



CLINICAL STUDY PROTOCOL

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)

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Investigational Product: KER-012

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Sponsor: Keros Therapeutics, Inc.
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Date of Protocol and Version: 18 December 2024, Version 6.0

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SIGNATURE PAGE

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I have read this clinical study protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), all applicable local Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, Regulation (EU) No. 536/2014, and all local and regional regulations and guidelines as applicable.

Principal Investigator:

Print/Type Name

Signature:

Date:

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LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWD	6-minute walk distance
6MWT	6-minute walk test
ActRIIB	activin receptor IIB
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AUC _{0-last}	area under the concentration-time curve from time 0 to last measured concentration
BMI	body mass index
BMP	bone morphogenic protein
BMPR2	bone morphogenic protein type 2 receptor
BP	blood pressure
BSAP	bone specific alkaline phosphatase
CI	cardiac index
C _{max}	maximum concentration
CO	cardiac output
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	connective tissue disease
DMC	Data Monitoring Committee
EC	Ethics Committee
ECD	extracellular domain
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study
EOT	End of Treatment
ERA	endothelin-receptor antagonist
ERC	European Respiratory Society
ESC	European Society of Cardiology

Abbreviation	Definition
ET	Early Termination
FAS	Full Analysis Set
FC	functional class
FEV1	forced expiratory volume in 1 second
FIH	first-in-human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GDF	growth differentiation factor
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	injection site reaction
IV	intravenous
IVC	inferior vena cava
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
mPAP	mean pulmonary arterial pressure
mRAP	mean right atrial pressure
NT-proBNP	N-terminal pro hormone B-type natriuretic peptide
NYHA FC	New York Heart Association functional class
PAC	pulmonary artery compliance

Abbreviation	Definition
PAH	pulmonary arterial hypertension
PAH-SYMPACT	Pulmonary Arterial Hypertension-Symptoms and Impact Questionnaire
PAWP	pulmonary artery wedge pressure
PD	pharmacodynamics
PDE5-I	phosphodiesterase 5 inhibitor
PFT	pulmonary function test
PH	pulmonary hypertension
PK	pharmacokinetics
PT	Preferred Term
PVR	pulmonary vascular resistance
Q4W	every 4 weeks
QTcF	QT interval corrected by Fridericia
RHC	right heart catheterization
RV	right ventricular
SAD	single-ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
sGC	soluble guanylate cyclase
SOA	Schedule of Assessments
SUSAR	suspected unexpected serious adverse reaction
SV	stroke volume
SVI	stroke volume index
SvO ₂	mixed venous oxygen saturation
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TGF-β	transforming growth factor-beta
TLC	total lung capacity
ULN	upper limit of normal
V/Q	ventilation-perfusion
WHO	World Health Organization
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Protocol Number: KER-012-A201	
Title: 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)	
Investigational Medicinal Product Name: KER-012	
Sponsor: Keros Therapeutics, Inc.	
Study Centers: Multicenter (Global)	
Development Phase: Phase 2	
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 pulmonary vascular resistance (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	
Evaluate the safety and tolerability of KER-012 in participants on background PAH therapy	Incidence of treatment-emergent adverse events (TEAEs), treatment-related TEAEs and discontinuations due to TEAEs; change from baseline in clinical laboratory values, vital signs, and electrocardiogram (ECG); incidence of anti-drug antibodies (ADA)
Note: All other secondary and exploratory objectives and endpoints have been described in detail in Section 3 .	
Study Design: 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) (every 4 weeks [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.

Number of Participants (Planned):

Approximately 90 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 the 1.5 mg/kg, 3.0 mg/kg, and 4.5 mg/kg KER-012 doses and Placebo treatment arms.

Key Inclusion Criteria:

- Adult participants ≥ 18 years of age
- Symptomatic World Health Organization (WHO) Group 1 Pulmonary Hypertension (PAH) classified by one of the following subgroups:
 - Idiopathic pulmonary arterial hypertension (IPAH)
 - Heritable pulmonary arterial hypertension (HPAH)
 - Associated with drugs and toxins
 - PAH associated with:
 - Connective tissue disease (CTD)
 - Congenital systemic-pulmonary intracardiac shunt (must have surgical correction or repair with closure device at least 1 year prior to Screening, AND have no, or clinically insignificant, shunt fraction in the opinion of Investigator [$1.0 \leq$ pulmonary-systemic flow ratio ≤ 1.5])
- Has the following hemodynamic parameters that are consistent with the diagnosis of PAH:
 - Mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest, AND
 - Pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, AND

- $PVR \geq 5$ Wood units ($400 \text{ dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$)

Note: RHC to assess eligibility performed within 6 weeks from Visit 1 (Day 1).

- Has WHO/New York Heart Association (NYHA) functional class (FC) II or III symptoms as assessed by the Investigator at Screening and Day 1
- Must be on a stable PAH background therapy with either an endothelin-receptor antagonist (ERA) and/or a phosphodiesterase-5 inhibitor (PDE5-I) or soluble guanylate cyclase (sGC) stimulator and/or prostacyclin analogue or receptor agonist (oral/inhaled/SC/intravenous)
 - Stable therapy is defined as no change in dose/regimen for at least 90 days prior to baseline and would be expected to be maintained for the duration of the study.
- $6MWD \geq 150$ and ≤ 500 meters repeated twice at screening (measured at least 4 hours apart but no longer than 1 week), and both values within 15% of each other (calculated from the highest value). Note: Both 6MWD values must be within the allowed range and not averaged.
- Provide written (signed and dated) informed consent form before the initiation of any Screening tests or procedures
 - Sites in Germany: see [Appendix A7-1.2](#)

Key Exclusion Criteria:

- Evidence or history of left ventricular dysfunction and/or clinically significant cardiac disease
- Has pulmonary function tests (PFTs) at Screening or within 180 days prior to the Screening with evidence of significant obstructive or parenchymal lung disease
- Evidence of thromboembolic disease assessed by ventilation perfusion (V/Q) lung scan or other local standard of care diagnostic evaluation at the time of PAH diagnosis or after
- Has uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) > 160 mmHg or sitting diastolic BP > 100 mmHg at Screening
- Hemoglobin < 9 g/dL at Screening
- Prior heart or heart-lung transplants, active on the lung transplant list, or life expectancy of < 12 months per Investigator assessment
- Diagnosis of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis
- Initiation or discontinuation of an exercise program for cardiopulmonary rehabilitation within 90 days prior to baseline or planned initiation during the study
- Prior participation in a KER-012 study, or prior treatment with a therapy targeting TGF- β (e.g., sotatercept)
- Prior participation in another interventional clinical study with medicinal products within 30 days or 5 half-lives prior to Screening, whichever is longer
 - Sites in France: see [Appendix A7-1.1](#)

Detailed Inclusion/Exclusion Criteria are available in [Section 5.1](#) and [Section 5.2](#).

Investigational Product, Dosage and Mode of Administration:

Dosing Schedule: KER-012 will be injected SC once every 28 days (Q4W) based on volume by body weight collected at each visit. Planned dose levels are 1.5 mg/kg, 3.0 mg/kg, and 4.5 mg/kg (as of Protocol Amendment Version 6.0, treatment of all participants assigned to Arm 2 [3.0 mg/kg] and

Arm 3 [4.5 mg/kg], along with participants assigned to Arm 4 [placebo] who have crossed over to 3.0 mg/kg, will be halted).

Reference Therapy, Dosage and Mode of Administration:

Dosing Schedule: Placebo will be injected SC Q4W based on volume by body weight collected at each visit. Placebo will be administered in the volume equivalent to 3.0 mg/kg dose.

Duration of Study Participation: The Treatment Period is expected to be 24 weeks, with an Extension Period of 72 weeks, for a total of 96 weeks (i.e., approximately 2 years) on treatment. Of note, participant enrollment and randomization were closed on 27 September 2024 when the last participant was randomized. As of Protocol Amendment Version 6.0, treatment of all participants assigned to Arm 2 (3.0 mg/kg) and Arm 3 (4.5 mg/kg), along with participants assigned to Arm 4 (placebo) who have crossed over to 3.0 mg/kg, will be halted.

Treatment Period (24 weeks):

- Arm 1: KER-012 (1.5 mg/kg)
- Arm 2: KER-012 (3.0 mg/kg) (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) (as of Protocol Amendment Version 6.0, treatment in Arm 3 [4.5 mg/kg] will be halted)
- Arm 4: Placebo

Extension Period (72 weeks):

- Arm 1: KER-012 (1.5 mg/kg) (+ roll-over from Treatment Period Placebo arm as of Protocol Amendment 6.0)
- Arm 2: KER-012 (3.0 mg/kg) (+ roll-over from Treatment Period Placebo arm) (as of Protocol Amendment Version 6.0, treatment of all participants assigned to Arm 2 [3.0 mg/kg], along with participants assigned to Arm 4 [Placebo] who have crossed over to 3.0 mg/kg, will be halted)
- Arm 3: KER-012 (4.5 mg/kg) (as of Protocol Amendment Version 6.0, treatment in Arm 3 [4.5 mg/kg] will be halted)

Statistical Methods:

As of 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.

Analysis Populations:

Safety Population is defined as all randomized participants who received at least 1 dose of IMP. Participants will be analyzed according to the treatment received.

The Full Analysis Set (FAS) is defined as all randomized participants who received at least 1 dose of IMP. Participants will be analyzed according to the treatment to which they were randomized.

Baseline will be defined as the last assessment on or prior to first dose of IMP for all safety and efficacy analyses.

Efficacy Analysis: The primary endpoint of change from baseline in PVR at Week 24 will be analyzed using either parametric or non-parametric methods consistent with the statistical assumptions required to support the analyses. In the primary analysis of the primary estimand, analysis of covariance or aligned-rank stratified Wilcoxon test (based on the assessment of skewness) will be used to compare the pooled KER-012 and Placebo treatment arms, with the baseline PVR as the covariate or

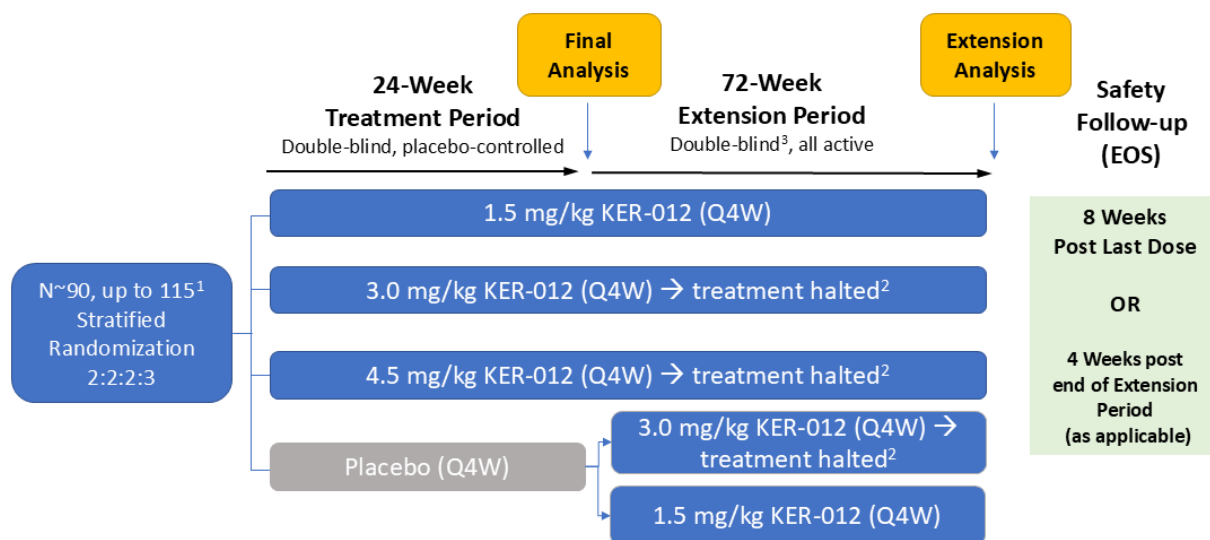
randomization stratification factor as strata. Analysis of the key secondary endpoint of change from baseline in 6MWD at Week 24 will be conducted in a similar manner as the primary analysis of the primary endpoint. A fixed sequence approach will be used to control the overall Type I error rate for the primary and key secondary endpoints.

