STATISTICAL ANALYSIS PLAN

Protocol Number GB002-2101

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)

FINAL
Version 1.0
27 October 2022

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LIST OF ABBREVIATIONS

Abbreviation Term	Description
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CO	Cardiac output
COVID-19	Coronavirus Disease 2019
CRO	Contract research organization
CSR	Clinical study report
C_t	Change from baseline to any timepoint t
CT	Computed tomography
CTD	Connective tissue disease
CTMS	Clinical Trial Management System
DBL	Database lock
DBP	Diastolic blood pressure
DLCO	Diffusing capacity of the lungs for carbon monoxide
DPI	Dry powder inhaler
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
EQ-5D-5L	European Quality of Life – 5 dimensions – 5 levels
ERA	Endothelin receptor antagonists
ERS	European Respiratory Society
ESC	European Society of Cardiology
FC	Functional class
FEV_1	Forced expiratory volume in 1 second
FRI	Functional respiratory imaging
FSH	Follicle stimulating hormone

Abbreviation Term	Description
FVC	Forced vital capacity
GGT	Gamma-glutamyl transferase
HbsAg	Hepatitis B virus surface antigen
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HRCT	High-resolution computed tomography
ICF	Informed consent form
ICH	International Conference for Harmonisation
IDMC	Independent Data Monitoring Committee
INR	International normalized ratio
IRT	Interactive response technology
ITT	Intent-to-Treat
IV	Intravenous
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
LLN	Lower limit of normal
LS	Least squares
LSMD	Least squares mean difference
LV	Left ventricular
LVEDP	Left ventricular-end diastolic pressure
LVEF	Left ventricular ejection fraction
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mmHg	Millimeters of mercury
MMRM	Mixed-effects model with repeated measures
MNAR	Missing not at random
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
NT-proBNP	N-terminal pro b-type natriuretic peptide
OLE	Open-label extension
PA	Pulmonary artery
PAC	Pulmonary arterial compliance
PAH	Pulmonary arterial hypertension
PAPi	Pulmonary artery pulsatility index
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic
PDE-5i	Phosphodiesterase type 5 inhibitors
PDGFR	Platelet-derived growth factor receptor
PFT	Pulmonary function test

Abbreviation Term	Description
PK	Pharmacokinetic
PRA	Prostacyclin receptor agonist
P_t	Percent change from baseline to any timepoint t
PT	Preferred term
PTT	Partial thromboplastin time
PVR	Pulmonary vascular resistance
PVRi	Pulmonary vascular resistance index
QOL	Quality of life
QTcF	Fridericia's correction formula for QT interval
RAA	Right atrial size
RBC	Red blood cell
REVEAL	Patient Registry for the Characterization of Primary Pulmonary Hypertension
REML	Restricted maximum-likelihood
RHC	Right heart catheterization
ROW	Rest of world
RV	Right ventricular
RVFAC	Right ventricular fractional area change
RVFWS	Right ventricular free wall strain
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDA	Study drug administration
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SE	Standard error
sGC	Soluble guanylate cyclase
SI	Standard international
SLE	Systemic lupus erythematosus
SOC	System organ class
sPAP	Systolic pulmonary artery pressure
SV	Stroke volume
SVRi	Systemic vascular resistance index
TAPSE	Tricuspid annular plane systolic excursion
TAS'	Tricuspid annular peak systolic velocity
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TLC	Total lung capacity
TR	Tricuspid regurgitation
TSH	Thyroid stimulating hormone
TTCW	Time to clinical worsening
ULN	Upper limit of normal

Abbreviation Term	Description
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization
WHODrug	World Health Organization Drug Classification Dictionary

1. INTRODUCTION

This clinical study is being conducted under the sponsorship of GB002, Inc. The data management and the statistical analyses are being performed under contract by [redacted] with oversight from GB002, Inc. [redacted] is a contract research organization (CRO).

This statistical analysis plan (SAP) has been developed based on protocol GB002-2101 version 4.0.0, dated 18 November 2021. This SAP presents a detailed plan of the statistical methods to be used during the analysis and reporting of efficacy and safety data collected under this protocol. This SAP does not include the planned analysis and reporting of pharmacokinetic (PK) assessments, selected biomarker assessments, the substudy of heart rate monitoring, and the substudy of changes in the pulmonary vasculature by high-resolution computed tomography (HRCT). Planned analyses of those results will be presented in separate analysis plans, as needed.

This SAP was prepared prior to database lock (DBL) to provide full details of the analyses to be presented in the clinical study report (CSR), including a technical and detailed elaboration of the efficacy and safety analysis methods presented in the protocol. Revisions can be made to this SAP while the study is ongoing; however, this SAP must be finalized prior to unblinding the study to perform the final analysis. Any deviations from the plan provided in this SAP will be considered post-hoc and will be documented as such in the final CSR.

This SAP is being written in accordance with the recommendations outlined in the International Conference for Harmonisation (ICH) E9 Guidance for Industry on Statistical Principles for Clinical Trials (FDA, 1998) and the ICH E3 Guidance for Industry on Structure and Content of Clinical Study Reports (FDA, 1996).

This SAP should be read in conjunction with the study protocol and the electronic case report forms (eCRFs).

2. PROTOCOL SUMMARY

This is a phase 2 study of GB002, a platelet-derived growth factor receptor (PDGFR) kinase inhibitor, in adult subjects with World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) who have WHO functional class (FC) II or III symptomatology and pulmonary vascular resistance (PVR) $\geq$ 400 dyne•s/cm^5 using right heart catheterization (RHC). This study aims to characterize the efficacy and safety of GB002 orally inhaled at doses of up to 90 mg twice daily (BID) in this subject population.

2.1. Study 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
Safety	
• Evaluate the safety of GB002 in this population	• Incidence of treatment-emergent adverse events (TEAEs), serious TEAEs (SAEs), and treatment-emergent adverse events of special interest (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 quality of life (QOL) – 5 Dimensions – 5 levels (EQ-5D-5L)
	  • 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, assessed by measuring the first occurrence of any of the following:
	  • 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
	  o Initiation of parenteral (IV infusion or subcutaneous injection) therapy with a prostacyclin (if not previously utilizing parenteral prostacyclin therapy)
	  • Disease progression, defined as:
	  o 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
	  o 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
	  o Worsening Risk Score Category, 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, electrocardiogram (ECG) parameters, pulmonary function and vital signs
• Evaluate the 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 during 6MWT – Substudy at select participating sites	• Change from Baseline in heart rate expenditure and heart rate recovery as 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)

2.2. Overall Study Design and Plan

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 ≥ 400 dyne•s/cm^5.

This study will consist of 3 periods: the screening period (up to 5 weeks), the treatment period (24 weeks), and the follow-up period (4 weeks) for a total study participation time of up to 33 weeks per subject. Subjects who complete the treatment period of this study and qualify for a separate open-label extension (OLE) study may enroll directly into the OLE study following the treatment period and those who do will not participate in the follow-up period of this study.

Subjects will initiate dosing with GB002 60 mg (4 inhalations) or placebo BID and, after 2 weeks, will up titrate to GB002 90 mg (6 inhalations) or placebo BID. Dose modifications downward to a minimum of 45 mg (3 inhalations) BID based on tolerability are permitted.

