CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	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)
Short Title:	GB002 in Adult Subjects with PAH
Protocol Number:	GB002-2101
Investigational Product:	GB002 (oral inhalation)
Study Phase:	Phase 2
Sponsor Name:	GB002, Inc.
Legal Registered Address:	3013 Science Park Road, Suite 200 San Diego, CA 92121, USA
Regulatory Agency Identifier Number(s):	[redacted]
Version:	4.0.0
Approval Date:	18 November 2021

SPONSOR'S AUTHORIZED REPRESENTATIVE SIGNATURE PAGE

Protocol Title: 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)

Protocol Number: GB002-2101, v4.0.0

INVESTIGATOR AGREEMENT

Protocol Title:	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)
Protocol Number:	GB002-2101, v4.0.0

I have read this protocol and agree to conduct this study in accordance with ethical principles as outlined in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice, any applicable laws and requirements and any additional conditions mandated by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I acknowledge that I am responsible for the overall study conduct and I agree to personally conduct or supervise the described clinical study.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of GB002, Inc.

_____

Signature

_____ _____

Name of Investigator Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Global Version number and Date	**Region #1 (UK)** Version Number and Date	**Region #2 (Spain)** Version Number and Date	**Region #3 (France)** Version Number and Date	**Region #4 (Germany)** Version Number and Date	**Region #5 (Canada)** Version Number and Date	**Region #6 (Czech Republic)** Version Number and Date
Original Protocol, Global v1.0.0, 10 April 2020	Region-specific, v1.1.0, 15 June 2020	NA	NA	NA	NA	NA
Global v2.0.0, 18 June 2020	Region-specific, v2.3.0, 08 October 2020	Region-specific, v2.1.0, 06 August 2020	Region-specific, v2.2.0, 08 October 2020	Region-specific, v2.4.0, 13 October 2020	Region-specific, v2.5.0, 19 October 2020	Region-specific, v2.6.0, 04 December 2020
Global v2.0.0, 18 June 2020	NA	NA	NA	Region-specific, v2.4.1, 24 November 2020	Region-specific v.2.5.1, 18 December 2020	NA
Global v3.0.0, 18 December 2020	NA	NA	NA	NA	NA	NA
Global v3.0.1, 15 January 2021	NA	NA	NA	NA	NA	NA
Global v4.0.0, 18 November 2021	NA	NA	NA	NA	NA	NA

Amendment 4 (v4.0.0; 18 November 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purpose of this amendment from v3.0.1 to v4.0.0 is to update the requirements relating to concomitant medications based on recent results from the drug-drug interaction study [redacted] and the human ADME study [redacted].

Additional minor changes have been made to the protocol which are summarized below.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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)

Short Title: GB002 in Adult Subjects with PAH

Rationale

Despite the use of multiple approved agents and the use of these agents in combination, the morbidity and mortality of pulmonary arterial hypertension (PAH) remains unacceptably high (Farber, 2015; Galie, 2015).

Increased platelet-derived growth factor receptor (PDGFR) signaling has been strongly implicated in playing an important role in the pathogenesis of PAH for a number of reasons. These include the expression of PDGFR and its ligands in human PAH lung tissue, the efficacy of platelet-derived growth factor (PDGF) pathway inhibitors in animal models of PAH, and the observation that imatinib, an orally administered PDGFR and Abelson murine leukemia viral oncogene homolog (Abl) kinase inhibitor, improved cardiopulmonary hemodynamics in patients with PAH in a Phase 2 and Phase 3 study (Ghofrani, 2010; Hoeper, 2013a; Medarametla, 2014; Wu, 2008). The animal model data particularly highlight that inhibiting the PDGFR pathway may prevent/reverse the cellular proliferation of the intimal lining of the pulmonary arteries, a key characteristic of PAH. Thus, drugs that target this pathway may have a clinical benefit distinct from the benefit observed with the currently approved vasodilators for the treatment of PAH. Although the studies of imatinib in PAH demonstrated proof of concept, imatinib was associated with poor tolerability and serious side effects (Frost, 2015; Hoeper, 2013a) suggesting that while targeting the PDGF pathway was relevant as a potential therapeutic for PAH, a drug with an improved therapeutic window would be more optimal.

Based on this rationale, GB002 was developed as a highly potent, small molecule PDGFR kinase inhibitor that is formulated to be delivered via inhalation to limit systemic exposure and thereby improve the tolerability and side effect profile of this class of drugs.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• Determine the effect of GB002 on improving pulmonary hemodynamics in subjects with World Health Organization (WHO) Group 1 PAH who are WHO Functional Class (FC) II or III	• Change in pulmonary vascular resistance (PVR) using right heart catheterization (RHC) from Baseline to Week 24
Secondary	
• Determine the effect of GB002 on improving exercise capacity in this population	• Change in distance achieved on the six-minute walk test (6MWT), (Δ6MWD) from Baseline to Week 24
Safety	
• Evaluate the safety of GB002 in this population	• Incidence of treatment-emergent adverse events (TEAEs), serious TEAEs (SAEs), and treatment-emergent adverse event of special interest (AESIs)

Overall Design

This is a double-blind, placebo-controlled, randomized Phase 2 study. This study will evaluate the oral inhalation of GB002 in adult subjects with WHO Group 1 PAH who are WHO FC II and III and have a PVR of ≥ 400 dyne•s/cm^5.

After signing an informed consent form (ICF), subjects will be screened for study eligibility for up to a 5-week screening period. Subjects must continue on stable doses of background PAH medications from 4 weeks before consent and throughout the treatment period. Dose modification of background PAH medications will not be allowed during the screening period.

On Day 1 (Baseline visit), eligible subjects will be randomized 1:1 to 1 of 2 treatment groups to receive GB002 twice per day (BID) or placebo (Table 1). Subjects will initiate dosing with 60 mg BID and, after 2 weeks, will up titrate to 90 mg BID (6 inhalations BID). Investigational product (IP) dose may be reduced due to tolerability or AEs as described in Section 6.5. Randomization will be stratified by PVR. Subjects will receive IP, BID, over 24 weeks inhaled orally with a dry powder inhaler (DPI). Following initiation of IP in the clinic on Day 1 (Visit 2), subjects will have study visits every 4 weeks through Week 12 and subsequent visits at Weeks 18 and 24; subjects will be evaluated as specified in the Schedule of Activities (SoA), see Table 2. Subjects will also be contacted by phone at Weeks 2 (Visit 3) and 6 (Visit 4) and, for those subjects not willing or not eligible to participate in the open-label extension study, an in person Week 28 (Visit 9) Follow-up visit at the clinic is required. For the Week 4 (Visit 3.5),

Week 8 (Visit 5), and Week 18 (Visit 7) visits, subjects or study personnel may choose to have a home-health visit rather than an in-clinic visit. For home-health care visits, IP shipment to the subject's home may be arranged.

An Independent Data Monitoring Committee (IDMC), comprised of external expert physician(s) and an external biostatistician, will regularly monitor overall safety and emerging efficacy results, as well as general aspects of study conduct, to ensure that the benefits and risks to subjects of study participation remain acceptable.

Subjects may be eligible to participate in an open-label extension (OLE) study under a different protocol provided they have completed study treatment and all assessments and procedures required at the Week 24 visit.

Treatment Groups, Number of Subjects and Duration:

Subjects will be randomized 1:1 to 1 of 2 treatment groups described in Table 1.

Table 1: Treatment Groups

Treatment Group	Dose Level, Schedule and Route of Administration	Number of Subjects
GB002	90 mg BID orally inhaled (see Section 6.5.1) Subjects with tolerability issues at 90 mg BID will be permitted to down titrate to 60 mg or 45 mg BID, as appropriate.	40
Placebo	BID, orally inhaled placebo	40

Duration

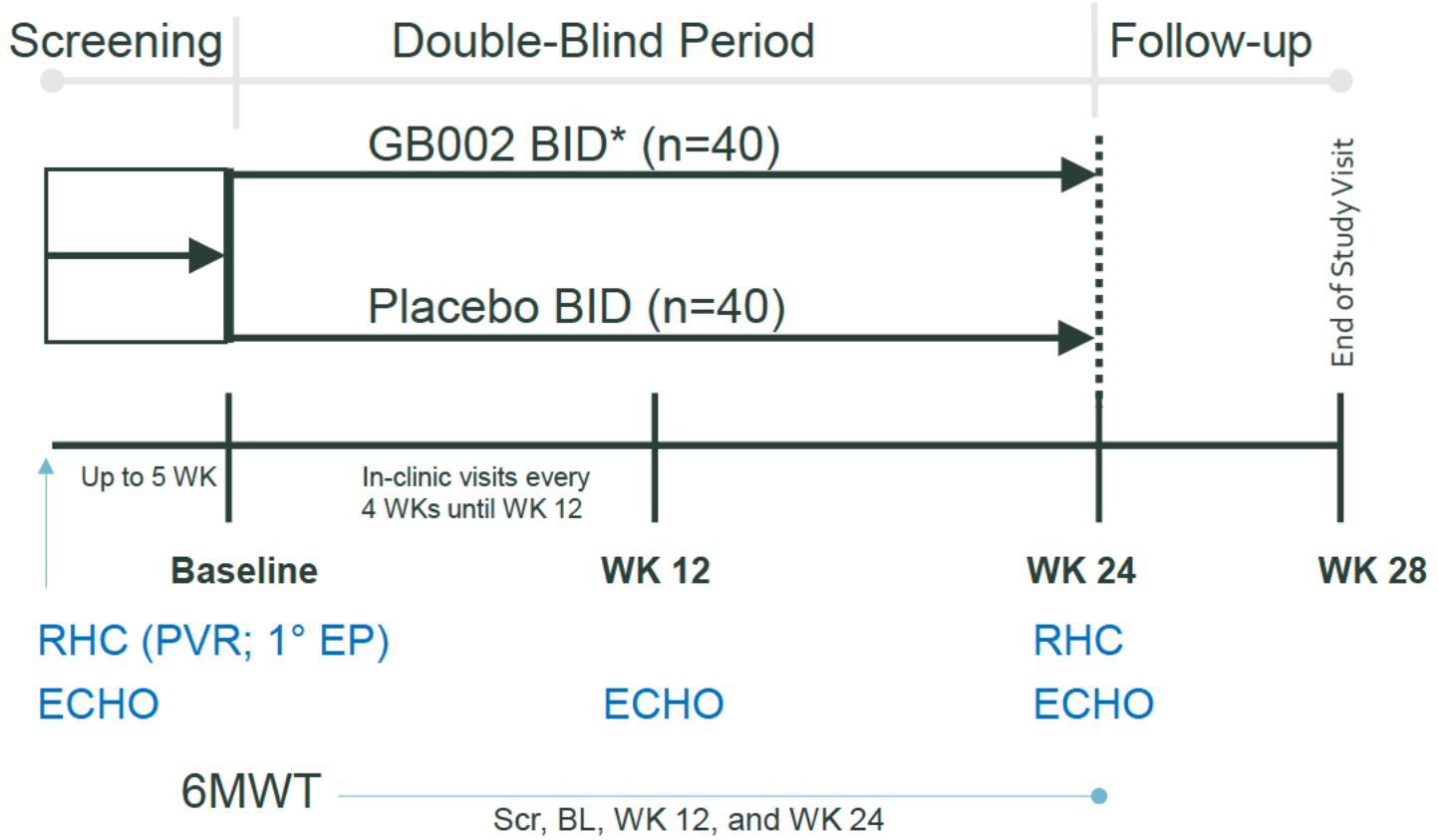
For each subject, study participation is expected to last up to 33 weeks as follows:

Screening:	up to 5 weeks
Treatment period:	24 weeks (-3, to +14 days)
Follow-up:	For subjects not enrolling in the OLE, 4 weeks (±7 days) after the last dose of IP. This will be defined as the last study visit (Week 36 for male subjects participating in the semen analysis).

Independent Data Monitoring Committee: Yes

1.2. Study Scheme

Figure 1: Study Scheme



* After 2 weeks, all subjects should be dose escalated, as tolerated, to 90 mg BID. Should a dose reduction be required, after discussion with the Sponsor's Medical Monitor (or designee), dose reduction to 60 mg BID, and if not tolerated, further dose reduction to 45 mg BID will be allowed.
* A 4-week safety follow up will not be required for subjects transitioning to OLE.

1.3. Schedule of Activities (SoA)

Table 2: Schedule of Activities

	Screening	Baseline	Treatment Period [a]									Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled						EOT Visit	Follow-Up	ET	
Visit Number	**1**	**2**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-5 to -1 [b,e]**	**Day 1 [e]**	**2 [c]**	**4 [d]**	**6 [c]**	**8 [d]**	**12 [e]**	**18 [d]**	**24 [c]**	**28 [f]**	**ET [g]**	[b] Screening period is from -5 weeks to -1 day; assessments may be performed at any time during the screening period, as needed. [c] Telephonic Contact: ✓ Collection of AEs and concomitant medications. At the discretion of the investigator, an unscheduled visit may also be scheduled for additional assessments. ✓ Confirm dosing compliance and proper use of dry powder inhaler (DPI). Book unscheduled visit for dosing re-training, if necessary [d] In-clinic visit with home-health visit option (defined in Section 8) [e] Mandatory in-clinic visit. [f] At least 4 weeks after last dose of IP. A 28-day safety follow-up will not be required for subjects transitioning to OLE. [g] If needed. Last dose at the Early Termination visit will be at the discretion of the study physician based on subject safety and dependent on subject's continued consent.
Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Written informed consent	X											May be obtained prior to Visit 1.
Eligibility criteria	X	X*										* Confirm eligibility prior to randomization.
Demography	X											
Medical history	X	X*										* Update prior to dosing, as applicable.
PAH diagnosis and PAH background medication history	X											

	Screening	Baseline	Treatment Period [a]									Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled						EOT Visit	Follow-Up	ET	
Visit Number	**1**	**2**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-5 to -1** [b,e]	**Day 1** [e]	**2** [c]	**4** [d]	**6** [c]	**8** [d]	**12** [e]	**18** [d]	**24** [c]	**28** [f]	**ET** [g]	[b] Screening period is from -5 weeks to -1 day; assessments may be performed at any time during the screening period, as needed. [c] Telephonic Contact: ✓ Collection of AEs and concomitant medications. At the discretion of the investigator, an unscheduled visit may also be scheduled for additional assessments. ✓ Confirm dosing compliance and proper use of dry powder inhaler (DPI). Book unscheduled visit for dosing re-training, if necessary [d] In-clinic visit with home-health visit option (defined in Section 8) [e] Mandatory in-clinic visit. [f] At least 4 weeks after last dose of IP. A 28-day safety follow-up will not be required for subjects transitioning to OLE. [g] If needed. Last dose at the Early Termination visit will be at the discretion of the study physician based on subject safety and dependent on subject's continued consent.
Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
WHO FC assessment	X	X					X		X		X	
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Vital signs and body weight	X*	X		X		X	X	X	X	X	X	* Measure height at screening
Physical examination	X						X		X		X	
12-lead electrocardiogram	X	X		X		X	X	X	X		X	Conduct prior to 6MWT for weeks where 12-lead electrocardiogram and 6MWT are both done.
V/Q lung scan, CT-angiogram, or pulmonary angiogram	X*											*If clinically indicated at screening or if not performed at any point prior to screening. Computed tomography (CT); ventilation-perfusion (V/Q)

	Screening	Baseline	Treatment Period [a]									Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled						EOT Visit	Follow-Up	ET	
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Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Six-minute walk test (6MWT)	X*	X					X		X		X	*Two 6MWTs at least 2 hours apart will be done at Screening according to the 6MWT manual. Continuous heart rate monitoring during the 6MWT will be conducted as a substudy at select participating sites.
Pulmonary function tests (PFTs) and diffusion capacity of the lungs for carbon monoxide (DLCO)	X								X		X	
Echocardiogram (ECHO)	X						X		X		X*	* For subjects who withdraw from the study Week 12 or later

	Screening	Baseline	Treatment Period [a]						EOT Visit	Follow-Up	ET	Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled									
Visit Number	**1**	**2**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**		
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Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Right heart catheterization	X								X**		X*	* For subjects who withdraw from the study Week 12 or later ** Refer to Section 10.8.
Dispense handheld device if all screening criteria are met		X										Handheld device will be used by patient at home to complete daily dosing diary.
Collect handheld device									X		X	
EQ-5D-5L survey		X					X		X		X	Perform predose at the clinic using ePRO tablet.

	Screening	Baseline	Treatment Period [a]									Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled						EOT Visit	Follow-Up	ET	
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Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Serology and urine drug screen	X*											Serology includes: Hepatitis B virus surface antigen (HbsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody, tuberculosis (TB). Urine drug screen includes amphetamines, methamphetamines, cocaine, and phencyclidine. *If a subject has a positive test, confirmatory serology will be performed.
TSH, free T4	X						X		X		X	Thyroid stimulating hormone (TSH)

	Screening	Baseline	Treatment Period [a]									Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
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Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Clinical laboratory tests	X	X*		X		X	X	X	X	X	X	Fasting required *After randomization, collect predose.
Testosterone, LH, FSH, estradiol, and inhibin B		X				X	X	X	X	X	X	For male subjects only. To be collected in the morning under fasting conditions.
Male fertility assessment*		X					X		X	X‡		*Optional: Samples will be collected from male subjects who are willing and able to provide semen samples (see Section 8.2.4.1). ‡ Male subjects who provided semen samples during the study will be asked to provide a final semen sample at 12 weeks (+2 weeks) after the Week 24 visit.

	Screening	Baseline	Treatment Period [a]						EOT Visit	Follow-Up	ET	Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled									
Visit Number	**1**	**2**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**		
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Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Coagulation laboratory tests	X			X		X	X		X		X	
Urinalysis	X*						X		X*		X	*Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the screening and EOT visits.
Pregnancy test (WOCBP)	S	U*		U		U	U**	U**	U	U	U	Women of childbearing potential (WOCBP) If urine (U) is positive, collect serum (S) to confirm. **At-home urine pregnancy tests will be provided for required monthly pregnancy testing. Any positive at-home urine pregnancy test should be confirmed with an on-site serum pregnancy test. *A negative result must be observed before dosing.

	Screening	Baseline	Treatment Period [a]						EOT Visit	Follow-Up	ET	Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled									
Visit Number	**1**	**2**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-5 to -1** [b,e]	**Day 1** [e]	**2** [c]	**4** [d]	**6** [c]	**8** [d]	**12** [e]	**18** [d]	**24** [c]	**28** [f]	**ET** [g]	[b] Screening period is from -5 weeks to -1 day; assessments may be performed at any time during the screening period, as needed. [c] Telephonic Contact: ✓ Collection of AEs and concomitant medications. At the discretion of the investigator, an unscheduled visit may also be scheduled for additional assessments. ✓ Confirm dosing compliance and proper use of dry powder inhaler (DPI). Book unscheduled visit for dosing re-training, if necessary [d] In-clinic visit with home-health visit option (defined in Section 8) [e] Mandatory in-clinic visit. [f] At least 4 weeks after last dose of IP. A 28-day safety follow-up will not be required for subjects transitioning to OLE. [g] If needed. Last dose at the Early Termination visit will be at the discretion of the study physician based on subject safety and dependent on subject's continued consent.
Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Serum digoxin concentration*	X											*Only for subjects taking digoxin To be checked locally as clinically indicated to adjust dosing for therapeutic monitoring of digoxin levels used in PAH
Exploratory biomarkers sample		X					X		X		X	Blood samples will be collected as specified in Table 9.
GB002 pharmacokinetic (PK) sample		X					X		X		X	Blood samples will be collected as specified in Table 8.
PAH background medication PK sample		X					X		X		X	Blood samples will be collected as specified in Table 5.

