16.1.9 DOCUMENTATION OF STATISTICAL METHODS

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STATISTICAL ANALYSIS PLAN

A Randomized, Phase 2, Double-blind, Placebo-controlled Study to Investigate the Safety and Efficacy of KER-012 in Combination with Background Therapy in Adult Participants with Pulmonary Arterial Hypertension (TROPOS Study)

Protocol Number:	KER-012-A201
National Clinical Trial Identification Number:	NCT05975905
EudraCT Number:	2022-502378-17-00
UTN Number:	U1111-1290-3167
Investigational Product:	cibotercept (also known as KER-012)
Sponsor:	Keros Therapeutics, Inc. 1050 Waltham Street Suite 302 Lexington, MA 02421 USA
Document Version:	Final Version 1.0
Based on:	Protocol Version 6.0, Dated 18 December 2024

Compliance: The study described in this report was performed according to the principle of Good Clinical Practice (GCP).

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REVISION HISTORY

SAP Version	Approval Date	Change	Rationale
1.0	02Apr2025	Not Applicable	Original Version

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LIST OF ABBREVIATIONS

Abbreviation	Definitions
6MWD	6-minute walk distance
6MWT	6-minute walk test
ADA	antidrug antibody
AE	adverse event
AEI	Adverse event of interest
AESI	Adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	blood pressure
BUN	Blood urea nitrogen
CFB	change from baseline
CI	confidence interval
CI	cardiac index
CO	cardiac Output
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
CS	clinically significant
CSP	Clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Connective tissue disease
CV	coefficient of variation
DBL	database lock
DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate

E10	emPHasis-10
EOS	end of study
EOT	end of treatment
ERA	endothelin receptor antagonist
ESC/ERS	European Society of Cardiology/ European Respiratory Society
FAS	full analysis set
FC	functional class
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hct	Hematocrit
Hgb	Hemoglobin
HPAH	Hereditable Pulmonary Arterial Hypertension
HR	hazard ratio
HRQoL	Health-related Quality of Life
IA	interim analysis
ICH	International Conference on Harmonization
IMP	investigational medicinal product
IPAH	Idiopathic pulmonary arterial hypertension
ISR	injection site reaction
MAP	Mean arterial pressure
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Non-clinically significant
NT-proBNP	N-terminal pro–brain natriuretic peptide
NYHA	New York Heart Association
PAC	pulmonary artery compliance
PAH	pulmonary arterial hypertension
PAWP	pulmonary arterial wedge pressure
PD	pharmacodynamic(s)
PDE5-I	phosphodiesterase-V inhibitor
PK	pharmacokinetic(s)
PRO	patient reported outcome
PT	Preferred Term

PVR	pulmonary vascular resistance
Q1	25% percentile
Q3	75% percentile
Q4W	Once every 28 days
RAP	right atrial pressure
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RHC	Right Heart Catheterization
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SBP	systolic blood pressure
SC	subcutaneous
SE	standard error
sGC	soluble guanylate cyclase
SI	The International System of Units
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
sPAP	Systolic pulmonary artery pressure
SpO2	Pulse Oximetry
SV	stroke volume
SVI	stroke volume index
PAH-SYMPACT	Pulmonary Arterial -Hypertension Symptoms and Impact Questionnaire
TAPSE	tricuspid annular plane systolic excursion
TEAE	treatment-emergent adverse event
TLFs	Tables, listings, and figures
TRG	tricuspid regurgitation gradient
ULN	upper limit of normal
ULQ	upper limit of quantification
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
vs	versus

1. INTRODUCTION

The Phase 2 study KER-012-A201 was planned for a total of 96 weeks on treatment which consists of two periods: a 24-week treatment period, and a 72-week extension period for those participants who complete the 24-week treatment period.

As of 27 September 2024, the study was fully enrolled, with 113 participants randomized to one of four treatment arms: 1.5 mg/kg, 3.0 mg/kg, 4.5 mg/kg KER-012 or placebo in a 2:2:2:3 fashion.

On 11 December 2024, Keros discontinued the dosing of 3.0 mg/kg and 4.5 mg/kg KER-012 for safety reasons, in consultation and agreement with the study's independent Data Monitoring Committee (DMC), due to adverse events (AEs) of Pericardial effusion occurring more frequently on the active study drug arm than placebo arm, thus altering the benefit-risk profile of KER-012. Keros distributed the Dear Investigator Letters to all clinical sites on the 11 December 2024. Keros also amended and finalized the Protocol Version 6.0 on 18 December 2024 to implementation of an Urgent Safety Measure. To inform the changes outlined in Protocol Version 6.0, an ad hoc unblinded analysis was conducted to assess the benefit-risk of KER-012 in participants with PAH by a selected group of Sponsor team members. This group was kept small and consisted of members who are not involved in site-facing study activities to ensure protection of the entire study's blind.

On 14 January 2025, Keros discontinued the study for the safety reasons, similarly in consultation and agreement with the DMC. Keros distributed the Dear Investigator Letters to all clinical sites on the 14 Jan 2025. This statistical analysis plan (SAP) describes the statistical methods and data presentations of the entire study. The SAP is based on the Protocol Version 6.0, dated 18 December 2024 and decision to discontinue the study on 14 Jan 2025.

Due to the ad hoc unblinded benefit-risk analysis and early termination of the study, the analysis will be descriptive and exploratory in nature.

The SAP will be finalized prior to the study database lock (DBL). Any deviations from these guidelines will be documented in the clinical study report (CSR).

The population PK analysis and other exploratory analysis including actigraphy, biomarkers, and ADA assay may be prepared in separate analysis plans.

2. STUDY OVERVIEW

2.1. STUDY OBJECTIVES

The objectives and their supporting endpoints are presented in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the effect of KER-012 on pulmonary hemodynamics compared to Placebo in Participants on background pulmonary arterial hypertension (PAH) therapy	Change from Baseline in PVR at Week 24
Key Secondary	
Evaluate the effect of KER-012 on exercise capacity compared to Placebo in Participants on background PAH therapy	Change from Baseline in the 6-minute walk distance (6MWD) at Week 24
Secondary	
Treatment Period: • Evaluate the safety and tolerability of KER-012 in Participants on background PAH therapy • Evaluate the effect of KER-012 on pulmonary hemodynamics compared to Placebo in Participants on background PAH therapy • Evaluate the effect of KER-012 on NT-proBNP in Participants on background PAH therapy • Evaluate improvement in functional assessment of KER-012 compared to Placebo in Participants on background PAH therapy • Evaluate the attenuation of clinical worsening of KER-012 compared to Placebo • Evaluate population PK of KER-012 in Participants on background PAH therapy • Evaluate improvement in risk stratifications of KER-012 in Participants on background PAH therapy	**Treatment Period:** • Incidence of TEAEs, treatment-related TEAEs, and discontinuations due to TEAEs; change from Baseline in clinical laboratory values, vital signs, and ECG; incidence of ADA • Change from Baseline in mean pulmonary artery pressure (mPAP), cardiac output (CO), cardiac index (CI), pulmonary artery wedge pressure (PAWP), right atrial pressure (RAP), mixed venous oxygen saturation (SvO2), stroke volume (SV), stroke volume index (SVI), and pulmonary artery compliance (PAC) at Week 24 • Change from Baseline in NT-proBNP by visit • Proportion of Participants who achieved improvement from Baseline in NYHA/WHO FC by visit • Incidence and time to clinical worsening • Population PK-derived parameters of KER-012 will be assessed as possible • Proportion of Participants who achieve improvement /or maintain low risk in ESC/ERS 4-strata risk category assessment -strata risk category assessment

Table 1: Study Objectives and Endpoints (Continued)

Objectives	Endpoints
Extension Period: • Evaluate the safety and tolerability of KER-012 in Participants on background PAH therapy • Evaluate the effect of KER-012 on exercise capacity in Participants on background PAH therapy • Evaluate the effect of KER-012 on pulmonary hemodynamics in Participants on background PAH therapy • Evaluate the PD effects of KER-012 in Participants on background PAH therapy • Evaluate improvement in functional assessment of KER-012 in Participants on background PAH therapy • Evaluate population PK of KER-012 in Participants on background PAH therapy • Evaluate improvement in risk stratifications of KER-012 in Participants on background PAH therapy	**Extension Period:** • Incidence of TEAEs, treatment-related TEAEs, and discontinuations due to TEAEs; change from Baseline in clinical laboratory values, vital signs, and ECGs; incidence of ADA • Change from Baseline in 6MWD by visit • Change from Baseline in PVR, mPAP, CO, CI, PAWP, RAP, SvO2, SV, SVI, and PAC at Week 96 • Change from Baseline in NT-proBNP by visit • Proportion of Participants who achieved improvement from Baseline NYHA/WHO FC by visit • Population PK-derived parameters of KER-012 will be assessed as possible • Proportion of Participants who achieve improvement /or maintain low risk in ESC/ ERC 4-strata risk category assessment
Exploratory*	
Treatment and Extension Period: • Evaluate physical activity • Evaluate improvement in additional risk stratification measures • Evaluate the effect of KER-012 on clinical worsening • Evaluate the PD effect of KER-012 on biomarkers • Evaluate health-related quality of life (HRQoL)	**Treatment and Extension Period:** • Change from Baseline in overall activity as measured by actigraphy • Proportion of Participants who achieve improvement in REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) Lite 2 and COMPERA 2.0 by visit • Incidence of and time to first clinical worsening • Change from Baseline in PAH-related biomarkers and other biomarkers by visit • Change from Baseline in HRQoL measures by visit (Pulmonary Arterial Hypertension-Symptoms and Impact [PAH-SYMPACT] and emPHasis-10)

* KER-012 evaluations will be compared against Placebo in the Treatment Period only.