Safety Analysis: All safety assessments will be summarized using descriptive statistics. Safety will be evaluated based on adverse events (AEs), clinical laboratory parameters, vital signs, ECGs, and ADA. The number and percentage of participants with treatment-emergent AEs (TEAEs), treatment-emergent serious AEs (TESAEs), treatment-related TEAEs, treatment-related TESAEs, and AEs leading to treatment discontinuation will be summarized by treatment arm. The observed value and change from baseline in clinical laboratory, ECGs, vital signs, and incidences of ADA will be summarized by treatment arm.

Sample Size Considerations: Approximately 90 and up to 115 participants diagnosed with PAH and on stable 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 $200 \text{ dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$ decrease between pooled KER-012 treatment arm and Placebo with a common standard deviation of $300 \text{ dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$, a premature discontinuation rate of 10%, and with 1-sided alpha of 0.10.

Interim Analysis: 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; hence, this amendment will not incur any potential operational bias for the analysis results.

1.2. 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

1.3. SCHEDULE OF ASSESSMENTS

Schedule of Assessments – Screening and Treatment Period

Study Visit (Week)	V0 Screening ^a	Treatment Period												Safety Follow- Up (8 weeks)
		V1 (Wk0)	V2 ^b (Wk1)	V3 (Wk2)	V4 ^b (Wk3)	V5 (Wk4)	V6 (Wk8)	V7 (Wk12)	V8 ^b (Wk13)	V9 (Wk16)	V10 (Wk20)	V11 ^b (Wk22)	V12 EOT/ET ^c (Wk24)	EOS
Day ^d	D-28 to D-1	D1	D5 ±2 days	D15 ±2 days	D22 ±2 days	D29 ±5 days	D57 ±5 days	D85 ±5 days	D95 ± 2 (10 ±2 days after D85 actual visit)	D113 ±5 days	D141 ±5 days	D155 ±5 days	D169 ±5 days	56 days (±5 days) after last dose of IMP
Informed consent	X													
Inclusion/exclusion criteria	X	X											X ^e	
Demographics	X													
Medical history	X													
Physical examination ^f	X	X		X		X	X	X		X	X		X	X
Vital signs ^g	X	X		X		X	X	X		X	X		X	X
PAH history ^h	X												X	
Optional genetic testing ⁱ	X													
Proteomics, metabolomics and transcriptomics	X												X	
Right heart catheterization	X ^j												X ^k	
V/Q scan ^l	X													
Pulmonary function test ^m	X													

Schedule of Assessments – Screening and Treatment Period (Continued)

Study Visit (Week)	V0 Screening ^a	Treatment Period												Safety Follow- Up (8 weeks)
		V1 (Wk0)	V2 ^b (Wk1)	V3 (Wk2)	V4 ^b (Wk3)	V5 (Wk4)	V6 (Wk8)	V7 (Wk12)	V8 ^b (Wk13)	V9 (Wk16)	V10 (Wk20)	V11 ^b (Wk22)	V12 EOT/ET ^c (Wk24)	EOS
Day ^d	D-28 to D-1	D1	D5 ±2 days	D15 ±2 days	D22 ±2 days	D29 ±5 days	D57 ±5 days	D85 ±5 days	D95 ± 2 (10 ±2 days after D85 actual visit)	D113 ±5 days	D141 ±5 days	D155 ±5 days	D169 ±5 days	56 days (±5 days) after last dose of IMP
Pregnancy test ⁿ	X	X				X	X	X		X	X		X	X
Serology (HIV, HBsAg, HCV)	X													
12-lead electrocardiogram ^o	X	X		X		X	X	X		X	X		X	X
Echocardiogram ^{p,q}		X				X	X	X		X	X		X	X
Clinical laboratory tests ^q	X	X	X	X	X	X	X	X		X	X		X	X
ADA assessment ^q		X		X	X	X	X	X		X	X		X	X
PK assessment ^r		X	X	X	X	X	X	X	X	X	X	X	X	
Biomarker assessments ^s		X		X		X	X	X		X	X	X	X	X
Randomization		X												
IMP administration		X				X	X	X		X	X			
Prior/concomitant medications	X	X												X
Adverse event and clinical worsening reporting	X	X												X
6-minute walk test ^t	X					X		X					X	
WHO/NYHA FC assessment ^u	X	X				X	X	X		X	X		X	
PAH-SYMPACT ^v		X						X					X	
EmPHasis-10 ^v		X						X					X	
Actigraphy ^w	X	X												X

Abbreviations: 6MWT = 6-minute walk test; ADA = anti-drug antibody; AE = adverse event; BMPR2 = bone morphogenetic protein type II receptor; BSAP = bone specific alkaline phosphatase; CTGF = connective tissue growth factor; D = day; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IMP = investigational medicinal product; NT-proBNP = N-terminal pro hormone B-type natriuretic peptide; NYHA FC = New York Heart Association functional class; PAH = pulmonary arterial hypertension; PFT = pulmonary function test; PK = pharmacokinetic(s); Q4W = every 4 weeks; QoL = quality of life; RHC = right heart catheterization; SYMPACT = symptoms and impact; V = visit; V/Q = ventilation perfusion; Wk = week; WHO = World Health Organization.

- ‡ At the time the Dear Investigator Letter is received regarding the changes made with Protocol Amendment Version 6.0, all participants in Arm 2 and Arm 3, along with participants in Arm 4 who have crossed over to 3.0 mg/kg, will be unblinded, must have an echocardiogram and other EOT/ET assessments, and must halt dosing. In addition to scheduled echocardiograms, all other participants may have additional echocardiograms at the Investigator's discretion.
- ^a All Screening activities are to be completed within 28 days (unless otherwise specified) before dosing on D1 and results are to be available for eligibility approval at least 48 hours prior to planned randomizations.
- ^b V2, V4, V8, and V11 assessments may be collected during home visits.
- ^c EOT only for study participants not continuing into the Extension Period.
- ^d Visits may be completed over multiple days, provided they are within the allowable visit window.
- ^e Eligibility for Extension Period, if applicable. Participants who have missed > 1 dose of treatment during the Treatment Period are not eligible for the Extension Period (see [Section 6.3](#)).
- ^f A full physical examination will be performed at Screening. Symptom-directed physical examinations will be conducted at all other visits.
- ^g Vital sign measurements (blood pressure, heart rate, respirations, body temperature, and pulse oximetry [SpO₂]; taken in supine position after 5-minute rest) will be taken at Screening and pre-dose during each visit. Vital sign measurements should be taken first if they coincide with the timing of a required blood draw. Height will be recorded at Screening only. Weight will be recorded at Screening, every dosing visit, and at Safety Follow-up.
- ^h Full history of PAH diagnosis, medications, and associated illness and disease.
- ⁱ Genetic testing (i.e., BMPR2) ([Section 9.17](#)).
- ^j An RHC procedure completed prior to joining the study may be utilized if it occurred within 6 weeks prior to D1. If more than 6 weeks prior to D1, then an RHC must be completed during the 28-day screening period ([Section 4.2](#)).
- ^k Week 24 RHC should be performed prior to Week 24 IMP administration. If RHC was performed as part of an EOT/ET visit, it does not need to be repeated at the Week 24 visit.
- ^l V/Q Scan will be performed at Screening if no historical scan was performed prior to Screening. If V/Q scan is not possible, a chest CT scan or pulmonary angiogram can be performed as outlined in ([Section 9.3.2](#) and [Section 9.3.3](#)). The selective pulmonary angiography will also be performed if the V/Q scan shows anything other than “normal” or “low-probability” of chronic thromboembolic disease. In cases where selective pulmonary angiography is unable to be performed, the local standard of care to rule out chronic pulmonary thromboembolic disease is allowed.
- ^m PFTs will be completed only if a test is not available within 180 days prior to the Screening Visit.
- ⁿ For participants of childbearing potential only; a serum pregnancy test must be performed at Screening. During the study, pregnancy tests may be serum or urine and will be performed at all other times indicated. If urine test is positive, confirmatory serum test is required, and dosing should be withheld until the serum test is negative.
- ^o ECG measurements are to be completed at Screening, pre-dose and 2 hours post-dose ($\pm$ 15 minutes) on D1, and pre-dose at every subsequent clinic visit.
- ^p Echocardiograms are to be done per local standards and to be completed prior to the 6MWT. In addition to the time points indicated in the table, an echocardiogram must be performed if a participant has a clinical worsening event (see [Section 9.7](#)). For participants in the 1.5 mg/kg or Placebo arms who will continue to receive study drug, the echocardiogram must be performed Q4W (and reviewed to confirm that there is no Pericardial effusion) prior to study

drug administration at each dosing visit. For participants no longer receiving study drug, echocardiograms should be performed every 12 weeks, or more frequently, if clinically indicated. The specific echocardiogram parameters that must be collected can be found in [Section 9.11](#). See [Section 6.3](#) for additional required echocardiograms and dose modifications if Pericardial effusion is present.

- ^q Clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis) and ADA sampling will be performed pre-dose when assessed on dosing days. All participants will have coagulation performed at Screening and D1. Subsequent evaluations are only performed on participants taking anti-coagulation medication.
- ^r PK samples will be collected at pre-dose and 2 hours post-dose ($\pm$ 5 minutes) on D1, and pre-dose at every subsequent clinic visit.
- ^s A listing of planned biomarker assessments are available in [Section 9.15](#) and [Appendix 3](#), however other biomarkers may be evaluated as determined by additional data. On days when IMP is administered, a biomarker blood sample should be collected within 1 hour prior to dosing. NT-proBNP to be collected at Visits 1, 3, 5, 6, 7, 9, 10, 12, and EOS (if applicable); BSAP to be collected at Visits 1, 3, 5, and 11; CTGF, galectin, and osteopontin to be collected at Visits 1, 7, and 12.
- ^t 6MWT during Screening Period must be performed twice, at least 4 hours but no longer than 1 week apart. 6MWT has to be performed before study drug administration during dosing visits. 6MWT may also be done twice based on criteria outlined for clinical worsening ([Section 9.7](#)). See [Appendix 5](#). If occurring on the same day, 6MWT should be performed before RHC.
- ^u WHO/NYHA FC will be assessed prior to dosing at the denoted study visits. See [Appendix 4](#).
- ^v If occurring on the same day, QoL assessments should be performed prior to other assessments.
- ^w Participants should wear the actigraphy device for a minimum of 14 days during the Screening period to establish a baseline.