	Screening	Baseline	Treatment Period [a]									Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled						EOT Visit	Follow-Up	ET	
Visit Number	**1**	**2**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-5 to -1** [b,e]	**Day 1** [e]	**2** [c]	**4** [d]	**6** [c]	**8** [d]	**12** [e]	**18** [d]	**24** [c]	**28** [f]	**ET** [g]	[b] Screening period is from -5 weeks to -1 day; assessments may be performed at any time during the screening period, as needed. [c] Telephonic Contact: ✓ Collection of AEs and concomitant medications. At the discretion of the investigator, an unscheduled visit may also be scheduled for additional assessments. ✓ Confirm dosing compliance and proper use of dry powder inhaler (DPI). Book unscheduled visit for dosing re-training, if necessary [d] In-clinic visit with home-health visit option (defined in Section 8) [e] Mandatory in-clinic visit. [f] At least 4 weeks after last dose of IP. A 28-day safety follow-up will not be required for subjects transitioning to OLE. [g] If needed. Last dose at the Early Termination visit will be at the discretion of the study physician based on subject safety and dependent on subject's continued consent.
Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Pharmacogenetic sample		X*										* If consent provided, sample can be collected at any visit post-randomization.
NT-proBNP sample		X*		X		X	X		X	X	X	N-terminal pro b-type natriuretic peptide (NT-proBNP) *After randomization, collect predose.
Randomization		X										
Dispense IP		X		X		X	X	X				Investigational product (IP)
Inhalation and DPI device training*		X										* As needed during the treatment period

	Screening	Baseline	Treatment Period [a]									Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled						EOT Visit	Follow-Up	ET	
Visit Number	**1**	**2**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-5 to -1** [b,e]	**Day 1** [e]	**2** [c]	**4** [d]	**6** [c]	**8** [d]	**12** [e]	**18** [d]	**24** [c]	**28** [f]	**ET** [g]	[b] Screening period is from -5 weeks to -1 day; assessments may be performed at any time during the screening period, as needed. [c] Telephonic Contact: ✓ Collection of AEs and concomitant medications. At the discretion of the investigator, an unscheduled visit may also be scheduled for additional assessments. ✓ Confirm dosing compliance and proper use of dry powder inhaler (DPI). Book unscheduled visit for dosing re-training, if necessary [d] In-clinic visit with home-health visit option (defined in Section 8) [e] Mandatory in-clinic visit. [f] At least 4 weeks after last dose of IP. A 28-day safety follow-up will not be required for subjects transitioning to OLE. [g] If needed. Last dose at the Early Termination visit will be at the discretion of the study physician based on subject safety and dependent on subject's continued consent.
Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Administer IP		X*	←======= Daily (BID) =======→									At the clinic; for all clinic visits, morning dose will be administered at the clinic * Observe subject for 2 hours post-dose.
Dose escalation*				←============→								*May occur at any point up until Week 20, including phone call check-in. Refer to Section 6.5.1.
Administer oral PAH background medications in the clinic		X					X		X		X	The morning doses of oral PAH disease-specific background medications should be taken immediately prior to GB002 dosing in clinic on PK sampling days.
Complete dosing diary		←======= Daily (BID) =======→										To be completed on handheld device daily from Baseline to Week 24.

	Screening	Baseline	Treatment Period [a]									Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled						EOT Visit	Follow-Up	ET	
Visit Number	**1**	**2**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-5 to -1** [b,e]	**Day 1** [e]	**2** [c]	**4** [d]	**6** [c]	**8** [d]	**12** [e]	**18** [d]	**24** [c]	**28** [f]	**ET** [g]	[b] Screening period is from -5 weeks to -1 day; assessments may be performed at any time during the screening period, as needed. [c] Telephonic Contact: ✓ Collection of AEs and concomitant medications. At the discretion of the investigator, an unscheduled visit may also be scheduled for additional assessments. ✓ Confirm dosing compliance and proper use of dry powder inhaler (DPI). Book unscheduled visit for dosing re-training, if necessary [d] In-clinic visit with home-health visit option (defined in Section 8) [e] Mandatory in-clinic visit. [f] At least 4 weeks after last dose of IP. A 28-day safety follow-up will not be required for subjects transitioning to OLE. [g] If needed. Last dose at the Early Termination visit will be at the discretion of the study physician based on subject safety and dependent on subject's continued consent.
Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Collect used investigational product/conduct accountability				X		X	X	X	X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	
Assessment of Risk Score		X					X		X			Refer to Table 7.
Assessment of Clinical Worsening		X					X		X			Refer to Section 8.1.5.
User Device Survey									X		X	
Functional Respiratory Imaging Substudy		X							X		X*	At selected sites (Section 8.1.8) *ET only to be collected if ET occurs after 16 weeks of study drug.

	Screening	Baseline	Treatment Period [a]						EOT Visit	Follow-Up	ET	Notes: End of Treatment (EOT) Early termination (ET) Investigational product (IP)
			Double-Blind, Placebo-Controlled									
Visit Number	**1**	**2**	**3**	**3.5**	**4**	**5**	**6**	**7**	**8**	**9**		
Week	**-5 to -1** [b,e]	**Day 1** [e]	**2** [c]	**4** [d]	**6** [c]	**8** [d]	**12** [e]	**18** [d]	**24** [c]	**28** [f]	**ET** [g]	[b] Screening period is from -5 weeks to -1 day; assessments may be performed at any time during the screening period, as needed. [c] Telephonic Contact: ✓ Collection of AEs and concomitant medications. At the discretion of the investigator, an unscheduled visit may also be scheduled for additional assessments. ✓ Confirm dosing compliance and proper use of dry powder inhaler (DPI). Book unscheduled visit for dosing re-training, if necessary [d] In-clinic visit with home-health visit option (defined in Section 8) [e] Mandatory in-clinic visit. [f] At least 4 weeks after last dose of IP. A 28-day safety follow-up will not be required for subjects transitioning to OLE. [g] If needed. Last dose at the Early Termination visit will be at the discretion of the study physician based on subject safety and dependent on subject's continued consent.
Visit window (days)			**±3**	**±7**	**±3**	**±7**	**±7**	**±7**	**-3 to +14**	**+7**		
Heart Rate Monitoring Substudy		X					X		X		X*	At selected sites (Section 8.1.8) * ET only to be collected if ET occurs after 16 weeks of study drug.

[a] Guidance to address a pandemic or other global health emergencies and potential impact on this clinical study are provided in Section 10.8, Appendix 8.

2. INTRODUCTION

GB002, formulated for oral inhalation delivery as a dry powder for treatment of pulmonary arterial hypertension (PAH), is a highly potent, small molecule platelet-derived growth factor receptor (PDGFR) kinase inhibitor. PDGFR is a tyrosine kinase receptor that induces cell proliferation when activated by its agonist ligands.

2.1. Study Rationale

Despite the use of multiple approved agents and the use of these agents in combination, the morbidity and mortality of PAH remains unacceptably high (Farber, 2015; Galie, 2015).

Increased PDGFR signaling has been strongly implicated in playing an important role in the pathogenesis of PAH for a number of reasons. These include the expression of PDGFR and its ligands in human PAH lung tissue, the efficacy of platelet-derived growth factor (PDGF) pathway inhibitors in animal models of PAH, and the observation that imatinib, an orally administered PDGFR and Abelson murine leukemia viral oncogene homolog (Abl) kinase inhibitor, improved cardiopulmonary hemodynamics in patients with PAH in a Phase 2 and Phase 3 study (Ghofrani, 2010; Hoeper, 2013a; Medarametla, 2014; Wu, 2008). The animal model data particularly highlight that inhibiting the PDGFR pathway may prevent/reverse the cellular proliferation of the intimal lining of the pulmonary arteries, a key characteristic of PAH. Thus, drugs that target this pathway may have a clinical benefit distinct from the benefit observed with the currently approved vasodilators for the treatment of PAH. Although the studies of imatinib in PAH demonstrated proof of concept, imatinib was associated with poor tolerability and serious side effects (Frost, 2015; Hoeper, 2013a) suggesting that while targeting the PDGF pathway was relevant as a potential therapeutic for PAH, a drug with an improved therapeutic window would be more optimal.

Based on this rationale, GB002 was developed as a highly potent, small molecule PDGFR kinase inhibitor that is formulated to be delivered via inhalation to limit systemic exposure and thereby improve the tolerability and side effect profile of this class of drugs.

2.2. Background

PAH is an orphan disease associated with high morbidity and mortality (Fisher, 2006; Launay, 2013; Simonneau, 2013). Despite recent advances in vasodilator therapy for PAH, more effective treatments are needed. PAH has been defined by parameters obtained at right heart catherization (RHC): a mean pulmonary arterial pressure (mPAP) of $\geq$ 25 mm Hg and a pulmonary capillary wedge pressure (PCWP) of $\leq$ 15 mm Hg (Hoeper, 2013b). The 6th World Symposium on Pulmonary Hypertension Task Force has proposed revising this definition as follows: an mPAP > 20 mm Hg, PCWP $\leq$ 15 mm Hg, and a pulmonary vascular resistance (PVR) $\geq$ 3 Wood Units (Simonneau, 2019).

The clinical manifestations of PAH result from an increase in resistance to blood flow through the pulmonary circulation due to a decrease in the cross-sectional area of the pulmonary arterioles and pulmonary vasoconstriction (Humbert, 2014). This decrease is due to in large part to proliferative remodeling of the pulmonary artery vasculature (Galie, 2010). Pulmonary vascular remodeling consists of two major components: (1) concentric and plexiform lesions in

small precapillary pulmonary arterioles that decrease overall cross-sectional area of the pulmonary arterioles, and (2) abnormal muscularization, hypertrophy, and hyperresponsiveness of pulmonary arterioles (Cool, 1997; Tuder, 1994). The proliferative component of pulmonary vascular remodeling may be due to a clonal expansion of apoptosis-resistant endothelial cells, as well as abnormal proliferation of myofibroblasts (Rai, 2008; Yi, 2000). Both primary and secondary proliferation of smooth muscle cells in pulmonary arterioles also play an important role in the pathogenesis and progression of PAH (Eickelberg, 2007; Yi, 2000). The pulmonary vasoconstriction component is due to abnormal muscularization and hypertrophy of pulmonary arterioles as well as changes in calcium handling and regulation of actin-myosin interactions within the vascular smooth muscle cells of the vessel media (Wu, 2008).

A large body of basic and translational research, including genetic dissection studies, functional assays, animal models, and histopathologic analysis of human PAH lung samples has shown that PDGF signaling through the two major isoforms of the PDGFR receptor plays a critical role in the two major components of pulmonary vascular remodeling: (1) the abnormal muscularization, hypertrophy, and hyperresponsiveness of the pulmonary arterioles, and (2) the neointimal proliferative lesions that compromise the lumen of the pulmonary arterioles. Thus, by inhibiting PDGF signaling it should be possible to address these two key components of pulmonary vascular remodeling, restore a more normal phenotype of the pulmonary arterioles and thereby reverse the pathological remodeling in the PAH pulmonary vasculature. Clinically, this pulmonary vascular remodeling that results in an increase in resistance to blood flow through the pulmonary vasculature can be measured by the pulmonary vascular resistance at the time of right heart catheterization.

Consistent with this hypothesis, imatinib, a PDGF receptor kinase inhibitor, has been shown to inhibit PDGF homodimer (PDGF-BB)-induced proliferation and migration of primary pulmonary artery smooth muscle cells (PASMCs), and to ameliorate pulmonary vascular remodeling in animal models of PAH (Heldin, 1999; Perros, 2008). Because of these demonstrated favorable effects of imatinib, it would be expected that pulmonary vascular resistance would improve, accordingly. Although PVR may decrease in response to vasodilator therapies in responsive subjects, there is a subset of subjects with WHO FC II and III who, despite vasodilator therapy, suffer worsening disease as reflected in a high PVR. The inadequate response to vasodilator therapy in this resistant population is likely due to limited effects on the two key components of pulmonary vascular remodeling of currently available treatments. In this target population, it would be expected that an improvement in PVR would be a result of favorable effects on pulmonary vascular remodeling by PDGFR inhibition.

2.3. Benefit/Risk Assessment

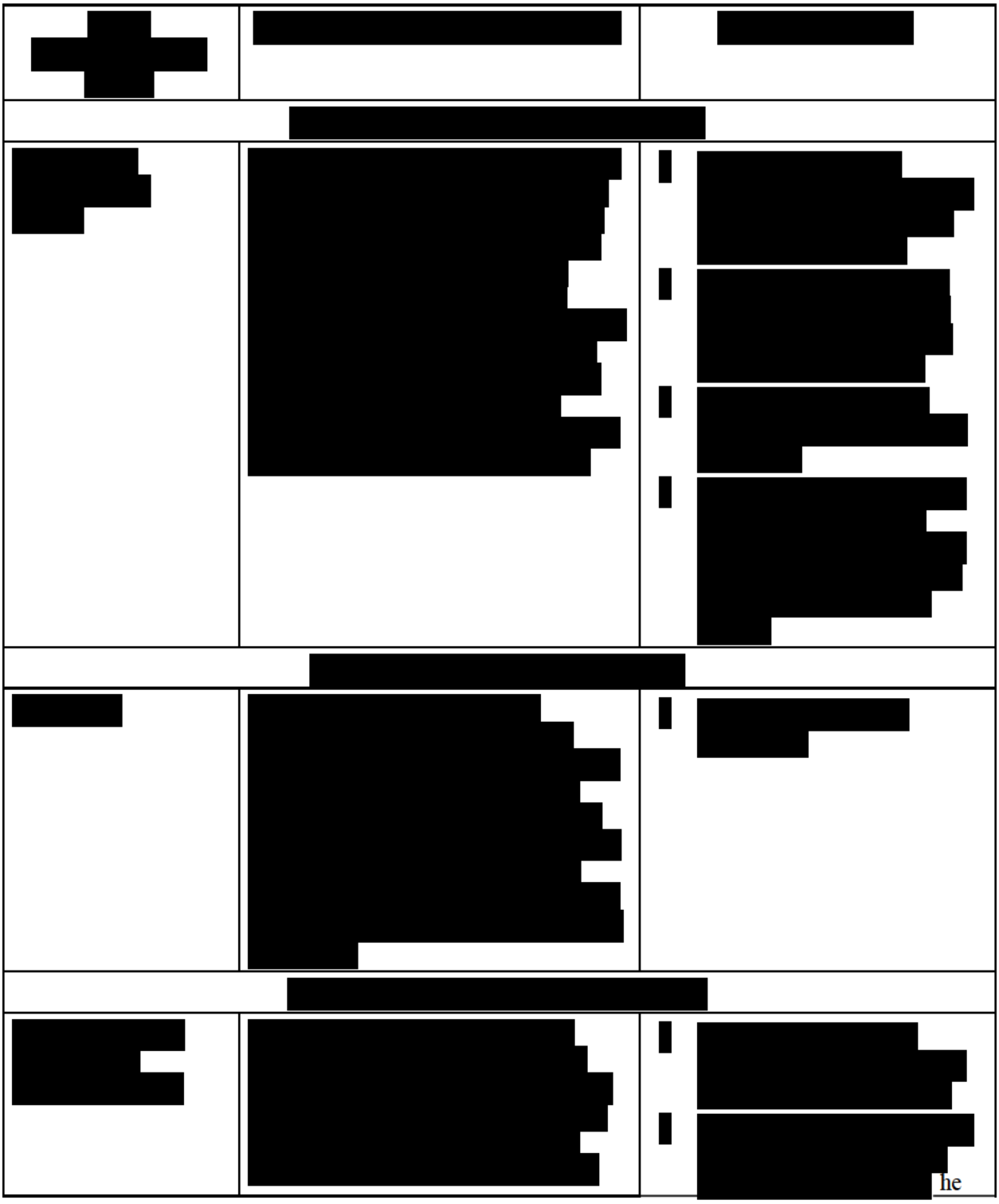
More detailed information about the known and expected benefits and potential risks of GB002 may be found in the Investigator's Brochure.

2.3.1. Risk Assessments

Orally inhaled GB002 has been well-tolerated in healthy subjects without drug-associated respiratory or cardiac effects in Phase 1 studies that evaluated up to 1 week of repeat dosing at both 48 mg three times per day (TID) and 90 mg BID. Review of available safety data confirms no findings with respect to electrocardiogram (ECG), chest X-rays, and pulmonary function

tests. The photosafety assessment is ongoing for GB002. Until completion of this assessment, light protective measures should be used to minimize exposure to direct sunlight, eg, sunglasses, wide-brimmed hat, sunscreen (if tolerable/not contraindicated) on any exposed skin. Safety considerations and mitigation strategies for GB002 in this study are described [redacted].

[redacted]



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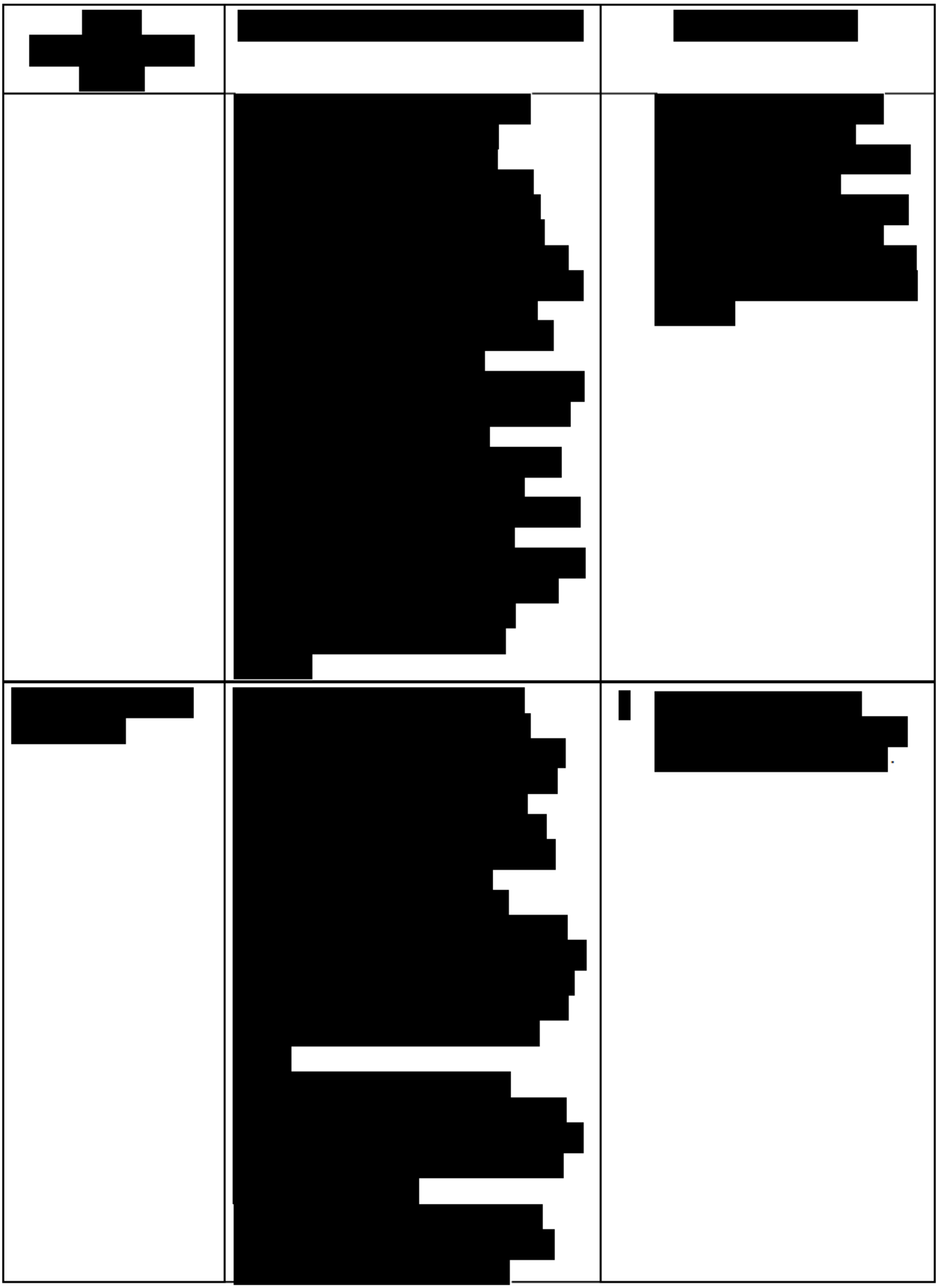
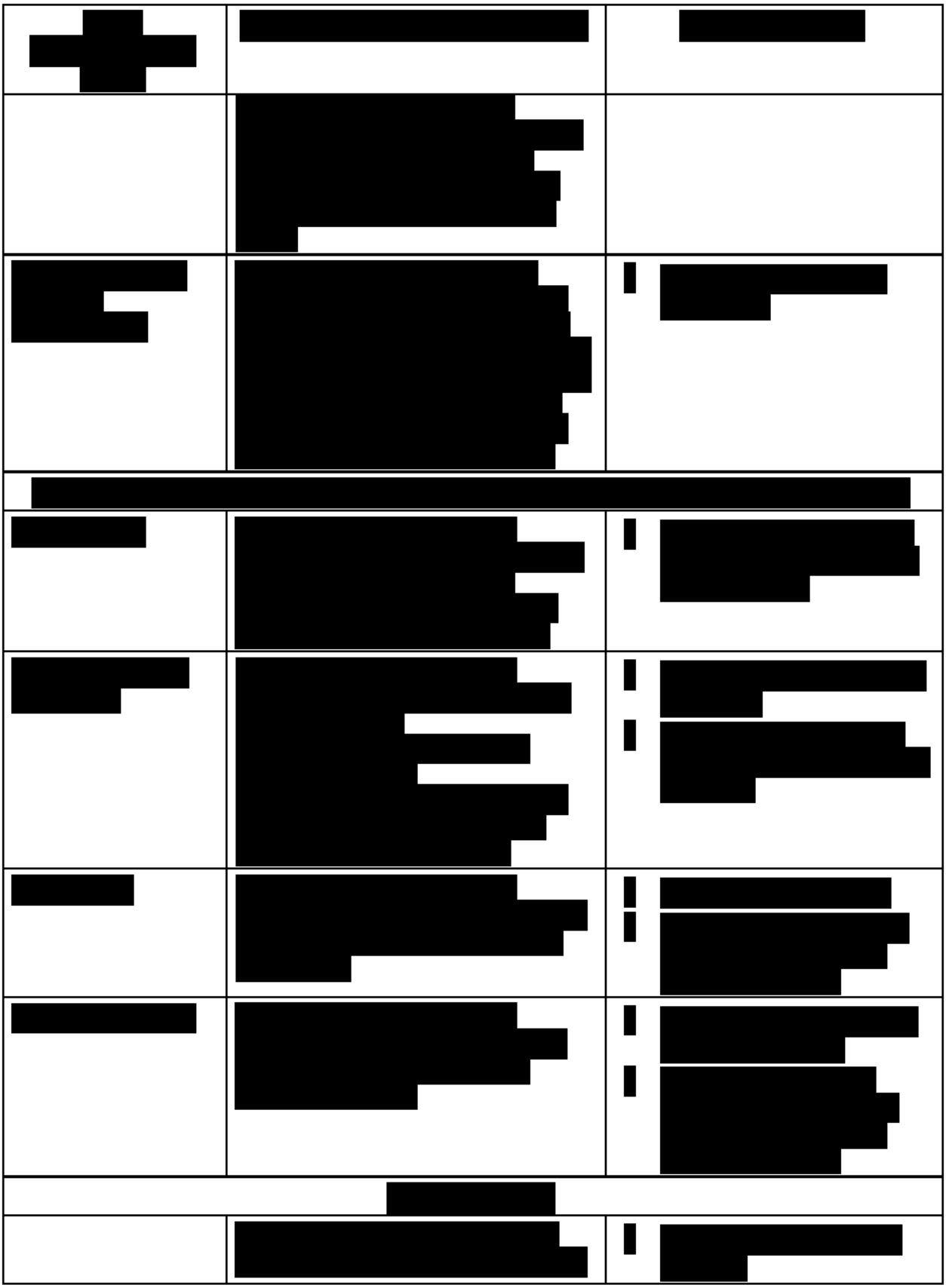




[redacted]	[redacted]	[redacted]
	[redacted]	

2.3.2. Benefit Assessment

The potential benefits of GB002 include an improvement of cardiopulmonary hemodynamics and pulmonary arterial vascular remodeling, which may improve morbidity and mortality in subjects with PAH. Reversal of the pathological pulmonary vascular remodeling is an important potential benefit of GB002, as it could modify the overall course of the disease. A proof of the concept that PDGFR antagonism can result in clinical benefits for PAH patients comes from the IMPRES study with imatinib (Hoeper, 2013a). Additionally, as GB002 utilizes a novel route of inhaled administration, there is potential for improved drug delivery to the pulmonary vessels with reduced systemic absorption. These potential benefits are supported by 2 in vivo nonclinical efficacy studies that demonstrate improvements in right ventricular systolic pressures and lumen size with GB002 both alone and in combination with PAH background medications.