ADA = antidrug antibody; COMPERA = Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; ESC/ERS = European Society of Cardiology/ European Respiratory Society; NYHA/WHO FC = New York Heart Association/World Health Organization functional class; NT-proBNP = N-terminal pro–brain natriuretic peptide; TEAE = treatment emergent adverse event.

2.2. STUDY DESIGN

The decision to discontinue the study prematurely was made as of 14 Jan 2025 (Section 1). The following described the study design as outlined in Protocol Amendment Version 6.0 dated 18 December 2024 prior to the early termination of the study.

This is a Phase 2, double-blind, randomized, placebo-controlled study of KER-012 compared to Placebo in adult participants with a primary diagnosis of PAH on stable background PAH therapy.

Participants will be randomly assigned in a 2:2:2:3 ratio to 1 of 4 treatment arms:

- Arm 1: KER-012 (1.5 mg/kg) subcutaneously (SC) (Q4W)
- Arm 2: KER-012 (3.0 mg/kg) SC (Q4W) (as of Protocol Amendment Version 6.0, treatment of all participants assigned to Arm 2 [3.0 mg/kg] will be halted)
- Arm 3: KER-012 (4.5 mg/kg) SC (Q4W) (as of Protocol Amendment Version 6.0, treatment of all participants assigned to Arm 3 [4.5 mg/kg] will be halted)
- Arm 4: Placebo SC (Q4W)

Randomization will be stratified by PVR (> 640 vs ≤ 640 dyn·sec·cm−5) at baseline. The PVR value will be adjudicated by central review as outlined in the Right Heart Catheterization (RHC) Manual, and the eligibility of the participant will be determined by the Investigator before randomization. Screening assessments will be performed within 28 days prior to the first dose of the investigational medicinal product (IMP). Participants will receive a SC dose of either KER-012 or Placebo on Day 1 and remain at the study site at the discretion of the Investigator until all assessments have been collected. Participants will return during scheduled visits for study assessments through Week 24 (Treatment Period).

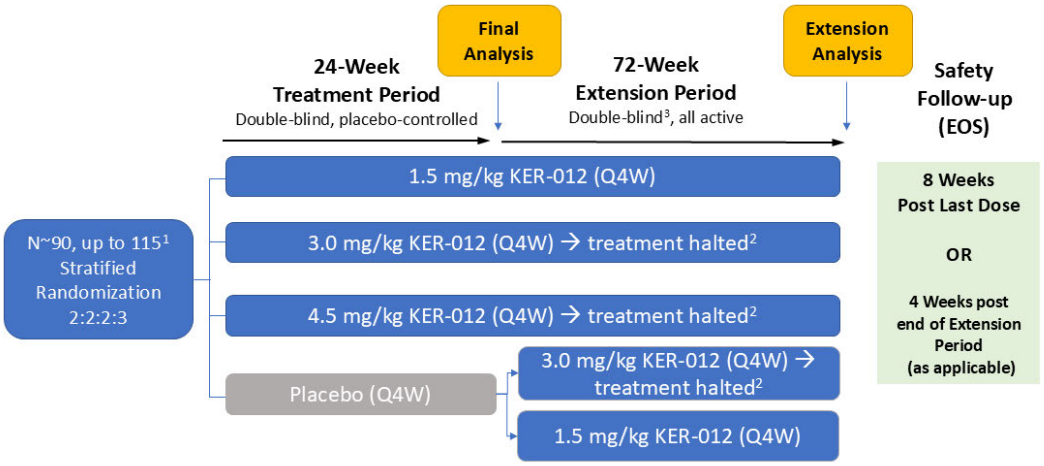
Participants who complete the Treatment Period will be eligible to continue into a 72-week Extension Period, for a total of 96 weeks on treatment. Participants who were in the Placebo group will enter the Extension Period with the 3.0 mg/kg KER-012 dose level and continue their background PAH therapy, while participants who were receiving KER-012 will continue at their current KER-012 dose level and continue their background PAH therapy. As of Protocol Amendment Version 6.0, treatment of participants in the Placebo group who have crossed over to 3.0 mg/kg KER-012 will be halted; other procedures will continue as outlined. Participants in the Placebo group who have not yet crossed over to the Extension Period (Week 24) will be allowed to continue into the Extension Period and will receive KER-012 at a dose level of 1.5 mg/kg. Administration of KER-012 will be open-label during the Extension Period.

Participants who discontinue IMP during the Treatment Period will have an End of Treatment (EOT) Visit/Early Termination (ET) Visit, in lieu of their next scheduled visit, at the time of discontinuing IMP. Participants should continue their scheduled visits to collect all other assessments through the end of the study, unless they withdraw consent from further participation. Participants who withdraw consent in the Treatment Period or Extension Period

and do not continue with scheduled monthly visits will be asked to attend an EOT/ET Visit and a Safety Follow-up Visit 8 weeks after the last dose of IMP.

The study schematic is presented in Figure 1.

Figure 1: Study Design Schematic



[1] Patients with a primary diagnosis of symptomatic PAH (WHO Group 1) on stable background PAH therapy
[2] As of Protocol Amendment Version 6.0, treatment of all participants originally randomized to 4.5 mg/kg KER-012 Q4W, and 3.0 mg/kg KER-012 Q4W, along with treatment of participants originally randomized to placebo who have crossed over to 3.0 mg/kg KER-012 Q4W, was halted for the duration of the study.
[3] As of Protocol Amendment Version 6.0, the 72-Week Extension Period will be open-label.
Abbreviations: EOS=End of Study; PAH=pulmonary arterial hypertension; Q4W=every 4 weeks; WHO=World Health Organization

On 14 January 2025, Dear Investigator Letter was sent to all investigator to terminate the study early with following updates in study procedures:

All participants should complete an End of Treatment (EOT) visit at their next scheduled visit, if one was not previously performed. As the Schedule of Assessments (SoA) in the Protocol outlines, the EOT visit includes a Right Heart Catheterization (RHC). This assessment is now considered optional, and investigators are asked to use their clinical judgement along with the participant's willingness in determining whether the EOT RHC will be completed or not. While the study is terminating, data collected from RHCs will be helpful to better understand the effects of KER-012 including safety.

Participants who received their last dose of IMP at or more than 8 weeks ago can have a combined EOT and End of Study (EOS) visit as their next visit. Participants who received their last dose of IMP less than 8 weeks ago should complete an EOT visit as their next visit and then a separate EOS visit, 8 weeks from the last IMP dosing.

Participants who have not had a study visit since the Dear Investigator Letter, dated 11 December 2024, should have an echocardiogram at their next visit. Any newly identified Pericardial effusion events should be reported using the Safety Event Reporting Form and the Adverse Event of Special Interest (AESI) Questionnaire.

Participants should not initiate therapy with another activin signaling inhibitor (e.g., sotatercept) for at least 56 days since the last dose of IMP (i.e., approximately 5 ½ half-lives of cibotercept) to ensure a full study drug washout.

All participants with new/ongoing AESIs or serious adverse events at their last visit, should be followed as clinically indicated until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up.

2.3. DETERMINATION OF SAMPLE SIZE

Approximately 90 participants and up to 115 participants diagnosed with PAH and on stable PAH background therapy will be randomized and assigned in a 2:2:2:3 ratio to 1.5 mg/kg, 3.0 mg/kg, and 4.5 mg/kg KER-012 doses and Placebo treatment arms. This sample size will provide at least 90% power to detect a significant difference in mean change from baseline in PVR at Week 24, assuming a 200 $dyn \cdot sec \cdot cm^{-5}$ decrease between pooled KER-012 treatment arm and Placebo with a common standard deviation of 300 $dyn \cdot sec \cdot cm^{-5}$, a premature discontinuation rate of 10%, and with 1-sided alpha of 0.10.

3. ANALYSIS POPULATIONS

3.1. FULL ANALYSIS SET

The Full Analysis Set (FAS) is defined to include all randomized participants. Participants will be analyzed according to the treatment to which they were randomized. The FAS will be used for evaluating efficacy endpoints and participants characteristics when applicable.

3.2. SAFETY POPULATION

The Safety Population is defined to include all participants who received at least 1 dose of IMP. Participants will be analyzed according to the actual treatment firstly received. The Safety Population will be used for all safety and exposure analyses.

3.3. PHARMACOKINETICS POPULATION

The Pharmacokinetics (PK) Population is defined to include all participants in the safety population and have at least one quantifiable plasma concentration of KER-012.

3.4. IMMUNOGENICITY POPULATION

The Immunogenicity Population includes all participants in the safety population, have a baseline assessment and at least one post-treatment immunogenicity result.

4. DATA ANALYSIS METHODS

Due to the early termination of the study, the analysis will be descriptive and exploratory in nature. Modeling approaches may be applied to estimate the treatment effect with consideration of missing data and covariates.

4.1. GENERAL STATISTICAL PRINCIPLES

In general, all efficacy and safety will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (sample size (n), mean, standard deviation, minimum, 25% percentile (Q1), median, 75% percentile (Q3), and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages).

Time to event variable will be analyzed using Kaplan-Meier method and summarized with median, 25% and 75% percentiles with their corresponding 95% confidence intervals (CI) which are calculated from a log-log transformation based on the method by (Brookmeyer and Crowley, 1982). Individual data will be presented in participant listings which will be provided for all participants.

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e., ICH-E3, will be used for all tables and listings. All summary tables, listings, and figures (TLFs) will be presented by treatment arms as defined in Table 2.