Schedule of Assessments – Extension Period

Study Visit ^a (Week)	Extension Period					EOS/ Safety Follow-Up (8 Weeks)
	V12 ^b (Wk24)	V13, V17, V21, V25, V29 (Wk28, 44, 60, 76, 92)	V14, V16, V18, V20, V22, V24, V26, V28 (Wk32, 40, 48, 56, 64, 72, 80, 88)	V15, V19, V23, V27 (Wk36, 52, 68, 84)	V30 EOT/ET (Wk96)	
Day	D169 ±5 Days	D197, D309, D421, D533, D645 Each ±5 Days	D225, D281, D337, D393, D449, D505, D561, D617 Each ±5 Days	D253, D365, D477, D589 Each ±5 Days	D673 ±5 Days	56 Days (±5 Days) After Last Dose of IMP
Inclusion/exclusion criteria	X					
Physical examination ^c	X	X	X	X	X	X
Vital signs ^d	X	X	X	X	X	X
Right heart catheterization	X ^e				X ^e	
Pregnancy test ^f	X	X	X	X	X	X
12-lead electrocardiogram ^g	X		X		X	X
Echocardiogram ^h	X	X	X	X	X	X
Clinical laboratory tests ⁱ	X	X	X	X	X	X
ADA assessment ^j	X	X	X	X	X	X
PK assessment ^j	X	X	X	X	X	
Biomarker assessments ^k	X	X	X	X	X	X
IMP administration	X	X	X	X		
Prior/concomitant medications	X					X

Schedule of Assessments – Extension Period (Continued)

Study Visit ^a (Week)	Extension Period					EOS/ Safety Follow-Up (8 Weeks)
	V12 ^b (Wk24)	V13, V17, V21, V25, V29 (Wk28, 44, 60, 76, 92)	V14, V16, V18, V20, V22, V24, V26, V28 (Wk32, 40, 48, 56, 64, 72, 80, 88)	V15, V19, V23, V27 (Wk36, 52, 68, 84)	V30 EOT/ET (Wk96)	
Day	D169 ±5 Days	D197, D309, D421, D533, D645 Each ±5 Days	D225, D281, D337, D393, D449, D505, D561, D617 Each ±5 Days	D253, D365, D477, D589 Each ±5 Days	D673 ±5 Days	56 Days (±5 Days) After Last Dose of IMP
Adverse event and clinical worsening reporting	X					X
6-minute walk test ^l	X		X		X	
WHO/NYHA FC assessment ^m	X	X	X	X	X	
PAH-SYMPACT	X			X	X	
EmPHasis-10 questionnaire	X			X	X	
Actigraphy	X					

Abbreviations: 6MWT = 6-minute walk test; ADA = anti-drug antibody; CTGF = connective tissue growth factor; D = day; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; IMP = investigational medicinal product; NT-proBNP = N-terminal pro hormone B-type natriuretic peptide; NYHA FC = New York Heart Association functional class; PAH = pulmonary arterial hypertension; PK = pharmacokinetic(s); RHC = right heart catheterization; SYMPACT = symptoms and impact; V = visit; Wk = week; WHO = World Health Organization; WOCBP = women of childbearing potential.

‡ At the time the Dear Investigator Letter is received regarding the changes made with Protocol Amendment Version 6.0, all participants in Arm 2 and Arm 3, along with participants in Arm 4 who have crossed over to 3.0 mg/kg, will be unblinded, must have an echocardiogram and other EOT/ET assessments, and must halt dosing. In addition to scheduled echocardiograms, all other participants may have additional echocardiograms at the Investigator's discretion.

^a Visits may be completed over multiple days, provided they are within the allowable visit window.

^b D169 (Wk 24/V12) is the beginning of the Extension Period for those participants who continue to the extension phase of the study. Participants who have been receiving Placebo will initiate treatment with the 3.0 mg/kg KER-012 dose and continue on background PAH therapy while participants who have been receiving KER-012 will continue at their current dose level and background PAH therapy.

^c Symptom-directed physical examinations will be conducted at all Extension Period visits.

^d Vital sign measurements (blood pressure, heart rate, respirations, body temperature, and pulse oximetry [SpO₂]; taken in supine position after 5-minute rest) will be taken at pre-dose during each visit. Vital sign measurements should be taken first if they coincide with the timing of a required blood draw. Weight will be recorded at every visit.

- ^e Week 24 RHC should be performed prior to Week 24 IMP administration. If RHC was performed as part of an EOT/ET visit, it does not need to be repeated at the Week 96 visit.
- ^f For WOCBP only (refer to [Appendix 6](#) for definition of fertility): Either a serum or urine pregnancy test may be completed during the Extension Period. If urine test is positive, confirmatory serum test is required, and dosing should be withheld until the serum test is negative.
- ^g Safety ECG measurements are to be completed at pre-dose at every clinic visit.
- ^h In addition to the time points indicated in the table, an echocardiogram must be performed if a participant has a clinical worsening event (see [Section 9.7](#)). For participants in the 1.5 mg/kg or placebo arms who will continue to receive study drug, the echocardiogram must be performed Q4W (and reviewed to confirm that there is no Pericardial effusion) prior to study drug administration for each dosing visit. For participants no longer receiving study drug, echocardiograms should be performed every 12 weeks, or more frequently, if clinically indicated. The specific echocardiogram parameters that must be collected can be found in [Section 9.11](#). See [Section 6.3](#) for additional required echocardiograms and dose modifications if Pericardial effusion is present.
- ⁱ Clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis) and ADA sampling will be performed pre-dose on dosing days. During the Extension Period, coagulation is only performed on participants taking anti-coagulation medication.
- ^j PK samples will be collected pre-dose on dosing days.
- ^k A listing of planned biomarker assessments are available in [Section 9.15](#) and [Appendix 3](#), however other biomarkers may be evaluated as determined by additional data. Biomarker blood sample should be collected within 1 hour prior to dosing. NT-proBNP to be collected at Visits 12, 15, 18, 21, 24, 27, and 30, and EOS (if applicable); CTGF, galectin, and osteopontin to be collected at Visits 12, 18, 24, and 30.
- ^l 6WMT may be done twice based on criteria outlined for clinical worsening ([Section 9.7](#)) and are to be completed at Visits 12, 18, and 24 (18 months post study start), and 30 (24 months post study start).
- ^m WHO/NYHA FC will be assessed prior to dosing at all visits.

2. INTRODUCTION

2.1. BACKGROUND AND SCIENTIFIC RATIONALE

KER-012 is being developed for the treatment of World Health Organization (WHO) Group 1 pulmonary hypertension (PH) (i.e., pulmonary arterial hypertension [PAH]). Dysregulated transforming growth factor-beta (TGF- β), specifically SMAD, signaling has been identified as a contributing factor to proliferative thickening of pulmonary arterioles, which leads to increased pressure and a compensatory right ventricular (RV) hypertrophy ultimately resulting in decompensated right heart failure. Dysregulation of SMAD signaling downstream of activin receptors results in an imbalance of SMAD2/3 and SMAD1/5/9, favoring SMAD2/3, which underlies vascular remodeling and leads to proliferative thickening of pulmonary arterioles in PAH (Lan, Massam, Kulkarni, & Lang, 2018; Yang et al., 2005; Yung et al., 2020).

KER-012 is a recombinant fusion protein comprised of a homodimer of a modified form of the human activin receptor type IIB (ActRIIB) extracellular domain (ECD) that is fused to a human immunoglobulin G1 (IgG1) Fc domain via a short linker sequence. The ECD is designed to trap select TGF- β superfamily ligands, including activin A, activin B, growth differentiation factor 8 (GDF8) and GDF11, which have been implicated in PAH (Long et al., 2015; Nikolic et al., 2019; Yndestad et al., 2009). KER-012 was designed with specificity to maximally inhibit SMAD2/3 (pro-proliferative) signaling, while permitting signaling of SMAD1/5/9 (anti-proliferative). This trapping is expected to rebalance the defective SMAD signaling in PAH and thereby potentially delay or reverse disease progression.

2.2. PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) is a debilitating disorder characterized by elevated pulmonary vascular resistance (PVR) due to severe constriction and progressive obliteration of pulmonary vessels, resulting in diminished oxygenation, impaired cardiac output, and RV overload (Tielemans, Delcroix, Belge, & Quarcq, 2019). The pathology of PAH is driven by endothelial dysfunction and vascular remodeling, which leads to increased wall thickening and resistance to blood flow.

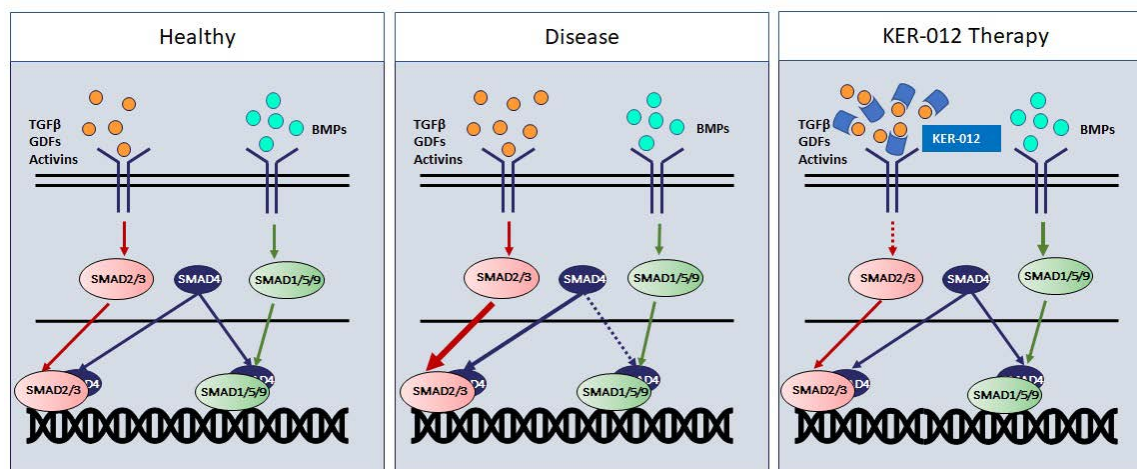
While the key physiologic and pathologic features of PAH include vasoconstriction, fibrosis, and vascular smooth muscle cell proliferation and inflammation, most currently approved therapies primarily target vasodilation. Approved PAH therapies include prostacyclin pathway agonists, endothelin receptor antagonists, and nitric oxide-cycle guanosine monophosphate enhancers (Galie et al., 2016). These therapies may modestly improve a patient's functional status, and in some cases may improve survival; however, none appear to halt or reverse disease progression. Accordingly, there is a significant unmet medical need for a PAH treatment that primarily targets the inflammatory, proliferative, and antifibrotic pathological processes of PAH.