Based upon these findings, GB002 may have a favorable effect on the pulmonary arteriolar intimal proliferation and other features of abnormal pulmonary vascular remodeling in patients with PAH, thus leading to an improvement in cardiovascular hemodynamics and ultimately to improved clinical outcomes.

Please refer to GB002 Investigator's Brochure for additional details.

2.3.3. Overall Benefit: Risk Conclusion

The potential benefits of GB002 for the treatment of PAH outweigh the potential risks. GB002 may offer improvements in cardiopulmonary hemodynamics that may translate to better functional outcomes.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Determine the effect of GB002 on improving pulmonary hemodynamics in subjects with WHO Group 1 PAH who are WHO FC II and III	• Change in PVR using RHC from Baseline to Week 24
Secondary	
• Determine the effect of GB002 on improving exercise capacity in this population	• Change in distance achieved on the six-minute walk test (6MWT), (Δ6MWD) from Baseline to Week 24

Objectives	Endpoints
Safety	
• Evaluate the safety of GB002 in this population	• Incidence of treatment-emergent adverse events (TEAEs), serious TEAEs (SAEs), and treatment-emergent adverse event of special interests (AESIs)
Exploratory	
• Evaluate the effect of GB002 on right heart function measures in this population	• Change from Baseline in tricuspid annular peak systolic velocity (TAS'), right ventricular (RV) Tei index and right ventricular free wall strain (RVFWS) by echocardiogram (ECHO)
• Evaluate the effect of GB002 on other measures of efficacy	• Changes in: – WHO FC – European QOL - 5 Dimensions - 5 Levels (EQ-5D-5L) – Right ventricle (RV) function by imaging (echocardiography) – Sub-study: Functional respiratory imaging (FRI) by computed tomography (CT) scan (in subjects with prior CT imaging) • Time from first dose of GB002 to first event of protocol-defined clinical worsening event, assessed by measuring the first occurrence of any one of the following events: – Death (all causes) – Hospital admission for worsening PAH, as a result of any of the following: o Non-elective hospitalization caused by clinical conditions directly related to PAH and/or right heart failure o Need for intravenous (IV) diuretics (more than a single dose in 24 hours) o Lung or heart/lung transplantation o Atrial septostomy

Objectives	Endpoints
	○ Initiation of parenteral (IV infusion or subcutaneous injection) therapy with a prostacyclin (if not previously utilizing parenteral prostacyclin therapy) – Disease progression, defined as: ○ Worsening symptoms of right heart failure requiring initiation of a new PAH disease-specific medication or an increase in dose, or change in disease-specific background PAH medications or initiation of chronic oxygen therapy (ie, requires oxygen for >24 hours with the intent of long-term use); or ○ A decrease in distance on 6MWT (6MWD) of at least 15% from Baseline, directly related to PAH progression, confirmed by 2 assessments of 6MWD performed at 2 consecutive visits and worsening in WHO FC for subjects with WHO FC I/II/III; or ○ Worsening Risk Score Category (as in Table 7) (Leuchte, 2018). Defined as a change in two components of the Risk Assessment to a worse risk category
• Evaluate the safety of GB002 on other measures of tolerability	• Change from Baseline in clinical laboratory parameters, ECG parameters, pulmonary function and vital signs
• Evaluate the pharmacokinetics (PK) of GB002	• Plasma concentrations of GB002 and its metabolites, if appropriate
• Evaluate the pharmacodynamics (PD) of GB002 in this population	• Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) • Changes from Baseline in biomarkers measured in blood samples
• Evaluate the effects of GB002 on Heart Rate Expenditure and Heart Rate Recovery	• Change from Baseline in heart rate expenditure and heart rate recovery as

Objectives	Endpoints
during 6MWT – Substudy at select participating sites	measured by continuous heart rate monitoring during the 6MWT
• Evaluate changes in the pulmonary vasculature by High-resolution CT – Substudy at select participating sites.	• Change from Baseline in pulmonary vasculature blood volume, pulmonary blood volume as a percent of total lung volume, fibrosis score, and image-based ventilation to perfusion score.
• Determine the effect of GB002 on Risk Score Category	• Change from Baseline in Risk Score Category based on REVEAL v2.0 and European Society of Cardiology (ESC)/European Respiratory Society (ERS)

4. STUDY DESIGN

4.1. Overall Study Design

This is a double-blind, placebo-controlled, randomized study of oral inhalation of GB002 in adult subjects with WHO Group 1 PAH who are WHO FC II and III and have a PVR of $\geq$ 400 dyne•s/cm^5.

After signing an informed consent form (ICF), subjects will be screened for study eligibility for up to a 5-week period. Standard of care tests/procedures that were performed prior to signing the consent may be used as part of the screening assessments as long as the procedures meet the protocol-required timelines (ie, within 5 weeks of randomization for these procedures). Subjects must continue on stable doses of background PAH medications from 4 weeks before consent and throughout the treatment period. Dose modification of background PAH therapy will not be allowed during the screening period; for dose adjustment during the study, refer to Section 6.5.2.

On Day 1 (Baseline visit), eligible subjects will be randomized 1:1 to 1 of 2 treatment groups described in Table 1. Subjects will initiate dosing with 60 mg BID and, after 2 weeks, will up titrate to 90 mg BID (6 inhalations BID). IP dose may be reduced due to tolerability or AEs as described in Section 6.5. Randomization will be stratified by PVR as described in Section 6.3.1. Subjects will receive IP, BID, over 24 weeks inhaled orally with a dry powder inhaler (DPI). Following initiation of IP in the clinic on Day 1 (Visit 2), subjects will have study visits every 4 weeks through Week 12 and subsequent visits at Weeks 18 and 24; subjects will be evaluated as specified in the Schedule of Activities (SoA), see Table 2. Subjects will also be contacted by phone at Weeks 2 (Visit 3) and 6 (Visit 4) and, for those subjects not willing or not eligible to participate in the open-label extension study, an in person Week 28 (Visit 9) Follow-up visit at the clinic is required. An interim analysis may be conducted as described in Section 9.5. For the Week 4 (Visit 3.5), Week 8 (Visit 5), and Week 18 (Visit 7) visits, subjects or study personnel may choose to have a home-health visit rather than an in-clinic visit. For home-health care visits, IP shipment to the subject's home may be arranged.

In addition to the Sponsor's regular monitoring of overall safety, an IDMC will meet to review overall safety and emerging efficacy results, as well as general aspects of study conduct, to ensure that the benefits and risks to subjects of study participation remain acceptable at intervals as defined under a separate charter (Section 9.5.1).

Subjects may be eligible to participate in an open-label extension (OLE) study under a different protocol provided they have completed study treatment and all assessments and procedures required at the Week 24 visit.

4.2. Scientific Rationale for Study Design

The study is designed as a double-blind, randomized, placebo-controlled study. All subjects will be on background PAH therapy. This approach is consistent with the development of new medications as add-on therapy in PAH studies (Abraham, 2010; Sitbon, 2010; Sitbon, 2019; Studer, 2014). The study is placebo-controlled to minimize bias and provide a control group to which the efficacy of GB002 can be compared. Comparisons between the GB002 and placebo treatment groups will facilitate differentiation of the GB002 safety profile from that of the background PAH therapy. A placebo group, in contrast to an active control, will help to

understand whether the occurrence of an AE in the GB002 group is different from that which would occur in this population in the absence of GB002. Lastly, there is an unmet need in this patient population, as most patients who are on 2-3 background therapies have exhausted active therapeutic classes.

This study will explore an expected clinically active dose of GB002 in comparison to placebo. To assess efficacy, parameters related to exercise tolerance (eg, 6MWT), vascular hemodynamics (eg, PVR), and measures of right heart function will be evaluated.

The primary endpoint is change in PVR by RHC from Baseline to Week 24. PVR is a clinically meaningful outcome correlated with morbidity and mortality (Wensel, 2013). Improvements in PVR have been demonstrated for all major classes of currently approved PAH therapies including phosphodiesterase type 5 (PDE-5) inhibitors, guanylate cyclase (GC) stimulators, endothelin receptor antagonists, and prostanoids (Blalock, 2010; Galie, 2015; Galie, 2017; Ghofrani, 2013; Klinger, 2011; Shapiro, 2017; Voswinckel, 2006). PVR is a relevant endpoint for drugs that target the PDGFR pathway and pulmonary remodeling, based on the IMPRES study (Hoeper, 2013a). Thus, based on these analyses, PVR is an acceptable indicator for clinical benefit in PAH and is acceptable as the primary endpoint.

The change in 6MWD is also a clinically important and relevant endpoint. Objective measures of improvement in exercise tolerance have been observed with every new major class of therapy approved for use in PAH. Additionally, the European Medicines Agency (EMA) guidance on the development of new therapeutic agents for PAH lists 6MWD as one of the important measures for evaluation (in combination with time to clinical worsening). (European Medicines Agency, 2010).

One of the exploratory endpoints is change from Baseline to Week 24 in right ventricular function as measured by ECHO. The key echocardiographic parameters will include evaluation of TAS', RV Tei index and RVFWS. The literature supports evaluating these parameters using ECHO (da Costa Junior, 2017; Fine, 2013; Hulshof, 2019; Li, 2013; Shukla, 2018).

4.2.1. Rationale for Study Population

The target patient population for GB002 represents a population with significant risk for worsening of their PAH and for whom there are few therapeutic options available; therefore, this target population has a significant unmet medical need. All subjects will be WHO FC II or III for whom current guidelines recommend treatment with 1, 2 or 3 medications as part of their background therapy. The IMPRES study utilized a cutoff of 800 dyne•s/cm^5 (Hoeper, 2013a). However, a lower threshold has been chosen for this study based upon literature that suggests that PVR is an independent risk factor for morbidity and mortality that increases in a continuous manner (Benza, 2019; Wensel, 2013). A PVR of ≥ 400 dyne•s/cm^5 is selected as a key eligibility criterion because this threshold has been shown to be associated with increased risk of mortality based on the REVEAL 2.0 risk score (Benza, 2019).

4.3. Dose Rationale

The study will explore the safety, tolerability and efficacy of 90 mg GB002 or placebo BID but allows for down titration to 60 mg or 45 mg BID based on safety and tolerability (refer to Section 6.5.1 for dose modifications). This dose range is anticipated to be clinically active and has been selected based upon the following:

- Comparison of the human PK to the rat PK of GB002 suggests human doses of 45 to 90 mg BID are projected to cover rat PAH model efficacious exposure range.
- Population PK/PD modeling/simulation comparing imatinib doses that were effective in the IMPRES study (Hoeper, 2013a) to GB002 predicts that GB002 between 45 and 90 mg BID doses would achieve similar inhibition of PDGFRα signaling and better inhibition of PDGFRβ signaling in the pulmonary region.
- GB002 was well tolerated and safe in Phase 1a studies in healthy volunteer subjects following 1 week of repeat dosing up to 90 mg BID doses.
- Data from an ongoing Phase 1B study in subjects with PAH has demonstrated adequate safety and tolerability at doses up to 90 mg BID.

4.4. Study Duration

For each subject, study participation is expected to last up to 33 weeks as follows:

Screening:	up to 5 weeks
Treatment period:	24 weeks (-3, to +14 days)
Follow-up:	For subjects not enrolling in the OLE, 4 weeks (+7 days) after the last dose of IP. This will be defined as the last study visit (or Week 36 for male subjects participating in the semen analysis).

4.5. End of Study Definition

A subject is considered to have completed the study if he/she has completed all study visits, including the Week 28 Follow-Up visit (+4 weeks after last dose of IP. A 4-week safety follow up will not be required for subjects transitioning to OLE). Note: Week 36 is the last visit for male subjects participating in the semen analysis who do not continue to participate in the OLE.

The end of the study is defined as the date of the last visit of the last subject in the study.

5. STUDY POPULATION

5.1. Inclusion Criteria

To be eligible for participation in this study, subjects must meet all the following:

Age and Sex

1. Adult female subjects aged 18 to 75 years, inclusive, or adult male subjects aged 50 to 75 years, inclusive, at the time of signing the ICF prior to initiation of any study-specific activities/procedures.

Type of Subject and Disease Characteristics

2. A current diagnosis of symptomatic PAH classified by one of the following:
   a. Idiopathic PAH (IPAH) or heritable pulmonary arterial hypertension (HPAH).
   b. PAH associated with connective tissue disease (CTD-APAH):
      – Systemic sclerosis,
      – Mixed CTD or overlap syndrome,
      – Systemic lupus erythematosus
      – Other CTD established by ACR/EULAR guidelines
   c. PAH associated with anorexigen or methamphetamine use.
   d. Congenital heart disease with simple systemic to pulmonary shunt at least 1 year after surgical repair.
3. 6MWD ≥ 150 meters and ≤ 550 meters at screening. The lower of 2 distances should be within 15% of the higher distance.
4. WHO FC II or III symptomatology.
5. Treatment with standard of care PAH background therapies. Medications should remain stable for the past 4 weeks prior to consent and throughout the screening period.

   Exception: As needed (PRN) diuretics for intermittent weight gain and/or edema are allowed and will be considered a stable dose for this study.
6. Documentation of cardiac catheterization within the screening period that is consistent with the diagnosis of PAH and meeting the following criteria, to be confirmed by the central hemodynamic core laboratory (note, mmHg and PVR [dyne·sec/cm^5] values below are rounded to the nearest whole number):
   a. mPAP ≥ 25 mmHg (at rest), **AND**
   b. PVR ≥400 dyne·sec/cm^5, **AND**
   c. PCWP or LVEDP ≤12 mm Hg if PVR ≥400 to <500 dyne·sec/cm^5
      OR
   d. PCWP or LVEDP ≤15 mmHg if PVR ≥500 dyne·sec/cm^5
7. Pulmonary function tests (PFTs) at screening with the following criteria met:

a. Forced expiratory volume in 1 second (FEV_1) divided by the forced vital capacity (FVC) ≥ 70%,
b. Total lung capacity (TLC) or FVC ≥ 70% predicted

If the subject uses continuous oxygen therapy, they must be able to complete PFTs without oxygen. Subjects who are unable to complete PFTs without oxygen therapy are not eligible for the study.

Contraception

Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

8. Women of childbearing potential must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) at screening and a negative urine pregnancy test on Day 1 before first administration of IP. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required, and results must be negative.
9. Women of nonchildbearing potential: Evidence of post-menopausal status. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, tubal ligation, or hysterectomy).
    - Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, tubal ligation, or hysterectomy).
10. Women of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must be willing to use a highly effective method of contraception (defined in Appendix 4 in Section 10.4 of the protocol) from consent through 30 days following the last administration of IP; acceptable methods include hormonal contraception (oral contraceptives – as long as on stable dose, patch, implant, or injection), intrauterine devices or other form of highly effective contraception.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable.

Note: A vasectomized partner is acceptable.

11. Male subjects: Non-sterilized male subjects who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom

from consent through 90 days after the last dose of IP. Male subjects should refrain from sperm donation throughout this period, except for the purpose of fertility analysis as part of this protocol.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable.

Informed Consent

12. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study prior to initiation of any subject-mandated procedures. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5.2. Exclusion Criteria

The subject must be excluded from participating in the study if he/she meets any of the following:

Medical Conditions

1. Evidence of chronic thromboembolic disease or acute pulmonary embolism as assessed by ventilation-perfusion (V/Q) scan, computed tomography (CT)-angiogram, or pulmonary angiogram prior to screening. If not available previously, then test should be performed during the screening period.
2. Uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg during screening visit after a period of rest.
3. Systolic blood pressure < 90 mm Hg during screening and baseline visits.
4. WHO Pulmonary Hypertension Group 2–5.
5. HIV-associated PAH.
6. History of left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:
    a. Aortic or mitral valve disease (stenosis or regurgitation) defined as greater than mild aortic insufficiency, mild aortic stenosis (AS), mild mitral stenosis (MS), moderate mitral regurgitation (MR);
    b. Mechanical cardiac valve requiring anticoagulation;
    c. Pericardial constriction or pericardial effusion with tamponade physiology;
    d. Restrictive cardiomyopathy;
    e. Left ventricular ejection fraction (LVEF) ≤ 50% by echocardiography (ECHO) within 6 weeks prior to screening; if ECHO from the prior 6 weeks is not available, the screening ECHO results may be used to establish this criterion.
    Note: If ECHO images are not adequate to provide an accurate estimate of LVEF then a multigated acquisition (MUGA) or cardiac magnetic resonance imaging

(cMRI) scan or single photon emission computed tomography (SPECT) imaging can be used to obtain an accurate LVEF.

f. Left Atrial Area greater than 29cm^2 by ECHO within 6 weeks prior to screening; if ECHO from the prior 6 weeks is not available, screening ECHO results may be used to establish this criterion.
g. Documented uncontrolled symptomatic coronary disease (ie, unstable angina or percutaneous coronary intervention or coronary artery bypass graft within 12 months prior to screening, or planned coronary intervention or coronary artery bypass surgery).

7. Untreated severe obstructive sleep apnea.
8. History of atrial septostomy within 180 days prior to screening.
9. Pulmonary venous occlusive disease (PVOD).
10. Subjects with a history of portopulmonary hypertension or portal hypertension due to cirrhosis classified as Child-Pugh Class A or higher; or baseline ALT or AST > 2 x ULN or Total Bilirubin ≥ 2 X ULN.
11. History of malignancy within 5 years prior to screening, with the exception of localized non-metastatic basal cell carcinoma of the skin and in-situ carcinoma of the cervix.
12. History of a potentially life-threatening cardiac arrhythmia with an ongoing risk.
13. Uncontrolled bacterial, viral, or fungal infections which require systemic therapy.
14. Severe acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or IP administration (eg, history of intracranial hemorrhage), or absolute neutrophil count (ANC) < 1x10^9/L or platelet count < 50x10^9/L.
15. Any musculoskeletal disease or any other disease that limits evaluation of 6MWT.
16. Pregnant or nursing or intends to become pregnant during the duration of the study.

Diagnostic Assessments

17. Body weight < 40 kg at screening.
18. Chronic renal insufficiency as defined by an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m^2 via CKD-epi (Levey, 2009) at screening or requires dialytic therapy or hemofiltration.
19. Hemoglobin (Hgb) concentration < 8.5 g/dL at screening.
20. Evidence of active human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C, or tuberculosis (TB) infections.