Table 2: Degree of Precision

Statistics	Degree of Precision
Mean, Median, Q1, Q3, Confidence limit boundaries	One more than the raw data, up to 3 decimal places
Standard deviation, Standard error	One more than the mean, up to 3 decimal places
Minimum, Maximum	The same as the raw data, up to 2 decimal places
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.
P-value	Three decimal places. If the p-value is less than 0.001 then it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.

Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 – 0.30).

For lab and biomarker parameters, standard units, when available, will be used in general with the following excepts:

- NT-proBNP will be analyzed using the unit of ng/L. The unit conversion between pg/mL and pmol/L is ng/L = pmol/L × 8.457.

- Hemoglobin and mean corpuscular hemoglobin (MCHC) will be analyzed using the unit of g/dL. The unit conversion between g/dL and g/L is g/dL =g/L / 10.

4.1.1. Missing Data Handling

In general, missing data will not be imputed unless otherwise specified.

The imputation methods of incomplete or missing dates for initial diagnosis, adverse events and concomitant medications are described in Appendix 3.

4.1.2. Adjustment of Covariates

Modeling approach, if appropriate, will include the randomization stratification factor of pulmonary vascular resistance (PVR) (> 640 vs ≤ 640 dyn·sec·cm^{-5}) as a covariate.

In addition, the other prognostic factors at baseline (e.g., baseline score) may be included in the modeling method. The details for the adjustment of covariates in the modeling will be provided in each relevant section.

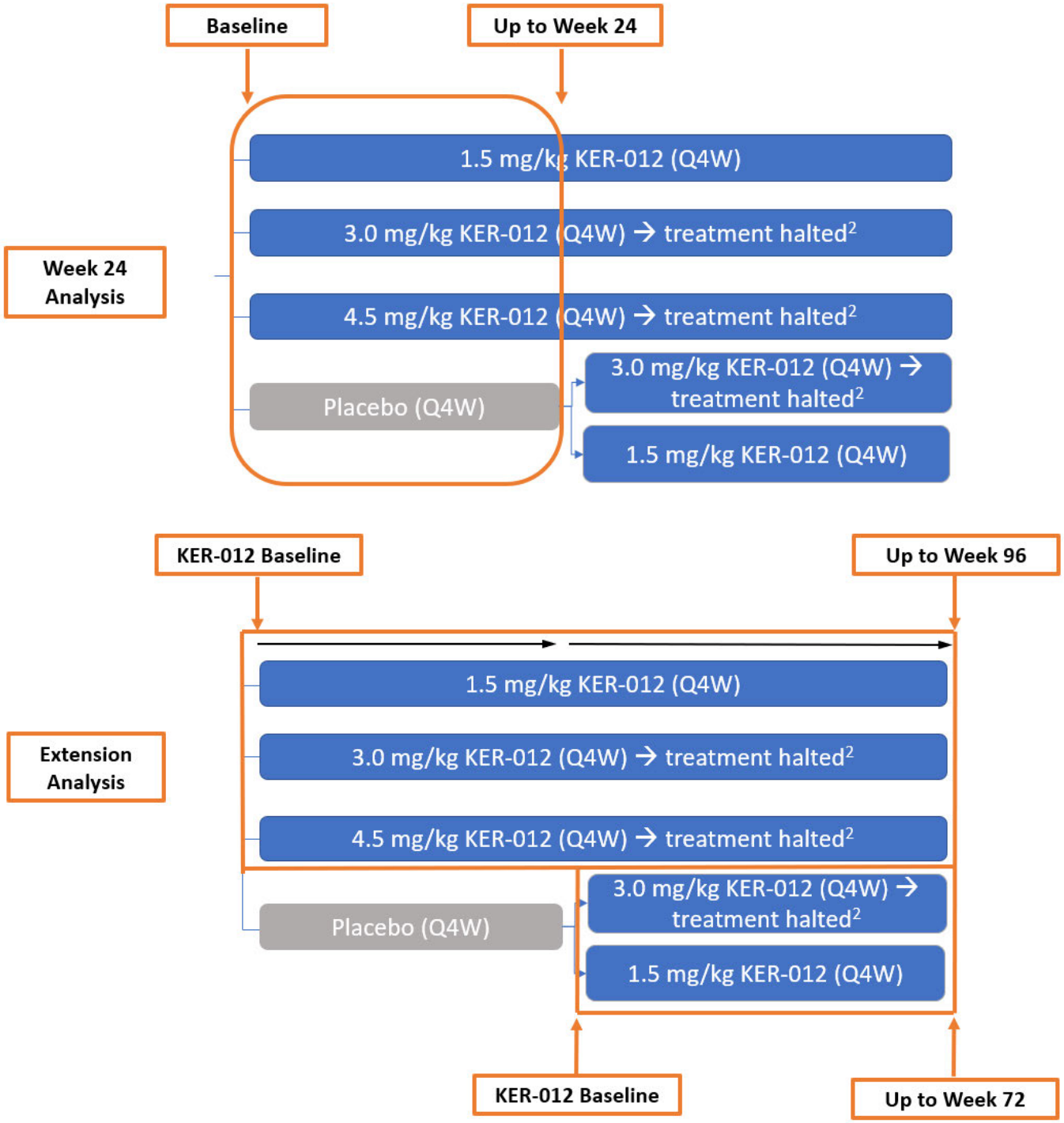
4.2. WEEK 24 AND EXTENSION ANALYSES

The study will be presented by the placebo-controlled Week 24 Analysis and the KER-012 only Extension Analysis, when appropriate. The analysis schema is presented in Figure 2. The two treatment periods are defined in Section 4.2.1; the presentation of treatment groups are detailed in Section 4.2.1; the baseline for each treatment periods are summarized in Section 4.2.3.

As of 11 December 2024, all placebo participants who completed the 24-week treatment period and rolled over to the extension period were assigned to receive KER-012 at dose level of 1.5 mg/kg, instead of the previously planned 3 mg/kg (detailed in Section 1).

Unless specified otherwise, all analysis will be presented for Week 24 and Extension Analyses separately.

Figure 2: Schema of Week 24 and Extension Analyses



4.2.1. Treatment Group

Treatment groups for Week 24 and Extension Analyses are defined in Table 3 and Table 4, respectively.

Table 3: Week 24 Analysis Treatment Grouping (placebo-controlled)

Display Order	1	2	3	4 Pool 1-3	5	6 Pool 4-5[a]
Header text	KER-012 1.5 mg/kg	KER-012 3.0 mg/kg	KER-012 4.5 mg/kg	All KER-012	Placebo	All Participants

[a] To be included in the tables for disposition, demographics, and baseline disease characteristics only

Table 4: Extension Analysis Treatment Grouping (all KER-012 treated)

Display Order	1	2	3	4	5	6 Pool 1-5
Header	PBO/KER-012 1.5 mg/kg[a]	KER-012 1.5/1.5 mg/kg	PBO/KER-012 3.0 mg/kg[a]	KER-012 3.0/3.0 mg/kg	KER-012 4.5/4.5 mg/kg	All Participants on KER-012

[a] KER-012 baseline for participants who rolled over from Placebo to KER-012 was defined in Table 4

4.2.2. Treatment Period and Study Day

Treatment periods and study days for Week 24 and Extension Analysis are defined in Table 5.

For a date after or on Study Day 1, the study day is defined as (date of interest) – Study Day 1 + 1. For a date before Study Day 1, it is defined as (date of interest) – Study Day 1.

Study day for Extension Analysis will be defined as (date of interest) – KER-012 Day 1 + 1.

Table 5: Definitions of Day 1, Treatment End Date and Treatment Periods

Category		Definition
Study Date	Study Day 1	The Date on which the participant in the study receives the first dose of IMP.
	Treatment End Date	Last dose date +60 days, the EOS visit date, whichever is earlier
Week 24 Analysis	Study Day 1	The Date on which the participant in the study receives the first dose of IMP.
	24-Week Treatment Period	From Study Day 1 to the Week 24 visit, or Treatment End Date (defined above), whichever is earlier
Extension Analysis	KER-012 Day 1	The Date on which the participant in the study receives the first dose of KER-012.
	KER-012 Treatment Period	From the first dose date of KER-012 to the Treatment End Date (defined above) for participants who received at least one dose of KER-012

4.2.3. Baseline

Baseline for Week 24 Analysis will be defined as the last available, valid, non-missing assessment prior to or on Study Day 1 (Table 5), except for 6MWD, which is defined separately in Section 4.2.3.1.

Baseline for Extension Analysis will be defined as the last available, valid, non-missing assessment prior to first dose of KER-012.

4.2.3.1. Baseline of 6MWD

During the Screening period, the 6MWT needs to be conducted twice at least 4 hours apart and no more than 1 week apart; the distance results must be within 15% of each other (calculated from the higher value). In the original protocol, 6MWT was initially conducted once at screening and once at randomization; the protocol was amended subsequently, so that the 6MWT was then conducted twice at screening, and no evaluation at randomization.

Baseline 6MWD for Week 24 Analysis will be defined as the mean of all 6MWD on or prior to the first dose of the IMP.

Baseline 6MWD for the Extension Analysis will be defined as follows:

- The mean of all 6MWD on or prior to the first dose of the KER-012 for the participants who were randomized to KER-012
- The last available, valid, non-missing assessment prior to the first dose of KER-012 for the participants who were randomized to placebo

4.2.4. Analysis Visit Windows for Early Termination Visit

Depending on the schedule of assessments, the analyses windows are different across endpoints. Section A3-1.2 provides a summary of the endpoints measured at each visit per schedule of events (Section 1.3) in the protocol.

