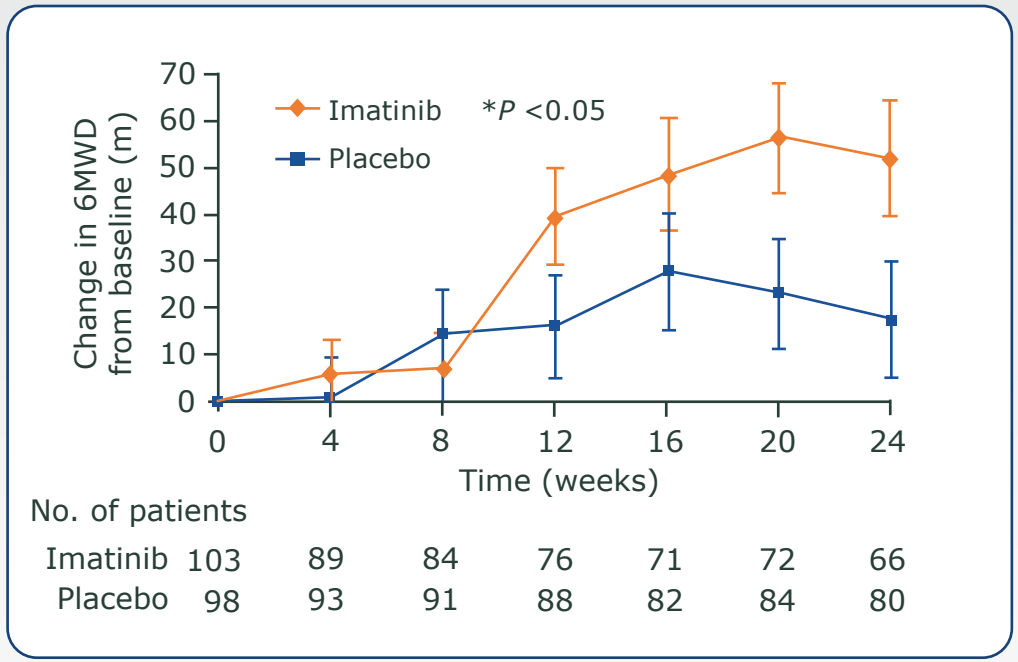
Photomicrograph shows increased phosphorylated PDGFRβ in PAH lesions[1]

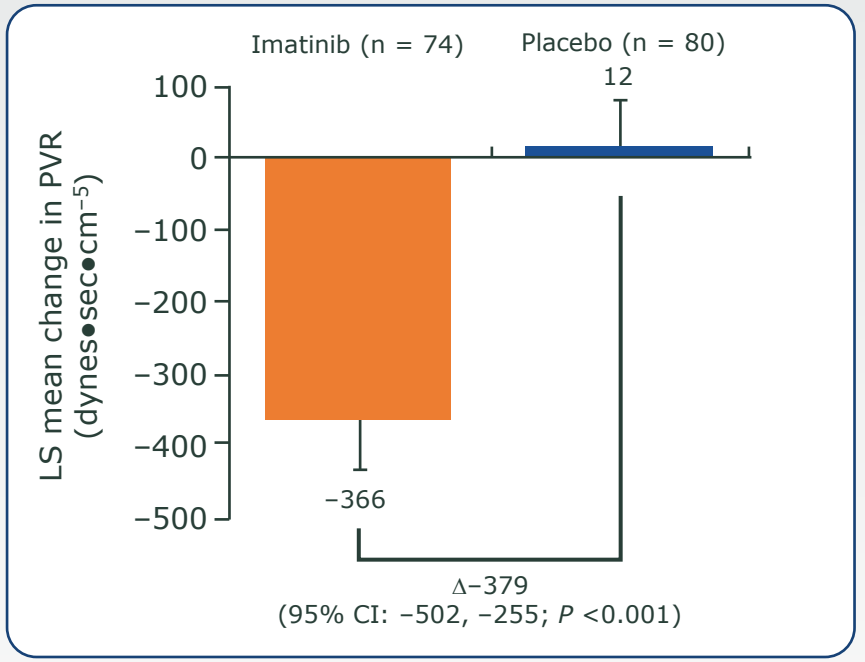
- Ablation of PDGFRβ signaling prevented hypoxia induced PAH[3]
- PDGFR inhibition is effective in animal models of PAH[2]
- Clinical studies of imatinib in PAH demonstrate efficacy[4-7]