Prior Therapy

21. Inhaled prostanoids; these drugs may be withdrawn ≥ 4 weeks prior to screening, if clinically indicated.
22. Use of oral anticoagulants (ie, warfarin or novel oral anticoagulants [NOAC]) at randomization; if on warfarin or a NOAC, these drugs can be withdrawn, if clinically

appropriate, during the screening period, and subjects should have normal coagulation parameters prior to the randomization (see Section 10.6 for examples of prohibited anticoagulants).

23. Requirement of intravenous (IV) inotropes (ie, levosimendan, dopamine, dobutamine, milrinone, norepinephrine) other than an IV prostanoid within 4 weeks of screening.

Prior/Concurrent Clinical Study Experience

24. Prior participation in GB002 studies and/or prior treatment with GB002.
25. Currently participating in or has participated in a study of an investigational agent or has used an investigational device for the treatment of PAH within 4 weeks prior to screening.

Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks or at least 5 half-lives (whichever is greater) after the last dose of the previous investigational agent.

Other Exclusion Criteria

26. Current use of inhaled tobacco and/or inhaled marijuana.
27. Current alcohol use disorder as defined by DSM-5, and/or a positive test for drugs of abuse (amphetamines, methamphetamines, cocaine, phencyclidine [PCP]). Retest may be performed for potential false positive results. Subjects with a history of methamphetamine abuse must be abstinent for a minimum of 1 year prior to screening, in the opinion of the investigator. Certain drugs may be allowed IF prescribed by medical personnel and is under medical supervision for documented medical conditions (ie, opioids for pain, benzodiazepines for anxiety). Ingestible or topical marijuana is allowed, per local restrictions and regulations.
28. Subjects with a history of severe milk protein allergy. In addition, subjects with known intolerance or hypersensitivity to lactose who, in the opinion of the investigator, may experience severe symptoms following the ingestion of lactose.
29. QTcF of > 480 msec recorded on a screening or baseline ECG or receiving concurrent treatment with medications that prolong QT interval. Please refer to Table 5.
30. Have any other condition or reason that, in the opinion of the Investigator or Medical Monitor, would prohibit the subject from participating in the study.

5.3. Screen Failure

Subjects will be assigned a subject number at the time of signing the ICF. Subjects who do not randomize will be labeled as screen failures.

A minimal set of screen failure information is required to ensure transparent reporting of Screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details (including eligibility criteria), and any SAE.

Subjects who are not randomized may be eligible to rescreen upon approval by the Medical Monitor (or designee). A new subject number will be assigned if approved to rescreen. One rescreen is permitted per subject.

6. INVESTIGATIONAL PRODUCT AND CONCOMITANT THERAPY

6.1. Investigational Product

The investigational product, GB002 Powder for Inhalation, is comprised of GB002 capsules (drug product) and the dry powder inhaler (device). GB002 capsules are comprised of GB002 spray-dried powder for inhalation in size 3 hydroxypropyl methylcellulose (HPMC) capsules. The device is a [redacted] dry powder inhaler (DPI). The placebo capsule is identical in size, shape, and color, with the same excipients and with the active drug replaced with lactose monohydrate.

Table 4: Investigational Product Description

Investigational Product Name	**Active: GB002**	**Control: Placebo**
Dose Formulation	Capsule containing GB002 spray-dried powder	Matching capsule containing placebo spray-dried powder
Inhaler Device	[redacted] dry powder inhaler (DPI)	
Unit Dose Strength(s)	15 mg per capsule	placebo capsule
Dose regimen	**45 mg:** 3 x 15 mg capsule, BID	3 capsules BID
	60 mg: 4 x 15 mg capsule, BID	4 capsules BID
	90 mg: 6 x 15 mg capsule, BID	6 capsules BID
Route of Administration and Instructions	Oral inhalation IP to be taken 12 hours apart (BID dosing) at approximately the same time each day, within ±2 hours. Subjects and/or caretaker will receive instructions and training regarding the correct use of the DPI devices. Subjects to be observed for 2 hours post first dose.	
Sourcing	IP will be provided to the site centrally by the Sponsor or designated representative.	
Packaging	GB002 and placebo capsules are contained within foil induction-sealed, child-resistant, high-density polyethylene (HDPE) bottles, which are enclosed in foil pouches. Each bottle contains 80 capsules. Foil pouches (and bottles) are uniquely numbered and will be dispensed in an appropriate quantity for each dosing period. All IP kits appear identical between GB002 and placebo. The DPI devices are packaged in a suitable secondary packaging kit appropriate for dispensing to subjects for each dosing period. Each device kit is uniquely numbered and closed with tamper-evident seals.	
Labelling	Label text will at a minimum include the protocol number, lot number, storage conditions, and Sponsor name and address. Labels will comply with local regulatory requirements for Ips.	

6.2. Shipping/Handling/Storage/Accountability

1. The kits containing GB002 capsules and placebo will be shipped using temperature monitoring devices and stored at controlled room temperature between 20°C and 25°C (68°F and 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before dispensation of the IP.
2. The kits containing DPI devices will be shipped at ambient conditions and stored indoors away from direct sunlight.
3. Only subjects enrolled in the study may receive IP, and only authorized site staff may supply or administer IP. All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
4. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization and Stratification

All subjects will be centrally randomized 1:1 to 1 of 2 groups as specified in Table 1 using interactive response technologies (IRT).

Randomization will be stratified by PVR (<800 dyne•s/cm^5, ≥ 800 dyne•s/cm^5).

Before the study is initiated, appropriate IRT training and the log-in information and directions will be provided to each site.

6.3.2. Assignment of Subject Number

At the screening visit, each subject will have a unique subject number assigned for subject identification in the study.

6.3.3. Assignment of Investigational Product Kit Number

IP(s) will be dispensed at the study visits as summarized in the SoA. The IP(s) kit number(s) will be assigned by the IRT system upon obtaining the subject's randomized treatment group.

For subsequent visits when IP is dispensed, the IRT system will assign IP kits based on the subject's randomized treatment group.

6.3.4. Unblinding of an Individual Subject

The IRT system will be programmed with blind-breaking instructions. In case of a medical emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's randomized treatment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator, when possible, should make efforts to contact the Sponsor's Medical

Monitor (or designee) to discuss unblinding a subject's treatment assignment before doing so, unless this could delay emergency medical treatment of the subject. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF).

Appropriate personnel at the Sponsor will unblind suspected unexpected serious adverse reactions (SUSARs) for the purpose of regulatory reporting. The Sponsor will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

Appropriate personnel at the Sponsor (or designee) will have access to unblinded individual subject treatment assignments for the purposes of study-required activities including management of IP inventory, production of summary tables and figures for IDMC review, and performance of bioanalytical analysis of PK concentrations. These personnel will not be involved in data collection or final analysis of safety and efficacy results. Subjects, investigators, other site personnel, and Sponsor (and/or designee) personnel who are directly involved in the conduct of the study, collection of the data, and analysis of the final safety and efficacy results will remain blinded to treatment assignments until after the completion of the study and the database has been locked.

6.4. Study Intervention Compliance

IP accountability will be assessed at each visit, as appropriate, by counting returned unused capsules. Deviation(s) from the prescribed dosage regimen will be evaluated. Subjects who demonstrate poor IP compliance should be reeducated on the importance of taking their medications as prescribed.

For visits where PK samples are collected, the subject will be instructed to take their dose in the evening before the visit at their regular dosing time and to record the time of dosing. For all clinic visits, the morning dose will be administered at the clinic.

Guidance for Missed Dose(s)

If a dose is missed, subjects should be instructed to skip the missed dose if there are less than 6 hours before the time of the next dose, resume dosing at their next scheduled dosing time ±2 hour and document the missed dose.

6.5. Dose Modifications

Please also refer to Section 7.1 for dose interruption and stopping rules for more details.

6.5.1. Investigational Product

All subjects will be randomized to 90 mg BID of GB002 or placebo administered via inhalation. Subjects will begin dosing with GB002 60 mg or Placebo BID. After 2 weeks, all subjects should be dose escalated, as tolerated, to 90 mg BID (Refer to Table 4 for acceptable dose levels). For those subjects who have not achieved a dose of 90 mg BID, dose escalation should be attempted approximately every 2 weeks until Week 20.

In the event of tolerability issues and/or an AE thought to be due to IP administration, dose reduction will be allowed to 60 mg BID (4 inhalations BID) with further reduction to 45 mg BID (3 inhalations BID), if required. Any dose reduction needs to be discussed with the Sponsor's Medical Monitor (or designee). If tolerated, the dose may be increased back to 90 mg BID at the discretion of the Investigator and discussion with the Sponsor's Medical Monitor.

Should a dose reduction be required, after discussion with the Sponsor's Medical Monitor (or designee), dose reduction to 60 mg BID, and if not tolerated, further dose reduction to 45mg BID will be allowed. If tolerated, the dose may be increased back to 90 mg BID at the discretion of the Investigator and discussion with the Sponsor's Medical Monitor.

Further up titrations should not be attempted after Week 20.

6.5.2. Background PAH Disease-Specific Therapy

Subjects should remain on their stable PAH disease-specific background therapy from 4 weeks prior to consent and for the duration of their time on study (if clinically appropriate). If a subject's condition worsens during the treatment period and this change meets the definition of the protocol's clinical worsening criteria (Section 8.1.5), they may need to increase dose of current disease-specific background PAH therapy above their baseline stable dose at the Investigator's discretion if it is in the best interest of the subject's health. Any increases in PAH disease-specific background therapies should be discussed with the Sponsor's Medical Monitor (or designee) if possible.

6.6. Treatment of Overdose

For this study, any dose of IP greater than the prescribed daily dose will be considered an overdose. There is no specific treatment recommended to treat an overdose of IP, and the subject should receive treatment directed towards any symptoms manifested.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor (or designee) as soon as possible.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor (or designee) based on clinical evaluation of the subject.

6.7. Concomitant Medications and Therapies

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Name of medication/therapy (generic name)
- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Concomitant medications necessary for the health and well-being of the subject and that do not interfere with study assessments are permitted during the study at the Investigator's discretion. This includes the use of appropriate medications for the treatment of AEs and/or concurrent illnesses under the direction of the Principal Investigator. All medications must be recorded in the source and on the appropriate electronic case report forms (eCRFs).

The Sponsor's Medical Monitor (or designee) should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.1. PAH Disease-Specific Background Medications

Review of the prescribing labels of these PAH disease-specific background medications listed in Table 5 revealed that no clinically relevant drug-drug interactions (DDIs) are expected and no dose adjustment is needed when they are co-administered with GB002 based on the completed DDI assessments summarized in the IB, except for sildenafil. When sildenafil is co-administered to patients receiving GB002, adjustment of sildenafil dose should be administered only after a careful benefit-risk assessment; a downward dose adjustment to 20 mg twice daily for tablet or oral suspension, or 10 mg twice daily for injection should be considered. Overall, these background medications are permitted for co-administration with GB002. The review also revealed that no clinically relevant DDIs are expected and no dose adjustment is needed for GB002 when it is co-administered with the PAH disease-specific background medications.

Table 5: Summary of Allowed PAH Background Medications

PAH Background Medication	Coadministration Permitted?	Background Medication Dose Adjustment?	GB002 Dose Adjustment?
Ambrisentan	Yes	No	No
Macitentan	Yes	No	No
Bosentan	Yes	No	No
Sildenafil	Yes	Should be considered[a]	No
Tadalafil	Yes	No	No
Riociguat	Yes	No	No
Treprostinil[b]	Yes	No	No
Epoprostenol	Yes	No	No
Selexipag	Yes	No	No
Iloprost[c]	Yes	No	No

[a] Any dose adjustment should be administered only after a careful benefit-risk assessment. A downward dose adjustment to 20 mg twice daily for tablet or oral suspension, or 10 mg twice daily for injection should be considered when sildenafil is co-administered to patients receiving GB002.

[b] Inhaled Treprostinil (not approved for marketing in the European Union) is prohibited; Treprostinil injection for SC or IV infusion or Treprostinil extended-release tablet for oral use (not approved for marketing in the European Union) are allowed.

[c] Iloprost solution for infusion is allowed; iloprost nebulizer solutions are prohibited.

6.7.2. CYP3A Substrate Drugs

GB002 is a moderate CYP3A inhibitor. For PAH background medications which are CYP3A substrates (sildenafil, tadalafil, riociguat, bosentan, and macitentan), refer to Section 6.7.1 for instructions.

For other CYP3A substrate drugs, consult their labels on how they should be co-administered with a moderate CYP3A inhibitor.

6.7.3. Digoxin

For subjects taking digoxin, measure serum digoxin concentrations before initiating GB002. When co-administering with GB002, modify dose and/or dosing frequency as required to keep digoxin within the therapeutic range typically used in PAH patients.

6.7.4. Prohibited Medications and Medications to be Used with Medical Monitor Advisement

Medications specifically prohibited in the exclusion criteria, such as anti-coagulants, are not allowed during the ongoing study.

However, if there is a clinical indication for any medication specifically prohibited during the study (Appendix 6), the Investigator should discuss these medications with the Sponsor's Medical Monitor (or designee), prior, if possible, to administration of prohibited medications and treatments.

The final decision on any supportive therapy rests with the Investigator and/or the subject's primary physician. However, the decision to dose a subject with IP or concomitant medications requires the mutual agreement of the Investigator, the Sponsor and the subject, this decision should be documented and retained in the local site records.

Please refer to Appendix 6 (Section 10.6) for prohibited medications. Any investigational agent, other than GB002, is also prohibited.

6.8. Intervention After the End of the Study

The final intervention in this protocol is the Week 24 visit followed by a Week 28 safety Follow-up Visit (Week 36 for male subjects participating in the semen analysis), or the Early Termination Visit, if applicable.

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND SUBJECT WITHDRAWAL FROM STUDY

7.1. Interruption of Investigational Product, Stopping Rules, and Discontinuation of Investigational Product

Dosing of IP must be interrupted for any serious adverse events assessed by the investigator as related to IP. Restart of dosing may be considered upon discussion with and approval by the Sponsor's Medical Monitor (or designee) after resolution of IP treatment-related events to baseline. In cases where subject has been off IP for more than 14 consecutive days, restart of IP may only be allowed with Sponsor's Medical Monitor approval.

Permanent discontinuation of IP does not mean withdrawal from the study, and the subject will be encouraged to remain in the study and continue to complete all study visits as per the SoA (Table 2).

If a subject discontinues IP for lack of efficacy (disease progression), background disease-specific PAH therapy may be adjusted, as needed.

A subject may discontinue IP(s) for reasons including but not limited to:

- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study drug
- Physician decision Section 7.1.2 Section 7.1.2
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject

The reason for subject discontinuation from IP will be recorded in the eCRF.

For liver function abnormalities, dose modification is based on guidelines in Section 7.1.1. For additional abnormalities, refer to Section 7.1.2 , Section 7.1.3, Section 7.1.4, Section 7.1.5, Section 7.1.7, Section 7.1.8 Section 7.1.9, and Section 7.1.10. A blood sample for PK analysis may be collected for subjects experiencing any of the below stopping rules, or as requested by the Sponsor.

Pregnancy is a mandatory criterion for permanent discontinuation of IP (see Section 7.1.6).

7.1.1. Liver Function: Actions

Liver function tests (LFTs) will be evaluated as specified in the SoA (Table 2). Scheduled and unscheduled liver function tests alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, will be evaluated and actions specified per the following criteria.

Weekly (or more frequently as clinically indicated) LFT values will be performed for confirmed results of ALT or AST ≥ 3 × upper limit of normal (ULN). The confirmation laboratory sample is collected ideally within 24 hours. After 4 weeks, the frequency and discontinuation of additional monitoring will be decided by the investigator and the Sponsor.

All ALT or AST ≥ 3 × ULN will be evaluated for an etiology (for example viral hepatitis, drug and herbal supplements, environmental exposure, and other) in consultation with the Sponsor.

Liver Function: IP Interruption

IP dosing will be paused for the following confirmed liver laboratory values:

- ALT or AST ≥ 5 × ULN

IP may be restarted if the ALT and/or AST return to baseline values or stabilize to < 3 x ULN. The decision to restart IP must be approved by the Sponsor.

Liver Function: IP Discontinuation

IP will be permanently discontinued for the following confirmed liver laboratory values:

- ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN, or
- ALT or AST ≥ 8 × ULN

7.1.2. Respiratory Function: Action

Respiratory Function: IP Interruption

If subject experiences signs and symptoms of moderate change from baseline in respiratory function (regardless of the investigator's reported relationship to IP), dosing with IP will be interrupted. Because changes in respiratory function may be due to factors other than IP (eg, worsening underlying disease, fluid overload, respiratory infection), further evaluation should be undertaken. After appropriate medical evaluation and management, IP dosing may be resumed if clinical status improves. Following agreement between the Sponsor's Medical Monitor (or designee) and the investigator, the same dose, a lower dose, or permanent discontinuation, in accordance with discontinuation criteria, of IP will occur depending on the clinical status of the subject.

Respiratory Function: IP Discontinuation

Adverse events related to respiratory function will be monitored. IP will be permanently discontinued for the following:

- Respiratory related adverse events considered by the Investigator as related to IP and resulting in hospitalization with need for intervention **or**
- If IP was interrupted per respiratory function interruption criterion and restart conditions were not achieved

7.1.3. Cardiac Function: Action

Cardiac Function: IP Interruption

If subject experiences signs and symptoms of moderate or severe change from baseline in cardiac function (regardless of the investigator's reported relationship to IP), dosing with IP will be interrupted. Because changes in cardiac function may be due to factors other than IP (eg, worsening underlying disease, fluid overload), further evaluation should be undertaken. After appropriate medical evaluation and management, IP dosing may be resumed if clinical status improves. Following agreement between the Sponsor's Medical Monitor (or designee) and the investigator, the same dose, a lower dose, or permanent discontinuation, in accordance with the discontinuation criteria, of IP will occur depending on the clinical status of the subject.

Cardiac Function: IP Discontinuation

Adverse events related to cardiac function will be monitored. IP will be permanently discontinued for the following:

- New onset heart failure that requires hospitalization and intervention and that is considered related to IP **or**
- If IP was interrupted per cardiac function interruption criterion and restart conditions were not achieved

7.1.4. Bleeding: Action

Bleeding: IP Interruption

If subject experiences signs and symptoms of minor bleeding (eg, limited epistaxis, mucocutaneous signs) which is an adverse event considered by the investigator as related to IP and which is not major hemorrhage meeting criteria for permanent IP discontinuation, dosing with IP should be interrupted, and further evaluation should be undertaken. After appropriate medical evaluation and management, IP dosing may be resumed following discussion with the Sponsor's Medical Monitor (or designee). A lower dose of IP should be considered depending on the outcome of clinical evaluation.

Bleeding: IP Discontinuation

Adverse events related to bleeding will be monitored. IP will be permanently discontinued for the following adverse event:

- Hemorrhage (other than traumatic injury) where invasive intervention or transfusion is required.

7.1.5. Immunosuppression: Action

Immunosuppression: IP Interruption

If subject experiences signs and symptoms of localized or systemic infection, dosing with IP may be interrupted and further evaluation should be undertaken. Because localized or systemic infections may be due to factors other than IP, further evaluation should be undertaken. After appropriate medical evaluation and management, IP dosing may be resumed depending upon the clinical status of the subject. Following agreement between the Sponsor's Medical Monitor (or

designee) and the investigator, the same dose, a lower dose, or permanent discontinuation of IP, in accordance with the discontinuation criteria, will occur depending on clinical status of the subject. If infection is accompanied by neutropenia, additionally refer to neutropenia actions (Section 7.1.8) for dose interruption and discontinuation criteria.

Immunosuppression: IP Discontinuation

Adverse events related to infections will be monitored. IP will be permanently discontinued for the following:

- Severe opportunistic infections requiring anti-fungal or anti-viral therapies or prolonged intravenous antibiotics regardless of whether it results in hospitalization or not **or**
- If IP was interrupted per immunosuppression interruption criterion and restart conditions were not achieved

7.1.6. Pregnancy

A subject with a positive urine pregnancy test must temporarily discontinue GB002. If the serum pregnancy test is negative, the subject may restart GB002. A subject must permanently discontinue IP if she becomes pregnant (as confirmed by serum pregnancy test). See Appendix 4 (Section 10.4.3) and Section 8.3.5 for additional details, including for female partners of male subjects).

See the SoA (Table 2) for data to be collected at the time of IP discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.7. Fluid Retention: Action

Fluid Retention: IP Interruption

If subject experiences signs and symptoms of severe fluid retention and/or experiences a 20% increase in weight from baseline, dosing with IP should be interrupted if considered by Investigator as related to IP, and further evaluation should be undertaken. After appropriate medical evaluation and management, IP dosing may be resumed following discussion with the Sponsor's Medical Monitor (or designee). A lower dose of IP should be considered depending on the outcome of clinical evaluation.