The first dose of study drug will be administered via oral inhalation using a dry powder inhaler (DPI) in the clinic on Day 1 (Visit 2). Subsequent doses will be taken via oral inhalation using a DPI twice daily at home.

Subjects who permanently discontinue study drug will be encouraged to complete any remaining study visits as per the protocol Schedule of Activities.

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

The study schema is shown in Appendix 13.1.

2.3. Study Population

This study will enroll adult female subjects aged 18-75 years, inclusive, and adult male subjects aged 50-75 years, inclusive, at the time of signing the Informed Consent Form (ICF). **Key** eligibility criteria include:

- Current diagnosis of symptomatic PAH with WHO FC II or III symptomatology
- Six-minute walk distance (6MWD) ≥ 150 meters and ≤ 550 meters at Screening
- Stable treatment (≥ 4 weeks) with standard of care PAH background therapies
- PVR ≥ 400 dyne•s/cm^5 via RHC
- Forced expiratory volume in 1 second (FEV_1) ≥ 70% and either total lung capacity (TLC) or forced vital capacity (FVC) ≥ 70% predicted

2.4. Randomization and Blinding

On Day 1 of the treatment period, subjects who meet the eligibility criteria will be randomized 1:1 to 1 of 2 treatment groups using interactive response technology (IRT):

- GB002 BID (40 subjects)
- Placebo BID (40 subjects)

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

This is a double-blind study. 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 completion of the study and the database has been locked.

2.5. Sample Size Determination

Based on the results from a Phase 2 study with the PDGFR inhibitor imatinib (Ghofrani, 2010), the mean (standard deviation [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.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

3.1. General Considerations

Continuous data will be presented using descriptive statistics: number of subjects (n), mean, SD, median, minimum, and maximum. Descriptive statistics on selected efficacy measures may also include the standard error (SE). Categorical data will be summarized by the number and percent of subjects. In general, data will be displayed in listings sorted by treatment group, subject number, and visit/study day. When count data are presented, the percent will be suppressed when the count is zero. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest, unless otherwise stated. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. Additional rounding rules are as follows:

- If the original value has 0 decimal places: mean and median will have one decimal place and SD and SE will have 2 decimal places
- If the original value has 1 decimal place: mean and median will have 2 decimal places and SD and SE will have 3 decimal places
- If the original value has 2 or more decimal places: mean, median, SD, and SE will all have 3 decimal places

Minimum and maximum will always have the same decimal places as the original measure, up to a maximum of 3 decimal places. The above rounding rules will not be applied to original measures displayed in listings.

Values that are collected with "<" or ">" signs will be analyzed as the numerical value without the sign in tables and figures. In listings, these data will be reported as collected with the sign.

All safety and efficacy data will be collected electronically. Datasets will be created using the Study Data Tabulation Model (SDTM) v. 1.7 or higher, conforming to the SDTM Implementation Guide (SDTMIG) v. 3.3 or higher. Datasets, tables, listings, and figures will be programmed using SAS® v 9.4 or higher (SAS Institute Inc., Cary, NC). All safety and efficacy data will be listed via the SDTM datasets and selected safety and efficacy data will be listed via programmed listings.

The following treatment groups will be presented:

- Placebo
- GB002

All subjects will be pooled into one of these 2 treatment groups regardless of how much they titrate up and/or down or how long they remain on a particular dose.

Selected tables will also present the following:

- Total (placebo and GB002 pooled together), for disposition, demographics, baseline characteristics, medical history, prior medications, and protocol deviation tables only

The order of columns presented in tables and figures will be as follows: Placebo first, GB002 second, and where applicable, Total third.

3.2. Definition of Baseline

Baseline data are defined as the last observed measurements collected, whether scheduled or unscheduled, prior to the start of the first dose of study drug (GB002 or placebo) administration on Day 1.

3.3. Calculation of Change and Percent Change from Baseline

Change from Baseline to any timepoint t (C_t) is calculated as follows:

- $C_t = M_t - M_B$, where:
  - M_t is the measurement of interest at timepoint t
  - M_B is the measurement of interest at Baseline

Percent change from Baseline to any timepoint t (P_t) is calculated as follows:

- $P_t = 100*(C_t/M_B)$

3.4. Study Day Calculation for Reporting Purposes

The following convention will be used to calculate study day for reporting purposes:

- The study day of the first dose of study drug administration (SDA) is Day 1

For measurements that are *on or after* the date of the first dose of SDA:

- Day = date of measurement – date of SDA + 1

For measurements that are *prior* to the date of the first dose of SDA:

- Day = date of measurement – date of SDA

There is no Day 0.

3.5. Visit Windowing

The designation of visits (or timepoints) will generally be based on the actual day of evaluation relative to the date of first dose of study drug (Day 1), rather than the nominal visit, for any analysis that are conducted by visit.

Mutually exclusive windows containing no gaps will generally be utilized to assign visits for by-visit analyses and will correspond to post-Baseline visits in the protocol. Visits for analysis will be assigned using the windowing scheme shown below.

For endpoints that are collected at every scheduled in-clinic/home-health option visit (vital signs, body weight, ECG, chemistry, hematology):

Nominal Visit	Target Day	Window
Baseline	Day 1 prior to first dose	Signing of ICF through Day 1 prior to first dose
Week 4	Day 29	Day 1 after first dose – Day 42
Week 8	Day 57	Day 43 – Day 70
Week 12	Day 85	Day 71 – Day 105
Week 18	Day 127	Day 106 – Day 147
Week 24	Day 169	Day 148 – Day 182
Week 28 (Follow-up)	Day 197	Day 183 or later

For endpoints that are collected at Baseline and Weeks 4, 8, 12, 24, 28 (coagulation, NT-proBNP):

Nominal Visit	Target Day	Window
Baseline	Day 1 prior to first dose	Signing of ICF through Day 1 prior to first dose
Week 4	Day 29	Day 1 after first dose – Day 42
Week 8	Day 57	Day 43 – Day 70
Week 12	Day 85	Day 71 – Day 126
Week 24	Day 169	Day 127 – Day 182
Week 28 (Follow-up)	Day 197	Day 183 or later

For endpoints that are collected at Baseline, and Weeks 12, 24 (WHO FC, 6MWT, ECHO, EQ-5D-5L, urinalysis, Patient Registry for the Characterization of Primary Pulmonary Hypertension (REVEAL) Lite 2 Risk Score, REVEAL 2.0 Risk Score):

Nominal Visit	Target Day	Window
Baseline	Day 1 prior to first dose	Signing of ICF through Day 1 prior to first dose
Week 12	Day 85	Day 1 after first dose – Day 126
Week 24	Day 169	Day 127 or later

For endpoints that are collected at Baseline and Week 24 (Pulmonary function tests [PFTs], RHC):

Nominal Visit	Target Day	Window
Baseline	Day 1 prior to first dose	Signing of ICF through Day 1 prior to first dose
Week 24	Day 169	Day 1 after first dose or later

If 2 or more evaluations occur in the same visit window, the evaluation closest to the target day will be selected for inclusion in the analysis. If 2 or more evaluations are equally close to the target day, then the latest evaluation will be selected for inclusion in the analysis. If multiple evaluations occur on the same day, the average of these evaluations will be used for analysis excluding maximum post-Baseline, abnormality, and outlier analyses.