1. Perros et al .AJRCCM 2008; **2.**Schermuly JCI 2005; **3**. Freyhaus et al. ATVB 2015; **4**. Ghofrani NEJM 2005; **5.** Ghofrani et al. AJRCCM 2010; **6.** Grimminger et al. Nat Rev Drug Disc 2010; **7**. Hoeper et al. Circ 2013

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





Hoeper M, et al. Circulation 2013.

GB002 Overview

	GB002	Imatinib
PDGFRα IC_{50} (nM)	7	12
PDGFRβ IC_{50} (nM)	6	74
Lung Exposure	++++	+++
Systemic Exposure	+	++

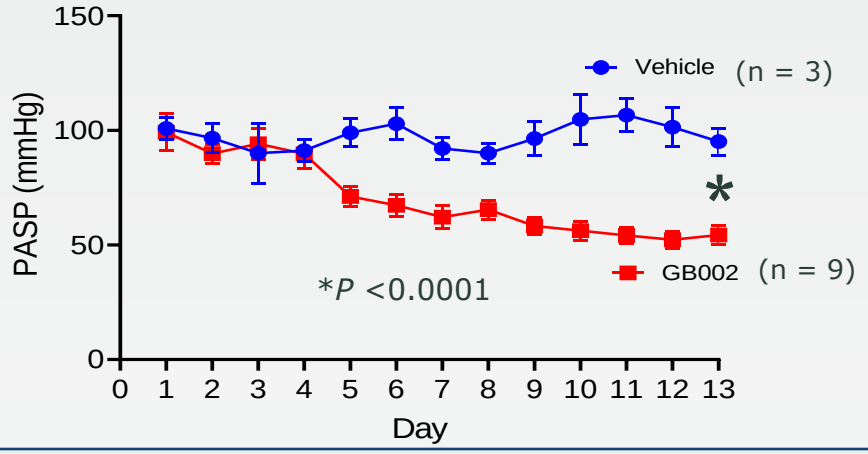
Dry Powder Inhaler From Plastiape

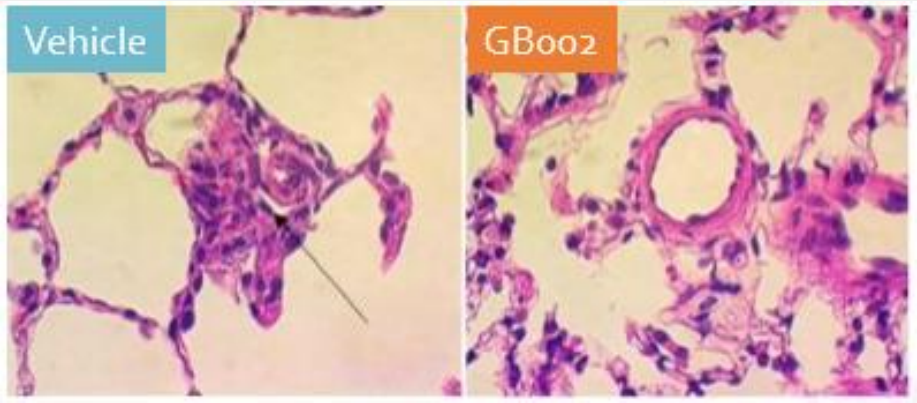
- GB002 is a novel chemical entity; small molecule platelet-derived growth factor receptor (PDGFR) kinase inhibitor
- Equipotent against PDGFRα and β; 10-fold more potent than imatinib against PDGFRβ in vitro; GB002 more potent in fibroblast assay
- In preclinical models, inhaled administration results in greater lung to systemic exposure
- GB002 formulation and administration via dry powder inhaler (DPI) designed to reach areas of the deep lung