Heritable forms of PAH are characterized by loss-of-function mutations in the bone morphogenic protein type 2 receptor (BMPR2), a member of the TGF- β superfamily. Mutations in ligands of

BMPR2, BMP9/GDF2 as well as the BMP-responsive genes, SMAD4 and SMAD9, have been implicated in deficient BMP signaling in PAH (Gräf et al., 2018; Soubrier et al., 2013). Alterations in the BMPR2 signaling pathway have also been linked to development of PAH in participants without a genetic predisposition (Guignabert & Humbert, 2021). Human PAH lung tissue and experimental PAH have shown diminished BMPR2 expression and BMP signaling in the presence or absence of BMPR2 loss-of-function mutations (Hodgson et al., 2021; Wang et al., 2016). Increased activin A levels, another TGF- β superfamily ligand, have been found in the PAH patients, as well as been shown to be overexpressed in the lungs from hypoxia-induced PH mice (Yndestad et al., 2009). Together, these observations support the important role for the TGF- β family in the development of PAH.

The TGF- β superfamily is comprised of > 30 ligands that can be broadly grouped into subfamilies including TGF- β s, activins, GDFs, and BMPs. These factors are critical in cell differentiation and the development and maintenance of many tissue systems. The signaling of these ligands occurs via the SMAD family of proteins and, in general, ligands act through 1 of 2 canonical pathways, SMAD1/5/9 or SMAD2/3. The BMP family, including BMP9, predominately signals through SMAD1/5/9 (anti-proliferative pathway), whereas activin and GDF ligands (including activin A, activin B, GDF8, and GDF11), signal through SMAD2/3 (pro-proliferative pathway). Ligands signaling through either of these SMAD pathways require binding of the co-SMAD (SMAD4) for signal transduction. The common need for binding of SMAD4 in both pathways results in competition between the two such that signaling through one pathway results in reduction of signaling through the other pathway. Balanced signaling between SMAD1/5/9 and SMAD2/3 is important to maintain cellular tissue homeostasis, and imbalanced signaling has been implicated in multiple disease states, including PAH (Ning et al., 2019; Yamazaki et al., 2009) (Figure 1).

Figure 1: KER-012 Designed to Rebalance Altered SMAD Signaling in Disease States



Abbreviations: BMP=bone morphogenetic protein; GDF=growth and differentiation factors; TGF β =transforming growth factor beta.

Dysregulation of TGF- β SMAD signaling downstream of activin receptors results in an imbalance of SMAD2/3 and SMAD1/5/9, which underlies vascular remodeling and leads to proliferative thickening of pulmonary arterioles in PAH and leads to increased pressure and a compensatory RV hypertrophy ultimately resulting in decompensated right heart failure (Lan et al., 2018; Yang et al., 2005; Yung et al., 2020). Mechanistically, insufficient signaling through SMAD1/5/9 (anti-proliferative) favors signaling through SMAD2/3 (pro-proliferative) and leads to enhanced myogenic and fibrogenic differentiation of blood vessels. The proliferation and differentiation cause pulmonary vascular remodeling involving arteriole wall thickening, which is a hallmark of PAH disease progression (Harper, Reynolds, Bonder, & Reynolds, 2016).

Thus, an investigational agent that could rebalance the aberrant SMAD signaling observed in PAH represents a promising therapeutic option.

2.3. STUDY RATIONALE

Study KER-012-A201 is Phase 2, double-blind, randomized, placebo-controlled study to determine the efficacy and safety of KER-012 compared to Placebo in adults with PAH (WHO Group 1 PH) on stable background PAH therapy. The study is divided into the Screening Period, Treatment Period, Extension Period, and Follow-Up Period.

The design of this study will control bias in the assignment of study treatment as well as in data interpretation, particularly of the measures that may have clinical variability (e.g., PVR and 6-minute walk distance [6MWD]).

2.3.1. Rationale for the Use of KER-012 in Treating PAH

KER-012 is a recombinant fusion protein that is comprised of a homodimer of a modified form of the human ActRIIB ECD fused to a human IgG1 Fc domain via a short linker sequence. The ECD acts as a soluble ligand trap for SMAD2/3-signaling ligands in the TGF- β superfamily, including activins A and B, GDF8, and GDF11. KER-012 is designed to target ligands that bind and signal through ActRIIs in a manner expected to be permissive for SMAD1/5/9 activity, potentially rebalancing the defective signaling in PAH. Furthermore, because activin A is known to decrease BMPR2 (Ryanto et al., 2021), inhibition of activin A by KER-012 could result in increased BMPR2 protein levels, which would be beneficial in treating PAH.

Rebalancing TGF- β signaling has been shown to be beneficial, with multiple therapeutic strategies targeting reduction of SMAD2/3 (pro-proliferative) signaling and/or facilitating SMAD1/5/9 (anti-proliferative) signaling providing benefit in participants with PAH (Long et al., 2009; Thomas et al., 2009; Yung et al., 2016; Yung et al., 2020; Zaiman et al., 2008). One investigational therapy currently being evaluated for the treatment of PAH is sotatercept, a ligand trap that binds and inhibits GDF11 and activins A and B that signal through SMAD2/3. In a Phase 3 study in PAH patients receiving stable background therapy, sotatercept treatment resulted in improvement in exercise capacity as assessed by 6MWD vs placebo. There were also improvements seen in PVR, WHO functional class (FC), and time to clinical worsening (Hoeper et al., 2022). As in the Phase 2 PAH study (M. Humbert et al., 2021), common adverse events (AEs) in the Phase 3 study included headache, diarrhea, dizziness and thrombocytopenia.

Adverse events of special interest, namely telangiectasias and bleeding events (epistaxis and bleeding gums), were also observed, thus adding further evidence that the intended effect of sotatercept on erythropoiesis may be dose-limiting ([Carrancio et al., 2014](#)) outside of diseases for which the erythropoietic effect is sought.

A Phase 1 study in healthy, postmenopausal women was recently completed (Study KER012-HV-101). KER-012 at single doses up to 5.0 mg/kg and multiple doses up to 4.5 mg/kg were generally well tolerated. Preliminary data indicate that KER-012, as intended by design, demonstrated maximal TGF- β signaling pathway target engagement by reducing follicle-stimulating hormone (FSH) and increasing bone specific alkaline phosphatase (BSAP). These data suggest that sequestration of activins by KER-012 potentially shifts the balance in favor of signaling via anti-proliferative SMAD1/5/9 pathway, which would then, in the background of PAH, be expected to result in vascular reverse-remodeling and clinical cardiopulmonary improvements in participants with PAH (For additional Phase 1 study information, refer to the Investigator's Brochure).

2.3.2. Rationale for Study Endpoints

The primary endpoint of change in PVR at 24 weeks from baseline is designed to assess reduction in resistance to flow across the pulmonary vasculature, which is anticipated based on the activity of KER-012 in animal models and the hypothesized mechanism of action and activity of KER-012 in participants with PAH. Secondary and exploratory objectives include evaluation of changes in 6MWD, changes in hemodynamic parameters, clinical worsening, changes in European Society of Cardiology (ESC)/European Respiratory Society (ERC) risk assessment, N-terminal pro hormone B-type natriuretic peptide (NT-proBNP) and other PAH-related biomarkers, pharmacokinetics (PK), and safety. ESC/ERC and other risk scores have been established as having significant mortality prognostic capacity ([Benza et al., 2021](#); [Galie et al., 2016](#); [Hoeper et al., 2022](#)).

2.3.3. Rationale for Comparator

The choice of placebo as the comparator is to enable robust assessments of the effectiveness and safety of KER-012 in a controlled setting. Participants in the Placebo group (and KER-012 groups) will be on stable doses of PAH background therapy prior to study entry and will maintain those therapies during the study ([Section 8.2.1](#)) thus ensuring that participants randomized to the Placebo arm are treated and managed as per established treatment guidelines.

2.4. PROFILE OF KER-012 AND PREVIOUS EXPERIENCE

2.4.1. Nonclinical Experience with KER-012

A robust nonclinical pharmacology package evaluating the effects of KER-012 has been conducted. Several rodent models have been utilized to evaluate the pharmacological activity of KER-012 for the treatment of PAH, bone loss, and erythropoietic effects. In these studies, KER-012 exhibited beneficial effects of reducing the development of PAH-associated pulmonary and

right ventricular dysfunction in cardiac inflammation and fibrosis, pulmonary remodeling, and cardiac damage in rodent models of cardiopulmonary disease. Also, KER-012 prevented and reversed bone loss in rodent models.

In addition, Good Laboratory Practice, repeat-dose toxicology studies have been performed with KER-012 up to 2-months in duration in Sprague-Dawley rats and up to 6-months in duration in cynomolgus monkeys. There were no KER-012-related adverse effects or changes in safety pharmacology parameters (central nervous system, respiratory, or cardiovascular) in any study. Results from the 2 embryo-fetal developmental studies in animals indicated the potential for KER-012 embryo-fetal toxicity.

For additional details please see the current KER-012 Investigator's Brochure.

2.4.2. Clinical Studies with KER-012

A Phase 1, first-in-human (FIH) study, KER-012-HV-101, was designed as a 2-part randomized, double-blind, placebo-controlled, single-ascending dose (SAD, Part 1) and multiple-ascending dose study (MAD, Part 2) of KER-012 in healthy postmenopausal women. This study was conducted in Australia. A starting dose of 0.75 mg/kg was supported by predicted human PK properties, expected human efficacious doses, and appropriate safety margins.

The primary objective of the study was to evaluate the safety and tolerability of escalating doses of KER-012 administered as single and multiple subcutaneous (SC) doses in healthy postmenopausal women. In addition, the study explored the effects of KER-012 on muscle, bone, and adipose tissues, and determined the PK/pharmacodynamic (PD) relationship of those effects.

A total of 40 participants were enrolled in Part 1 (SAD) of the study; of these, 32 received a single SC dose of KER-012 and 8 received a single SC dose of Placebo. One participant withdrew consent after receiving a single 1.5 mg/kg dose of KER-012 and did not complete the Safety Follow-up. All participants were females who were not of childbearing potential.

A total of 26 participants were enrolled in Part 2 (MAD) of the study; of these, 19 received 3 SC doses of KER-012 every 4 weeks (Q4W) (8 received 0.75 mg/kg, 5 received 1.5 mg/kg, and 6 received 4.5 mg/kg) and 5 received 3 SC doses of Placebo Q4W (on Days 1, 29, and 57). One participant withdrew consent after receiving 2 doses of 1.5 mg/kg KER-012. One participant discontinued the study after receiving 2 doses of Placebo due to Investigator's decision related to an AE of Grade 1 extrasystoles. All participants were females who were not of childbearing potential.

In healthy postmenopausal women, KER-012 has been generally well tolerated in Part 1 (SAD) and Part 2 (MAD). There were no dose-limiting toxicities, no treatment-emergent adverse events (TEAEs) that were Common Terminology Criteria for Adverse Events (CTCAE) Grade $\geq$ 3, no treatment-emergent serious adverse events (TESAEs) with KER-012 administration (1 TESAE in the Placebo arm), no discontinuations due to TEAEs with KER-012 administration (1 discontinuation due to TEAE in the placebo arm), and no TEAEs leading to death, either in Part 1 (SAD) or Part 2 (MAD). Injection site reactions (ISRs) were the most frequently reported TEAEs. Of the ISRs reported, injection site erythema had the highest incidence; these erythema

events were localized, mild to moderate in severity, self-limiting, and not associated with systemic hypersensitivity or anaphylaxis reactions.