4.3. DISPOSITION, DEVIATIONS AND SUBJECT CHARACTERISTICS

4.3.1. Participant Disposition

Based on FAS, the number and percentage of participants completing or prematurely discontinuing the study including reasons for discontinuation will be summarized for all participants for the following:

- Participants who were screened
- Participants who were screen failed
- Participants who were randomized (Full Analysis Set)
- Participants in the Safety Population
- Participants in the Pharmacokinetics Population
- Participants in the Immunogenicity Population
- Participants who completed the 24-week treatment period
- Participants who discontinued from 24-week treatment with primary reason for discontinuation
- Participants who continued into 72-week extension period
- Participants who completed from 72-week extension period
- Participants who discontinued from 72-week extension period with primary reason for discontinuation
- Participants who discontinued from End of Study Visit with primary reason for discontinuation

Frequency tabulation of participants enrolled by site, country, treatment group will be summarized.

4.3.2. Protocol Deviation

Important protocol deviations will be summarized by category and listed for the Full Analysis Set by Week 24 and Extension Analysis.

Listing will include all participants with important protocol deviations organized by clinical trial site.

Additionally, all protocol deviations will be included in the Study Data Tabulation Model (SDTM) Protocol Deviation (DV) domain with a variable that provides the determination of whether the protocol deviation was important.

4.3.3. Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be summarized by treatment arms using the FAS:

- Age (years)
  - age groups (< 65 years, ≥ 65-74 years, >=75 years)
- Sex
  - childbearing potential (female only)
- Race
- Ethnicity
- height (cm) at screening
- weight (kg) at screening
- BMI (kg/m^2)
  - BMI category (<18.5, ≥ 18.5 and <25, ≥ 25 and <30, ≥30 kg/m^2)

4.3.4. Disease Characteristics

The following baseline disease characteristics will be summarized by treatment arms using the FAS:

- Time (years) since diagnosis of PAH
  - calculated as (date of ICF – date of diagnosis of)/365.25
- Classification of PAH
- WHO Functional Class: Class II, Class III
- Background therapy type for PAH: monotherapy; double therapy; triple therapy
- Background therapy category for PAH: prostacyclin therapy; soluble guanylate cyclase (sGC) stimulator; phosphodiesterase-V inhibitor (PDE5-I); endothelin receptor antagonist (ERA)
  - Prostacyclin therapy will be further categorized by its route of administration
- REVEAL lite 2 risk stratification: low, intermediate, or high (Section 4.4.4.2)
- COMPERA 2.0 risk stratification: low, intermediate-low, intermediate-high, or high (Section 4.4.4.2)
- 6MWD (m), and its categories: > 440, 320-440, 165-319, < 165

- NT-proBNP (ng/L), and its categories: < 300, 300-649, 650-1100, > 1100
- Pulmonary vascular resistance (PVR) (dyn·sec·cm^{-5}), and its categories: > 640 vs. ≤ 640; > 800 vs. ≤ 800
- Cardiac output (CO) (L/min)
- Cardiac index (CI) (L/min/m^2), and its categories: ≥ 2.5; ≥2 - <2.5; < 2
- Stroke volume (mL)
- Stroke volume index (SVI) (mL/m^2), and its categories
- Mean pulmonary artery pressure (mPAP) (mmHg)
- Systolic pulmonary artery pressure (sPAP) (mmHg)
- Diastolic pulmonary artery pressure (dPAP) (mmHg)
- Mean Right atrial pressure (RAP) (mmHg)
- Mean Pulmonary arterial wedge pressure (PAWP) (mmHg)
- Mixed venous oxygen saturation (SvO2) (%), and its categories: >65%, ≥60-≤65%, <60%
- Pulmonary artery compliance (PAC) (mL/mmHg)
- Hemoglobin (g/dL)
- Total Bilirubin (umol/L)
- Alanine Aminotransferase (U/L)
- Aspartate Aminotransferase (U/L)
- BUN (mmol/L)
- Creatinine (mg/dL)
- eGFR (mL/min/1.73 m^2): < 60 vs ≥ 60

4.3.5. Medical History

The conditions/diseases from medical/surgical history are those conditions/diseases that stopped prior to the study entry. Medical history will be coded to SOC and PT using MedDRA version 26.0 or higher.

The number and percentage of participants with any past medical/surgical history within each SOC and PT will be provided by treatment arms on the Safety Population.

A participant will only be counted once within a particular SOC (PT) even if he/she has multiple conditions/diseases in the same SOC (PT).

4.3.6. Prior and Concomitant Medications/Procedures

Prior medications are defined as medications taken prior to the first dose of IMP. Concomitant medications are defined as medications taken on or after the date and time of first dose and through the treatment period. Prior medications that continue into the treatment period will also be reported as concomitant medications.

Concomitant procedures are defined as any procedures performed on or after the date of signing the informed consent form up to the End of Study visit date. They will be listed.

Prior and concomitant medications will be coded using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) Drug Dictionary Enhanced Version 01MAR2023 or higher. Concomitant procedures will be coded using MedDRA central coding dictionary, Version 26.0.

Prior and concomitant medications will be grouped by drug Preferred Name and summarized for the Safety Population.

Prior and concomitant PAH medications as identified by the following ATC code will be summarized for the Safety Population.

- PDE5-I (ATC=C02KX**)**
- Prostacyclin therapy (ATC=B01AC)
- ERA (ATC=C02KX**)**
- sGC (ATC=C02KX)
- diuretics (ATC2 = C03),
- antithrombotic agents (ATC2 = B01),
- calcium channel blockers (ATC2 = C08, ATC3 = C07B, ATC4 = C09BB, or ATC4 = C09DB),
- oxygen (ATC4 = V03AN),
- digoxin (ATC4 = C01AA), and
- antihypertensives for PAH (ATC3 = C02KX)

4.4. EFFICACY ANALYSIS

All efficacy endpoints will be analyzed using the FAS unless otherwise specified. In the change from baseline analyses, only participants who have non-missing baseline values will be included in the analyses.

Due to the early termination of the study (Section 1), multiplicity adjustment as specified in previous versions of the protocol, will not be conducted. Modeling approach may be applied to better assess the treatment effect by accounting of non-normality and adjust for baseline covariates for assessment of the treatment effect when appropriate. Any p-values presented will be nominal.

4.4.1. Primary Endpoint: Change from baseline in PVR at Week 24

Change and percent change from baseline in PVR at Week 24 will be analyzed using descriptive statistics and summarized by treatment group. Hodges-Lehmann estimate, their standard error (SE) and 80% CI will be provided to estimate the treatment effect in change from baseline in PVR at Week 24 between KER-012 and placebo. Only participants with both baseline and post-baseline PVR assessments at Week 24 will be included in this analysis.

Similar analysis will be conducted that will include the RHC assessments at Week 24 and/or at the early termination visits within Week 24 in the FAS with at least 3 doses of IMP.

Extension Analysis:

The durability of KER-012 treatment effect, measured as change from baseline in PVR, will be summarized by visit for the Extension analysis in the FAS.

4.4.2. Key Secondary Efficacy Endpoint: Change from baseline in 6MWD at Week 24

Baseline of 6MWD is defined in Section 4.2.3.1. Change and percent change from baseline in 6MWD will be analyzed using descriptive statistics and summarized by treatment group. Additionally, Hodges-Lehmann estimate, their standard error (SE) and 80% CI will be provided to estimate the treatment effect in change from baseline in 6MWD by visit between KER-012 and placebo.

Extension Analysis:

The durability of KER-012 treatment effect, measured as change from baseline in 6MWD, will be summarized by visit for the Extension analysis in FAS.

4.4.3. Other Secondary Efficacy Analyses

4.4.3.1. Change from baseline in Hemodynamic Parameters

Hemodynamic parameters collected from right heart catheterizations (RHCs) are adjudicated by central readers. The observed values and change from Baseline in mean pulmonary artery pressure (mPAP) (mmHg), cardiac output (CO) (L/min), cardiac index (CI) (L/min/m^2), pulmonary artery wedge pressure (PAWP) (mmHg), mean right atrial pressure (mRAP) (mmHg), mixed venous oxygen saturation (SvO2) (%), stroke volume (SV) (mL), stroke volume index (SVI) (mL/m2), pulmonary artery compliance (PAC) (mL/mmHg), and pulse pressure (PP) (mmHg) at Week 24 will be analyzed descriptively.

Proportion of participants who met the following criteria will be analyzed by treatment group.

- mPAP < 25 mmHg at Week 24
- mPAP < 20 mmHg at Week 24
- PVR < 240 dyn·sec·cm^{-5} at Weeks 24

- PVR < 160 dyn·sec·cm^{-5} at Weeks 24

Extension Analysis:

The durability of KER-012 treatment effect, measured as change from baseline in hemodynamic parameters, will be summarized by visit for the Extension analysis in FAS.

4.4.3.2. Change from baseline in NT-proBNP

The observed NT-proBNP, change, and percent change from baseline will be analyzed similarly as 6MWD as detailed in Section 4.4.3. Unit conversion of NT-proBNP is defined in Section 4.1.

Extension Analysis:

The durability of KER-012 treatment effect, measured as change from baseline in NT-proBNP, will be summarized by visit for the Extension analysis in FAS.

4.4.3.3. Proportion of participants with improvement in WHO/NYHA FC from baseline

The WHO/NYHA FC reports 4 classes from Class I to Class IV. Decreasing in class will be defined as improvement. Number and percentage of participants with improvement in WHO FC or maintenance of WHO FC II by treatment group will be summarized by visit and treatment arm.

Extension Analysis:

The durability of KER-012 treatment effect, measured as change from baseline in WHO/NYHA FC, will be summarized by visit for the Extension analysis in FAS.