4. ANALYSIS POPULATIONS

4.1. Enrolled Population

All subjects with a non-missing date of informed consent will be included in the Enrolled Population. This population will be used for summaries of disposition. The subset of subjects who enroll and fail screening will additionally be used in demographics reporting.

4.2. Intent-to-Treat Population

All subjects who are randomized will be included in the Intent-to-Treat (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

4.3. Safety Population

All subjects who receive any amount of study drug 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.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

A summary of disposition of subjects for the Enrolled Population will include the number and percentage of subjects in the following categories except where noted:

- Subjects enrolled (signed the ICF)
- Subjects who failed screening with reasons for screen failure
- Subjects randomized
- Subjects dosed
- Subjects completing dosing of study drug
- Subjects not completing dosing of study drug with reasons for discontinuation
- Subjects completing study overall and through Week 24 and Week 28
- Subjects not completing study with reasons for withdrawal

Only one reason for study drug discontinuation and only one reason for study withdrawal may be recorded for each subject.

Subjects enrolled will display the number only in the Total column. Subjects who failed screening will have percentages based on the number of subjects enrolled as the denominator. Subjects randomized will display the number only across the treatment group columns and the number and percentage in the Total column based on the number of subjects enrolled. The number and percentage of subjects in the ITT Population and in the Safety Population will be reported, based on the number of subjects randomized. Percentages in all other categories will be based on the ITT Population.

A listing of screen failures and a listing of disposition for all randomized subjects will be provided. The randomization scheme will also be listed.

5.2. Protocol Deviations

Protocol deviations will be identified and reviewed on an ongoing basis by the study team and entered into a Clinical Trial Management System (CTMS). Important protocol deviations are defined as those that can affect efficacy and/or safety assessments, the safety of a subject, or the scientific value of the study. Protocol deviations will be classified as important or non-important and will be assigned a protocol deviation type prior to unblinding the study. The number and percent of subjects with at least 1 important protocol deviation overall and for each protocol deviation type will be summarized for the ITT Population. In addition, Coronavirus Disease 2019 (COVID-19) related and non-COVID-19 related important protocol deviations will be summarized.

Protocol deviations will also be listed.

6. DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND MEDICAL HISTORY

6.1. Demographic and Baseline Characteristics

Demographics will consist of the following parameters:

- Age (years)
- Age category (≥ 18-49, ≥ 50-64, ≥ 65)
- Sex (female, male)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

Baseline characteristics will consist of the following parameters:

- Height (cm)
- Weight (kg)
- Body mass index (BMI) [kg/m^2]
- Country (Australia, Belgium, Czech Republic, France, Germany, Spain, United Kingdom, United States)
- Region (North America [United States], Western Europe [Belgium, France, Germany, Spain, United Kingdom], Eastern Europe [Czech Republic], Asia Pacific [Australia])

Demographics and baseline characteristics will be summarized by treatment group and Total for the ITT Population. Demographics only will separately be summarized in a single column for screen failure subjects. Demographics and baseline characteristics will also be listed.

6.2. Baseline Disease Characteristics

Baseline disease characteristics will be summarized for the ITT Population and include the following variables:

- Age at PAH diagnosis (years) – derived as follows:
  - Age – floor (time since PAH diagnosis)
- Time since PAH diagnosis (years) – derived as follows:
  - (date IC signed – date of PAH diagnosis)/365.25
- PAH classification (idiopathic, heritable, associated with connective tissue disease [CTD], associated with anorexigen use, associated with methamphetamine use, associated with congenital heart disease with simple systemic to pulmonary shunt)
- Type of connective tissue disease (if applicable – systemic sclerosis, mixed CTD, overlap syndrome, systemic lupus erythematosus [SLE])
- Time since CTD diagnosis (years) – derived as follows:

  - (date IC signed – date of CTD diagnosis)/365.25
- WHO functional classification at Screening and Baseline (Class II, Class III)
- PVR
  - randomized (< 800 dyne•s/cm5, ≥ 800 dyne•s/cm5)
  - actual (< 800 dyne•s/cm5, ≥ 800 dyne•s/cm5)
  - continuous (dyne•s/cm5)
  - continuous (wood units)
- 6MWD at Screening #1, Screening #2, and Baseline (m)
- NT-proBNP (ng/L)
- Number of PAH disease-specific background medications (< 3, ≥ 3)
- PAH disease-specific background medications category:
  1. Endothelin receptor antagonists (ERA)
  2. Phosphodiesterase type 5 inhibitors (PDE-5i)
  3. Soluble guanylate cyclase (sGC) stimulators
  4. Prostacyclins or prostacyclin receptor agonist (PRA)

For the background medications portion of the summary, the number and percent of subjects on each of those 4 categories alone (monotherapy) will be presented, along with the number and percent of subjects on the following combination therapies:

- ERA + PDE-5i
- ERA + PDE-5i + Prostacyclins/PRA
- ERA + sGC
- ERA + sGC + Prostacyclins/PRA
- PDE-5i + Prostacyclins/PRA
- sGC + Prostacyclins/PRA

See Appendix 13.2 for a list of PAH disease-specific background medications by category.

Baseline disease characteristics will also be listed.

6.3. Medical History

General medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or later. General medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the ITT Population. General medical history will also be listed.

7. TREATMENTS AND MEDICATIONS

7.1. Prior and Concomitant Medications

Prior medications are defined as medications with a stop date occurring before Day 1. Concomitant medications are defined as medications that are ongoing on Day 1 or with a start date occurring on or after Day 1. Medications with start and stop dates which bracket Day 1, or for which missing information makes it impossible to determine the prior or concomitant status, will be summarized as concomitant medications.

All medications will be coded with the World Health Organization Drug Classification Dictionary (WHODrug), March 2021 or later.

Incidence of prior and concomitant medications will be summarized separately for the Safety Population by drug class and PT. In addition, incidence of prior PAH disease-specific therapies, PAH disease-specific background medications, and concomitant PAH disease-specific medications will be summarized separately for the ITT Population by drug class and PT. At each level of summarization, a subject is counted once if that subject reports 1 or more medications at that level. Drug class will correspond to the Anatomical Therapeutic Chemical (ATC) Level 2 term.

All prior and concomitant medications, prior PAH disease-specific therapies, and background and concomitant PAH disease-specific medications will also be listed. In addition, all concomitant procedures and therapies will be listed

7.2. Extent of Time on Study, Study Drug Exposure, and Compliance

Duration of study treatment and time on study in subject-days, subject-weeks (subject-days/7), and subject-years (subject-days/365.25) will be summarized for the Safety Population. A subject's duration of study treatment in days will be calculated as last dose date – first dose date + 1. Drug holidays will be ignored for the purposes of calculating treatment duration. A subject's time on study in days will be calculated as last assessment date – first dose date + 1.

Dosing and time on study will also be summarized by the number of weeks completed for the following categories:

- < 12 weeks
- 12-15 weeks
- 16-19 weeks
- 20-23 weeks
- ≥ 24 weeks

For the purposes of this categorical summary, the duration in subject-weeks will be rounded to the nearest integer to determine the category for each subject.