Fluid Retention: IP Discontinuation

Adverse events related to fluid retention will be monitored. IP will be permanently discontinued for adverse events considered by the investigator as related to IP for the following:

- Severe fluid retention related events that do not respond to appropriate medical management or IP dose reduction

7.1.8. Neutropenia: Action

Neutropenia: IP Interruption

If subject has a confirmed absolute neutrophil count (ANC) $< 1 \times 10^9$/L, dosing with IP should be interrupted. ANC should be monitored weekly and GB002 dosing can resume when ANC $> 1.5 \times 10^9$/L. IP dosing should resume at a lower dose level and ANC monitored weekly for the

first 2 weeks and, if stable, every 2 weeks for the next month, then as per the protocol laboratory evaluation schedule.

Neutropenia: IP Discontinuation

Laboratory parameters will be monitored for the development of neutropenia. IP will be permanently discontinued for the following:

- Confirmed ANC < 1×10^9/L and persistence despite IP dose reduction

7.1.9. Thrombocytopenia: Action

Thrombocytopenia: IP Interruption

If subject has confirmed platelet count < 50×10^9/L, dosing with IP should be interrupted. Platelet count should be monitored weekly and GB002 dosing can resume when platelet count > 100×10^9/L. IP dosing should resume at a lower dose level and platelet count monitored weekly for the first 2 weeks and, if stable, every 2 weeks for the next month, then as per the protocol laboratory evaluation schedule.

Thrombocytopenia: IP Discontinuation

Laboratory parameters will be monitored for the development of thrombocytopenia. IP will be permanently discontinued for the following:

- Confirmed platelet count < 50×10^9/L and persistence despite IP dose reduction

7.1.10. ECG Changes Including Prolonged QTc: Action

ECG changes including prolonged QTc: IP Interruption

Not applicable.

ECG changes including prolonged QTc: IP Discontinuation

ECGs will be monitored for clinically significant abnormalities. IP should be permanently discontinued for the following:

- The development of a new life-threatening cardiac arrythmia
- QTcF > 500 msec or change from baseline > 60 msec

7.2. Subject Withdrawal from the Study

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the institution. A subject may withdraw from the study for reasons including but not limited to:

- Death
- Withdrawal by subject
- Lost to follow-up
- Study terminated by Sponsor.

The reason for subject withdrawal from the study will be recorded in the eCRF.

If a subject is withdrawing from the study and has previously discontinued IP, as soon as possible, an ET Visit should be conducted, as shown in the SoA (Table 2). If the subject is simultaneously discontinuing IP and withdrawing early from the study, the ET visit should be conducted at the time of IP administration. A last dose at the ET visit will be at the discretion of the Investigator based on subject safety and dependent on subject's continued consent. Subjects should be encouraged to return 4 weeks later for a Follow-up Visit. See the SoA for data to be collected at the time of study withdrawal and at follow-up and for any further evaluations that need to be completed.

If a subject withdraws from the study, he/she may request destruction of any biological samples collected and not yet assayed, and the Investigator must document this request in the site study records. The Sponsor should be notified of this request.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls to the subject's last known phone number, and, if necessary, a certified letter sent to the subject's last known mailing address, or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- The Sponsor may also attempt to ascertain vital status on subjects deemed lost to follow-up.
- Should the subject continue to be unreachable, he/she will be considered lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness of occurrence to determine if the subject should continue or discontinue IP(s).
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3) is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a log to record details of all subjects screened (including demographic data) and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- For the Weeks 4, 8, and 18 visits, subjects or study personnel may choose to have a home-health visit rather than an in-clinic visit. For home-health care visits, IP shipment to the subject's home may be arranged.

8.1. Efficacy Assessments

8.1.1. Right Heart Catheterization

RHC will be done to assess the severity of hemodynamic impairment and to subsequently help to identify risk status of subjects with a diagnosis of PAH. These data will also be used to evaluate the efficacy of GB002.

The key RHC parameters are as follows:

1. Right atrial pressure
2. RV systolic pressure
3. Pulmonary artery systolic and diastolic pressures
4. Mean pulmonary arterial pressure
5. End expiratory pulmonary capillary wedge pressure (PCWP), or if PCWP not accurate then left ventricular end diastolic pressure or mean left atrial pressure (mLAP) (in which case left heart catheterization to measure LVEDP may be needed)
6. Cardiac output and cardiac index
7. PVR, calculated as:

$$\frac{mPAP - PCWP}{CO} \; x \; 80 \text{ dyne} \bullet \text{s/cm5}$$

where mPAP = mean pulmonary arterial pressure in mm Hg, PCWP = pulmonary capillary wedge pressure in mm Hg, and CO = cardiac output in liters/minute.

RHC should be performed by an experienced operator in an appropriate cardiac catheterization laboratory. If access is obtained via the internal jugular vein, then ultrasound guidance should be used. Femoral or brachial vein access is permitted. Subclavian vein access should be avoided. Details are provided in the RHC Manual.

8.1.2. Six Minute Walk Test (6MWT)

A standardized 6MWT will be performed in the clinic at specified visits, in accordance with the guidelines of the American Thoracic Society (American Thoracic Society Committee, 2002).

The 6MWT will be carried out by trained study staff. If an ECG is required at the same visit as a 6MWT, the 6MWT must be performed after the ECG. For further details, refer to the 6MWT manual.

8.1.3. Echocardiogram (ECHO)

A full echocardiogram (including two-dimensional, Doppler, and speckle tracking), assessed centrally, will be used to evaluate RV and LV function. The digital image and results will be available to the Sponsor; every effort should be made to include the appropriate images and results of RV and LV function. Further details are described in the imaging manual.

- The two-dimensional echocardiography parameters to be measured or calculated include: right and left heart chamber volumes, such as RV fractional area change (RVFAC), LV eccentricity index, and tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular peak systolic velocity (TAS'). In addition, presence and size of a pericardial effusion will be determined.
- Doppler echocardiographic parameters will be measured or calculated to evaluate RV function, including Tei index (Tei, 1996).
- Speckle tracking echocardiography will be used to measure RV and LV strain.

For further details refer to ECHO manual.

8.1.4. Functional Class

Description of each WHO functional class for pulmonary hypertension is provided in Table 6.

Table 6: World Health Organization Function Class for Pulmonary Hypertension

WHO Functional Class	Description
I	Patients with pulmonary hypertension but without any resulting limitation of physical activity. Ordinary physical activity does not cause dyspnea, fatigue, chest pain or near syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea, fatigue, chest pain or near syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea, fatigue, chest pain or near syncope.
IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity. Syncope or near syncope can occur.

8.1.5. Assessments for Protocol-Defined Clinical Worsening Events and Risk Categorization

For assessment of clinical worsening, data will be captured related to the following:

- Death (all causes)
- Hospital admission for worsening PAH, as a result of any of the following:
  - Non-elective hospitalization caused by clinical conditions directly related to PAH and/or right heart failure
  - Need for IV diuretics (more than a single dose in 24 hours)
  - Lung or heart/lung transplantation
  - Atrial septostomy
  - Initiation of parenteral (IV infusion or subcutaneous injection) therapy with a prostacyclin (if not previously utilizing parenteral prostacyclin therapy)
- Disease progression, defined as
  - Worsening symptoms of right heart failure requiring initiation of a new PAH disease-specific medication or an increase in dose, or change in disease-specific background PAH medications or initiation of chronic oxygen therapy (ie, requires oxygen for >24 hours with the intent of long-term use); or
  - A decrease in 6MWD of at least 15% from Baseline, directly related to PAH progression, confirmed by 2 assessments of 6MWD performed at 2 consecutive visits and worsening in WHO FC for subjects with WHO FC I/II/III; or
  - Worsening Risk Score Category (as in Table 7) (Leuchte, 2018). Defined as a change in two components of the Risk Assessment to a worse risk category

Risk will be evaluated using the ESC/ERS guidelines (Galie, 2016) as well as the Registry for the Characterization of Primary Pulmonary Hypertension (REVEAL) 2.0 risk calculator as described by Benza et al (Benza, 2019; McGoon, 2012).

Risk assessment will be performed according to one or more of the approaches described by Leuchte et al (Leuchte, 2018) and may include variables recommended by the ESC/ERS guidelines (eg, WHO FC, 6MWD, right atrial pressure [RAP], cardiac index [CI], stroke volume [SV], right atrial [RA] area, presence of a pericardial effusion, and NT-pro-BNP).

For assessment of Risk Score, the date of determination that a change in two Risk Assessment components has occurred (in the case of NT-proBNP, the date of the laboratory result) will be reported in the case report form as the date of the Clinical Worsening Event.

Table 7: Risk Score Categories

Risk Assessment Score	Low risk	Intermediate risk	High risk
WHO functional class	I, II	III	IV
6MWD	> 440 m	165–440 m	< 165 m
NT-proBNP plasma levels	NT-proBNP <300 ng·L^{-1}	NT-proBNP 300–1400 ng·L^{-1}	NT-proBNP >1400 ng·L^{-1}

Source: Leuchte, 2018

8.1.6. Oxygen Saturation

Oxygen saturation will be measured using pulse oximetry.

8.1.7. Pulmonary Function Testing

Pulmonary function tests (PFTs) will be measured using electronic spirometry, with the highest of three technically acceptable measurements recorded in the eCRF. Measurements will include forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and DLCO.

If the subject uses continuous oxygen therapy, they must be able to complete PFTs without oxygen.

8.1.8. Substudies

8.1.8.1. Functional Respiratory Imaging (Sub-study)

A functional respiratory imaging (FRI) by high-resolution chest CT sub-study using specialized software to determine change from baseline in pulmonary vasculature blood volume, pulmonary blood volume as a percent of total lung volume, fibrosis score, and image-based ventilation to perfusion score will be performed at Baseline and Week 24 at select participating sites. For further information, please refer to the corresponding sub-study manual.

8.1.8.2. Heart Rate Monitoring Sub-Study

A heart rate monitoring sub-study utilizing a wearable ECG device (VivaLNK) during the 6MWT will be conducted to evaluate the change in heart rate expenditure and heart rate recovery from Baseline to Week 24 at select participating sites. For further information, please refer to the 6MWT sub-study manual.

8.1.9. Patient Reported Outcomes

8.1.9.1. EuroQol – 5 Dimensions – 5 Levels (EQ-5D-5L)

EQ-5D-5L (five severity levels EQ-5D), developed by the EuroQoL Group, is a standardized instrument to be completed by the subject for use as a measure of health outcome applicable to a wide range of health conditions (Herdman, 2011). It comprises five dimensions of health:

mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. Based on qualitative and quantitative studies conducted by the EuroQol Group, there are five options (levels) under each domain: 'no problems', 'slight problems', 'moderate problems', 'severe problems' and 'unable to/extreme problems'. The responses to all five dimensions, can be converted to a single summary index, utility (range: 0 to 1), by using value sets. Higher index values represent better health states. The EQ-5D-5L also includes a 20 cm vertical, visual analog scale for recording the subject's self-rated health from 'the best health you can imagine' and 'the worst health you can imagine'.

The EQ-5D-5L will be captured at the clinic via an ePRO device (tablet).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 2). Study procedures should be completed within the windows provided in the SoA and as specified in this section.

8.2.1. Physical Examinations

- A complete physical examination will be performed and will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs, Body Weight, and Height

- Vital signs (pulse rate, respiratory rate, temperature and blood pressure) will be measured after 5 minutes rest and prior to ECG measurements.
- Blood pressure and pulse measurements will be assessed with the subject in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).
- Body weight will be measured and recorded. Subjects will be encouraged to weigh themselves at home as part of standard of care; if a subject experiences abnormal lower extremity swelling and/or weight gain, they will be instructed to contact the clinical study site or primary care physician for further evaluation.
- Height will be measured and recorded only at screening.

8.2.3. Electrocardiograms

- Assessment of a single 12-lead ECG will be obtained as outlined in the SoA (see Table 2) to determine heart rate and measure PR, QRS, QT, and QTc intervals.
- ECGs must be performed prior to the 6MWT.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed at the visits designated in the SoA (Table 2). Details for collection, processing and shipping of samples to the central laboratory are provided in a separate Laboratory Manual.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The signed laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered abnormal and clinically significant during participation in the study should be repeated per standard practices until the values return to normal or baseline or are no longer considered clinically relevant by the Investigator or Sponsor's Medical Monitor (or designee).

  Note: If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the SoA (Table 2).
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator, then the events must be recorded in the eCRF and retained in source documents.

8.2.4.1. Male Fertility Assessment (Optional)

The male fertility assessment will be done in male subjects who are willing and able to provide a semen sample to evaluate semen volume, total sperm per ejaculate, sperm concentration, sperm progressive motility, and sperm morphology. Collected specimens will be evaluated by a local laboratory. Participating male subjects with abnormal values at baseline will not be included in further fertility assessments.

Semen samples will be collected at Baseline, Week 12 and Week 24. A follow-up semen sample will be collected at approximately Week 36 (12 weeks after the last dose of IP at Week 24).

For all semen samples, subjects should abstain from ejaculation for 48 hours before and a maximum 1 week before each semen collection.

8.3. Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

The definitions of an AE, SAE, and AESI can be found in Appendix 3 (Section 10.3).

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of AE, SAE, or AESI. A review of all system organ classes, including the reproductive system, should be performed at the time of Adverse Event assessment.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from the first dose of IP until the end of study follow-up. SAEs will be collected beginning at the time of consent until the end of study follow-up. All medical occurrences, with the exception of SAEs, that begin after obtaining ICF and before the first dose of IP will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately upon the site learning of an event, and under no circumstance should the initial notification exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs that start after conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care is to be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire whether AEs occurred.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to the Sponsor is essential so that the Sponsor's legal obligations and ethical responsibilities towards the safety of subjects and the safety of IP under clinical investigation can be met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation.

The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) (defined in Section 10.3.3) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies will be collected as outlined in Appendix 4 (Section 10.4).
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Participating male subjects who are willing and able to provide semen samples will undergo fertility assessments. Sperm samples will be collected at the timepoints specified in the SoA (Table 2) and will be evaluated for semen volume, total sperm per ejaculate, sperm concentration, sperm progressive motility and sperm morphology.

8.3.6. Death Events

Timelines for reporting of death events are identical to the requirements for SAE reporting. (Appendix 3, Section 10.3).

8.3.7. Adverse Events of Special Interest

Bleeding and cardiac effects (as described below) are considered potential risks and are deemed AESIs. Additional information will be required for AESIs and recorded on the CRFs. All AESIs will be followed to resolution or stabilization. The Sponsor will review all AESIs and may report these events as expedited to regulatory authorities.

Bleeding

Risk of bleeding is a class safety concern for PDGFR kinase inhibitors. Bleeding is an AE of interest and will include preferred terms in the Standard Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) of Haemorrhage terms (excluding laboratory terms) that are assessed as severe, defined as indicating a transfusion or invasive intervention or necessitating a hospitalization.

Cardiac effects

Risk of cardiac effects, specifically congestive heart failure, have been observed within the class of kinase inhibitors. These effects are AESIs and will include the preferred term of heart failure that is assessed as severe, defined as the new onset of symptoms at rest or with minimal activity or necessitating a hospitalization.

8.4. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of GB002 and its metabolites, if applicable, as specified in Table 8. The actual time and date of each sample collection will be recorded in eCRF. The actual time and date of the morning dosing of GB002 (start and stop times) and oral PAH on the PK days and the last dosing of them before the PK days will be recorded in eCRF. A more detailed description of plasma sample preparation will be provided in the Laboratory Manual.

PK samples will be analyzed with a validated method; for metabolites, the samples may be analyzed with a fit-for-purpose method(s). The samples may be used for metabolite profiling or bioanalytical method development and validation. The samples may also be used for measuring concentrations of PAH background medications.

Table 8: Pharmacokinetic Collection Schedule

Visit	Timepoint	Dose	Time	PK Collection	PK Collection Time Window
2	Day 1/Baseline	morning	Predose*	X	-1 hour
			2 hours postdose	X	± 10 minutes
6	Week 12	morning	Predose*	X	-1 hour
			2 hours postdose	X	± 10 minutes
8	Week 24	morning	Predose*	X	-1 hour
			5 minutes postdose	X*	± 2 minutes
			3 hours postdose	X	± 10 minutes
Early Termination Visit	any time after Baseline	none	Anytime	X	
*Five minutes at Week 24. If the dose administration takes more than 5 minutes, the 5-minute blood sample will be collected within 1 minute of the completion of the dose administration.					

* The predose sample may be collected anytime within 1 hour prior to dosing. PAH-disease specific background medication should be dosed ahead of GB002.

8.5. Pharmacodynamics and Biomarkers

Samples for exploratory biomarker analysis will be collected as specified in Table 9 and may be used as the basis for multiple exploratory assays to evaluate the effect of GB002 on a range of potential target engagement and PD biomarkers.

Samples may be stored at a facility selected by the Sponsor, to enable further analysis of biomarker responses to GB002, for a maximum of 8 years (or according to local regulations) following the last subject's last visit for the study.

Residual blood may be stored for potential future identification of factors or profiles that correlate with measures of response to GB002.

Table 9: Biomarkers Collection Schedule

Assay	Collection Schedule
mRNA assay (disease modification [DM])	At Day 1/Baseline, Weeks 12, 24, and ET[1] visit: • Predose (-1 hour)[1] • 2 hours postdose (± 10 minutes)[1]
Proteomics and methylation patterns assays (DM)	At Day 1/Baseline, Weeks 12 and 24, and ET visit: • Predose (-1 hour)

[1] Biomarkers for the early termination visit will be collected at any time during the visit.

8.6. Pharmacogenetics

8.6.1. Use and Analysis of DNA

Germ line variation may impact a subject's response to IP, susceptibility to, and severity and progression of disease. Variable response to IP may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion (ADME), the mechanism of action of the drug, disease etiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, and subjects consent, a pharmacogenetic sample may be collected for DNA analysis.

Pharmacogenetic samples may be analyzed for genetic variations in genes which have the potential to affect the PK of GB002, the safety, and/or efficacy profile. Often, a large variability in the plasma concentration–time profiles of any medicine can be linked to loss of function mutations in the drug metabolizing enzymes and/or transporters. For example, substantial efforts have been made in reducing the risk of drug-drug interactions related to cytochrome P450 (CYP) enzymes and variability caused by polymorphic expression of metabolizing enzymes (eg, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 & CYP3A5) and transporter proteins (eg, P-glycoprotein [P-gp], breast cancer resistance protein [BCRP], organic anion transporting polypeptide [OATP]1B1, OATP1B3, ornithine aminotransferase [OAT]3, organic cation transporter [OCT]2, multidrug and toxin extrusion [MATE]1 & MATE2K). The effects of single nucleotide polymorphisms (SNPs) on the PK of GB002 uncovered in the course of this study may help guide future clinical studies and regulatory review of GB002. Additional pharmacogenetic analyses may be conducted if it is hypothesized that doing so may help resolve issues with the clinical data (eg, safety and/or PD observations) during the study.

The results of these analyses may be reported in a separate study summary.

The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on GB002 continues but no longer than 8 years or other period as per local requirements.

The Sponsor may elect to measure the naturally occurring variation across a range of relevant pharmacogenetic markers using a laboratory test such as the ThermoFisher DMETTM Plus Solution. This assay would cover 1,936 genetic variants across 231 relevant genes using a single array. This particular assay, for example, would include many genetic variants that cannot easily be detected, eg, SNPs and insertion and deletions (INDELs) with secondary polymorphisms in close proximity, triallelic markers, and variants from multi-gene families. Particular emphasis would, in this case, be placed on covering the PharmaADME "Core ADME Genes" (32 genes) and PharmaADME "Core Markers" (185 variants). If the Sponsor finds it necessary, it may move beyond the PharmaADME core content to cover common and functional variants associated with hepatic detoxification for processing xenobiotics and environmental toxins (eg, markers associated with newly described adverse drug events–CYP3A4 [392A>G]; structural variants in transporter genes which are important pharmaceutical targets–ABCG2 [421C>A]; enrichment for mutations in ADME regulatory genes–PPARD; inclusion of many population specific markers–VKORC1).

8.6.2. N-Terminal Pro B-Type Natriuretic Peptide (NT-proBNP)

N-terminal pro b-type natriuretic peptide (NT-proBNP) may be elevated in subjects with PAH and is an independent risk predictor in these subjects (Galie, 2016; Leuchte, 2007). Blood samples will be collected to assess change in NT-proBNP from baseline will be assessed to provide potential prognostic information at the time of screening and during follow-up assessments (Warwick, 2008).

8.7. Other Assessments

8.7.1. User Device Survey

All subjects will be requested to complete a User Device Survey as specified in the SoA to evaluate ease of use of the DPI.

9. STATISTICAL CONSIDERATIONS

Unless specified otherwise, all statistical analyses will be performed using a 2-sided hypothesis test at the 5% level of significance. Continuous data will be presented using descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. Descriptive statistics on continuous efficacy measures will also include the standard error (SE). Categorical data will be summarized by the number and percent of subjects. Time-to-event data will be summarized using the median (if estimable) and the 25^{th} and 75^{th} percentiles. Confidence intervals (CI) will be 95% and two-sided, unless otherwise stated. All efficacy and safety data will be summarized by treatment group.