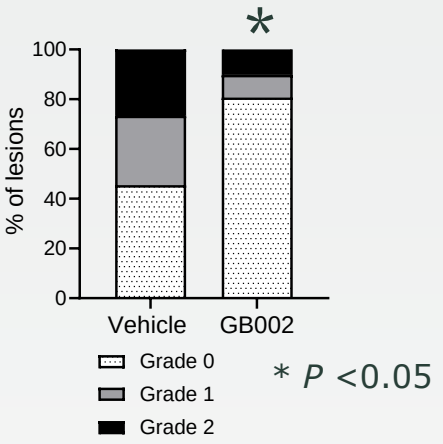
Galkin A, et al. Circulation 2019;140: A11102.

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

SU5416/H telemetry study[1]

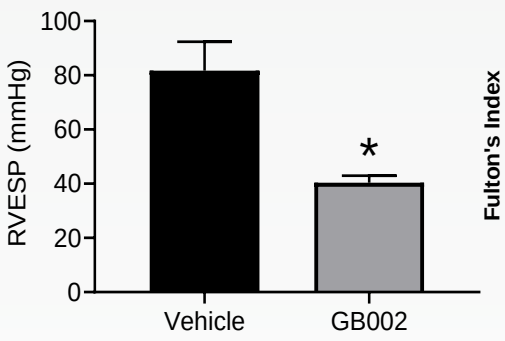


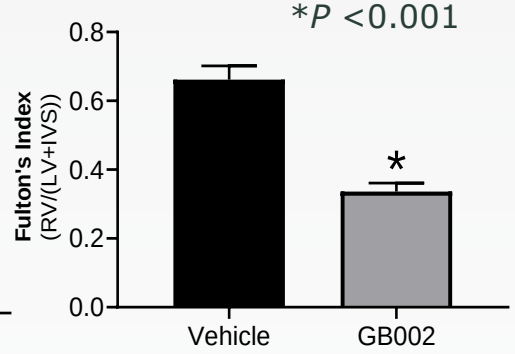


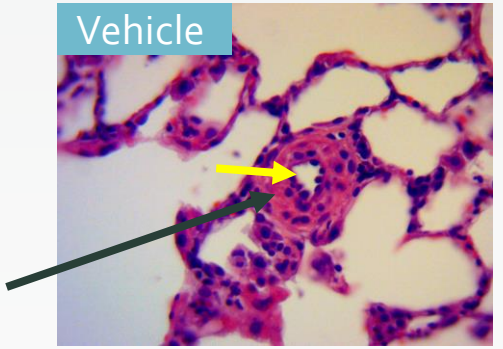


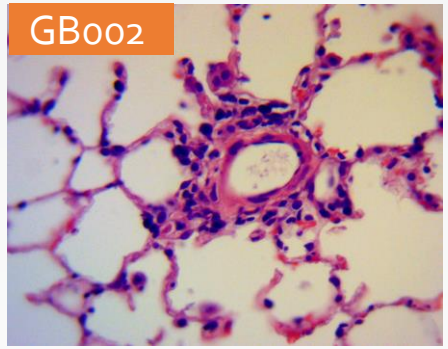
MCT/PN study[2]

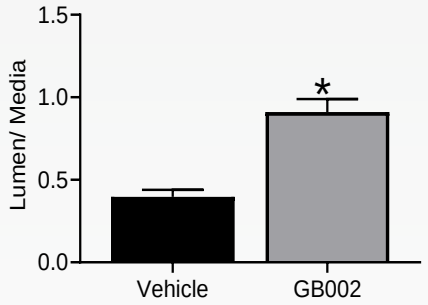
Vehicle (n = 6)
GB002 (n = 11)
*P <0.001