For each dose level, the expected number of capsules taken *per dose* is as follows (15 mg active pharmaceutical ingredient [API] per capsule):

- 45 mg: 3 capsules

- 60 mg: 4 capsules
- 75 mg: 5 capsules
- 90 mg: 6 capsules

The study is designed such that each subject starts on 60 mg BID and then titrates to 90 mg BID after 14 days. Therefore, the expected number of capsules for a subject that completes dosing on schedule (168 days) without further titration is as follows:

- (4 capsules x 2 [BID] x 14 days) + (6 capsules x 2 [BID] x 154 days) = 1,960 capsules

For subjects that discontinue early or that titrate the dose other than scheduled will have their expected number of capsules adjusted accordingly.

Note: Protocol v2 specified a maximum dose of 60 mg BID. Any subjects enrolled under that amendment and not titrating to 90 mg BID will have their expected number of capsules adjusted accordingly.

Compliance 100*(capsules taken/expected), average BID dose in mg, and total cumulative dose in mg will be summarized. Compliance will also be summarized for the following categories:

- < 80%
- 80-100%
- > 100%

Extent of time on study, study drug exposure, and compliance will be listed. Study treatment administration, titrations, and lot numbers will also be listed.

8. EFFICACY EVALUATION

All analyses of efficacy data will be conducted using the ITT Population. Unless specified otherwise, all statistical analyses will be performed using 2-sided hypothesis tests at the 5% level of significance. Confidence intervals (CI) will be 95% and 2-sided, unless otherwise stated. All efficacy data will be summarized by randomized treatment group and visit, where applicable.

8.1. Primary Endpoint

8.1.1. Statistical Hypothesis and Estimand

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

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

The primary estimand to address the statistical hypothesis 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 PVR values at Week 24 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 treatment, Baseline PVR, and Baseline WHO FC. 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 disease-specific medication or increase in dose of a background PAH disease-specific medication, death, or discontinuation due to disease progression. Intercurrent events affecting Week 24 PVR values will be classified and documented prior to DBL.

8.1.2. Primary Efficacy Analysis

PVR in units of dyne•s/cm^5 is calculated as:

$$PVR = \frac{mPAP - PCWP}{CO}\ x\ 80$$

where mPAP = mean pulmonary arterial pressure in millimeters of mercury (mmHg), PCWP = pulmonary capillary wedge pressure in mmHg, and CO = cardiac output in L/min. In cases where PCWP is missing, left ventricular-end diastolic pressure (LVEDP) in mmHg will be used instead.

RHC from which PVR is collected is scheduled at Baseline and Week 24. The primary analysis of change in PVR from Baseline to Week 24 will be carried out using an ANCOVA model adjusted for treatment, Baseline PVR, and Baseline WHO FC. Results will be expressed as least squares (LS) mean changes in PVR and associated SEs, LSMDs and SEs with associated 95% CI, and p-values. Missing PVR values at Week 24 and observed PVR values affected by intercurrent events will be imputed using MI. Fifty imputations will be performed, and the resulting 50 complete datasets will be combined to produce a single inference that incorporates

uncertainty due to missing data (Rubin, 1987). Values that are affected by intercurrent events and therefore subject to imputation in the primary analysis will be documented prior to DBL.

A bar graph showing the LS mean and SE for each treatment group along with the LSMD and associated p-value will be produced. PVR results will also be listed.

The normality of the primary analysis model will be assessed using the Shapiro-Wilk test. If the test indicates that the assumption of normality is violated, then the primary analysis of PVR effects will be repeated in 2 ways: first by repeating the primary analysis model on the difference in log transformed PVR values and second by using a Wilcoxon rank sum test on non-transformed PVR changes.

8.1.3. Sensitivity and Supplemental Analyses

Sensitivity and supplemental analyses will include the following:

- Repeating the primary analysis on percent change in PVR
- Repeating the primary analysis (without MI) on the subgroup of subjects with observed post-Baseline PVR values
- Repeating the primary analysis (without MI) on the subgroup of subjects who complete at least 20 weeks of treatment and have an observed Week 24 PVR
- Repeating the primary analysis on the following subgroups:
  - Females
  - Number of PAH disease-specific background medications (< 3, ≥ 3)
  - Presence of Prostacyclins at Baseline (yes, no)
  - Age groups ($<$ median, $\geq$ median; < 65, ≥ 65)
  - Race (white, non-white)
  - Region (North America, rest of world [ROW])
  - PVR strata ($<$ 800 dyne•s/cm5, $\geq$ 800 dyne•s/cm5)
  - WHO FC at Baseline (II, III)
  - CTD (yes, no)
  - Risk Score using REVEAL 2.0 (< 6, ≥ 6)

A forest plot showing the primary analysis result along with each of the subgroup results will be produced.

Note: the expected number of males enrolled in the study is ≤ 12 (15%), so no supplemental analysis is planned on males. If the actual male enrollment is ≥ 8 per group, then an analysis of ΔPVR in males will also be performed.

8.1.4. Other Analyses of RHC Results

Changes from Baseline to Week 24 in the following parameters will be analyzed using an ANCOVA model adjusted for treatment, Baseline value of the parameter of interest, PVR strata,

and Baseline WHO FC. Results will be expressed as LS mean changes and associated SEs, LSMDs and SEs with associated 95% CI, and p-values. Missing values will not be imputed.

- Mean right atrial pressure (mRAP)
- RV systolic pressure
- PCWP or LVEDP
- Pulmonary artery (PA) systolic pressure
- PA diastolic pressure
- mPAP
- CO
- Cardiac index
- PVR index (PVRi)
- Stroke volume (SV) (calculated as 1000*CO/heart rate)
- PA pulsatility index (PAPi) (calculated as [PA systolic pressure – PA diastolic pressure]/mRAP)
- PA compliance (PAC) (calculated as SV/[PA systolic pressure – PA diastolic pressure])
- Systemic vascular resistance index (SVRi)

Other RHC results will also be listed. A bar graph showing the LS mean and SE for each treatment group along with the LSMD and associated p-value will be produced for mPAP and CO.

8.2. Secondary Endpoint

The 6MWT is scheduled at Screening, Baseline, Week 12, and Week 24. If the 6MWT is not done at a post-Baseline visit due to PAH disease progression, the change from Baseline value will be imputed to the worst observed value across all subjects. The secondary endpoint of change from Baseline to Week 24 in 6MWD will be analyzed using a mixed-effects model with repeated measures (MMRM) with treatment, Baseline 6MWD, Baseline WHO FC, PVR strata, visit, Baseline 6MWD by visit interaction, and treatment by visit interaction as fixed effects. MMRM will be performed using a restricted maximum-likelihood (REML) based approach with unstructured covariance to model within-subject error. Parameters will be estimated via REML using the Newton-Raphson algorithm. Results will be expressed as LS mean changes in 6MWD and associated SEs, LSMDs and SEs with associated 95% CI and p-values with the Kenward-Roger adjustment (Kenward, 1997). If the model fails to converge due to the complexity of the model specification, alternative methods to enable model convergence will be explored, such as employing a log transformation of the 6MWT results.