Following single and multiple (3 doses) SC administration of KER-012, the median time from dosing to maximum observed concentration (T_{max}) ranged between 2 to 4 days. Serum KER-012 exposure was generally dose proportional between low to mid dose, while exposure achieved at the high dose levels was somewhat less than dose proportional. The median elimination half-life ($t_{1/2}$) was approximately 7 to 11 days, independent of dose. Apparent clearance (CL) was low, with mean CL values ranging between 0.9 and 1.8 L/day and mean apparent volume of distribution (V_d) between approximately 11 to 25 L.

Consistent with the design of KER-012 to inhibit activins and GDFs in the bone, which potentially results in reduced SMAD2/3 signaling and shifts the balance in favor of signaling via the BMP pathway (SMAD1/5/9), KER-012 administration elicited rapid and robust increases in multiple bone formation biomarkers starting at the lowest dose tested. Both as a single dose and as multiple Q4W doses, KER-012 increased BSAP, suggesting activation/recruitment of bone forming osteoblasts and increased osteocalcin suggesting osteoblastic bone formation. In addition to bone turnover markers, dose-dependent reductions in FSH were also observed after the first dose in both Part 1 (SAD) and Part 2 (MAD), further suggestive of target engagement via inhibition of activin as designed. No clinically meaningful changes in hemoglobin or red blood cells were observed, supportive of a tolerability profile suitable for further development in participants with PAH.

For additional details please see the current KER-012 Investigator's Brochure.

2.5. BENEFIT/RISK ASSESSMENT

Study KER-012-A201 is designed to evaluate the safety, tolerability, efficacy, PK, and PD of KER-012 in combination with current background therapy in participants with PAH.

It is not known if participants in this study will benefit from treatment with KER-012. However, in the Phase 1 FIH study, a robust PD effect on markers of activin inhibition (BSAP and FSH) was demonstrated, suggestive of target pathway engagement at the proposed Phase 2 dose levels. Participants randomized to the KER-012 arms may therefore experience improvement in their PAH as evident by reduction in PVR and other associated endpoints. Overall, the increased understanding of the effect of KER-012 in this population may potentially result in new treatment options for participants with PAH that go behind the current standard therapies.

The potential risks to study participants associated with KER-012 are described in the Guidance to Investigator section of the Investigator's Brochure and will be provided in the Informed Consent Form (ICF). To evaluate and mitigate the potential risk of KER-012, the following safety measures and monitoring requirements will be implemented:

- Developmental and reproductive effects: There are no clinical data available regarding effects of KER-012 on reproductive function or on the use of KER-012 in pregnant women. Based on animal studies and mechanism of action (on-target inhibition of activin), KER-012 is anticipated to reduce reproductive function in both men and women. Results from the 2 embryo-fetal developmental studies in animals indicated the potential for KER-012 embryo-fetal toxicity. Study documents provide recommendations to investigators for pregnancy testing, pregnancy monitoring and informing the participants about options for cryopreservation of germ cells (sperms or ova) and refraining from donating germ cells for the protocol-specified time period. Males and females of childbearing potential will be required to follow the contraception guidelines outlined in the study protocol.
- Anti-drug antibodies (ADA): As with all biologics, there is potential for ADA that can be associated with increased drug clearance and hypersensitivity reactions. There was no apparent difference in the incidence of the AEs between the participants testing ADA positive and those testing ADA negative in the Phase 1 Study KER012-HV-101. Safety effects will be monitored closely through AE reporting and periodic review of AE data including but not limited to clinical laboratory tests, including assay for ADA over the course of the study, vital signs, and physical examinations. ADA will be measured throughout the study and best efforts will be made to monitor the participant's ADAs until they return to baseline.
- Injection site reactions (ISRs): As with many drugs administered SC, ISRs may occur following administration of KER-012 that are expected to be mild and transient in nature. To date, these reactions have presented following multiple doses, have been mostly limited to erythema, and have resolved within 1 to 21 days. Safety effects will be monitored closely through AE reporting and periodic review of AE data.
- Pericardial effusions: Based on a review of unblinded study data by the independent Data Monitoring Committee (DMC) and select unblinded Sponsor team members who were not part of the direct study team, an increased frequency of Pericardial effusion events in participants being treated at the dose levels of 3.0 mg/kg and 4.5 mg/kg of KER-012 in Study KER-012-A201 was observed. Considering this observation, as of Protocol Amendment Version 6.0, treatment of all participants assigned to the KER-012 4.5 mg/kg and KER-012 3.0 mg/kg arms, along with participants assigned to the Placebo arm who crossed over to 3.0 mg/kg at Week 24, will be halted.

The benefit-risk potential was assessed for the 1.5 mg/kg KER-012 dose through a review of available unblinded data and information on an interim basis. Based on this assessment and in agreement with the DMC, it was decided to continue dosing in the 1.5 mg/kg KER-012 and Placebo arms and to maintain blinding for these arms during the 24-week Treatment Period. Participants assigned to the Placebo arm 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 1.5 mg/kg will be open-label during the Extension Period. Safety events will continue to be monitored closely through echocardiograms and targeted safety information will be requested as part of the adverse event of special interest (AESI) reporting.

The protocol for the proposed study will identify potential risks associated with KER-012 treatment and these can be mitigated by routine and enhanced pharmacovigilance monitoring. In addition, an independent DMC will be convened at regular intervals to observe unblinded safety and efficacy data throughout the conduct of the study. Thus, exposure of participants in this study is justified by the potential benefits that may be observed in participants with PAH by continued development of KER-012.

More detailed information about the known and expected benefits and risks and possible adverse events of KER-012 may be found in the current KER-012 Investigator's Brochure.

3. 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 6MWD at Week 24
Secondary*	
<u>Treatment Period:</u> - 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 FC 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	<u>Treatment Period:</u> - Incidence of TEAEs, treatment-related TEAEs, and discontinuations due to TEAEs; change from baseline in clinical laboratory values, vital signs, and electrocardiogram (ECG); incidence of ADA - Change from baseline in mean pulmonary artery pressure (mPAP), cardiac output (CO), cardiac index (CI), pulmonary artery wedge pressure (PAWP), mean right atrial pressure (mRAP), 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 FC/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

Objectives	Endpoints
<u>Extension Period:</u> • 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 FC 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	<u>Extension Period:</u> • 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, mRAP, SvO₂, SV, SVI, and PAC at Week 96 • Change from baseline in NT-proBNP by visit • Proportion of participants who achieved improvement from baseline in NYHA FC/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/ERS 4-strata risk category assessment
Exploratory *	
<u>Treatment and Extension Period:</u> • 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)	<u>Treatment and Extension Period:</u> • Change from baseline in overall activity as measured by actigraphy (Section 9.12.3) • 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 (Section 9.14) • 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.

4. INVESTIGATIONAL PLAN

4.1. STUDY OVERVIEW AND PLAN

Study KER-012-A201 is Phase 2, double-blind, randomized, placebo-controlled study to determine the efficacy and safety of KER-012 compared to Placebo in adults with PAH (WHO Group 1 PH) on stable background PAH therapy. The study is divided into the Screening Period, Treatment Period, Extension Period, and Follow-up Period.

The Study Design Schematic is available in [Section 1.2](#). Refer to [Section 9](#) for a complete list of study assessments.

4.2. SCREENING PERIOD

Upon giving written informed consent, participants will enter the Screening Period to determine eligibility. During the Screening Period, participants will undergo assessments to determine eligibility for the randomized study and assessments for baseline measures, including right heart catheterization (RHC) for assessment of baseline PVR (if participants do not have a recent RHC defined as being performed within 6 weeks of planned Day 1). RHC must have been performed in accordance with the procedures outlined in the RHC Manual. Procedures also include review of participant's medical, surgical, and family history; collecting of demographics, race, and ethnicity; and medical record requests for external procedures. All Screening activities are to be completed within 28 days prior to dosing on Day 1 (unless otherwise stated). RHC results will be adjudicated by the central reviewer and then these results will be used to determine eligibility and stratification by the Investigator. Screening procedures are to be performed as per the Schedule of Assessments (SOA) ([Section 1.3](#)).

4.3. TREATMENT PERIOD

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) 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 RHC Manual, and the eligibility of the participant will be determined by the Investigator before randomization. Participants with a diagnosis of PAH on stable PAH background therapy 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. Certain visits may be conducted via home visit as described in [Section 1.3](#) and [Section 9.19](#).

4.4. EXTENSION PERIOD

Participants who complete the Treatment Period will continue into a 72-week Extension Period, for a total of 96 weeks on treatment. Participants who were in the Placebo group will begin 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.

4.5. DATA MONITORING COMMITTEE

An external, independent DMC will be established to review unblinded safety and efficacy data after at least 10% of participants have been enrolled and completed Visit 6, and at periodic intervals (approximately 25%, 50% and 75% enrolled) thereafter. Concurrently, the DMC will review the safety data of participants enrolled in the Extension Period. Upon completion of the Treatment Period enrollment, the DMC will continue to review safety data for participants in the Extension Period on a semiannual basis. Based on these reviews, the DMC will make a recommendation to the Sponsor to continue the study, continue with modification, or to terminate the study. In addition, the DMC may be asked by the Sponsor to independently review data on an ad hoc basis.

A detailed DMC Charter will provide further details of membership, role, function, responsibilities of the committee, and frequency of meetings.

4.6. FOLLOW-UP PERIOD

Participants will enter into a Follow-Up Period for 8 weeks after the last dose of study treatment in either the Treatment Period or the Extension Period.

Participants who discontinue investigational medicinal product (IMP) during the Treatment Period will have an End of Treatment (EOT)/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 (as indicated in [Section 1.3](#)) through the end of the study, unless they withdraw from the study.

Participants who withdraw from 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.

4.7. OVERALL PARTICIPATION AND STUDY DURATION

The Treatment Period is expected to be 24 weeks, with an Extension Period of 72 weeks, for a total of 96 weeks (i.e., approximately 2 years) on treatment. Screening assessments will be performed within 28 days prior to the first dose of the IMP.

For participants who complete the Extension Period, consultation with their treating physician is recommended to determine the appropriate treatment based on local standard of care. Ongoing treatment with KER-012 may be available as a part of another clinical study or post-study access program.

4.8. DOSE JUSTIFICATION

The doses proposed for the Phase 2 study are 1.5 mg/kg, 3 mg/kg, and 4.5 mg/kg KER-012, administered SC Q4W.

As discussed in [Section 2.4.2](#), all KER-012 doses in Part 1 (SAD) and Part 2 (MAD) cohorts were generally well tolerated in the Phase 1 study, with no clinically significant dose dependent TEAEs. While there was a higher incidence of ISRs (5/6 participants [83%]) at the 4.5 mg dose, all ISRs were mild to moderate in severity, transient, and limited to local erythema with no evidence of systemic hypersensitivity or anaphylaxis. No dose-dependent clinically significant effects on any laboratory parameters, including hemoglobin, were seen at these doses, nor were there any clinically significant effects on vital signs or ECG findings. Additionally, the proposed study includes an independent DMC that will monitor safety data frequently throughout the study as outlined in [Section 4.5](#).