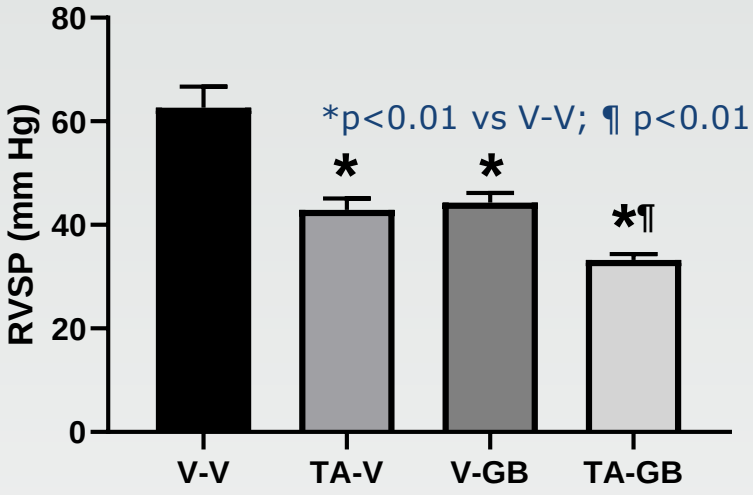


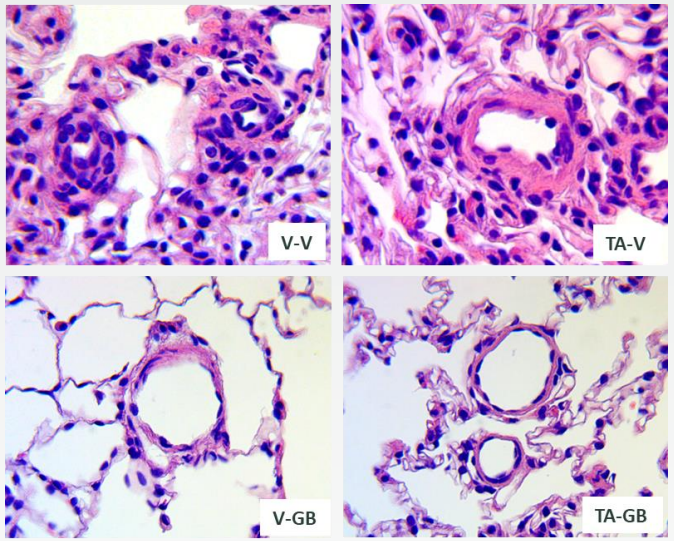


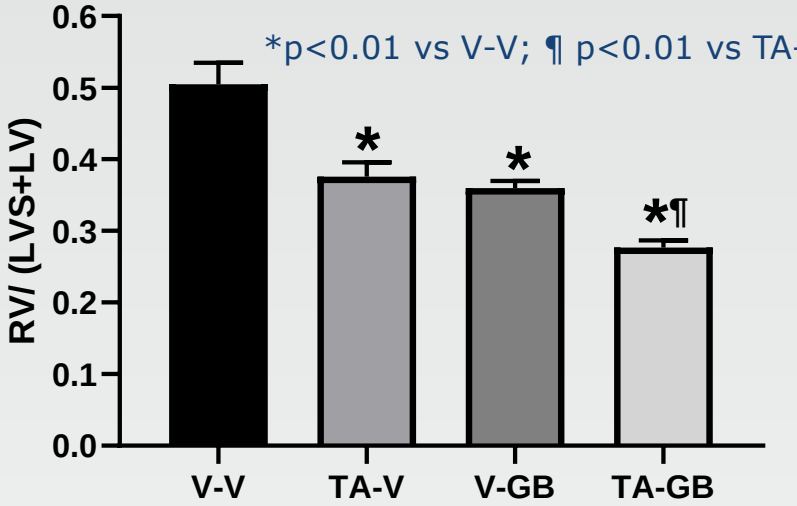