Sensitivity and supplemental analyses will include the following:

- Performing MI for missing 6MWT results and repeating the primary analysis of 6MWD on the full dataset (MMRM with MI)
- Running ANCOVA on both the Week 12 and Week 24 6MWD results adjusted for treatment, Baseline 6MWD, Baseline WHO FC, and PVR strata on the full dataset after performance of MI (ANCOVA with MI)
- Repeating the ANCOVA model (without MI) on the subset of subjects with observed post-Baseline values at, or carried forward to, each timepoint
- Repeating the primary analysis on the subset of subjects who complete at least 20 weeks of treatment and have an observed Week 24 6MWT
- Repeating the primary analysis on the same subgroups listed in Section 8.1.3

A forest plot showing the primary analysis result along with each of the subgroup results will be produced. A bar graph showing the LS mean and SE for each treatment group along with the LSMD and associated p-value will also be produced.

6MWT results will also be listed.

8.3. Exploratory Endpoints

Sensitivity and supplemental/subgroup analyses indicated for the primary and secondary endpoints are not planned to be performed on any of the exploratory endpoints.

8.3.1. Echocardiography Endpoint

ECHO is performed at Screening, Week 12, and Week 24. ECHO endpoints include the following:

- Change from Baseline in:
  - TAS'
  - RVFWS
  - Right ventricular fractional area change (RVFAC)
  - Tricuspid annular plane systolic excursion (TAPSE)
  - Tricuspid regurgitation (TR) velocity
  - Right atrial size (RAA)
  - Pericardial effusion
  - estimated systolic PA pressure (sPAP)
  - TAPSE:sPAP Ratio
  - RV:left ventricular (LV) Basal Diameter Ratio
  - Left ventricular ejection fraction (LVEF)

Results will be analyzed for subjects with a Baseline and at least one post-Baseline ECHO. Missing values will not be imputed.

Each of these endpoints will be analyzed using an ANCOVA model adjusted for treatment, Baseline value of the response parameter, PVR strata, and Baseline WHO FC. Results will be expressed as LS mean changes and associated SEs, LSMDs and SEs with associated 95% CI, and p-values.

ECHO results will also be listed.

8.3.2. Time to Clinical Worsening

Time to clinical worsening (TTCW) is defined as the time from the date of the first dose of study drug to the first date that any of the following components of the TTCW endpoint is met:

- 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 medication 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 defined as a change in at least two components (variables) of the French Non-invasive Risk Assessment to a worse risk category (see table below)

	Risk Category		
Variable	**Low Risk**	**Intermediate Risk**	**High Risk**
WHO FC	I, II	III	IV
6MWD	> 440 m	165 – 440 m	< 165 m
NT-proBNP level	< 300 ng/L	300 – 1400 ng/L	> 1400 ng/L

Abbreviations: 6MWD, six-minute walk distance; FC, functional class; NT-proBNP, N-terminal pro b-type natriuretic peptide; WHO, World Health Organization.
Source: Leuchte, 2018

Subjects who do not progress to clinical worsening during the study will be censored on the date of their last study visit.

TTCW will be compared between treatment groups via a Cox proportional hazards model using the exact method to handle ties in event times, adjusted for treatment, PVR strata, and Baseline WHO FC. The estimated hazard ratio with corresponding 95% CI and p-values will be reported. The percent reduction in hazard and corresponding 95% CI will also be reported. A Kaplan-Meier analysis will be run to report the median TTCW, 25th and 75th percentiles (if estimable), along with associated 95% CI. Kaplan-Meier curves will be produced, and the logrank test stratified by PVR strata and Baseline WHO FC will be used to compare differences in the curves.

The number and percentage of subjects who progress to clinical worsening in each treatment group along with the 95% binomial CI (or exact CI if the number of subjects is small) will be reported. The difference in proportion between the treatment groups, 95% CI, and p-value will be reported using the Cochran-Mantel-Haenszel (CMH) method adjusted for treatment, PVR strata, and Baseline WHO FC, using modified ridit scores. The number and percentage of subjects meeting each one of the clinical worsening components will also be presented in a table, with subjects counted only once for the component first met.

Clinical worsening results will also be listed.

Note: if the number of clinical worsening events is so low that the 25th percentile cannot be estimated, TTCW analyses will not be performed and will be listed only.

8.3.3. WHO Functional Class

WHO FC is assessed at Screening, Baseline, Week 12, and Week 24. For the analysis of change in WHO FC, subjects will be assigned to one of the 3 categories as follows:

1. Improved: II → I; III → II; III → I
2. No Change: II → II; III → III
3. Worsened: II → III; III → IV; II → IV

The distribution of subjects in each category by visit will be analyzed using the CMH method adjusted for treatment, PVR strata, and Baseline WHO FC, using modified ridit scores. The number and percentage of subjects in each category will be reported, along with p-values. The number and percentage of subjects by WHO FC will also be reported. Missing values will not be imputed.

WHO FC results will also be listed.

8.3.4. EQ-5D-5L

The EQ-5D-5L is collected at Baseline, Week 12, and Week 24. This questionnaire is designed to profile a subject's current health state across 5 dimensions:

- Mobility
- Self-Care
- Usual Activities

- Pain/Discomfort
- Anxiety/Depression

Each dimension is comprised of a single question with 5 possible responses that are scored 1-5 (EQ-5D-5L User Guide v 3.0, Sept. 2019). In addition, there is a 6th question asking the subject to assess their overall health on a visual analogue scale (VAS) with a range of 0-100.

Change from Baseline for each dimension will be analyzed using an ANCOVA model adjusted for treatment, Baseline dimension response, PVR strata, and Baseline WHO FC. Results will be expressed as LS mean changes and associated SEs, LSMDs, and SEs with associated 95% CI, and p-values. Missing values will not be imputed.

Change from Baseline in overall health VAS responses will be analyzed using an ANCOVA model adjusted for treatment, Baseline VAS response, PVR strata, and Baseline WHO FC. Results will be expressed as LS mean changes and associated SEs, LSMDs, and SEs with associated 95% CI, and p-values. Missing values will not be imputed.

EQ-5D-5L results will also be listed.

8.3.5. NT-proBNP

NT-proBNP is measured at Baseline and Weeks 4, 8, 12, 24 and Follow-up. Change from Baseline in NT-proBNP will be analyzed using a MMRM similar to that described in Section 8.2, with treatment, Baseline NT-proBNP, Baseline WHO FC, PVR strata, visit, Baseline NT-proBNP by visit interaction, and treatment by visit interaction as fixed effects. Mean and SE for actual values and changes from Baseline over time will be plotted.

The distribution of NT-proBNP will be analyzed by visit using the CMH method adjusted for treatment, Baseline NT-proBNP, PVR strata, and Baseline WHO FC, using modified ridit scores. The categories are as follows:

- Low: < 300 ng/L
- Medium: 300 – <1100 ng/L
- High: ≥ 1100 ng/L

The number and percentage of subjects in each category will be reported, along with p-values. Missing values will not be imputed.

NT-proBNP results will also be listed.

8.3.6. Risk Score

Components of the Risk Score are assessed at Baseline, Week 12, and Week 24. Risk Score will be evaluated 2 ways: the first using REVEAL 2.0 criteria (Benza, 2019), and the second using the REVEAL Lite 2 criteria (Benza, 2021).