9.1. Statistical Hypotheses

The superiority of GB002 over placebo will be evaluated by testing the following null hypotheses (H_0) vs. the alternative hypotheses (H_a).

- H_0: There is no difference in ΔPVR after 24 weeks in PAH subjects treated with GB002 compared to placebo
- H_a: This is a difference in ΔPVR after 24 weeks in PAH subjects treated with GB002 compared to placebo

9.2. Sample Size Determination

Based upon the results from a Phase 2 study with the PDGFR inhibitor imatinib (Ghofrani, 2010), the mean (SD) decrease from baseline in PVR over 24 weeks is assumed to be 300 (340) dyne•s/cm^5 for the GB002 group and 79 (270) dyne•s/cm^5 for the placebo group, resulting in a GB002 treatment effect (SD) of 221 (305) dyne•s/cm^5. Assuming this treatment effect, 40 subjects per treatment group has approximately 90% power to detect a statistically significant difference between GB002 and placebo using Satterthwaite's t-test with $\alpha = 0.05$, two-sided.

9.3. Population for Analyses

The following populations are defined:

- Intent-to-Treat (ITT) Population: All subjects who are randomized will be included in the ITT Population. This population will be used as the primary analysis population for all efficacy endpoints. Subjects will be grouped in this population according to their randomized treatment assignment.
- Safety Population: All subjects who receive any dose amount of IP will be included in the Safety Population. This population will be used for all summaries of safety data. Subjects will be grouped as follows: any subject that receives only placebo doses will be in the placebo group. Any subject that receives at least one dose of GB002 will be in the GB002 group.

9.4. Statistical Analyses

The number and percentage of subjects in each analysis population will be summarized. Subject disposition, including the number of subjects screened, randomized, dosed, taking at least 80% of their expected number of doses for their time on study, completing study treatment, not completing study treatment by reason for discontinuation, completing study, and not completing study by reason for withdrawal will be summarized. Subject demographics will be summarized for the ITT Population and will include age, age category, sex, race, ethnicity, height, weight, and body mass index (BMI). Age, age category, sex, race, and ethnicity will also be summarized for consented subjects who fail screening. Baseline disease characteristics will be summarized for the ITT population and will include WHO FC, age at PAH diagnosis, duration of PAH, previous PAH-specific therapy, type of PAH-specific background therapy, pulmonary hemodynamic parameters, and 6MWD.

9.4.1. Efficacy Analyses

9.4.1.1. Primary Endpoint

The primary estimand to address the efficacy objective with respect to PVR is the change in PVR from Baseline to Week 24 for each subject in the ITT Population with missing Week 24 PVR values imputed using multiple imputation (MI) techniques under the assumption that missing data are missing at random (MAR), comparing the estimated least-squares mean differences (LSMDs) between the GB002 group and the placebo group using an analysis of covariance (ANCOVA) model adjusted for Baseline PVR. Possible intercurrent events that could affect whether a post-Baseline PVR value is missing not at random (MNAR) or that could affect an observed post-Baseline value itself are initiation of a new PAH medication or increase in dose of a background PAH medication, death, or discontinuation due to disease progression.

The primary analysis of mean change in PVR from Baseline to Week 24 will be carried out using an ANCOVA model adjusted for Baseline PVR. Results will be expressed as mean changes in PVR and associated SDs, LSMDs and SEs with associated 95% CIs, and p-values. Missing PVR values at Week 24 will be imputed using MI. The resulting complete datasets obtained through MI will be analyzed and the estimates combined to produce a single inference that incorporates the uncertainty due to missing data (Rubin, 1987). A sensitivity analysis will be conducted using the tipping point approach (Ouyang, 2017) to both assess the appropriateness of the MAR assumption and whether patients with any of the intercurrent events noted above who have observed post-baseline PVR data might have had their results affected by the intercurrent event. In this analysis, the same analytic model will be used as in the primary analysis, however the MI approach will be expanded to allow for varying impact of missing data and intercurrent events by incorporating a shift parameter in the imputation model exploring the varying missing data assumptions from MAR to MNAR. Supplementary analyses will include repeating the primary and sensitivity analyses on percent change in PVR and analyzing the subgroup of subjects with observed PVR values at Week 24.

9.4.1.2. Secondary and Exploratory Endpoints

Secondary and exploratory endpoints involving continuous measurements will be analyzed using ANCOVA or mixed-effects models for repeated measures (MMRM) adjusted for PVR strata and

baseline value of the measurement of interest, or a Wilcoxon rank sum test as appropriate. Categorical endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusted for PVR strata. Time-to-event endpoints will be analyzed using Kaplan-Meier methods and Cox proportional hazards models.

9.4.2. Safety Analyses

All safety analyses will be performed using the Safety Population. All safety data will be summarized by treatment group.

AEs that start during or after the first dose of IP administration, or AEs with an onset prior to the first dose of IP administration that worsen during or after the first dose of IP administration will be considered TEAEs. All TEAEs will be coded and tabulated by system organ class (SOC) and preferred term (PT). Incidence of TEAEs, SAEs, and AESIs will be summarized and presented in descending order of frequency according to the GB002 treatment group. Aes leading to IP discontinuation and/or study withdrawal will be summarized and listed separately.

Associated laboratory parameters such as hepatic profile, lipid profile, renal function, and hematology values will be grouped and presented together in summary tables. For each laboratory test, individual subject values will be listed and values outside of the standard reference range will be flagged. Shift tables will be produced showing the frequency of shifts from Baseline to the lowest and to the highest on-study value in and out of normal range as well as by visit. The change from Baseline in laboratory parameters will also be summarized by visit.

The change from Baseline to each visit for each of the vital sign variables will be summarized. Abnormal vital sign values will be flagged and listed. Changes from Baseline in ECG results will be summarized.

9.4.3. Pharmacokinetic Analyses

GB002 concentrations may be summarized descriptively by PK sampling times and visits. The GB002 concentration data obtained in this study may be used for population PK and exposure-response analyses (including PK-PD, as appropriate) and may be reported separately. Analyses may be performed to assess if co-administration of GB002 affects the concentrations of PAH background medications and if there is a correlation between the concentrations and efficacy endpoints; these analyses may be reported separately.

9.5. Interim Analyses

An unblinded interim analysis may be conducted after at least 40 subjects undergo the Week 24 RHC. If the interim analysis is conducted, the conditional power (CP) for the primary and secondary endpoint will be estimated assuming the interim analysis treatment effect. If $50\% \leq CP < 80\%$, the sample size may be adjusted upward to recover the planned statistical power of approximately 90%. If the CP falls outside of this “promising zone”, the sample size may not be adjusted. Following the Haybittle-Peto α-spending function, $\alpha = 0.001$ will be spent at the interim analysis, resulting in a final α-level of 0.050. Results of this unblinded interim analysis will be reviewed by a small group of Sponsor employees who are not part of the study team as well as by the IDMC.

9.5.1. Independent Data Monitoring Committee

An IDMC, comprised of 2 independent external expert physicians (including the Chair) and an independent biostatistician will regularly monitor overall safety and emerging efficacy results, as well as general aspects of study conduct, to ensure that the benefits and risks to subjects of study participation remain acceptable. Based on these regular reviews of emerging results, the IDMC will recommend to the Sponsor continuation, modification, or termination of the study. Makeup of the IDMC, meeting structure, schedule, and procedures, including communication between the Sponsor and the IDMC, the content and format of IDMC reports, and other relevant details, are detailed in the IDMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations (Site Responsibilities)

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, Dosing Diary and other relevant subject-facing documents (eg, surveys, instructions for use, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of title 21 Code of Federal Regulations (CFR) (or equivalent for non-IND sites), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (or equivalent for non-IND sites), local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject entered the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

A pharmacogenetics consent form must be offered to all subjects, and the process must be documented, unless prohibited by local regulations.

10.1.3. Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law(s). The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

A clinical study report will be developed by the Sponsor at completion of data analysis. This report will be an integrated clinical and statistical report prepared according to the ICH E3 guidelines.

Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

10.1.5. Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain attributable, legible, contemporaneous, original, and accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Details describing monitoring strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality review of the data.

The Sponsor maintains ultimate responsibility for the quality and integrity of study data, even if study-related duties and functions are transferred to other individuals or organizations (eg, contractors or contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are attributable, legible, contemporaneous, original, and accurate from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per ICH-GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6. Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents should be generated utilizing good documentation practices and are filed at the Investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.7. Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further IP development.

10.1.8. Publication Policy

The publication policy is located within the Clinical Study Agreement with the Investigator and/or Institution.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10 and Table 11 will be performed by the central laboratory, unless otherwise noted.
- Protocol-specific requirements for inclusion or exclusion of subjects, including those based on selected laboratory test results, are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report in subject's source records.

Table 10: Protocol-Required Safety Laboratory Assessments

Hematology	
• White blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) • Hemoglobin • Hematocrit	• Red blood cell (RBC) with indices (mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]) • Platelet count
Clinical Chemistries (fasting)	
• Alanine Aminotransferase (ALT) • Alkaline phosphatase • Total and direct bilirubin (fractionated) • Calcium • Sodium • Chloride • Glucose • Phosphorus • Uric acid/Urate • Bicarbonate • Cholesterol	• Aspartate Aminotransferase (AST) • Gamma-glutamyl transferase (GGT) • Albumin • Blood urea nitrogen (BUN) • Creatinine • Potassium • Lactic dehydrogenase • Total protein • Magnesium • Lipids and triglycerides
Coagulation	
• Partial thromboplastin time (PTT)/Activated Partial thromboplastin time (APTT) • Prothrombin time (PT)	• International normalized ratio (INR)

Urinalysis	
• Basic urinalysis (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen); to be collected predose after randomization as specified in Schedule of Activities (SoA)	• Full urinalysis (dipstick plus microscopic evaluation) to be performed only at the screening and EOT visits

Other Laboratory Assessments
1. Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential
2. In women: follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only)
3. Serology (hepatitis B virus surface antigen [HbsAg], hepatitis C virus antibody, human immunodeficiency virus [HIV] antibody, tuberculosis [TB]; (interferon-based testing either via Quantiferon via central lab or local interferon-based test method such as T-SPOT.TB)). If hepatitis C virus antibody is positive, hepatitis C virus RNA will be tested.
4. Thyroid stimulating hormone (TSH), free T4
5. Drugs of abuse (amphetamines, methamphetamines, cocaine, and phencyclidine)
6. Serum digoxin for subjects currently on digoxin (local laboratory)
7. Male subjects: testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, and inhibin B (to be collected in the morning under fasting conditions)
8. Male fertility assessments (optional): semen volume, total sperm per ejaculate, sperm concentration, sperm progressive motility and sperm morphology (local or central laboratory)

The additional tests listed in Table 11 will be collected only as part of liver safety actions and follow-up (see Section 7.1.1).

Table 11: Liver Safety Laboratory Assessments

Hematology
Expanded viral hepatitis serology: 9. Hepatitis A immunoglobulin M (IgM) antibody 10. HbsAg and hepatitis C virus antibody 11. Hepatitis C RNA 12. Cytomegalovirus IgM antibody 13. Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) 14. Hepatitis E IgM antibody 15. Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, quantitative total immunoglobulin G (IgG) or gamma globulins, and serum acetaminophen assay
Chemistry
16. Serum creatine phosphokinase (CPK) 17. Lactate dehydrogenase (LDH)

The above assessments will be conducted only if required.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow up, and Reporting

10.3.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence in a subject or clinical study subject, whether or not considered related to the IP. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated).

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition other than the disease under study including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after IP administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Suspected and Unsuspected Adverse Reaction

Suspected adverse reactions are defined as:

- Any AE for which there is a reasonable possibility that the IP caused the AE. For the purposes of Sponsor regulatory safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by IP(s).

Unexpected Adverse events are defined as:

- AE which is not listed in the Investigator's brochure or approved label of the IP or is not listed at the specificity or severity that has been observed

10.3.4. Recording and Follow Up of Adverse Events and Serious Adverse Events

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE/AESI information in the eCRF.

It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both Aes and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between IP and each occurrence of each AE/SAE.

Related – The AE is known to occur with the IP, there is a reasonable possibility that the IP caused the AE, or there is a temporal relationship between the IP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP and the AE.

Not Related – There is not a reasonable possibility that the administration of the IP caused the event, there is no temporal relationship between the IP and event onset, or an alternate etiology has been established.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration will be considered and investigated.

The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the Investigator **must** document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always assesses causality for every event before the initial transmission of the SAE data to the Sponsor.**

The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Aes and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology, if available.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

The mechanism for reporting an SAE to the Sponsor will be the electronic data capture system.

If the electronic system is unavailable, then the site will contact the Medical Monitor (or designee) in order to report the event and submit the paper SAE report form via the contacts below within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information via contact to the Medical Monitor (or designee) and submitting the paper SAE report form via the contacts below.

Contacts for SAE reporting are:

PPD Pharmacovigilance Group
Safety hotline phone **+1 888 483 7729**
Safety hotline fax **+1 888 529 3580**

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterilized (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IP, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Male Subjects:

Male subjects 50 years and older are eligible to participate if they agree to the following from informed consent through 90 days after the last dose of IP:

- Refrain from donating sperm, except for the purpose of fertility analysis as part of this protocol

  PLUS, either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier (a male condom)

Female Subjects:

- A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency (see table below), from consent through 30 days after the last dose of IP, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of IP.
  - A WOCBP must have negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 72 hours prior to receiving the first administration of IP and a negative urine pregnancy test before first administration of IP. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required and results must be negative.

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly Effective Methods[a] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[b]
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[a] That Are User-Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

[a] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[b] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

10.4.3. Collection of Pregnancy Information

Male subjects with partners who become pregnant:

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.
- After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The Sponsor will attempt to follow the female partner to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. The Sponsor will follow the female partner until birth or termination of pregnancy when possible. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

Any female subject who becomes pregnant while participating in the study will discontinue IP(s). Additionally:

- The investigator will collect pregnancy information, which will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. The subject will be followed until birth or termination of pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the IP by the investigator will be reported to the Sponsor as described in Section 10.3.5. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: Genetics

Pharmacogenetic samples will be collected from subjects who have consented to participate in the genetic analysis component of the study, where permitted by law and local authorities and allowed by IRB/IEC. Participation is a subject-level decision, and those subjects who do not wish to participate in the genetic research may still participate in the overall study. While a particular biosample may be collected from consenting subjects to facilitate the ease of the genetic analysis, consent would apply to all biosamples provided by the subject.

The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality.

If the samples are assayed, the resulting data will be coded with a specific number, and neither subject name nor other personally-identifying information (initials, date of birth, Social Insurance number) will be used. This process allows the Sponsor to connect the assay results with other study results for research purposes, and to more securely store the data. Data obtained from this study is for research purposes only. The results may be shared with the site, upon request of the Investigator, if available, with the understanding that the results cannot be used for diagnostic and/or therapeutic purposes. The subject will not be identified in any reports or publications resulting from this study. The results and other information from this study may be submitted to the U.S. Food and Drug Administration (FDA) and governmental agencies in other countries where GB002 may be considered for approval. Unless required by law or regulatory authorities for the purpose of verifying the legitimacy of data obtained from this study, only the Sponsor and its authorized personnel and agents will have access to the data.

The results of these analyses may be reported in in independent, post hoc study report, without identifying the subject donor.

The samples will be retained while research on GB002 continues, but no longer than 8 years from end of study (as defined in Section 4.5) or other period so as to comply with local requirements.

10.6. Appendix 6: Prohibited Medications and Medications to be Used with Agreement of Medical Monitor

Medication	Washout time prior to screening visit
Anticoagulants	
Examples of anticoagulants: argatroban bivalirudin dalteparin drotrecogin alfa enoxaparin fondaparinux heparin administered intravenously or subcutaneously hirudin 4-hydroxycoumarin lepirudin warfarin ximelagatran Direct-acting oral anticoagulants (DOACs)	Use of anticoagulants (ie, warfarin or DOACs); if on warfarin or a DOACs, it is clinically acceptable to be withdrawn 1 month prior to start of IP. Discontinue use a minimum of 10 days prior to screening laboratories and until the end of treatment.
Medications that are inducers of CYP3A such as those listed below (not all inclusive)	
Moderate inducers: modafinil	Stop on first day of screening visit until the end of treatment
Strong inducers: phenytoin rifampin carbamazepine St. John's wort	
Medications that are inhibitors of CYP3A such as those listed below (not all inclusive)	
Strong inhibitors: cobicistat grapefruit juice itraconazole ketoconazole posaconazole telithromycin troleandomycin voriconazole	Stop on first day of screening visit or 3 half-lives prior to Day 1, whichever is longer, until the end of treatment

Medication	Washout time prior to screening visit
clarithromycin nefazodone	
Other Medications	
BCRP substrates (not all inclusive): rosuvastatin, sulfasalazine	Stop on first day of screening visit until the end of treatment
MATE-2K substrates (not all inclusive): dofetilide, metformin	
CYP2B6 substrates (not all inclusive): bupropion,	
Oral kinase inhibitors (not all inclusive): imatinib gefitinib erlotinib sorafenib dasatinib nilotinib	Within 3 months of screening visit until end of treatment
Medications Associated with QT Interval Prolongation (not all inclusive)	
Anti-arrhythmics: amiodarone, disopyramide, flecainide, ibutilide, procainamide, propafenone, quinidine, sotalol, dofetilide Antidepressants: amitriptyline, desipramine, doxepin, imipramine, maprotiline, nortriptyline, citalopram	Within 14 days (or 5 half-lives, whichever is longer) prior to Screening until end of treatment
Anti-infectives: erythromycin, pentamidine, azithromycin, clarithromycin, ciprofloxacin, gemifloxacin, levofloxacin Antipsychotics: haloperidol, pimozide, ziprasidone, thioridazine, olanzapine, risperidon, quetiapine Others: arsenic trioxide, probucol, droperidol, methadone, ondansetron	Within 14 days (or 5 half-lives, whichever is longer) prior to Screening until end of treatment

10.7. Appendix 7: Abbreviations

Abbreviation Term	Description
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
Abl	Abelson murine leukemia viral oncogene homolog
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APAH	Associated pulmonary arterial hypertension
AS	Aortic stenosis
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
BUN	Blood urea nitrogen
cfDNA	Cell free DNA
CFR	Code of Federal Regulations
CI (clinical)	Cardiac index
CI (Stat)	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
cMRI	Cardiac magnetic resonance imaging
CO	Cardiac output
CONSORT	Consolidated Standards of Reporting Trials
CP	Conditional power
CPK	Creatine phosphokinase
CT	Computed tomography
CTD	Connective tissue disease
CTFG	Clinical Trial Facilitation Group
CYP P450	Cytochrome P450
DDI	Drug-drug interaction

Abbreviation Term	Description
DLCO	Carbon monoxide diffusing capacity
DM	Disease modification
DMC	Data Monitoring Committee
DPI	Dry powder inhaler
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	European Quality of Life – 5 dimensions – 5 levels
ERS	European Respiratory Society
ESC	European Society of Cardiology
ET	Early termination
FC	Functional class
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
FWLS	free wall longitudinal strain
GC	Guanylate cyclase
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLS	Global longitudinal peak systolic strain
H_0	Null hypothesis
HA	Health authority
H_a	Alternative hypothesis
HbsAg	Hepatitis B virus surface antigen

Abbreviation Term	Description
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HFpEF	Heart failure with reserved ejection fraction
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPAH	Heritable pulmonary arterial hypertension
HR	Hazard ratio
HRT	Hormonal replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INDEL	Insertion and deletion
INR	International normalized ratio
IPAH	Idiopathic pulmonary arterial hypertension
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LAM	Lactational amenorrhoea method
LDH	Lactate dehydrogenase
LFT	Liver function test
LH	Luteinizing hormone
LSMD	Least-squares mean difference
LV	Left ventricle
LV GCS	Left ventricular global circumferential strain
LVEDP	Left ventricular-end diastolic pressure

Abbreviation Term	Description
LVEF	Left ventricular ejection fraction
MAR	Missing at random
MATE	Multidrug and toxin extrusion
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mLAP	Mean left atrial pressure
MMRM	Mixed-effects model for repeated measures
MNAR	Missing not at random
mPAP	Mean pulmonary arterial pressure
MR	Mitral regurgitation
MS	Mitral stenosis
MUGA	Multigated acquisition scan
NOAC	Novel oral anticoagulant
NT-proBNP	N-terminal pro b-type natriuretic peptide
OAT	Ornithine aminotransferase
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OLE	Open-label extension
PAH	Pulmonary arterial hypertension
PASMC	Pulmonary artery smooth muscle cell
PCP	Phencyclidine
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PDE-5	Phosphodiesterase type 5
PDGF	Platelet-derived growth factor
PDGF-BB	Platelet-derived growth factor homodimers
PDGFR	Platelet-derived growth factor receptor
PFT	Pulmonary function test
P-gp	P-glycoprotein
PK	Pharmacokinetic

Abbreviation Term	Description
PRN	Pro re nata (Latin for as needed)
PT (lab parameter)	Prothrombin time
PT (safety coding)	Preferred term
PTT	Partial thromboplastin time
PVOD	Pulmonary venous occlusive disease
PVR	Pulmonary vascular resistance
QOL	Quality of life
RA	Right atrial
RAP	Right atrial pressure
RBC	Red blood cell
REVEAL	Patient Registry for the Characterization of Primary Pulmonary Hypertension
RHC	Right heart catheterization
RV	Right ventricular
RVEF	Right ventricular ejection fraction
RVFAC	Right ventricular fractional area change
RVFWS	Right ventricular free wall strain
RVLS	Right ventricular longitudinal strain
SAE	Serious treatment emergent adverse event
SD	Standard deviation
SE	Standard error
SMQ	Standard MedDRA Query
SNP	Single nucleotide polymorphism
SoA	Schedule of Activities
SOC	System organ class
SPECT	Single photon emission computed tomography
SpO_2	Peripheral capillary oxygen saturation
SSc-APAH	PAH associated with systemic sclerosis
SUSAR	Suspected unexpected serious adverse reactions
SV	Stroke volume
TAPSE	Tricuspid annular plane systolic excursion
TAS'	Tricuspid annular peak systolic velocity

Abbreviation Term	Description
TB	Tuberculosis
TE	Target engagement
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TID	Three times per day
TSH	Thyroid stimulating hormone
TTCW	Time to clinical worsening
ULN	Upper limit of normal
V/Q	Ventilation-perfusion
WBC	White blood cells
WHO	World Health Organization
WOCBP	Women of childbearing potential
Δ6MWD	Change in distance achieved on the six-minute walk test

10.8. Appendix 8: Guidance to Address a Pandemic or Other Global Health Emergencies and Potential Impact on the Clinical Study

In the occurrence of a global health pandemic affecting the conduct of the ongoing study, such as COVID-19, the study may be adjusted due to trial subjects being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks. [Source: EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 3 (28 April 2020).]