In the Phase 1 study, robust PD changes indicating target engagement as result of TGF- β ligand trapping were observed. Specifically, dose-dependent increases in BSAP were observed at the proposed doses following the initial dose and with each repeated dose (See Investigator's Brochure for additional details). Importantly, significant changes in BSAP were observed starting at the proposed low dose of 1.5 mg/kg.

Administration of KER-012 also elicited a dose-dependent reduction in FSH after the first dose in both the SAD and MAD portions of the study, with maximal suppression observed at the highest doses tested, further suggestive of achieving robust target engagement. A correlation between systemic exposure (maximum concentration [C_{max}] and area under the concentration time curve from time 0 to last measured concentration [AUC_{0-last}]) and 2 distinct PD parameters (FSH and BSAP) in healthy postmenopausal women is suggestive that higher doses (i.e., 1.5, 3, and 4.5 mg/kg vs the lowest Phase 1 dose tested [0.75 mg/kg]) are likely to result in a pharmacological effect in participants with PAH and supports the selection of doses proposed for our planned Phase 2 study.

A Q4W dosing regimen is proposed, as it was the dosing interval used in the Phase 1 study. In addition, the available nonclinical toxicity data provide adequate assurance of the safety of this dosing interval. While the terminal elimination half-life of KER-012 was approximately 7 to 11 days in the Phase 1 study, there was no evidence of serum KER-012 accumulation across the proposed dose range following administration in a Q4W regimen.

4.9. END OF STUDY DEFINITION

End of Study (EOS) is defined as completion of the last participant completing the last visit or last procedure shown in the SOA ([Section 1.3](#)).

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

To be eligible for study entry, participants must satisfy all the following criteria:

1. Adult participants ≥ 18 years of age.
2. Primary diagnosis of symptomatic PAH (WHO Group 1 PAH) in any of the following subgroups:
 - Idiopathic pulmonary arterial hypertension (IPAH)
 - Hereditary pulmonary arterial hypertension (HPAH)
 - Drug or toxin-induced PAH
 - PAH associated with:
 - i. Connective tissue disease (CTD),
 - ii. Congenital systemic-pulmonary intracardiac shunt (must have surgical correction or repair with closure device at least 1 year prior to Screening, AND have no, or clinically insignificant, shunt fraction in the opinion of Investigator [$1.0 \leq \text{pulmonary-systemic flow ratio} \leq 1.5$])
3. Has the following hemodynamic parameters that are consistent with the diagnosis of PAH:
 - mPAP > 20 mmHg at rest, AND
 - PAWP ≤ 15 mmHg, AND
 - PVR ≥ 5 Wood units ($400 \text{ dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$).

Note: RHC to assess eligibility performed within 6 weeks from Visit 1 (Day 1).

4. Has WHO/NYHA FC II or III symptoms as assessed by the Investigator at Screening and Day 1.
5. Participant must be on a stable PAH background therapy with either an endothelin-receptor antagonist (ERA) and/or a phosphodiesterase-5 inhibitor (PDE5-I) or soluble guanylate cyclase (sGC) stimulator and/or prostacyclin analogue or receptor agonist (oral/inhaled/SC/intravenous [IV]), as further described in [Section 8.2.1](#).
 - Stable therapy is defined as no change in dose/regimen for at least 90 days prior to baseline and would be expected to be maintained for the duration of the study.
 - Participants may be either on PDE5-I or an sGC stimulator, but not on both nitric oxide pathway agents.
 - If participant's PAH therapy does not include a PDE5-I, the use of a PDE5-I for erectile dysfunction is permitted if dosing does not exceed 3 times a week and is not taken within 48 hours prior to the study visits.
 - Received no IV inotropes (e.g., dobutamine, dopamine, norepinephrine, vasopressin) within 30 days prior to the Screening period.

6. If participant is taking concomitant medications that may affect clinical PAH symptoms (i.e., calcium channel blockers, diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, digoxin, L-arginine supplements), the participant must be on a stable dose for at least 30 days prior to baseline, and the dose would be expected to be maintained during the study. Diuretics must be stable for at least 10 days prior to baseline.
7. 6MWD ≥ 150 and ≤ 500 meters repeated twice at Screening (measured at least 4 hours apart but no longer than 1 week), and both values within 15% of each other (calculated from the highest value) (see [Appendix 5](#)). Note: Both 6MWD values must be within the allowed range and not averaged. The last 6MWD performed must be the one used as the baseline value for purposes of assessing potential clinical worsening ([Section 9.7](#)).
8. Women of childbearing potential (WOCBP), defined as participants who have not undergone hysterectomy or bilateral oophorectomy or not had natural menopause (absence of menses for at least 24 consecutive months), must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative serum or urine hCG pregnancy test at all other study visits as indicated in the Schedule of Assessments ([Section 1.3](#)) and as clinically indicated.
9. WOCBP and male participants with a partner of childbearing potential must agree to use at least 1 highly effective contraception without interruption (as defined in [Appendix 6](#)), from the signing of the ICF at Screening, during the study treatment (including dose interruptions), and for at least 8 weeks after the last dose of study treatment.
10. Provide written (signed and dated) ICF before the initiation of any Screening tests or procedures.
 - Sites in Germany: see [Appendix A7-1.2](#)
11. Willing to comply with study visit schedule and all the protocol-related procedures and restrictions.

5.2. EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

1. Body mass index (BMI) ≥ 35 kg/m²
2. Have 3 or more of the following risk factors for left ventricular dysfunction:
 - a. BMI ≥ 30 kg/m²
 - b. History of systemic hypertension as evidenced by being on anti-hypertensives and sitting systolic blood pressure (BP) > 140 mmHg or sitting diastolic BP > 90 mmHg
 - c. History of diabetes mellitus
 - d. Recurrent or persistent atrial fibrillation
3. Based upon pulmonary function tests (PFTs) conducted at Screening or within 180 days prior to Screening, the participants must not have:

- a. Forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio < 0.70 AND/OR,
 - b. Total lung capacity (TLC) $< 60\%$ (predicted) or FVC $< 60\%$ (predicted), if plethysmography not available, AND,
 - i. If TLC or FVC is between 60% and 70% (predicted), confirmatory high-resolution computed tomography (CT) is required within 180 days prior to Screening to rule out moderate to severe interstitial lung disease as per Investigator interpretation.
 - a. A high-resolution CT chest scan is preferred but if not available at the clinical site, a CT chest scan is acceptable.
4. Evidence of thromboembolic disease assessed by ventilation-perfusion (V/Q) lung scan or other local standard of care diagnostic evaluation at the time of PAH diagnosis or after.
5. Ongoing, more than mild obstructive sleep apnea that is untreated.
6. Has uncontrolled systemic hypertension as evidenced by sitting systolic BP > 160 mmHg or sitting diastolic BP > 100 mmHg at Screening.
7. Systolic BP < 90 mmHg at Screening.
8. QT interval corrected by Fridericia (QTcF) recorded on ECG at Screening as follows:
 - a. Male participants with QTcF > 450 msec
 - b. Female participants with QTcF > 470 msec
 - c. Participants with intraventricular conduction delay defined as QRS > 110 msec will be excluded if QTcF is > 500 msec (both male and female).
 - d. Known personal or family history of long QTc syndrome
9. History of cerebrovascular accident within 3 months before Screening
10. History of cardiac disease including:
 - a. Restrictive or obstructive cardiomyopathy
 - b. Systolic cardiomyopathy with left ventricular ejection fraction $< 45\%$ on echocardiogram (if one has been performed prior to Screening), diastolic heart failure, or acutely decompensated heart failure (diastolic or systolic) within 30 days prior to Screening
 - c. Moderate to severe aortic, or mitral valvular disease, according to the Investigator assessment
 - d. Historical evidence of myocardial infarction, angina, percutaneous coronary intervention, coronary artery bypass graft surgery, angiographic evidence of coronary artery disease ($> 50\%$ stenosis in at least 1 coronary artery), or positive stress test with imaging
11. Known history of portal hypertension or chronic liver disease, defined as mild-to-severe hepatic impairment (Child-Pugh Class A-C).

12. Confirmed active infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C.
 13. History of HIV infection–associated PAH.
 14. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3 \times$ upper limit of normal (ULN) or total bilirubin $\geq 2.0 \times$ ULN at Screening.
 15. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m² (CKD-EPI, [Levey et al. \(2009\)](#)) or requiring dialysis at Screening.
 16. Hemoglobin < 9 g/dL at Screening.
 17. History of opportunistic infection (e.g., invasive candidiasis or pneumocystis pneumonia) within 6 months prior to Screening or serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., septicemia) within 3 months prior to Screening.
 18. Prior heart or heart-lung transplants, active on the lung transplant list, or life expectancy of < 12 months per Investigator assessment.
 19. Diagnosis of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis.
 20. Initiation or discontinuation of an exercise program for cardiopulmonary rehabilitation within 90 days prior to baseline or planned initiation during the study.
 21. Prior participation in a KER-012 study or prior treatment with a therapy targeting TGF- β (e.g., sotatercept).
 22. Prior participation in another interventional clinical study with medicinal products within 30 days or 5 half-lives prior to Screening, whichever is longer.
 23. History of severe allergic or anaphylactic reaction or hypersensitivity to recombinant proteins or excipients in investigational product.
 24. Pregnant or breastfeeding female participants.
 25. History of active malignancy within 5 years prior to Screening, except for fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or ≤ 2 squamous cell carcinomas of the skin.
 26. History of clinically significant (as determined by the Investigator), non-PAH–related disease that may limit participation in the study in the opinion of the Investigator.
 27. Participants who are investigational site staff members directly involved in the conduct of the study and their immediate family members, site staff members otherwise supervised by the Investigator, or participants who are Sponsor or contract research organization (CRO) employees directly involved in the conduct of the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- Sites in France: see [Appendix A7-1.1](#)

5.2.1. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment. Certain electronic case report forms (eCRFs)

need to be completed for all participants who sign the informed consent. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from Regulatory Authorities. Minimal information includes demography, reason for screen failure (i.e., eligibility criteria not met), and study procedure-associated adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once with the approval of the study Medical Monitor (MM) or designee. Rescreened participants must be re-consented and will be assigned a new participant number. In addition, laboratory assessments can be independently repeated once within the Screening Period to determine participant eligibility. If laboratory assessments are repeated within the Screening Period, participant is not considered rescreened, and remains assigned the same participant number.

6. INVESTIGATIONAL MEDICINAL PRODUCT

IMP is defined as any investigational treatment, or Placebo, intended to be administered to a study participant according to the study protocol.

6.1. IMP(S) PREPARATION AND ADMINISTRATION

The unblinded pharmacist or designee will prepare the required volume per participant weight collected at each visit (mg/kg) in a syringe for administration by the site staff. The vials are allowed to equilibrate at room temperature (15-25°C) for 30 min to 1 hour prior to withdrawal into the syringe. Multiple syringes may be used to accommodate the dose/volume required. The syringes should be prefilled by the pharmacist or designee not to exceed 2.0 mL per syringe/injection site. The recommended SC injection site is the abdomen with rotation amongst quadrants and the thigh to accommodate volume of injections and/or alternate between different visits.