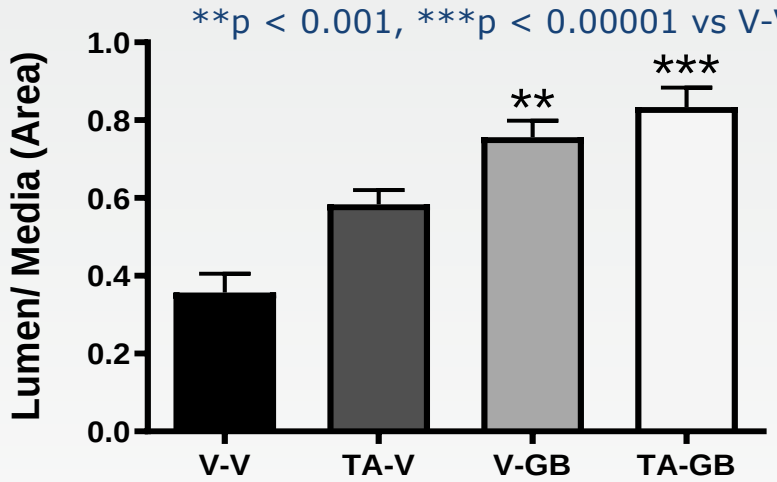
1. Manuscript in preparation **2.** Sitapara R, et al. Circulation 2019;140:A12947.