Vaccines for the SARS-CoV-2 virus should be recorded as described in protocol section 6.7. Please discuss timing of first vaccine dose administration with the medical monitor.

The GB002-2101 protocol assessments may be conducted as described below, in line with Regulatory Authorities Guidance in order to assure the safety of study participants, maintain compliance with good clinical practice (GCP), and minimize the risks to trial integrity during the COVID-19 pandemic. Source: EMA, April 2020; FDA, March 2020; Health Canada, 03 April 2020; MHRA, 22 April 2020); the FDA guidance was amended 04 December 2020

Informed Consent

- If written consent by the study subject is not possible (for example because of physical isolation due to COVID-19 or other global health emergencies), consent could be given orally by the study subject.
- Study subjects and the person obtaining consent could sign and date separate ICFs.
- In case a written informed consent cannot be obtained at the clinical site, electronic informed consent can be obtained remotely. Alternatively, the consent form may be sent to the subject or the subject's legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone/teleconference when the subject or subject's legally authorized representative can read the consent form during the discussion; the subject or subject's legally authorized representative will be requested to sign and date a blank piece of paper with a written statement affirming that they agree to participate in the study.
- If re-consent is necessary for the implementation of **new urgent changes in study conduct** (mainly expected for reasons related to global health emergencies or important safety issues for other studies), alternative ways of obtaining consent may include contacting the study subject via phone or video-calls and obtaining oral consents, to be documented in the study subjects' medical records, supplemented with e-mail confirmation.
- The informed consent procedure is to remain compliant with the study protocol as well as local regulatory requirements. All relevant records should be archived in the Investigator's site master file. A correctly signed and dated informed consent form should be obtained from the study subjects later, as soon as possible.

Study Visits and Procedures

- In the case of missed visits due to COVID-19 (or other health pandemic)-related reasons:
  - The site should make every effort to contact the subject to confirm and document the reason for the missed visit, and at minimum evaluate AEs/SAEs, concomitant medications, Functional Class and a complete review of symptoms (modified physical exam) in order to assess subject safety.
  - Week 24 RHC may be scheduled up to 8 weeks beyond the Week 24 visit with the subject remaining in this study and on IP. An optional IP dispensing visit may be necessary to support the additional 8 weeks. Further delays require discussion with the Sponsor's Medical Monitor.
  - Delays with any other Week 24 assessments require discussion with the Sponsor's Medical Monitor.
- In order to maintain the integrity of the study, alternative methods of collecting data from study procedures, such as questionnaires, may be considered where possible.
  - EQ-5D-5L survey will be administered via telephone by qualified site personnel following a documented process.
  - The dosing diary will continue to be self-recorded by the subject at home.
- Alternative methods of supplying IP to enrolled study subjects (eg, direct-to-subject shipment from site) may be considered where possible.
  - Additional IP will not be released to the subject without an evaluation of subject safety by the Principal Investigator and clearance verbally communicated to the subject with minimum clinical safety laboratory assessments including hematology, coagulation, chemistry (Protocol Section 10.2 , Table 7), NT-proBNP and, for women of child-bearing potential, a urine or serum pregnancy test with confirmed negative result.
  - A local laboratory or mobile nurse (e.g., home-health or site nurse) may be utilized for collection of laboratory assessments, if available.
- In the event a subject has a confirmed positive test for SARS-COV-2 (test approved by local Health Authority), the infection should be recorded as an AE/SAE, and the PI should consult with the medical monitor regarding continuation of IP.

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

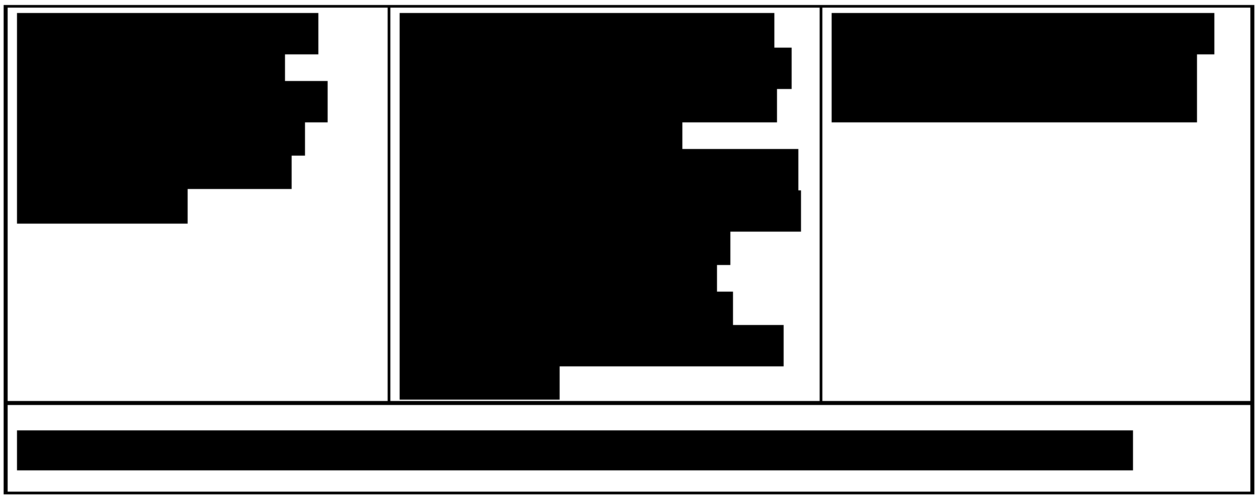
Amendment 3, Global (v3.0.1; 15 January 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purposes of this amendment from v2.0.0 to v3.0.1 are to update the maximum dose to be evaluated to 90 mg, to incorporate changes from a recent letter of amendment (LoA) dated 06 August 2020, provide updates and clarifications based on feedback received from health authorities (HA), and provide details for two substudies to be performed under the protocol.

Version 3.0.1 was issued to correct a typographical error in v3.0.0. Protocol v3.0.1 replaces v3.0.0 and no patients will be enrolled under v3.0.0. All changes compared to v2.0.0 that were summarized in v3.0.0 are reflected in this minor amendment (v3.0.1) and are summarized below.

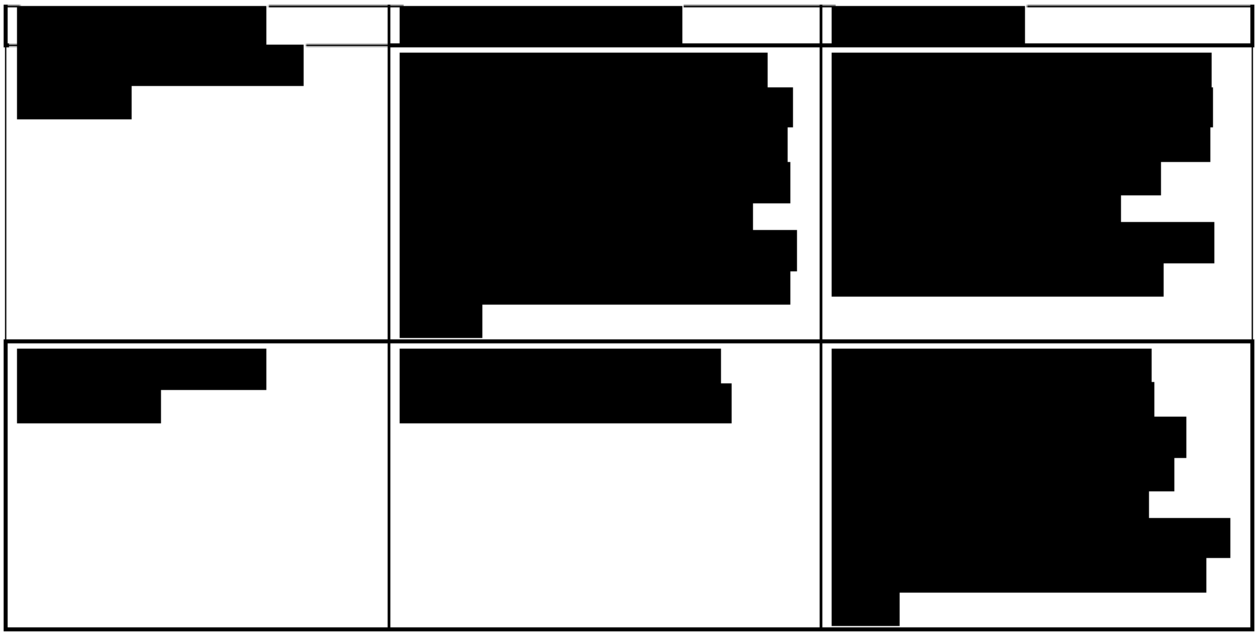


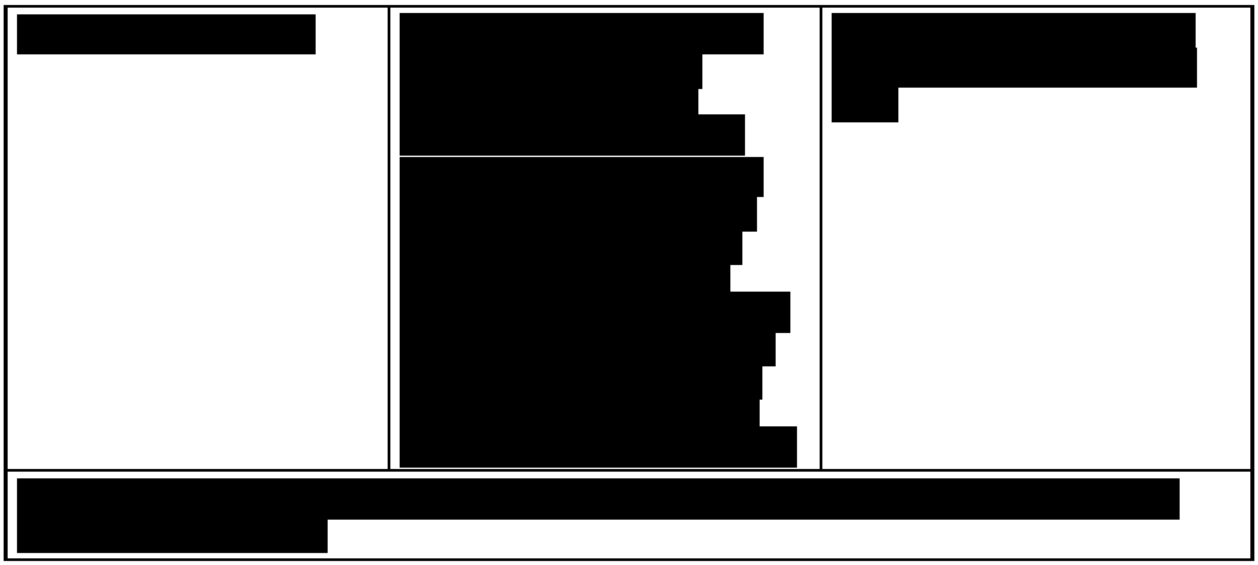
v2.0.0; 18 June 2020 and v2.5.1 (Canada); 18 December 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purposes of this amendment from v2.5.0 to v2.5.1 are to update the protocol in response to feedback obtained from the Health Canada.



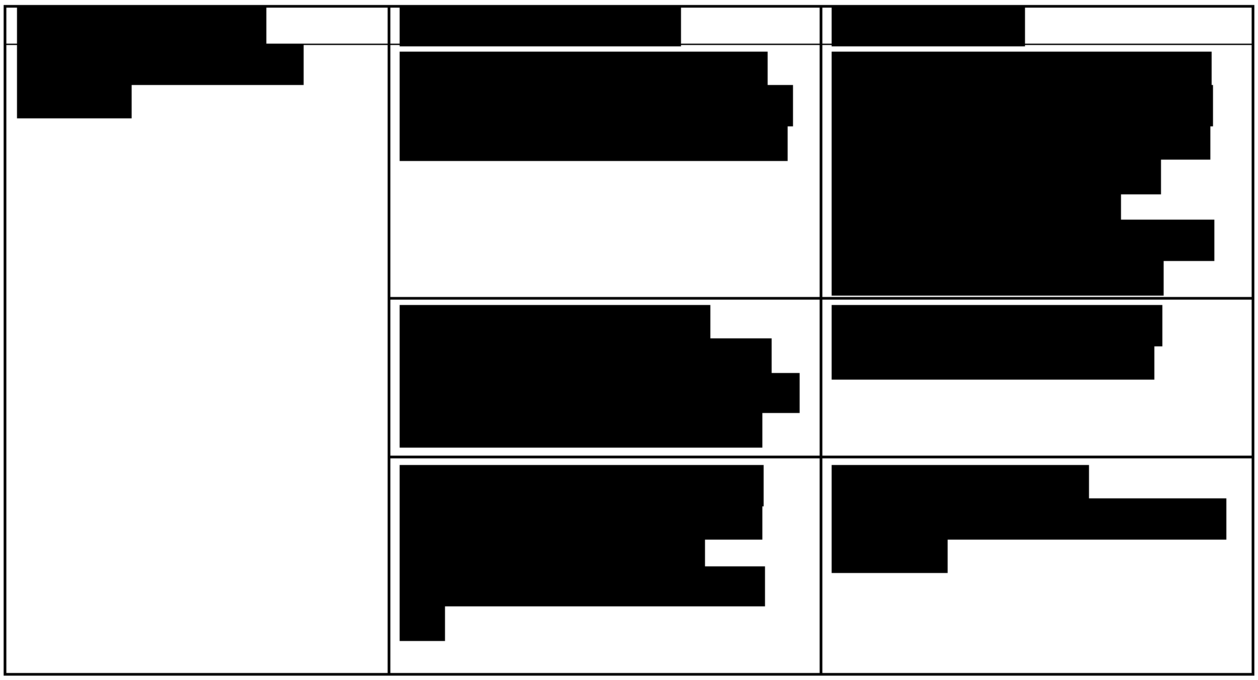


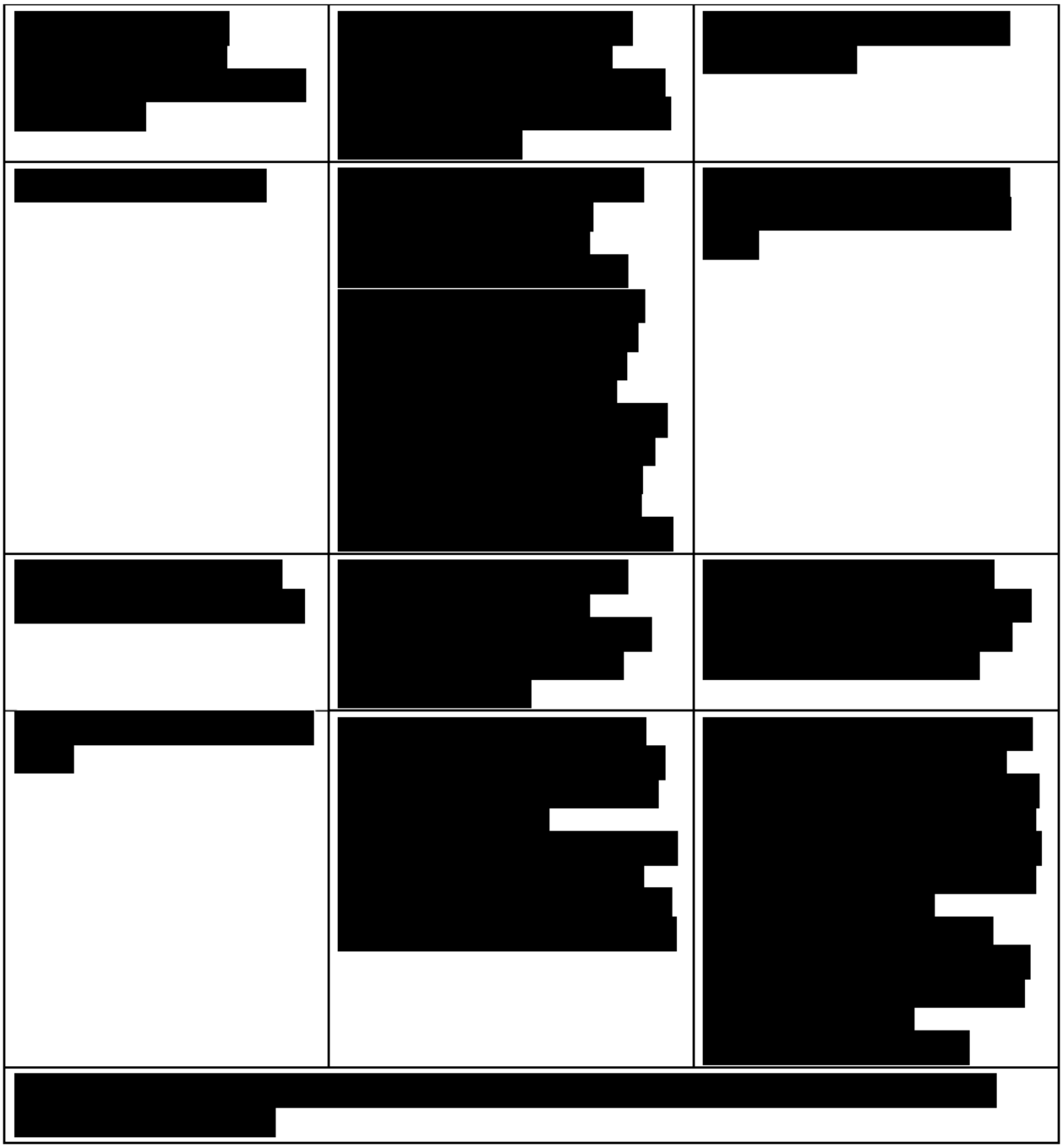
v2.0.0; 18 June 2020 and v2.4.1 (Germany); 24 November 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purposes of this amendment from v2.0.0 to v2.4.1 are to update the protocol in response to feedback obtained from the German Heath Authority, Federal Institute of Drugs and Medical Device (BfArM).





v2.0.0; 18 June 2020 and v2.6 (Czech Republic); 24 November 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