Risk Score using the REVEAL 2.0 criteria is calculated using 13 variables across 11 categories (see Appendix 13.3) resulting in a score that ranges from 0-23, with a minimum of 7 of 13

variables required to generate a score. Risk of clinical worsening is then assigned to one of 3 categories based on the score:

1. 0-6: Low Risk
2. 7-8: Intermediate Risk
3. ≥ 9: High Risk

Risk Score using REVEAL 2.0 includes components of the RHC and as such will only be analyzed at Baseline and Week 24. The distribution of subjects across the 3 categories will be reported at both Baseline and Week 24. The exploratory endpoint of change from Baseline in Risk Score will be analyzed using an ANCOVA model adjusted for treatment, Baseline Risk Score, PVR strata, and Baseline WHO FC. Results will be expressed as LS mean changes and associated SEs, LSMDs and SEs with associated 95% CI, and p-values.

Risk Score using the REVEAL 2.0 Lite criteria is calculated using 6 variables (see Appendix 13.4) resulting in a score that ranges from 1 to 14, with a minimum of 3 variables required to generate a score where at least 2 are of the most predictive variables (NT-proBNP, 6MWT, WHO FC). Risk of clinical worsening is then assigned to one of 3 categories based on the score:

1. ≤ 5: Low Risk
2. 6-7: Intermediate Risk
3. ≥ 8: High Risk

Risk Score using REVEAL 2.0 Lite can be calculated at Baseline, Week 12, and Week 24. The distribution of subjects across the 3 categories will be reported at all 3 visits. The exploratory endpoint of change from Baseline in Risk Score will be analyzed using a MMRM similar to that described in Section 8.2, with treatment, Baseline Risk Score, Baseline WHO FC, PVR strata, visit, Baseline Risk Score by visit interaction, and treatment by visit interaction as fixed effects.

Risk Score results will also be listed.

9. SAFETY EVALUATION

All analyses of safety data will be conducted using the Safety Population. No statistical hypothesis testing of any safety results will be performed. All safety data will be summarized by actual treatment group as described in Section 4.3.

9.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical study subject, whether considered related to the study drug or not. A SAE is an AE occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing inpatient hospitalization, results in persistent or significant disability/incapacity, or is a congenital abnormality/birth defect. Important medical events that may not be immediately life-threatening or result in death, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed above.

For an event to be a TEAE, it must meet one of the following conditions:

- Begins on Day 1, during or after administration of the first dose of study drug
- Begins after Day 1
- Begins before Day 1 and worsens in severity during or after the administration of the first dose of study drug

AEs with unknown start dates or unknown end dates will be counted as TEAEs unless the event resolves before Day 1.

AEs will be coded using MedDRA version 24.0 or higher. Only TEAEs will be presented in AE tables, according to the SOC and/or PT. Any AEs that occur and resolve prior to Day 1 or are ongoing but do not worsen on or after Day 1 will be considered pretreatment AEs and will appear in the AE listing but not in TEAE tables.

9.1.1. Treatment-Emergent Adverse Events

The incidence of TEAEs table will include only 1 occurrence of a PT per subject. If a subject reports the same PT multiple times, then that PT will only be incremented by 1 since subject counts will be presented. As with the PT, if a subject reports multiple TEAEs within the same SOC, then that SOC will only be incremented by 1 since subject counts will be presented. For tables showing incidence by SOC and PT, SOCs will be sorted by the internationally agreed order (see Appendix 13.6) and PTs will be sorted within SOC in descending order of incidence in the GB002 column. For tables showing incidence by PT only, the PTs will be sorted in descending order of incidence in the GB002 column.

An overall summary of TEAEs will be presented, and will include the following:

- Number of TEAEs
- Number and percent of subjects with:
  - at least 1 TEAE

  - at least 1 severe TEAE
  - at least 1 related TEAE
  - at least 1 TEAE leading to study drug discontinuation
  - at least 1 TEAE leading to study withdrawal
  - at least 1 AESI
- Number of SAEs
- Number and percent of subjects with:
  - at least 1 SAE
  - at least 1 related SAE
  - a fatal TEAE

The following additional adverse event summaries will be presented:

- Incidence of TEAEs by SOC and PT
- Incidence of TEAEs by PT
- Incidence of Severe TEAEs by SOC and PT
- Incidence of Related TEAEs by SOC and PT
- Incidence of TEAEs leading to study drug discontinuation by SOC and PT
- Incidence of TEAEs leading to study withdrawal by SOC and PT
- Incidence of AESIs by SOC and PT
- Incidence of SAEs by SOC and PT

AESIs fall into 2 categories based on safety concerns seen in the class of PDGFR kinase inhibitors: bleeding and cardiac effects and are collected directly on the eCRF.

All AEs will be presented in a listing. TEAEs leading to study drug discontinuation and/or study withdrawal, AESIs, SAEs and fatal TEAEs will be presented in separate listings.

9.2. Clinical Laboratory Evaluation

Summary tables for serum chemistry, hematology, coagulation, and quantitative and qualitative urinalysis values including actual values and change from Baseline values will be presented for clinical laboratory tests with numeric results. These tables will include each visit (Baseline, Weeks 4, 8, 12, 18, 24, Follow-up), highest postdose value, and lowest postdose value. For urinalysis results with categorical values, summary tables will present the number and percentage of subjects in each category at each visit. All laboratory values will be reported in standard international (SI) units, where available.

Shift tables will be presented for serum chemistry, hematology, and coagulation parameters showing shifts from Baseline to highest and lowest post-Baseline values, whether scheduled or unscheduled, based on laboratory normal ranges.

Listings of laboratory values will include flags for values outside the central laboratory normal ranges that indicate how far out of the normal range an abnormal value is. For example, a value that is ≥ 3 times the upper limit of normal (ULN) but below 4 times the ULN will have a "3H" flag. Flag multipliers will show values that are 1, 2, 3, 4, 5, 8, 10, and 20 times relative to the ULN if high (> for all ULNs except ≥ 3). Values that are below the lower limit of normal (LLN) will be flagged simply with "L". Normal ranges from the central laboratories will also be listed.

9.2.1. Serum Chemistry

The following parameters will be included in the serum chemistry summary tables: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, cholesterol, creatinine, direct bilirubin, gamma-glutamyl transferase (GGT), glucose, lactate dehydrogenase (LDH), lipids, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, triglycerides, and uric acid.

Associated serum chemistry parameters such as hepatic profile (ALT, albumin, ALP, AST, direct bilirubin, GGT, total bilirubin), electrolytes (bicarbonate, calcium, chloride, magnesium, phosphorus, potassium, sodium), lipid profile (cholesterol, lipids, and triglycerides), renal profile (BUN, creatinine), and other (glucose, LDH, total protein, uric acid) will be sorted/grouped together in table and listing presentations.

A summary table of maximum post-Baseline values for hepatic profile serum chemistry parameters by ULN category will be presented. Evaluation of drug-induced serious hepatotoxicity (eDISH) scatterplots of the highest postdose ALT vs. total bilirubin observed at the same draw as the high ALT value, of the highest postdose AST vs. total bilirubin observed at the same draw as the high AST value, and of the highest of either ALT/AST vs. total bilirubin observed at the same draw as the high value will also be produced.

9.2.2. Hematology

The following parameters will be included in hematology summary tables: hematocrit, hemoglobin, platelet count, red blood cell (RBC) count with mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), and total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils).

9.2.3. Coagulation

The following laboratory tests will be included in coagulation summary tables: partial thromboplastin time (PTT), prothrombin time, and international normalized ratio (INR).

9.2.4. Urinalysis

The following laboratory tests will be included in urinalysis summary tables: pH and specific gravity (numeric summary), and appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, protein, and urobilinogen (categorical summary).