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





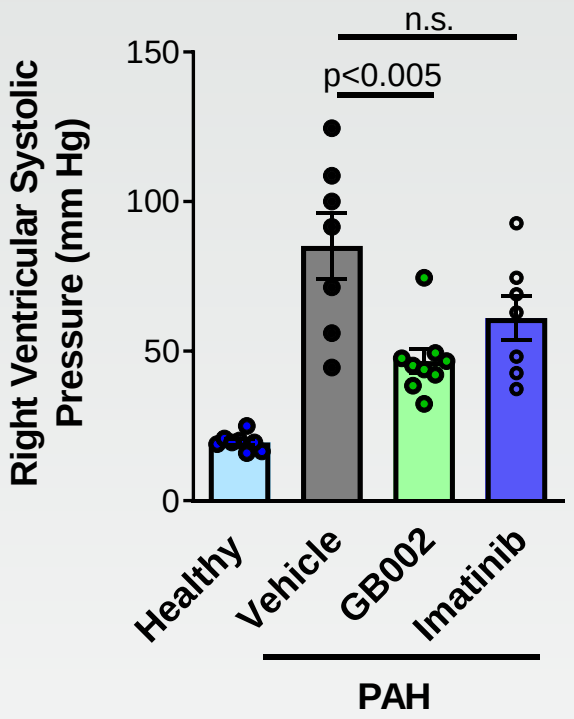


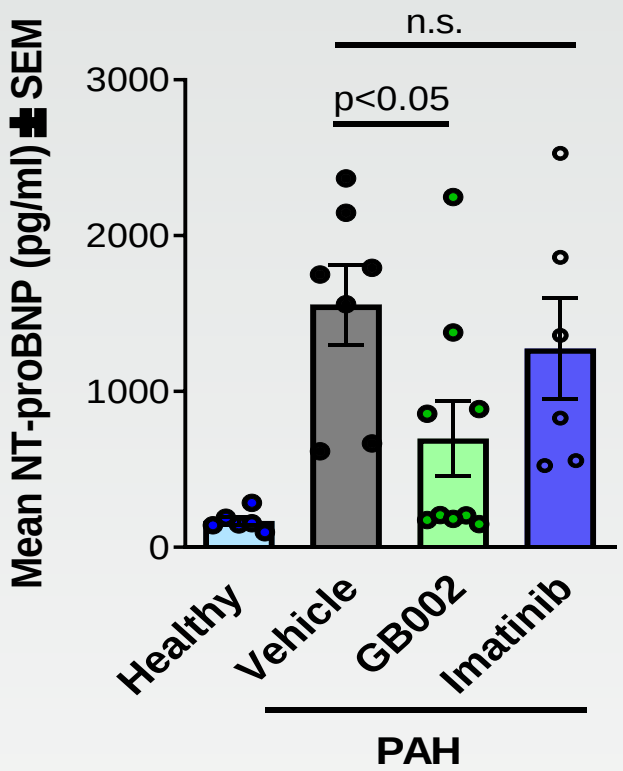


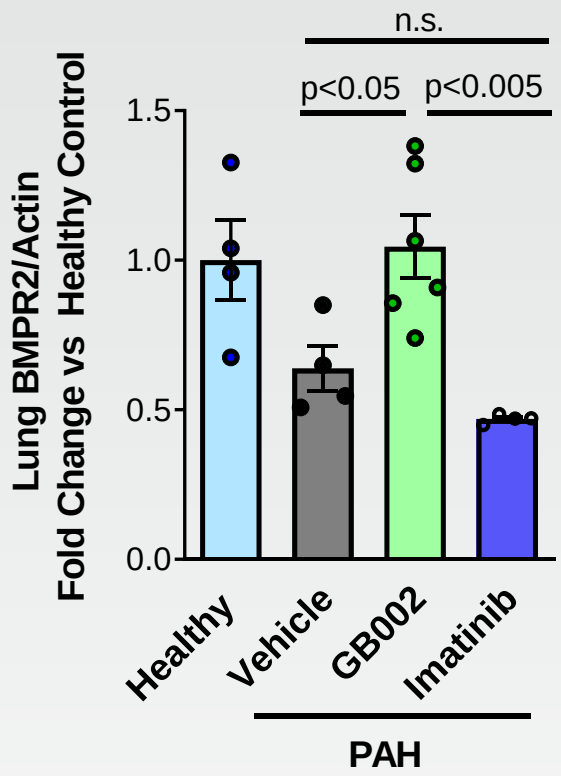
V-V, vehicle gavage + vehicle inhalation; TA-V, tadalafil + ambrisentan gavage + vehicle inhalation; V-GB, vehicle gavage + GB inhalation; TA-GB, tadalafil + ambrisentan gavage + GB inhalation

Sitapara R, et a. AJRCCM 2017; 195: A6897.

Inhaled GB002 Outperformed Gavage Imatinib in Head-to-Head Preclinical SuHx PAH Study