4.4.3.4. Proportion of participants with multi-component Improvement

Multi-component improvement is defined as participants meeting all three criteria relative to baseline:

- Improvement in 6MWD (increase ≥ 30 m)
- Improvement in NT-proBNP (decrease in NT-proBNP ≥ 30%) or maintenance/achievement of NT-proBNP level < 300 ng/L
- Improvement in WHO FC or maintenance of WHO FC II

Proportion of participants with improvement in multi-component improvement will be summarized by visit. Additionally, the proportion of participants with improvement in individual components—based on 6MWD, NT-proBNP, or WHO FC—will also be summarized to assess the effect of KER-012 on each component.

Extension Analysis:

The durability of KER-012 treatment effect, measured as proportion of participants with multi-component Improvement, will be summarized by visit for the Extension analysis in FAS.

4.4.3.5. Clinical worsening

Participants with clinical worsening will be listed. Number and percentage of participants will be summarized for overall clinical worsening and for each component, by treatment group for Week 24 and Extension Analysis.

4.4.4. Exploratory Efficacy Analyses

4.4.4.1. REVEAL Lite 2 risk assessment

The six items included in REVEAL Lite 2 (Benza et al, 2021) and their corresponding scores are detailed in Table 6. All results should be collected from the same visit.

Table 6: Derivation of REVEAL Lite 2 Score

Item		Score value if condition is met for each item				
No.	**Description**	**-2**	**-1**	**0**	**1**	**2**
1	eGFR <60 mL/min/1.73 m^2 or renal insufficiency			No	Yes	
2	Systolic BP from vital sign (mmHg)			≥110	< 110	
3	Heart rate from vital sign (bpm)			≤ 96	> 96	
4	WHO FC		I	II	III	IV
5	6MWD (m)	≥440	≥320-<440	≥165-<320	< 165	
6	NT-proBNP (ng/L)	< 300		300 - 1100		≥ 1100

Abbreviations: 6MWD = 6-minute walk distance; BP = blood pressure; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro–brain natriuretic peptide; WHO FC = World Health Organization functional class

REVEAL Lite 2 score will be calculated for each participant as the sum of the scores for the 6 items. To calculate a non-missing score, a minimum of 3 items are required to calculate a score where at least 2 are of the most predictive items from items of NYHA/WHO FC, 6MWD and NT-proBNP. Missing score will not be imputed.

Then, at each assessment visit, based on the calculated REVEAL Lite 2 score, participant can be assigned REVEAL Lite 2 risk stratification as follows. Missing categories will not be imputed.

- Low [≤5]
- Intermediate [6-7]
- High [≥8].

For each visit, a binary (Yes or No) endpoint of improvement in REVEAL Lite 2 risk stratification for a participant is defined as at least 1 category decrease from the baseline in the REVEAL Lite 2 risk stratification based on the observed value. Number and percentage of

participant with improvement in REVEAL Lite 2 risk stratification or maintenance of low risk will be summarized by visit for Week 24 and Extension Analysis.

4.4.4.2. COMPERA 2.0

Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) 2.0 (Hoeper et al., 2022) is a European pulmonary hypertension registry. Three items are included in COMPERA 2.0, and its scoring schedule is provided in Table 7 for each item. The definition is the same as ESC/ ERC 4-strata risk category assessment.

All results should be collected from the same visit.

Table 7: Derivation of COMPERA 2.0 Score

Item		Score value if condition is met for each item			
No.	**Description**	**Low Risk 1**	**Intermediate-Low Risk 2**	**Intermediate-High Risk 3**	**High Risk 4**
1	WHO FC	I, II	—	III	IV
2	6MWD (m)	> 440	320-440	165-319	< 165
3	NT-proBNP (ng/L)	< 300	300-649	650-1100	> 1100

Abbreviations: 6MWD = 6-minute walk distance; NT-proBNP = N-terminal pro–brain natriuretic peptide; WHO FC = World Health Organization functional class

COMPERA risk score will be calculated for each participant as the division of the sum of the scores for the 3 items by 3. All 3 values are required to calculate score. Missing value will not be imputed.

Then, at each assessment visit, based on the calculated COMPERA risk score, participant will be assigned COMPERA risk stratification as: low [1 to <1.5], intermediate-low [1.5 to <2.5], intermediate-high [2.5 to <3.5], or high [3.5 to 4]. Missing category will not be imputed.

For each visit, a binary (Yes or No) endpoint of improvement in COMPERA risk stratification for a participant is defined as at least 1 category decrease from the baseline in the COMPERA risk stratification based on the observed value, under this situation, the response “Yes” will be assigned, otherwise, it will take value of “No”.

Number and percentage of participant with improvement or maintenance of low risk in REVEAL Lite 2 risk stratification will be summarized by visit for Week 24 and Extension Analysis.

4.4.4.3. PAH-related biomarkers and other biomarkers

Observed values and change from Baseline in PAH-related biomarkers and other biomarkers, such as BSAP, Connective tissue growth factor, galectin, osteopontin will be summarized by descriptive statistics.

4.4.5. Subgroup Analysis of selected Efficacy endpoints

Subgroup analyses will be conducted for the following endpoints in Week 24 Analysis:

- Change from baseline in PVR at Week 24
- Change from baseline in CI at Week 24
- Change from baseline in CO at Week 24
- Change from baseline in 6MWD
- Change from baseline in NT-proBNP
- Proportion of participants with improvement in WHO/NYHA FC from baseline
- Proportion of participants with multi-component Improvement

A list of the subgroup factor may include but not limited to the following:

- Sex (male vs female)
- Classification of PAH (IPAH, HPAH, Drug or toxin-induced PAH, CTD, PAH associated with congenital systemic-pulmonary intracardiac shunt)
- WHO Functional Class: II vs III
- Background therapy type for PAH
  - Prostacyclin therapy
    - Yes vs No
    - Prostacyclin Infusion vs Prostacyclin non-infusion
  - Monotherapy/double therapy vs. triple therapy
- PVR
  - > 640 vs. ≤ 640 dyn·sec·cm^{-5}
  - > 800 vs. ≤ 800 dyn·sec·cm^{-5}
- REVEAL Lite 2 : Low vs. Intermediate/High
- COMPERA 2.0: Low vs. Intermediate-low/Intermediate-high/High
- Pericardial effusion: Yes vs No

  Pericardial effusions are collected from various sources, such as those reported as adverse events (Section 4.6.2.3) or identified through echocardiograms (Section 4.6.5). However, because participants may lack baseline echocardiogram assessments, it can be challenging to determine whether the effusion is pre-existing or newly developed. To address this, our subgroup analysis will account for multiple factors, including timing, effusion size, location, and associated symptoms, providing flexibility in interpreting the results and ensuring a more thorough understanding of the findings.

Mean and standard error of change from baseline will be presented as bar charts, comparing KER-012 (overall and by individual treatment group) versus Placebo. Each bar chart will include FAS and subgroups of WHO FC III, on Prostacyclin therapy, on triple therapy, PVR > 800 dyn·sec·cm^{-5}, Intermediate/high on REVEEAL Lite 2, Intermediate-low/Intermediate-high/High on COMPERA 2.0, and no Pericardial Effusion. It will be conducted for the following continuous endpoints:

- Change from baseline in PVR, CO, CI at Week 24
- Change from baseline in 6MWD at Week 12
- Change from baseline in NT-proBNP at Week 12

Similarly, percent of participant will be graphed as bar chart for these subgroups for the following two categorical endpoints:

- Proportion of participants with improvement in WHO/NYHA FC from baseline at Week 12
- Proportion of participants with multi-component Improvement and by individual component at Week 12

4.5. QUALITY OF LIFE ANALYSIS

4.5.1. Pulmonary Arterial Hypertension Symptoms and Impact

The PAH-SYMPACT is a 23-item instrument for assessing the presence and severity of symptoms associated with PAH and their impact on physical and emotional/cognitive functioning in adult PAH patients, detailed in Appendix 1 (Chin et al., 2018). Briefly, the PAH-SYMPACT consists of 11 symptom items with a 24-h recall period, 11 impact items with a 7-day recall period, and one item on oxygen use in the previous 24 h. Scores for the individual items ranged from 0 to 4 on a 5-point Likert scale, with higher scores indicating greater symptom severity or worse impact. Appendix 1:

- **Symptoms** (cardiopulmonary and cardiovascular): The cardiopulmonary symptoms subscale consists of 6 items and cardiovascular symptoms subscale is evaluated based on 5 items. All the items are reported on a 5-point Likert scale with score range from 0 = best to 4 = worst.
- **Impact** (physical impacts and cognitive/emotional): The physical impacts subscale consists of 7 items reported on a 5-point Likert scale (from 0 to 4) with value 0 = "with no difficulty at all" and value 4 = "not able at all". The cognitive/emotional subscale consists of 4 items reported on a 5-point Likert scale (from 0 to 4) value 0 = "not at all" and value 4 = "extremely".

There is no global score for PAH-SYMPACT, instead, 4 composite subscale scores (i.e., cardiopulmonary symptoms [total score range from 0 to 24], cardiovascular symptoms [total score range from 0 to 20], physical impact [total score range from 0 to 28], and cognitive/emotional impact [total score range from 0 to 16]) can be calculated for each participant as the sum of the scores for the non-missing items included in the subscale divided by

the number of non-missing items in the subscale, then multiply it by the number of items in the subscale. For example, physical impacts have 7 items, assuming there are 5 items with non-missing response, then the score for physical impacts will be the sum of the scores from these 5 non-missing items divided by 5, then multiply it by 7. For a participant, to calculate a non-missing score for a subscale, it is expected that physical impacts have ≥ 4 non-missing items, cognitive/emotional has ≥ 2 non-missing items, cardiopulmonary symptoms have ≥ 4 non-missing items, and cardiovascular symptoms have ≥ 2 non-missing items; for a subscale, if the requirement is not met, the subscale score will be set as missing. For all subscales, a higher score indicates more severe symptoms/impacts.