9.2.5. Other Laboratory Assessments

Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential), follicle stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only), serology (hepatitis B virus surface antigen [HbsAg], hepatitis C virus antibody, human immunodeficiency virus [HIV] antibody, and tuberculosis [TB]), thyroid stimulating hormone (TSH), free T4, drugs of abuse (amphetamines, methamphetamines, cocaine, and phencyclidine), serum digoxin for subjects currently on digoxin (local laboratory), in male subjects: testosterone levels, luteinizing hormone (LH), FSH, estradiol, and inhibin B, and optional male fertility assessments (local laboratory: semen volume, total sperm per ejaculate, sperm concentration, sperm progressive motility, and sperm morphology) will be listed.

9.3. Vital Signs

Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, body temperature, respiration rate, and body weight will be collected on the eCRF at Screening, Baseline, Weeks 4, 8, 12, 18, 24, and Follow-up.

A summary table including actual values and changes from Baseline will be presented for vital signs. Vitals signs results will also be listed.

The number and percentage of subjects with clinically relevant abnormalities will be presented using data from any postdose visit (including unscheduled visits). The criteria for clinically relevant abnormalities are as follows:

Vital Sign Parameter	Abnormality Criteria
Temperature	> 38 degrees C and an increase from Baseline of at least 1 degree C.
Heart Rate	High or Increased: > 120 bpm post-Baseline if ≤ 120 bpm at Baseline, or an increase from Baseline of > 20 bpm. Low or Decreased: < 50 bpm post-Baseline if ≥ 50 bpm at Baseline, or a decrease from Baseline of > 20 bpm.
SBP	High or Increased: > 180 mmHg post-Baseline if ≤ 180 mmHg at Baseline, or an increase from Baseline of > 40 mmHg. Low or Decreased: < 90 mmHg post-Baseline if ≥ 90 mmHg at Baseline, or a decrease from Baseline of > 30 mmHg.
DBP	High or Increased: > 105 mmHg post-Baseline if ≤ 105 mmHg at Baseline, or an increase from Baseline of > 30 mmHg. Low or Decreased: < 50 mmHg post-Baseline if ≥ 50 mmHg at Baseline, or a decrease from Baseline of > 20 mmHg.

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; mmHg, millimeters of mercury; SBP, systolic blood pressure.

Abnormal vital signs results will be flagged in the listing.

9.4. 12-Lead ECGs

ECG parameters include heart rate (beats/min), PR interval (ms), QRS duration (ms), QT interval (ms), and Fridericia's correction formula for QT interval (QTcF) interval (ms) and will be collected at Screening, Baseline, Weeks 4, 8, 12, 18, and 24. Overall interpretations of ECG results are also included.

A summary table including actual values and changes from Baseline will be presented for ECG results. ECG results will also be listed.

The number and percentage of subjects with the following clinically relevant abnormalities will be summarized at each visit and overall.

- QTcF values:
  - > 450 ms
  - > 480 ms
  - > 500 ms
- Change from Baseline in QTcF values:
  - > 30 ms
  - > 60 ms

Clinically relevant ECG abnormalities will be flagged in the listing.

9.5. Pulmonary Function Tests

PFTs will be performed at Screening and Week 24. The following PFTs will be collected:

- FVC
- FEV_1
- Diffusing capacity of the lungs for carbon monoxide (DLCO)
- FEV_1/FVC ratio
- Percent predicted for each of the above parameters

A summary table including actual values and changes from Baseline will be presented for PFTs. PFT results will also be listed.

10. INTERIM ANALYSES AND DATA MONITORING

No formal interim analyses will be performed.

An IDMC, comprised of 2 independent external expert physicians 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 IMDC, the content and format of IDMC reports, and other relevant details can be found in the IDMC Charter and the IDMC SAP.

11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

The formal interim analysis described in the protocol will not be performed. The estimand and primary analysis model specified in the protocol inadvertently left out the WHO FC covariate; it has been added to the SAP. The tipping point analysis specified in the protocol has been eliminated due to the anticipated low amount of missing RHC data. The endpoint regarding change from Baseline in risk score category will be analyzed using REVEAL 2.0 and the REVEAL Lite 2, as opposed to REVEAL 2.0 and the ESC/ERS criteria. RV Tei index was not collected and therefor the endpoint regarding change from Baseline in RV Tei index will not be performed. As of the writing of this SAP there are no other changes to the analyses and endpoints disclosed in the protocol.

12. REFERENCES

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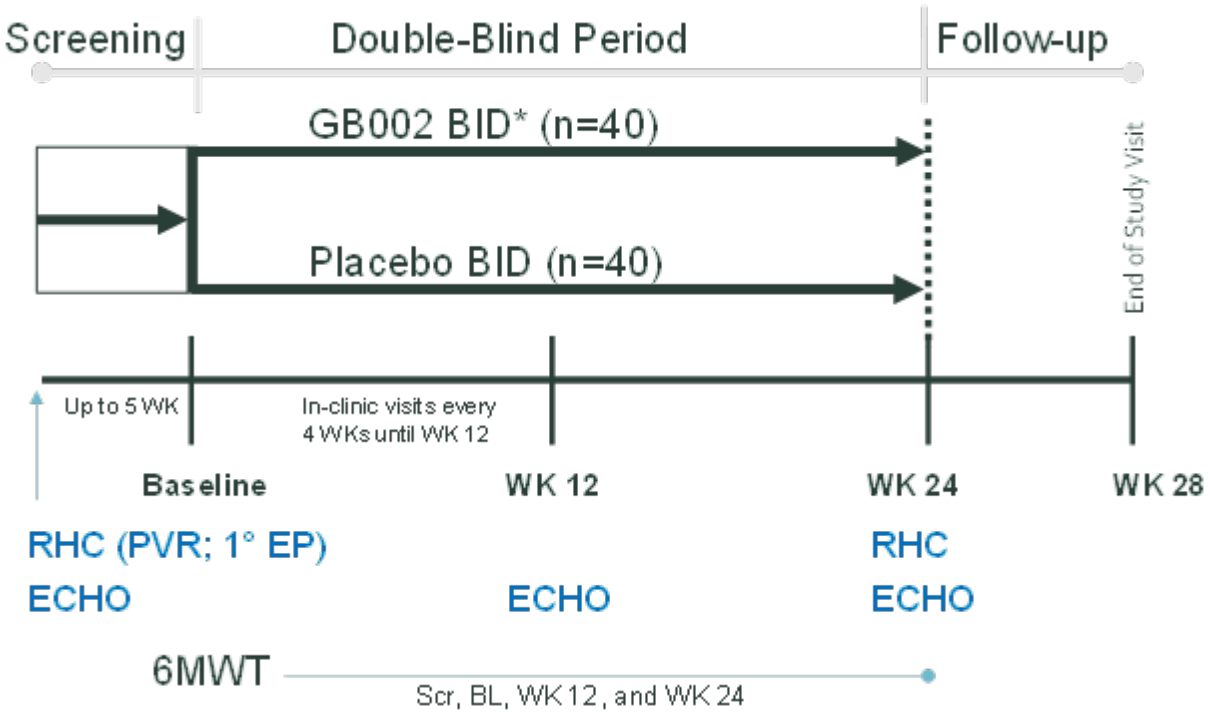
13. APPENDICES

13.1. Study Schema



Abbreviations: 1° EP, primary endpoint; BID, twice daily; ECHO, echocardiogram; BL, Baseline; PVR, pulmonary vascular resistance; RHC, right heart catheterization; Scr, Screening; 6MWT, six-minute walk test; WK, week.
* 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.