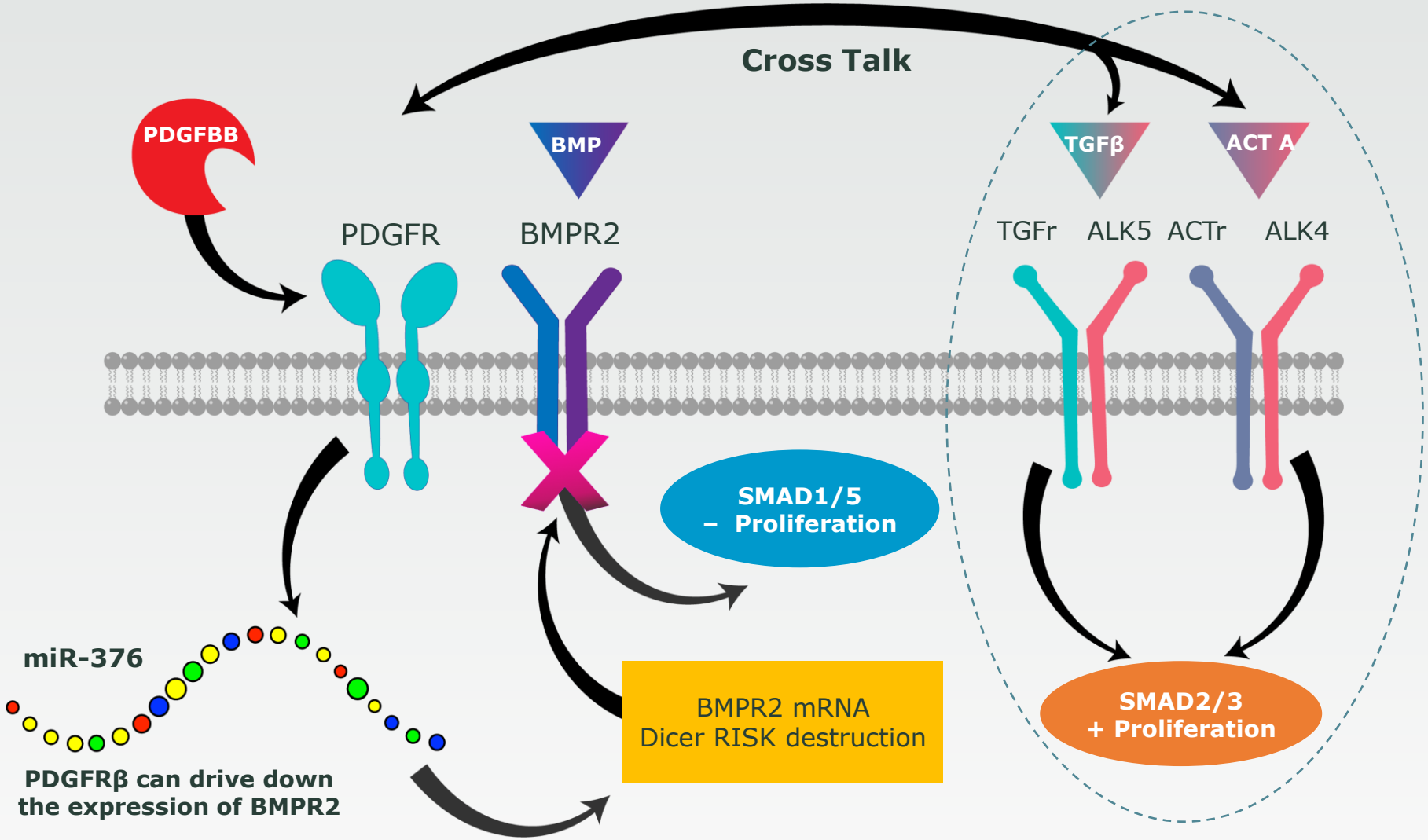


Data presented as mean ± SEM. Statistical analysis was performed using one-way ANOVA with Dunnett's multiple comparisons test.
(Healthy n = 8, Vehicle n = 7, GB002 n = 9, Imatinib n = 7)

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

Galkin A, et al. Circulation 2019;140: A11102.

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[1]

COMPLETE

- SAD/MAD in Healthy Volunteers
- ATS 2020 Abstract/Poster

Phase 1b[2] (NCT03926793)

ONGOING

- Objectives:
  - Examine safety and tolerability in PAH subjects
  - Examine early PK/PD relationships
  - Identify potential biomarkers for Phase 2