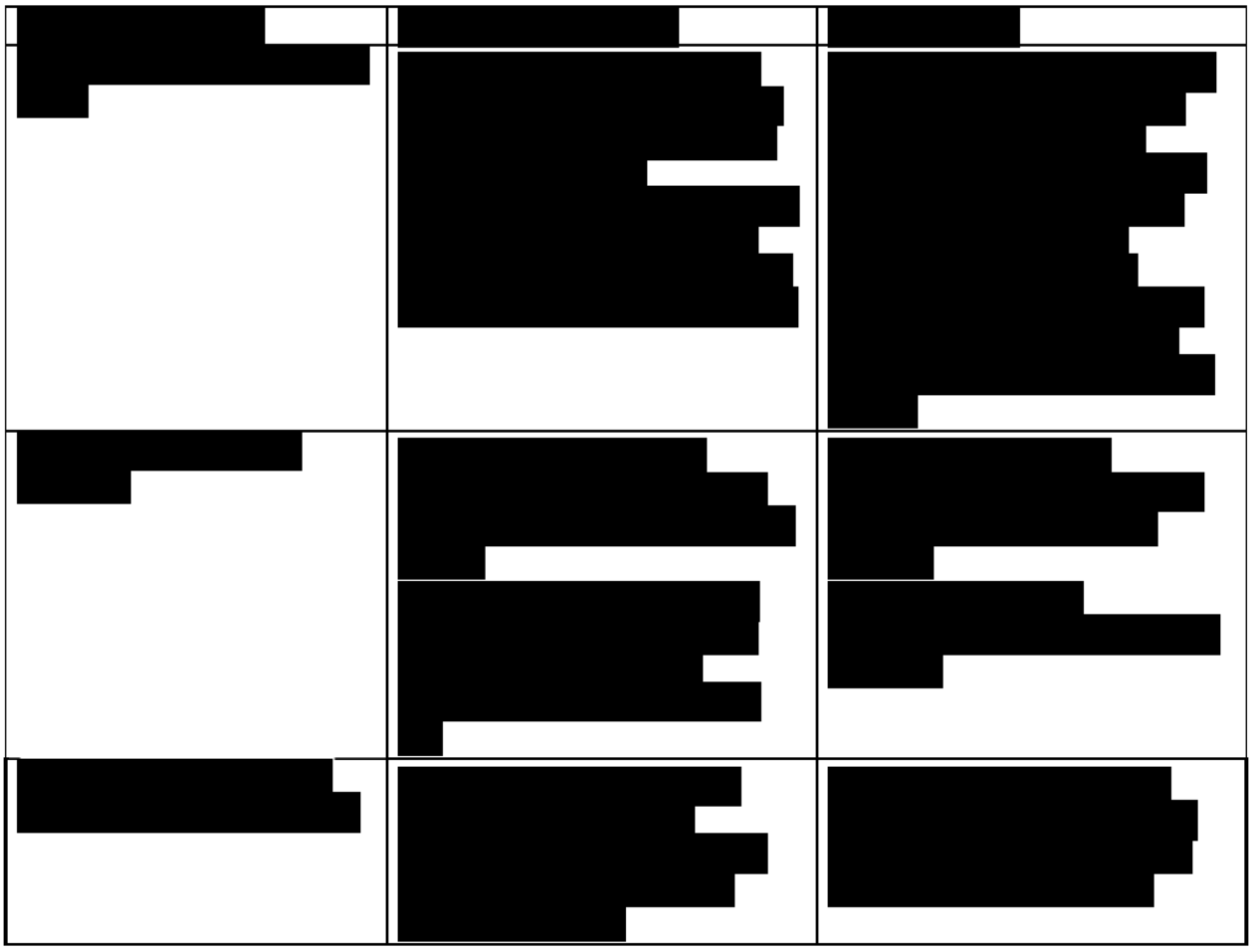
The primary purposes of this amendment from v2.0.0 to v2.6.0 are to update the protocol in response to feedback obtained from the State Institute of Drug Control (SUKL).

v2.0.0; 18 June 2020 and v2.5.0 (Canada); 19 October 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purposes of this amendment from v2.0.0 to v2.5.0 are to update the protocol with changes described in Letter of Amendment #1, dated 06 August 2020.



v2.0.0; 18 June 2020 and v2.4.0 (Germany); 13 October 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

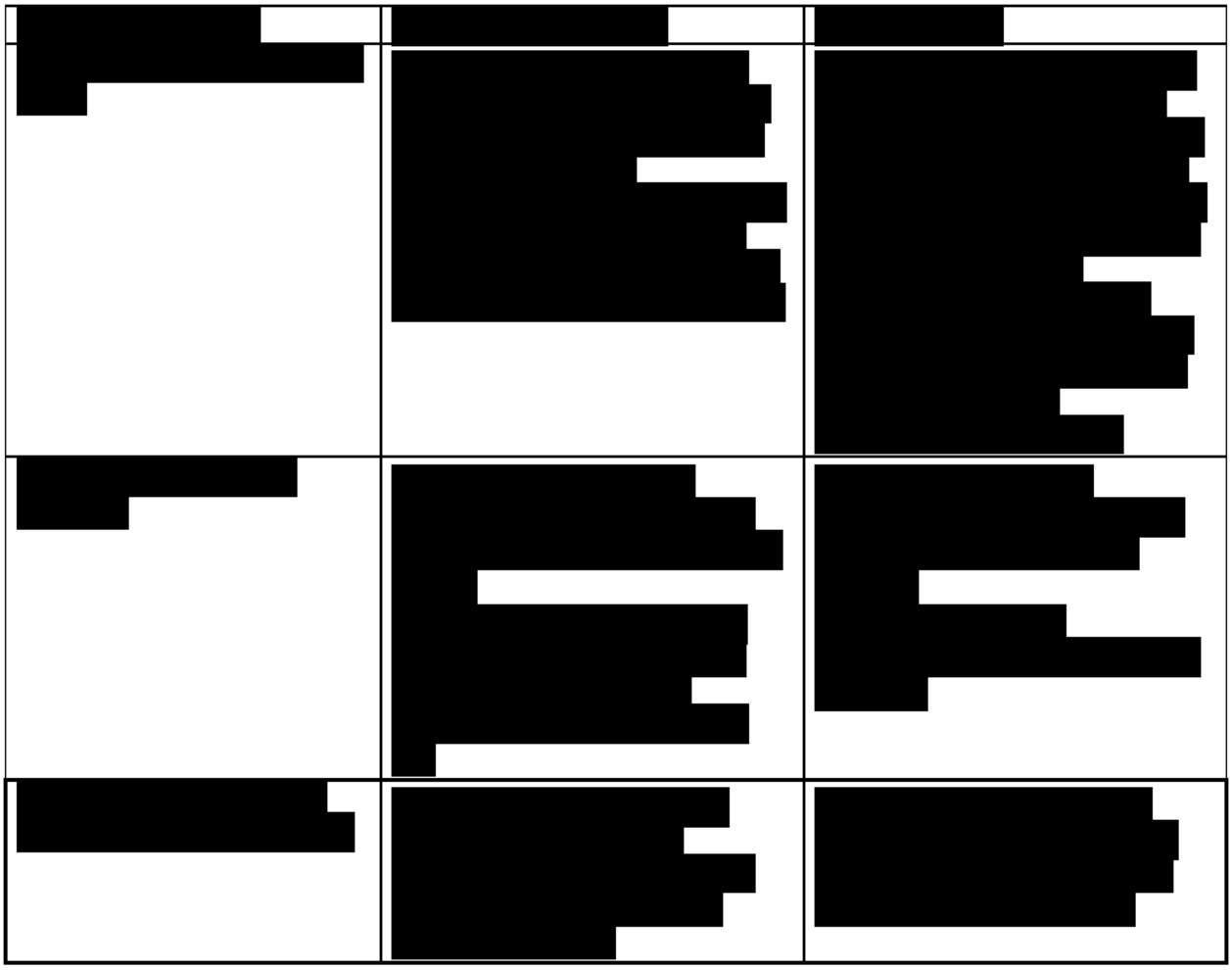
The primary purposes of this amendment from v2.0.0 to v2.4.0 are to update the protocol in response to feedback obtained from the German Heath Authority, Federal Institute of Drugs and Medical Device (BfArM).

v2.0.0; 18 June 2020 and v2.3.0 (UK); 08 October 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purposes of this amendment from v2.0.0 to v2.30 are to update the protocol with changes described in Letter of Amendment #1, dated 06 August 2020.

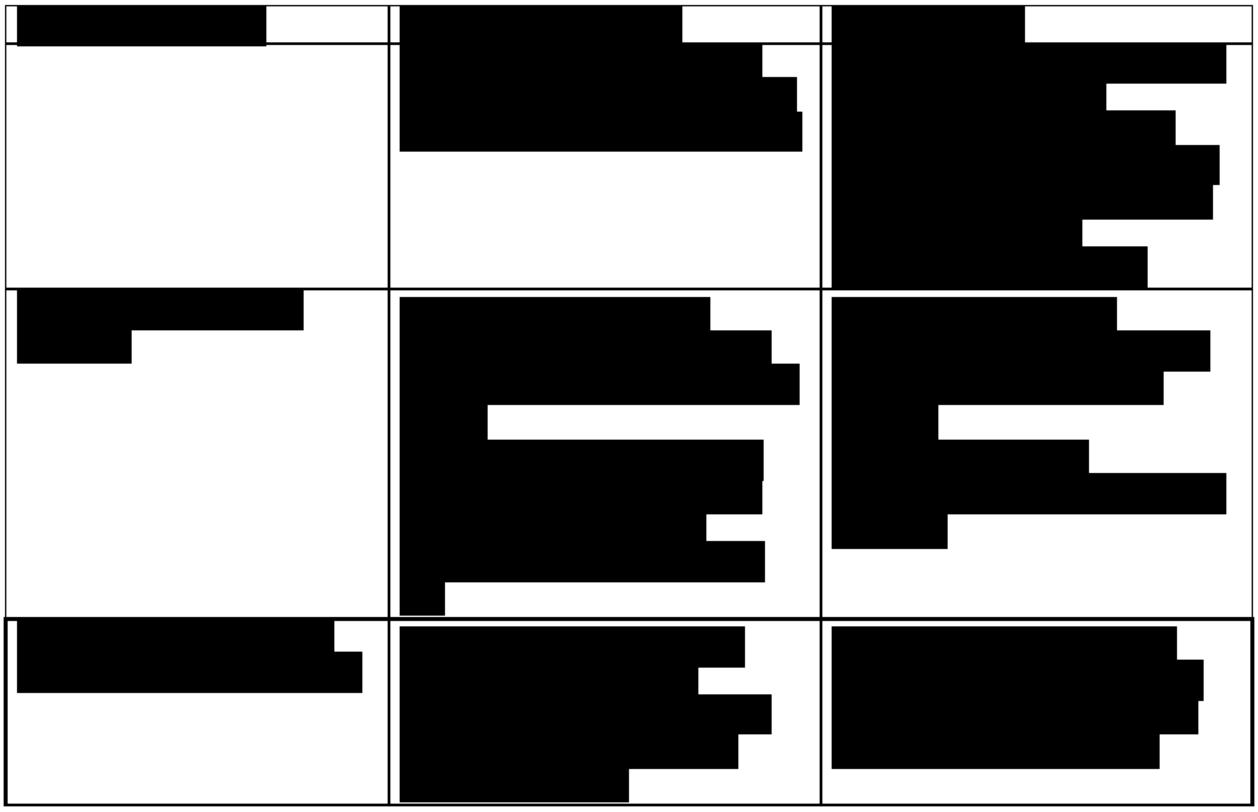


v2.0.0; 18 June 2020 and v2.2.0 (France); 08 October 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purposes of this amendment from v2.0.0 to v2.2.0 are to update the protocol with changes described in Letter of Amendment #1, dated 06 August 2020.

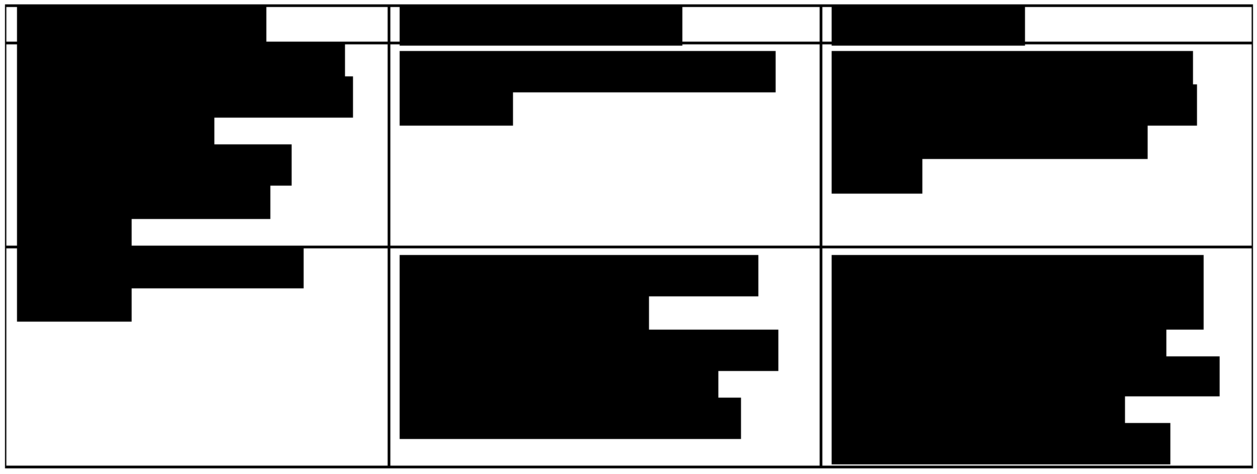


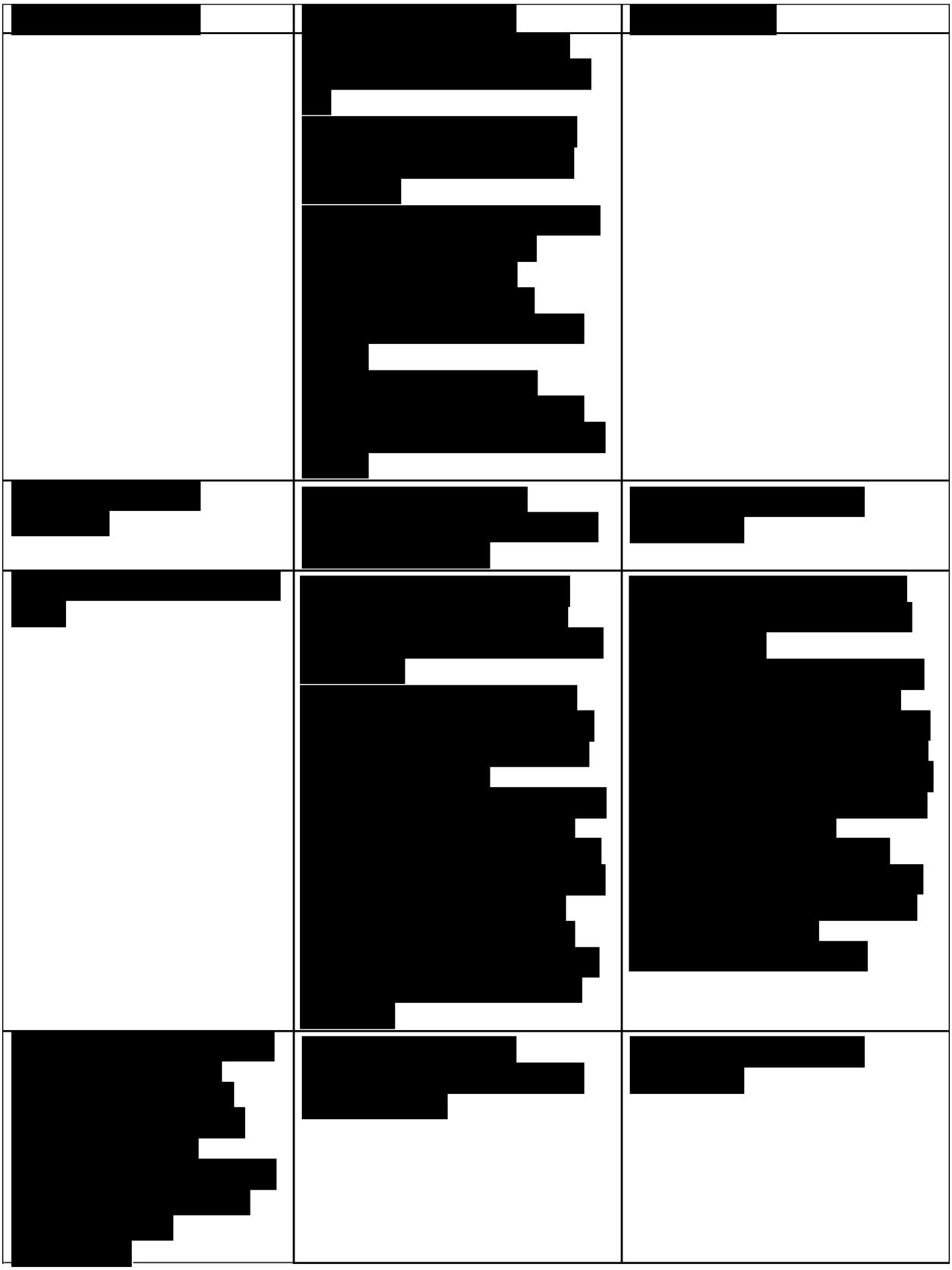
v2.0.0; 18 June 2020 and v2.1.0 (Spain); 06 August 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purposes of this amendment from v1.0.0 to v2.1.0 are to update the dose to be evaluated to 60 mg and adjust the Schedule of Activities (SoA) to reduce patient burden and allow for flexibility. In addition, this amendment addresses specific queries from Spanish health authorities upon review of Version 1.0.0 of the Global Protocol.



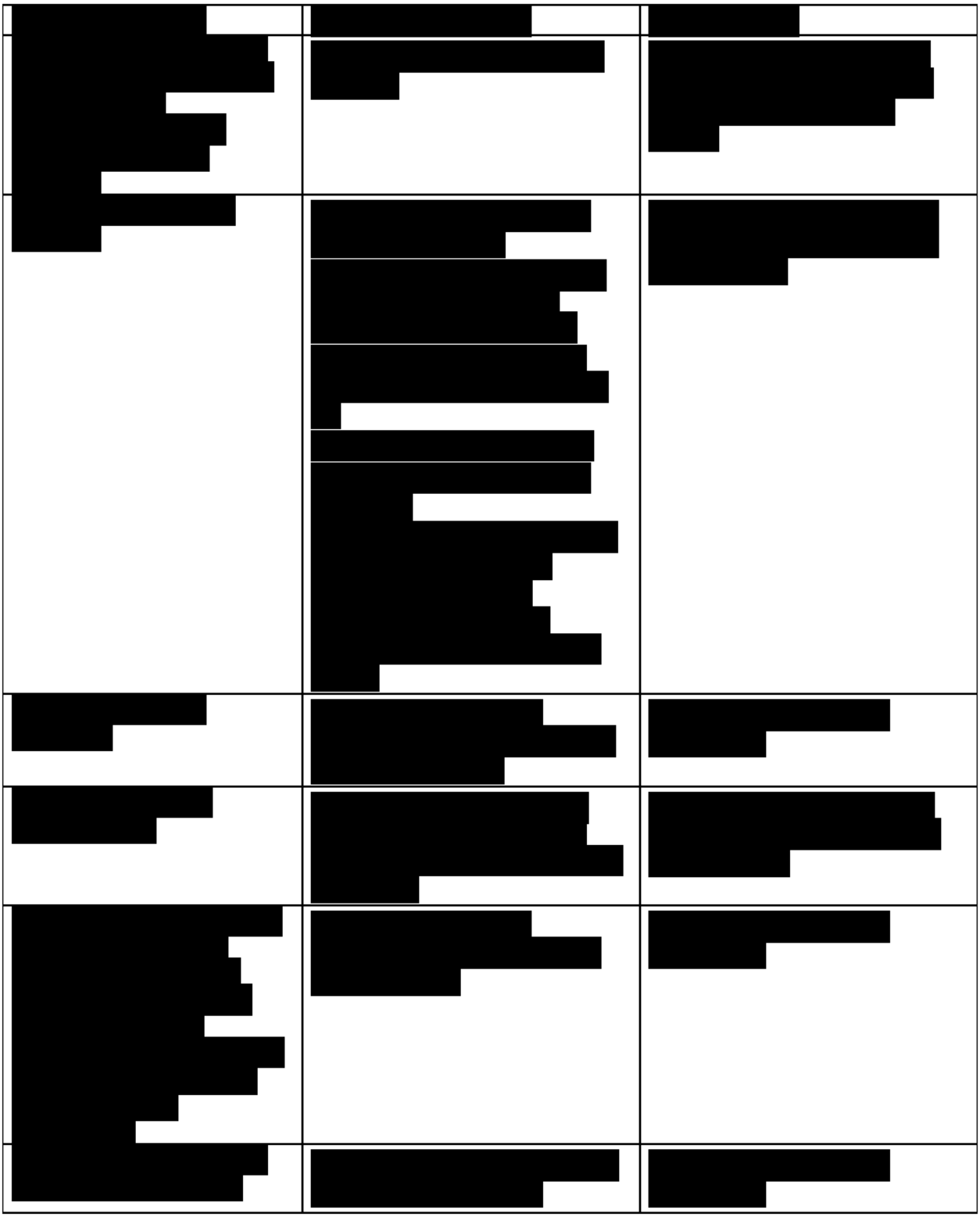


Amendment 2, Global (v2.0.0; 18 June 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purposes of this amendment from v1.1.0 to v2.0.0 are to update the dose to be evaluated to 60 mg and adjust the Schedule of Activities (SoA) to reduce patient burden and allow for flexibility.



Amendment 1 (v1.1.0 [UK]; 15 June 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purpose of this amendment is to add language regarding photosafety.

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