6.1.1. KER-012

[REDACTED] . It is supplied in a volume of 1.2 mL aseptically filled into 2R glass vials.

KER-012 will be manufactured, packaged, and labeled in accordance with Good Manufacturing Practice for Medicinal Products for use in human clinical trials, International Council for Harmonisation (ICH) Good Clinical Practice Guidelines (GCP) guidelines, and applicable laws/regulations, and provided with a certificate of analysis. Each package will bear a label conforming to regulatory guidelines that identify contents as an investigational drug.

KER-012 will be supplied to the study site's pharmacy for preparation for SC administration. KER-012 SC injections will be administered to participants by study staff at the clinical site and administration will be documented in the participant's eCRF. KER-012 is stable at ambient temperature for up to 8 hours and is compatible with polypropylene syringes.

6.1.2. Placebo

[REDACTED] will be supplied to the study site's pharmacy for preparation for SC administration. Placebo SC injections will be administered to participants by study staff at the clinical site and administration will be documented in the participant's eCRF. Placebo will be administered in the volume equivalent to the 3.0 mg/kg dose. Placebo is stable at ambient temperature for up to 8 hours and is compatible with polypropylene syringes.

6.2. IMP ADMINISTRATION AND SCHEDULE

All participants will receive KER-012 or Placebo as shown in Table 1 for the Treatment Period and in Table 2 for the Extension Period, as referenced in Section 4. The recommended SC injection site is the abdomen, with rotation amongst quadrants, and the thigh. No fasting or dietary restrictions are required for KER-012 or Placebo administration. Additional instructions are included in the Pharmacy Manual.

Table 1: Treatment Period IMP Administration Schedule (Double-blind)

IMP	Route of administration	Dose* (mg/kg)	Dose Frequency
KER-012	Subcutaneous, abdomen or thigh	Arm 1: 1.5 mg/kg Arm 2: 3.0 mg/kg* Arm 3: 4.5 mg/kg*	Q4W
Placebo	Subcutaneous, abdomen or thigh	Arm 4: Volume equivalent to 3.0 mg/kg	Q4W

Abbreviations: IMP = investigational medicinal product; Q4W = every 4 weeks (28 days)

* As of Protocol Amendment Version 6.0, treatment of all participants assigned to Arm 2 (3.0 mg/kg) and Arm 3 (4.5 mg/kg) will be halted.

Table 2: Extension Period IMP Administration Schedule (Open-label)

IMP	Route of administration	Dose (mg/kg)	Dose Frequency
KER-012	Subcutaneous, abdomen or thigh	Arm 1: 1.5 mg/kg Arm 2*: 3.0 mg/kg Arm 3**: 4.5 mg/kg	Q4W

Abbreviations: IMP = investigational medicinal product; Q4W = every 4 weeks (28 days)

* Includes roll-over from Treatment Period Placebo arm. As of Protocol Amendment Version 6.0, treatment of all participants assigned to Arm 2 (3.0 mg/kg), along with participants assigned to Arm 4 (placebo) who have crossed over to 3.0 mg/kg, will be halted.

** As of Protocol Amendment Version 6.0, treatment of all participants assigned to Arm 3 (4.5 mg/kg) will be halted.

6.3. MODIFICATION OF DOSE AND/OR TREATMENT SCHEDULE

Dosing must adhere to the Q4W schedule (± 5 day per window in SOA [[Section 1.3](#)]). If a participant is unable to receive a dose within the scheduled dosing window, it should be recorded as a missed dose. Study visits and assessments should be conducted during missed doses as described in [Section 6.4](#).

During the Treatment Period, participants who miss > 1 dose must be discontinued from treatment. Participants who discontinue treatment during the Treatment Period due to > 1 missed dose are not eligible for the Extension Period.

During the Extension Period, participants who miss ≥ 3 doses should be discontinued from treatment. Participants who have ≥ 2 consecutive missed doses due to AEs must be discontinued from treatment.

As of Protocol Amendment Version 6.0, all participants will undergo echocardiograms Q4W. For participants in the 1.5 mg/kg or Placebo arms who continue to receive study drug, an echocardiogram must be performed (and reviewed to confirm that there is no Pericardial effusion) prior to study drug administration for each dosing visit.

If no Pericardial effusion is noted at the most recent echocardiogram prior to dosing, administration of IMP can proceed with scheduled dosing (see [Figure 2](#)).

If a Pericardial effusion is noted, then the following rules apply (using CTCAE v5.0 per [Table 3](#)):

- If the Pericardial effusion is Grade 2, then dosing must be paused. Dosing may be resumed at the next study visit if the Pericardial effusion has resolved, and the Investigator assesses that it would be safe to administer study treatment. The medical monitor should also be consulted, but the clinical assessment of whether it would be safe to dose will be made by the Investigator. As with all dosing visits, Q4W echocardiograms must continue to be performed prior to dosing to confirm the absence of Pericardial effusion. If a Pericardial effusion recurs following prior resolution during the study, the study treatment must be permanently discontinued.

- If the Pericardial effusion is Grade 3, then study treatment must be permanently discontinued, and intervention instituted as clinically indicated in accordance with standard of care.
- If the Pericardial effusion is Grade 4, then study treatment must be permanently discontinued, and urgent intervention must be instituted, in accordance with standard of care.

Figure 2: Echocardiogram Decision Tree

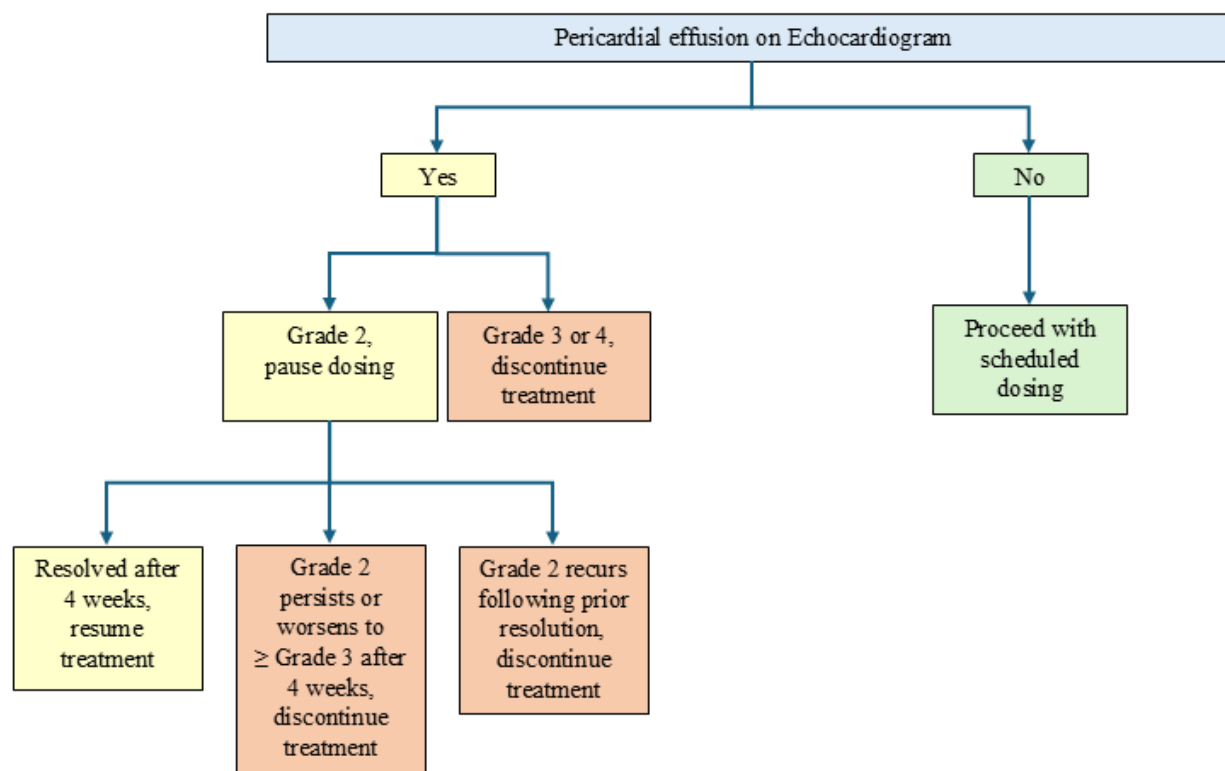


Table 3: CTCAE Grading of Pericardial Effusions

Grade*	CTCAE v5.0 Definition
2	Asymptomatic effusion size small to moderate
3	Effusion with physiologic consequences
4	Life-threatening consequences; urgent intervention indicated

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

* CTCAE v5.0 does not include a Grade 1 Pericardial effusion.

6.4. STUDY ASSESSMENTS DURING MISSED DOSES

All planned assessments, as outlined in the SOA ([Section 1.3](#)), should be performed during a visit, even when a dose is missed. If a participant misses a dose because they are unable to attend a visit, all assessments, except for IMP administration, should be performed at their earliest return.

Additional visits outside of the scheduled visits detailed in the SOA ([Section 1.3](#)) are to be recorded as an unscheduled visit.

6.5. METHOD OF IMP ASSIGNMENT

6.5.1. Randomization

Participants who have signed the informed consent and meet all eligibility criteria will be stratified by PVR (> 640 vs ≤ 640 dyn·sec·cm⁻⁵) at baseline (Day 1) and then randomized to receive Placebo, 1.5 mg/kg KER-012, 3.0 mg/kg KER-012, or 4.5 mg/kg KER-012. Of note, the participant enrollment and randomization were closed on 27 September 2024 when the last participant was randomized. A computer-generated randomization schedule will be prepared by an unblinded statistician prior to the start of the study. KER-012 and Placebo will be prepared in accordance with the randomization list. After the completion of the 24-week Treatment Period, Placebo participants will receive 3.0 mg/kg KER-012 and KER-012-treated participants will continue on their current dose in the Extension Period in a blinded manner.

As of Protocol Amendment 6.0, treatment of all participants assigned to receive 4.5 mg/kg or 3.0 mg/kg (including participants who crossed over to 3.0 mg/kg from the Placebo arm) will be halted; all other study 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 open-label KER-012 at a dose level of 1.5 mg/kg.

6.5.1.1. Assignment of Participant Numbers

After signing the ICF, each participant will be assigned, via the Interactive Response Technology (IRT) system, a participant number according to the screening order. The participant number will comprise the site number (e.g., 101), followed by a 4-digit number (e.g., 0001) according to the screening order at each site. (Example of a participant number: 101-0001).

The participant numbers will be used to identify the participant throughout the study period and on all study-related documentation.

6.5.2. Blinding

This is a double-blind study in which treatment assignment will be blinded for the Investigators and any personnel (other than the unblinded pharmacist or designee) involved with the study conduct or evaluation at the investigational sites, the CRO, and the Sponsor.

All participants will be centrally assigned to randomized treatment using an IRT system. Before the study is initiated, the login information and directions for the IRT system will be provided to each site.

The randomization scheme will only be disclosed to selected personnel to ensure correct preparation of the IMP, correct set-up of the IRT, and safety monitoring by the DMC. All aspects of blinding and unblinding for the study is outlined in the study-specific Blinding and Unblinding Plan.