The symptoms domain is evaluated every day in a week (i.e., 7 days), hence, the two mean weekly symptom subscale scores (i.e. cardiopulmonary symptoms, cardiovascular symptoms) are calculated as the average across the days in a given week; a minimum of 4 out of 7 days of symptom data are needed in order to calculate a weekly score. If there are ≥ 4 days of missing symptom data, the weekly score is set to missing.

For each of the 4 subscales (i.e., cardiopulmonary symptoms, cardiovascular symptoms, physical impact, and cognitive/emotional impact), the total score at each visit (i.e. Week 12 and Week 24) and its change from baseline in the scores of will be calculated.

4.5.2. EmPHasis-10

The emPHasis-10 (E10) (Yorke et al, 2014) score is a 10-item questionnaire for assessing health-related quality of life in PAH patients and has been designed specifically for use in routine clinical practice. The E10 global score consists of 10 questions scored in a semantic 6-point scale (from 0 to 5), for a total maximum score of 50 (the higher the score, the worse the quality of life). The E10 total score at each visit and its change from baseline in the scores of will be calculated.

For each participant, the E10 total score is calculated as the sum of the scores for the non-missing items divided by the number of non-missing items, then multiply it by 10. For example, if there are no missing item scores, the E10 total score is the sum of the 10 individual item scores; if there is one missing item score, the total score is the sum of the 9 non-missing items score multiplied by 10/9. For a participant, to calculate a non-missing E10 total score, it is expected to have ≥ 5 non-missing items.

The total score of EmPhasis-10 and its change from baseline will be summarized by visit, treatment group for Week 24 and Extension Analysis.

4.6. SAFETY ANALYSES

Unless otherwise specified, the safety analyses will be conducted based on Safety Population.

4.6.1. Exposure

Duration of exposure is defined as the time (days) between the first dose and last dose dates of IMP, i.e., Treatment end date (defined in Section 4.2.2) – Day 1 date + 1.

The duration of exposures, number of doses received, and total dose will be summarized by treatment group in the Safety Population for Week 24 and Extension Analysis.

4.6.2. Adverse Events

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 26.0 and graded by the Investigator according to the CTCAE, Version 5.0.

A Treatment-emergent Adverse Event (TEAE) is defined as an AE with an onset date on or after the IMP start date and within 60 days after the last dose of IMP or the end of the analysis period as defined in Section 4.2.2, whichever is earlier. TEAEs will be grouped by System Organ Class (SOC) and PT and summarized to present the number and percentage of participants with events.

For the summaries of TEAEs, participants who experience the same AE (in terms of the MedDRA PT) more than once will only be counted once for that event in the number of participants but all occurrences of the same event will be counted in the number of events.

The AE summaries will be provided as number and percentage of participants with events in the following categories:

- Overview of TEAEs, including:
  - TEAEs
  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - TEAEs leading to IMP discontinuation
  - TEAE of special interest (defined in Section 4.6.2.3)
  - TEAE of interest (defined in Section 4.6.3)
  - Related TEAEs
  - Related TEAEs of ≥ CTCAE Grade 3
  - TEAEs by toxicity grade
  - Related TEAEs by toxicity grade
- TEAEs by SOC and PT
- TEAEs by PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs by PT

- TEAEs of ≥ CTCAE Grade 3 by SOC and PT
- Treatment-related TEAEs of ≥ CTCAE Grade 3 by SOC and PT
- Serious TEAEs by SOC and PT
- Treatment-related serious TEAEs by SOC and PT
- TEAEs leading to discontinuation of IMP by SOC and PT
- TEAEs after first positive ADA result in ADA positive Participants
- TEAEs of Telangiectasia with the following PTs:
  - Telangiectasia
  - Spider vein
  - Spider naevus
- TEAEs of Bleeding events with the following SMQ and PTs:
  - SMQ Haemorrhages (narrow, excluding laboratory terms)
  - PT Anaemia
- TEAEs of Increased hemoglobin (increased hematocrit, increased RBC count) with the following PTs:
  - Haemoglobin increased
  - RBC count increased
  - Full blood count increased
  - Haematocrit increased
  - Polycythaemia
  - Stress polycythaemia
- TEAEs of Increased blood pressure / hypertension with the following SMQ
  - Hypertension (broad)
- TEAEs of Thrombocytopenia
  - SMQ Haematopoietic thrombocytopenia (narrow)

The analysis of TEAEs will be based on the onset date of AE to determine the time period. Any AE occurring before the first dose of IMP or beyond the Treatment Period will be included in the data listings but will not be included in the summary tables of AEs. Summary tables will include only TEAEs.

Time to the onset of the first Telangiectasia and Bleeding events as defined above will analyzed by treatment group using Kaplan-Meier Approach.

Additional graphical presentations of selected adverse events (AEs) may be created to visualize the time of onset, duration, and severity grade for each participant by the treatment group.

4.6.2.1. Death

Death data will be presented in data listing.

4.6.2.2. AE of Special Interest

The number and percentage of participants experiencing the treatment-emergent AESI of Pericardial Effusion will be also summarized by PT and by CTCAE grade for each treatment arm.

- AESI of Pericardial effusion is defined with the following PTs:
  - Pericardial effusion
  - Pericardial effusion malignant
  - Cardiac tamponade
  - Pericardial drainage
- AESI of pericardial effusion will be analyzed by:

  Background therapy category for PAH: prostacyclin therapy (including prostacyclin infusion vs prostacyclin non-infusion); soluble guanylate cyclase (sGC) stimulator; phosphodiesterase-V inhibitor (PDE5-I); endothelin receptor antagonist (ERA)

Time to the onset of the first pericardial effusion as defined above will be analyzed by treatment group using Kaplan-Meier Approach.

Echocardiogram data will be summarized separately as in Section 4.6.4

4.6.2.3. AE of Interest

Injection site reaction (ISR) is defined as a reaction developing at the site of an injection of the IMP, will be considered as adverse event of interest (AEI). ISR includes AEs with High Level Term (HLT) as “Injection site reactions”. All ISRs will be reported and summarized.

4.6.3. Laboratory Evaluations

All individual clinical laboratory results will be presented in data listings. Values outside the laboratory reference range will be flagged (low-L, high-H). Observed values and change from Baseline for clinical laboratory data (hematology, coagulation, and chemistry) will be summarized at each protocol specified time point.

Change from baseline in laboratory test results to each assessment will be calculated. The non-protocol specified tests (if any reported) and urinalysis results will not be summarized; they will only be included in listings.

Data recorded by the laboratory will be converted to the International System of Units (SI) and all presentations will use SI units except for hgb, MCHC, where g/dL will be used (Section 4.1).

Additionally, the last assessment on treatment period for each participant over the entire treatment period for each haematology and chemistry laboratory parameter will also be derived. The change from baseline will be calculated and summarized.

Clinical laboratory results will be graded according to CTCAE criteria, CTCAE v5.0 criteria (see Appendix 2). Any graded abnormality that occurs following the initiation of IMP and represents at least a 1-grade increase from the baseline assessment is defined as treatment emergent. Any assessment for which CTCAE toxicity grades are not available will not be included in any analyses for which toxicity grades are required. Moreover, any occurrence of Grade 3 or Grade 4 will be summarized, and shift in grade from baseline to the worst post-baseline value will be summarized. Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

Analysis of Abnormal Hepatic Laboratory Values

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments.

- AST > 3,5, 8 × ULN
- ALT > 3,5, 8 × ULN
- Total bilirubin elevations > 2 × ULN
- ALP >3 × ULN
- Listing of Participants who met Hy's Law per FDA guidance, defined as Participants met all three of the following: AST and/or ALT > 3 × ULN and total bilirubin ≥ 2 × ULN and ALP < 2 × ULN
- The maximum of post baseline value of Total bilirubin [× ULN] vs. ALT [× ULN] on a log/log scale, group by elevated ALP (≥ 1xULN) versus non-elevated ALP (< 1xULN) in different color, treatment versus control by panel, will be presented in eDISH figure. Total bilirubin vs. AST will be also presented in eDISH figure similarly.

A summary table will be also provided for abnormal hepatic laboratory values by treatment arm. Abnormal hepatic laboratory values are based on the pre-specified thresholds. An eDISH plot presenting peak total bilirubin and peak ALT values will also be produced.

Listings of all laboratory data with normal reference ranges, and CTCAE grades (when possible) will be provided.

Proportion of participants with change from baseline in hgb exceeding the thresholds (> 2, 3 and 4 g/dL) at any time during the 24-week period will be summarized by treatment group for the Safety Population. This analysis will include both scheduled and unscheduled assessments.

4.6.4. Vital Signs

Vital signs parameters (height, body weight, BMI, heart rate, respiratory rate, body temperature, systolic blood pressure [SBP], diastolic blood pressure [DBP], Pulse Oximetry [SpO2]) will be reported for this study.

Mean arterial pressure (MAP) will be calculated using formula as (SBP + 2 × DBP) / 3.

Observed values and actual change from Baseline for vital signs parameter values will be summarized at each protocol specified time point. If repeated measurements are performed for SBP/DBP, the mean value will be presented for this visit.

Mean±SE change from Baseline by treatment group will be plotted for selected parameters including SBP, DBP, MAP, SpO2, and body weight.