Phase 2

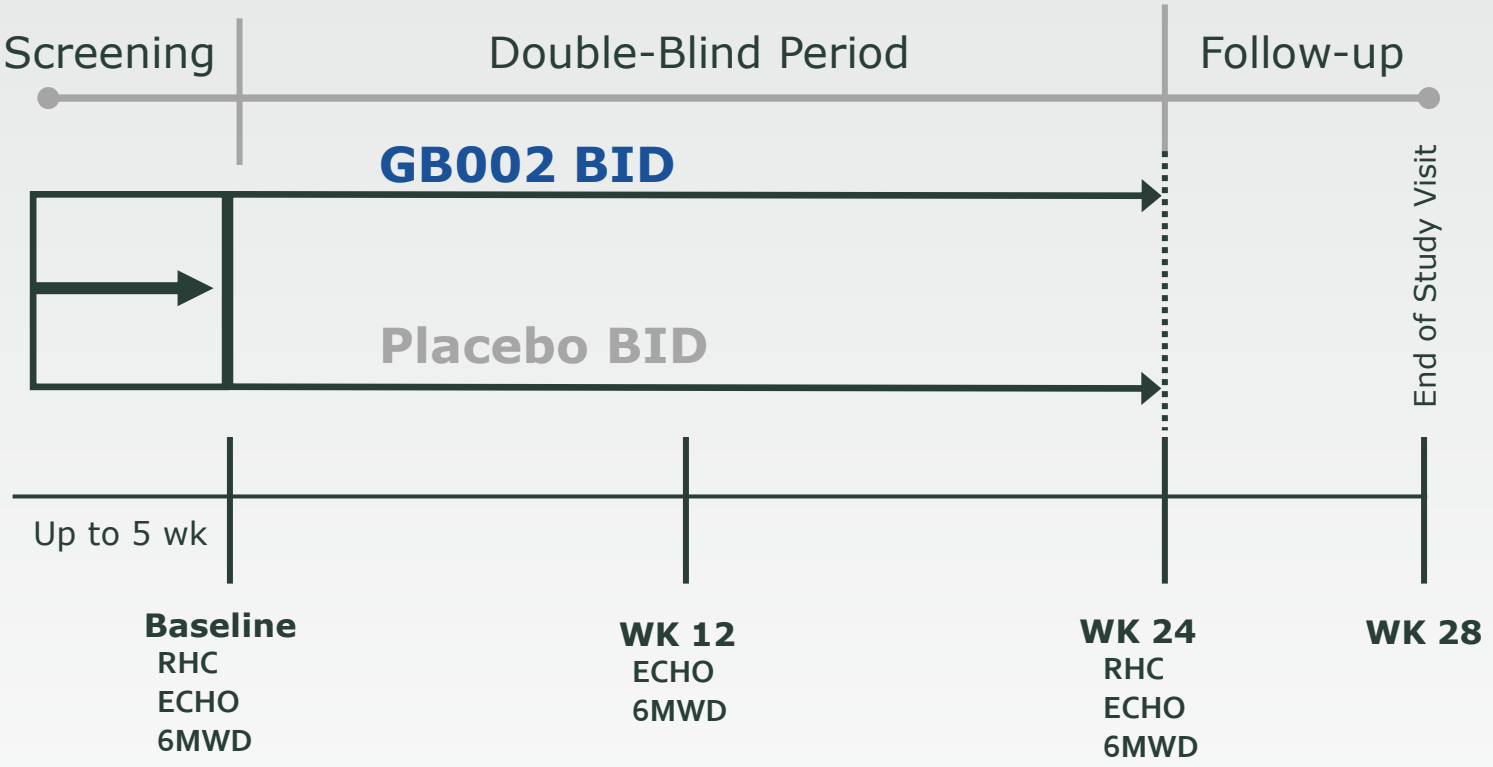
PLANNED

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

1. Li J, et al. AJRCCM 2020;201:A2907. **2.** https://clinicaltrials.gov/ct2/results?cond=&term=NCT03926793&cntry=&state=&city=&dist=

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

1. Data on file; Trials in Progress abstract submitted to AHA 2020.

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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Federal Ministry of Education and Research

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ECCPS Excellence Cluster Cardio-Pulmonary System

DFG

Cardio Pulmonary Institute

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Henning Gall
Khodr Tello
Manuel Richter
Akyl Sydykov
Astrid Weiss
Prakash Chelladurai
Dijana Iloska
Swati Dabral

Thank you,
Come and visit us next time at the UGMLC/DZL

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DZL Deutsches Zentrum für Lungenforschung

UGMLC Universities of Giessen & Marburg Lung Center

ECCPS Excellence Cluster Cardio-Pulmonary System

Max-Planck-Institute for Heart and Lung Research W.G. Kerckhoff-Institute

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