13.2. Categories of PAH Disease-Specific Background Medications

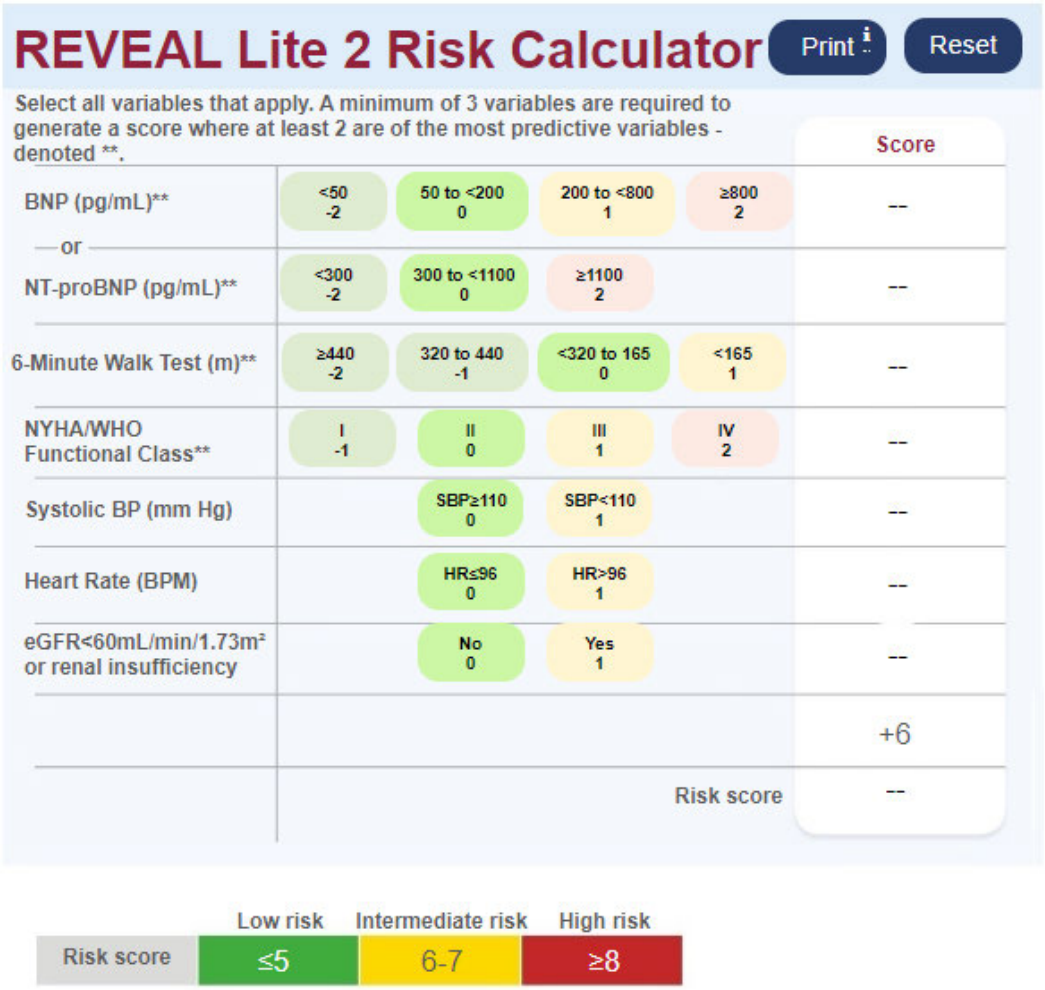
Category	Medication Name
ERA	Ambrisentan
	Bosentan
	Macitentan
PDE-5i	Sildenafil
	Tadalafil
sGC stimulators	Riociguat
Prostacyclins	Epoprostenol
	Iloprost
	Selexipag
	Treprostinil

Abbreviations: ERA, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type 5 inhibitors; sGC, soluble guanylate cyclase.

13.3. REVEAL 2.0 Risk Score Calculator

Source: Benza, 2019

13.4. REVEAL Lite 2 Risk Score Calculator



Source: Benza, 2021

13.5. Imputation of Partial and Missing Data

Incomplete Start Dates of Adverse Events

All AE start dates must be entered on the eCRF as complete dates. In the rare case that all or part of an AE start date is missing but an AE resolution date is present and after SDA then the AE start date will be imputed as follows:

Year of start	Month of start	Day of start	Start date to be imputed as
Missing	Missing	Missing	Date of first dose of SDA
year = year of SDA	Missing	Nonmissing	Date of first dose of SDA
year = year of SDA	Missing	Missing	Set month and day to those of first dose of SDA
year < year of SDA	Missing	Nonmissing	set month to December
year < year of SDA	Missing	Missing	set month and day to December 31
year > year of SDA	Missing	Nonmissing	set month to January
year > year of SDA	Missing	Missing	set month and day to January 1
year = year of SDA	Month = month of SDA	Missing	Set day as day of first dose of SDA
year = year of SDA	Month < month of SDA	Missing	Set day as last day of start month
year = year of SDA	Month > month of SDA	Missing	Set day as first day of start month
year < year of SDA	Nonmissing	Missing	Set day as last day of start month
year > year of SDA	Nonmissing	Missing	Set day as first day of start month

Abbreviation: SDA, study drug administration.

If AE resolution date is present and prior to the first dose of SDA, no need to impute incomplete AE start date, as the AE is not treatment-emergent and the event should be in the medical history.

Incomplete Dates of Concomitant Medications and PAH Diagnosis

- If year and month are present and day is missing then set day to first day of month for start date, and set day to last day of month for end date
- If year and day are present and month is missing then set month to January for start date, and set month to December for end date
- If year is present and month and day are missing then set month and day to January 1 for start date, and set month and day to December 31 for end date
- Completely missing dates will not be imputed

If start date is completely missing and end date is not prior to the first dose of SDA, then the medication will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are completely missing will be classified as concomitant.

13.6. MedDRA Terminology SOC List: Internationally Agreed Order

Order	SOC
1	Infections and infestations
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3	Blood and lymphatic system disorders
4	Immune system disorders
5	Endocrine disorders
6	Metabolism and nutrition disorders
7	Psychiatric disorders
8	Nervous system disorders
9	Eye disorders
10	Ear and labyrinth disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
14	Gastrointestinal disorders
15	Hepatobiliary disorders
16	Skin and subcutaneous tissue disorders
17	Musculoskeletal and connective tissue disorders
18	Renal and urinary disorders
19	Pregnancy, puerperium and perinatal conditions
20	Reproductive system and breast disorders
21	Congenital, familial and genetic disorders
22	General disorders and administration site conditions
23	Investigations
24	Injury, poisoning and procedural complications
25	Surgical and medical procedures
26	Social circumstances
27	Product issues

Abbreviation: SOC, system organ class.
Source: Introductory Guide, MedDRA Version 21.0, March 2018.

13.7. Document Revision History

Version Number	Date	Comments/Changes
1.0	27 October 2022	Final