Maximum post-baseline increases in SBP and DBP from Baseline will be summarized for the following categories:

- Change from baseline in SBP ≥ 20 mmHg and SBP ≥ 160 mmHg
- Change from baseline in SBP ≥ 40 mmHg and SBP ≥ 160 mmHg
- Change from baseline in DBP ≥ 10 mmHg and DBP ≥ 100 mmHg
- Change from baseline in DBP ≥ 20 mmHg and DBP ≥ 100 mmHg

Shift table will be presented for the following categories:

- SBP shift from normal at Baseline to ≥ 160 mmHg anytime post-baseline
- DBP shift from normal at Baseline to ≥ 100 mmHg anytime post-baseline
- Normal SBP is defined as SBP of 100 to 130 (inclusive) at baseline; Normal DBP is defined as DBP of 60 to 800 (inclusive) at baseline.

Maximum post-baseline decreases in SBP and DBP from Baseline will be summarized for the following categories:

- Change from baseline in SBP ≥ 20 mmHg and SBP ≤ 90 mmHg.
- Change from baseline in SBP ≥ 20 mmHg and SBP ≤ 80 mmHg.
- Change from baseline in DBP ≥ 10 mmHg and DBP ≤ 50 mmHg.
- Change from baseline in DBP ≥ 10 mmHg and DBP ≤ 40 mmHg.

Maximum post-baseline increases or decrease of at least 5% and at least 10% in weight will be summarized using the number and percentage.

4.6.5. Electrocardiogram

Electrocardiogram (ECG) parameters (heart rate, PR interval, QRS duration, QT interval and QTcF and QTcB) will be reported for this study. All ECG data will be presented in data listings.

Observed values and actual change from Baseline for ECG parameter values will be summarized at each protocol specified time point.

In addition, clinical assessment of the ECG (Normal, Abnormal NCS, Abnormal CS) will also be summarized at each protocol specified time point using frequency tabulations. Shifts in ECG interpretation at Baseline versus any post-baseline values (including values from unscheduled visit) will be presented.

The QTcF will be categorized into the following categories:

- QTc interval > 450 msec and ≤ 480 msec
- QTc interval > 480 msec and ≤ 500 msec
- QTc interval > 500 msec

The change from Baseline in QTcF will also be categorized separately as follows:

- QTc interval increases from Baseline by > 30 msec and ≤ 60 msec
- QTc interval increases from Baseline by > 60 msec

Shift table will be provided for the QTcF analysis as follows. For the number of participants meeting each category for the post-baseline results, the numerator is the number of participants meeting the criterion at post-baseline and the denominator is the number of participants with normal Baseline and at least one post-baseline assessment in the Safety Population. For the number of participants meeting each category for the change from Baseline, the numerator is the number of participants meeting the criterion at post-baseline and the denominator is the number of participants with Baseline and at least one post-baseline assessment in the Safety Population.

4.6.6. Echocardiogram

An echocardiogram must be performed at baseline (Visit 1) and subsequently according to the SOA (CSP Section 1.3) and per local standards. An echocardiogram must be performed anytime a participant meets the protocol definition of clinical worsening (CSP Section 9.7). A by-participant data listing of echocardiogram values at each time point will be presented.

The size of effusion will be collected if a pericardial effusion is observed, it will be categorized as follows:

- Trivial: Presence during cardiac cycle in systole only
- Small: <10 mm (corresponding to 50-100 mL pericardial fluid)
- Moderate: 10-20 mm (corresponding to 100-500 mL pericardial fluid)
- Large: >20-≤25 mm (corresponding to >500 mL pericardial fluid)
- Very large: >25 mm (usually indicating >700 mL pericardial fluid)

The number and percentage of participants with any pericardial effusion, as identified by echocardiogram, will be presented overall by treatment group, and categorized by the maximum

size of the effusion (as defined above). The analysis will be conducted in the Safety Population and including only participants who had at least one post-baseline echocardiogram assessment. Both scheduled and unscheduled echocardiogram assessments will be included. This analysis will be conducted for the Week 24 and Extension Analyses.

4.7. IMMUNOGENICITY ANALYSIS

The immunogenicity analysis will be based on Immunogenicity Population for both Week 24 and Extension Analysis.

The number and percentage of participants who developed ADA will be presented at each scheduled time point.

The number and percentage of the participants and median (range) titer for binding ADA to KER-012 will be presented by treatment group and visit.

The ADA status of a participant during Treatment Period is determined based on the ADA results as following:

- Negative: All samples (Baseline and post-baseline) are negative.
- Positive to treatment-emergent ADA:
  - At least one post-baseline sample is positive if the Baseline sample is negative, or
  - At least one post-baseline sample is positive with a titer ≥ 4-fold of the Baseline titer if the Baseline sample is positive.
- Positive to preexisting ADA:
  - Baseline sample is positive and all post-baseline samples are negative, or
  - Both Baseline and post-baseline samples are positive, but all positive post-baseline sample have a titer < 4-fold of the Baseline titer.

In addition, the following tables may be provided by ADA status

- Serum concentration
- Number and percentage of participants with AESI (defined in Section 4.6.2.2)

Additional analysis for results from additional ADA assays may be performed outside of the statistical analysis plan if applicable.

4.8. PHARMACOKINETIC ANALYSIS

The PK analysis will use the PK Population. Concentrations of KER-012 will be provided as by-participant listings and will be summarized using descriptive statistics (n, arithmetic mean, SD, percent coefficient of variation [CV%], median, minimum, and maximum) by treatment group. Additional PK/PD analysis may be performed outside of this analysis plan (Section 1).

5. PLANNED ANALYSES

5.1. INTERIM ANALYSES

To inform the changes outlined in Protocol Version 6.0, an ad hoc unblinded analysis was conducted to assess the benefit-risk of KER-012 in participants with PAH by a selected group of Sponsor team members. This group was kept small and consisted of members who are not involved in site-facing study activities to ensure protection of the entire study's blind.

A blinded interim analysis (IA) may be conducted to assess if sample size needs to be increased due to higher than assumed variability of change from baseline in PVR at Week 24.

The IA was not performed due to fast enrollment in the study.

6. CHANGES TO PROTOCOL-PLANNED ANALYSES

As detailed in Protocol Amendment Version 6.0, details regarding the statistical methodology will be included in the Statistical Analysis Plan which will supersede the analysis presented in the protocol and will be finalized prior to any database lock.

Due to the early termination of the study, the analysis will be descriptive and exploratory in nature including the changes to Section 10.6 in the Protocol Amendment Version 6.0.

- Multiplicity adjustment approach to control the overall Type I error rate for primary and key secondary endpoints will no longer be applicable (Section 4.4).
- The primary analysis of the primary endpoints and key secondary endpoints of the protocol will no longer be performed (Section 4.4.1 and Section 4.4.2).
- Responder analysis will be included as a more clinically meaningful measure in the presence of small sample size and outliers (Section 4.4)
- Analysis of AESI for Pericardial Effusion was added to AE, echocardiogram and subgroup analysis (Section 4.6.2.2, Section 4.4.5, Section 4.6.6)

REFERENCES

Dear Investigator Letter: Study KER-012-A201 (dated 11 December 2024)

Dear Investigator Letter: Study KER-012-A201 (dated 14 January 2025)

Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG. Predicting survival in pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). *Circulation*. 2010; 122(2):164-72.

Benza RL, Kanwar MK, Raina A, Scott JV, Zhao CL, Selej M, Elliott CG, Farber HW. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. *Chest*. 2021; 159(1):337-46.

Chin KM, Gomberg-Maitland M, Channick RN, Cuttica MJ, Fischer A, Frantz RP, Hunsche E, Kleinman L, McConnell JW, McLaughlin VV, Miller CE, Zamanian RT, Zastrow MS, Badesch DB. Psychometric Validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Questionnaire: Results of the SYMPHONY Trial. *Chest*. 2018 Oct;154(4):848-861

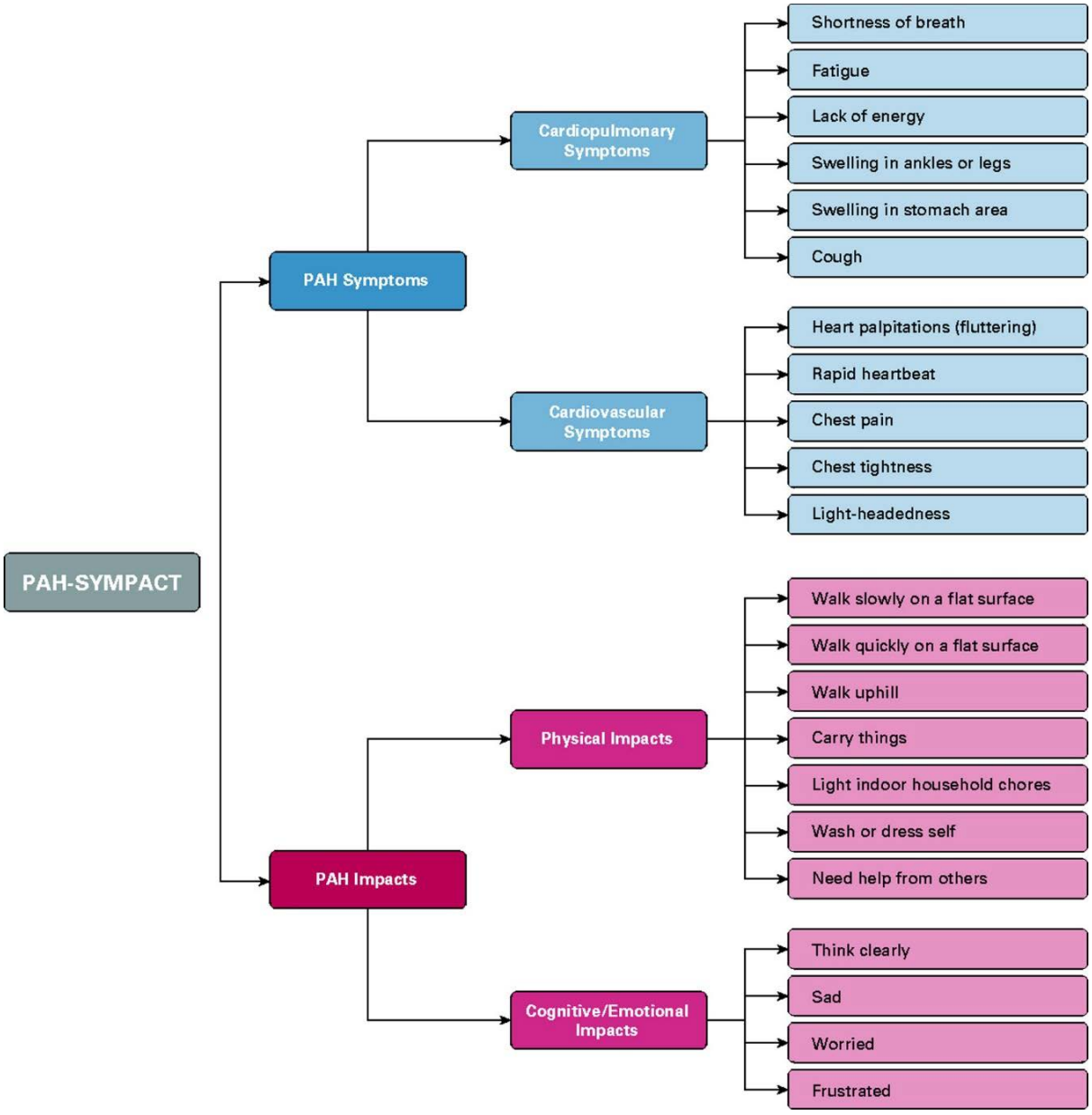
Hoeper MM, Pausch C, Olsson KM, Huscher D, Pittrow D, Grünig E, Staehler G, Vizza CD, Gall H, Distler O, Opitz C. COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension. *European Respiratory Journal*. 2022;60(1).

McCollister D, Shaffer S, Badesch DB, Filusch A, Hunsche E, Schüler R, Wiklund I, Peacock A. Development of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) questionnaire: a new patient-reported outcome instrument for PAH. *Respiratory Research*. 2016; 17: 72.

Yorke J, Corris P, Gaine S, Gibbs JS, Kiely DG, Harries C, Pollock V, Armstrong I. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *European Respiratory Journal*. 2014;43(4):1106-13.

APPENDIX 1. PULMONARY ARTERIAL HYPERTENSION SYMPTOMS AND IMPACT (PAH-SYMPACT)

The PAH-SYMPACT is a 23-item instrument for assessing the presence and severity of symptoms associated with PAH and their impact on physical and emotional/cognitive functioning in adult PAH patients. The structure of the PAH-SYMPACT is graphically displayed below, and more detailed derivation of the score for a subscale is included in Section 4.4.5.



APPENDIX 2. CTCAE VERSION 5.0 FOR SELECTED LAB PARAMETERS

PARAM (SI Unit)	Hypo	Hyper	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Hemoglobin (g/L)		Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	NA
	Anemia		Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L	NA
Platelets (10^9/L)	Platelet count decreased		<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Leukocytes (10^9/L)	White blood cell decreased		<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
Neutrophils (10^9/L)	Neutrophil count decreased		<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Lymphocytes (10^9/L)	Lymphocyte count decreased		<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
		Lymphocyte count increased	NA	>4000/mm3 - 20,000/mm3	>20,000/mm3	NA
White blood cells (WBC) (10^9/L)	White blood cell decreased		<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
Albumin (g/L)	Hypoalbuminemia		<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	NA
Glucose (mmol/L)	Hypoglycemia		<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Creatinine (umol/L)		Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline if baseline was abnormal; >1.5 - 3.0 x ULN if baseline was normal	>3.0 x baseline- 6.0xULN if baseline was abnormal; >3.0 - 6.0 x ULN if baseline is normal	>6.0 x ULN
Creatine phosphokinase (IU/L)		CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN- 5 x ULN	>5.0 X ULN - 10.0 x ULN	>10.0 x ULN

PARAM (SI Unit)	Hypo	Hyper	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Alkaline Phosphatase (uKat/L)		Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate Aminotransferase (uKat/L)		Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alanine Aminotransferase (uKat/L)		Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Serum Calcium (mmol/L)		Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L
	Hypocalcemia		<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Magnesium (mmol/L)		Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	NA	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
	Hypomagnesemia		<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Potassium (mmol/L)		Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
	Hypokalemia		<LLN - 3.0 mmol/L	NA	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Sodium (mmol/L)		Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
	Hyponatremia		<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L
Total cholesterol (mmol/L)		Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L

PARAM (SI Unit)	Hypo	Hyper	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Bilirubin (umol/L)		Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Triglycerides (mmol/L)		Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
eGFR (mL/min/1.73 m^2)			<LLN - 60 ml/min/1.73 m2	30-59 ml/min/1.73 m2	15-29 ml/min/1.73 m2	<15 ml/min/1.73 m2

APPENDIX 3. HANDLING OF MISSING DATA

A3-1.1. DATE IMPUTATION RULES

Initial diagnosis date or other historical dates related to diagnosis/prior treatment (as applicable):

- If year is missing, do not impute.
- If only day is missing, impute day as 15th of the month.
- If day and month are missing, impute as July 1st of the year.

Concomitant medication start date:

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as January 1st.
- If year and month are present and day is missing, impute day as first day of the month.

Concomitant medication end date:

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing, impute as December 31st.
- If year and month are present and day is missing, impute day as last day of the *month.*
- If the imputed end date is earlier than the observed/imputed medication start date, the end date will be imputed as the same as the start date.

Missing Dates in Adverse Events

Start dates of adverse events will be imputed relative to the first dose in the Treatment Period or the Extension Period accordingly:

- Completely missing start date will be imputed as the date of first dose
- Start date missing both month and day will be imputed as:
  - the date of first dose if the year of the start date is the same as the date of first dose.
  - otherwise, Jan 1st of the year of the start date will be used.
- Start date missing day will be imputed as:
  - the date of first dose if the year and month of the start date are the same as the date of first dose.
  - otherwise, the 1st of the month of the start date will be used.

Stop dates of adverse events will be imputed as follows:

- Completely missing stop date will be imputed as the date of last dose in the corresponding study period.

- Stop date missing both month and day will be imputed as Dec 31st of the year of stopdate.
- Stop date missing day will be imputed as the last date of the month of the stop date.

After imputation, the imputed date will be compared against the date of death, if available. If the planned imputed date is later than the date of death, the date of death will be used as the imputed date instead.

A3-1.2. RELATIONSHIP AND SEVERITY IMPUTATION RULES FOR ADVERSE EVENTS

Missing relationship will be considered as 'Related' if the adverse event started on or after the date of first dose of study IMP. Missing severity will be considered as severe.

APPENDIX 4. VISIT WINDOW FOR EARLY TERMINATION VISIT MAPPING (WEEK 24 ANALYSIS ONLY)

If participants discontinue the 24-week treatment period early, the data collected during their Early Termination (ET) visit, if within the treatment period as defined in Section 4.2.2, will be assigned to the visit based on the study day as outlined in Table 8 below. However, if an assessment from a scheduled visit corresponding to that same time point already exists, the data from the scheduled visit will take precedence and be used instead.

ET visit beyond the 24-week treatment period will not be mapped.

Table 8: Visit Window to Map the Assessments From the Early Termination Visit within 24-week treatment period.

Visit	1	2	3	4	5	6	7	9	10	11	12
Week	0	1	2	3	4	8	12	16	20	22	24
Study Day	1	5	15	22	29	57	85	113	141	155	169
Vital Sign	Day 1		2 to 22		23 to 43	44 to 71	72 to 99	100 to 127	128 to 155		156 to TED
RHC	Day 1										155 to TED
12-lead ECG [g]	Day 1		2 to 22		23 to 43	44 to 71	72 to 99	100 to 127	128 to 155		156 to TED
Clinical laboratory	Day 1	2 to 10	11 to 18	19 to 25	26 to 43	44 to 71	72 to 99	100 to 127	128 to 155		156 to TED
NT-proBNP	Day 1		2 to 22		23 to 43	44 to 71	72 to 99	100 to 127	128 to 155		156 to TED
ADA	Day 1		2 to 18	19 to 25	26 to 43	44 to 71	72 to 99	100 to 127	128 to 155		156 to TED
Biomarkers	Day 1		2 to 22		23 to 43	44 to 71	72 to 99	100 to 127	128 to 148	149 to 162	163 to TED
6-minute walk test	Day 1				15 to 43		71 to 99				155 to TED
WHO/NYHA FC	Day 1				15 to 43	44 to 71	72 to 99	100 to 127	128 to 155		156 to TED
PAH-SYMPACT	Day 1						71 to 99				155 to TED
EmPHasis-10	Day 1						71 to 99				155 to TED

ECG = electrocardiogram; NT-proBNP = N-terminal pro hormone B-type natriuretic peptide; NYHA FC = New York Heart Association functional class; PAH = pulmonary arterial hypertension; RHC = right heart catheterization; SYMPACT = symptoms and impact; TED=treatment end day (defined in Table 5); WHO = World Health Organization.