Unblinding, i.e., breaking the code for an individual participant during the study, is restricted to emergency situations (e.g., in the case of undesirable events) and should only be used under circumstances where knowledge of the treatment is absolutely necessary for the proper care of the participant. In cases of absolute medical necessity (e.g., in the case of undesirable events), the Investigator may unblind the participant using the IRT system associated with the study. In these emergent cases, the decision to unblind the participant resides solely with the Investigator. In the event unblinding is necessary, the Investigator should contact the study MM or designee whenever possible and as long as it does not delay medical intervention. If not possible to contact prior to emergency unblinding, the study MM or designee must be informed about the code break as soon as possible. When a participant's treatment assignment is unblinded, the unblinding Investigator must complete a comprehensive source note that includes the date, time, and reason(s) the participant was unblinded. If the reason for unblinding was discussed with MM or designee, the source note must contain a record of the discussion. Detailed unblinding procedures are provided in a separate IRT system manual.

An unblinded pharmacist or designee will prepare the KER-012 and/or Placebo in syringes with a masking label for delivery to the Investigator or designee. Details of IMP preparation and administration will be found in the Pharmacy Manual.

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; hence, this amendment will not incur any potential operational bias for the analysis results.

6.6. PACKAGING AND LABELING

KER-012 and Placebo will be labeled in accordance with text that is in full regulatory compliance with the participating country. KER-012 product and Placebo labels will not bear any statement that is false or misleading in any manner. Please refer to the Pharmacy Manual for further details on labeling of KER-012 and Placebo.

6.7. IMP STORAGE

Study materials will be stored by the study site personnel according to the documentation provided with the study materials. Access must be limited to authorized site personnel. The Sponsor reserves the right to inspect the IMP storage area before and during the study. A written

record will be made of the storage condition of the study materials and retained for the Investigator's Site File.

6.7.1. KER-012 and Placebo

The recommended storage condition for KER-012 drug product is $\leq -60^{\circ}\text{C}$ with a defined expiry date based on available stability data. KER-012 drug product will be stored frozen prior to distribution at the clinical sites. Upon receipt at clinical sites, vials may be stored at 2 to 8°C if required per the defined expiry as outlined on the IMP label and/or in the Pharmacy Manual. The recommended storage condition of Placebo is 2 to 8°C at the clinical sites. Temperature monitoring is required at the storage location to ensure that KER-012 and Placebo are maintained within an established temperature range. The Investigator or designee is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained.

6.8. IMP HANDLING

KER-012 and Placebo accountability and traceability are ultimately the responsibility of the Investigator and Sponsor.

Detailed records will be maintained to allow for accurate accountability of KER-012 and Placebo per applicable Sponsor and clinical site procedures. Please refer to the Pharmacy Manual for further details on IMP handling.

6.9. IMP ACCOUNTABILITY AND DISPOSAL

The Investigator is responsible for KER-012 and Placebo accountability, reconciliation, and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain IMP accountability records throughout the course of the study. The amount of IMP received from the Sponsor, and the amount supplied and/or administered to participants will be documented.

Dispensing of KER-012 and Placebo will be carefully recorded on appropriate accountability forms and will be verified by the unblinded study monitor during monitoring visits.

The accountability logs should include dates, quantities, batch numbers, expiration dates, and any unique pack numbers assigned to the IMP and/or participant. The accountability logs will also include general details related to the study including the protocol number, Sponsor, and the Investigator.

The unblinded study monitor will review the IMP accountability logs and reconcile with all IMP, used and unused. After reconciliation, all IMP, unused and used/empty containers, will be returned to the drug depot or destroyed on site with prior approval from the Sponsor. Please refer to the Pharmacy Manual for further details on IMP destruction and return.

6.10. IMP COMPLIANCE

Each dose of study treatment will be administered by SC injection(s) at the clinical site by the study staff and will be documented in the study record. Accurate recording of all IMP administrations will be made in the appropriate section of the participant's eCRF and source documents.

7. DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL CRITERIA

The reason for treatment discontinuation must be recorded in the corresponding participant's eCRF. The Investigator must notify the MM or designee when a participant has discontinued treatment or been withdrawn from the study.

7.1. DISCONTINUATION OF IMP

Reasons that may lead to discontinuation of IMP administration include, but are not limited to:

- Clinical worsening or disease progression (see [Section 9.7](#))
- Adverse event
- Withdrawal of consent
- Sponsor request
- Lost to follow-up
- Pregnancy
- Protocol deviation
- Study terminated by the Sponsor
- Site terminated by the Sponsor

The Investigator has full discretion to stop KER-012 or Placebo administration at any time if clinically warranted or is in the participant's best interest. All participants who have received any amount of IMP will continue to be followed for safety. Participants who discontinue IMP at any time during the study should complete an EOT/ET visit, in lieu of their next scheduled visit, and return to the scheduled assessments for the remainder of respective study period. If participants express that they are not willing to participate in future visits, attempt should be made to ask participant to attend at minimum an EOT/ET and Safety Follow-up Visit which would include all assessments listed in the SOA ([Section 1.3](#)).

The Sponsor may terminate study treatment or a dose level after consultation with the DMC at any time for safety or administrative reasons.

- Sites in the European Union: see [Appendix A7-1.3](#) for additional discontinuation criteria.

7.2. WITHDRAWAL OF PARTICIPANTS FROM STUDY

Reasons that may lead to discontinuation of participants from study include any of the following reasons, but are not limited to:

- Withdrawal of consent
- Clinical worsening or disease progression (see [Section 9.7](#))
- Adverse event
- Lost to follow-up
- Study terminated by the Sponsor
- Site terminated by the Sponsor
- Pregnancy

The reason for study withdrawal is to be documented in the participant's eCRF.

Participants who withdraw from the Treatment or Extension Period and do not continue with scheduled 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 Sponsor may terminate the study if the occurrence of serious adverse events (SAEs) or other findings suggests unacceptable risk to the health of the participants.

7.3. LOST TO FOLLOW-UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make ≥ 3 attempts to contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up, which should be noted on the participant's eCRF.

The Investigator must maintain a record of all participants who fail to complete the study. A full explanation of the reason for study withdrawal or discontinuation will be made on the appropriate eCRF.

7.4. REPLACEMENT OF PARTICIPANTS

Participants who withdraw or are withdrawn early from the study will not be replaced.

7.5. CONTINUATION OF TREATMENT

Participants will discuss continued medical care with Investigator or designee (or will be referred back to their local treating physician if applicable) after ending participation in the study.

8. CONCOMITANT THERAPY AND PROCEDURES

8.1. CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken by the participant during the 30 days prior to Screening Period and up to the EOS Visit must be recorded on the appropriate eCRF along with:

- Indication
- Dates of administration including start date/time and end date/time
- Dosage information including dose and frequency

During Screening and throughout the study, participants may take stable doses of medications for chronic conditions and those that are not specifically excluded by the protocol ([Section 5.2](#)).

The Investigator may consult the MM or designee regarding what constitutes a stable dose or a chronic condition.

If there is an immediate clinical need during the study (e.g., for treatment of an AE) to prescribe a new medication or a new dosage of an existing medication to treat an AE, concurrent therapy may be administered at the discretion of the Investigator and administration details must be recorded in the source documents and the eCRF.

PAH background therapy treatment compliance will be the responsibility of each participant and Investigator or designee. The Investigator or designee should promote compliance by instructing the participant to take their PAH background therapy exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant should be instructed to contact the Investigator if they are unable for any reason to take their background medications as prescribed (see [Section 8.2.1](#) for more details).

If the participant requires a new PAH medication to be added or their current PAH medication dose to be increased for clinical worsening (please refer to [Section 9.7](#) for criteria), the Investigator will need to ensure that clinical worsening is captured appropriately as directed by the protocol.

Information regarding concomitant medications will be collected beginning after signing the ICF and will include all medications taken during the Screening Period through the EOS Visit.

8.2. ALLOWED CONCOMITANT THERAPY

Participants are allowed to continue taking any stable dose of prescription or over-the counter medications during the study as defined in the protocol ([Section 5.1](#)). Vaccinations, including COVID vaccines, are allowed per local guidelines. If possible, vaccines should be administered at least 2 weeks prior to planned Screening Visit to avoid confounding AEs at Screening. During the study, if possible, administration should occur at approximately a middle time point between 2 doses to avoid confounding AEs.

8.2.1. PAH Background Therapy

Participants will be permitted PAH therapy at a stable dose. Stable therapy is defined as no change in dose/regimen for at least 90 days prior to baseline and would be expected to be maintained for the duration of study. The PAH therapy medications taken 90 days prior to baseline must be recorded on the appropriate eCRF.

PAH background therapy refers to combination therapy consisting of at least 2 agents (each from a different class) or monotherapy (see below) from a list including, but not limited to: an ERA (e.g., ambrisentan, bosentan, macitentan), a PDE5-I or a sGC stimulator (e.g., sildenafil, tadalafil, riociguat), and/or a prostacyclin analogue or receptor agonist (SC/inhaled/oral/IV, e.g., epoprostenol, iloprost, treprostinil, beraprost, selexipag). Only medicinal products authorized by local Regulatory Authorities will be allowed as PAH background therapy. Monotherapy is permissible if combination therapy has failed, not been tolerated, or is unavailable.

Participants may be either on a PDE5-I or an sGC stimulator, but not on both nitric oxide pathway agents.

Participants with prior treatment with a therapy targeting TGF- β (e.g., sotatercept) will be excluded as described in [Section 5.2](#).

If a participant's PAH therapy does not include a PDE5-I, the use of a PDE5-I for erectile dysfunction is permitted if dosing does not exceed 3 times a week and is not taken within 48 hours prior to the study visits.

Participants cannot receive IV inotropes (e.g., dobutamine, dopamine, norepinephrine, vasopressin) within 30 days prior to the Screening period.

PAH background therapy treatments will be provided by the treating physician based on local treatment guidelines and must remain stable throughout the study. It will be the Investigator's or designee's responsibility to ensure participant's compliance with PAH background therapy. The information about PAH background therapy will be collected in an appropriate eCRF. If a participant has an event of clinical worsening requiring additional PAH therapy (see [Section 9.7](#)), background therapy may be altered as per the treating physician's decision. Any other changes (aside from therapy for clinical worsening) to a participant's background should be discussed with the MM on a case-by-case basis to determine if participant may stay on study treatment.

8.3. DISALLOWED CONCOMITANT THERAPY

Prohibited medication criteria for enrollment are listed in [Section 5.2](#). Participants with prior treatment with a therapy targeting TGF- β (e.g., sotatercept) will be excluded as described in Section 5.2. Prohibited medications, including activin-signaling inhibitors (e.g., sotatercept), and the initiation of new investigational therapies should be avoided for 5 half-lives (8 weeks [56 days]) after the last administration of IMP because of the potential for residual pathway inhibition.

The following concomitant medications are specifically excluded during the study:

- Simultaneous administration of PDE5-I and sGC stimulator

8.4. CONCOMITANT PROCEDURES

Any concomitant procedures that the participant reports from signing the informed consent up to the EOS Visit must be recorded on the eCRF along with:

- Reason for procedure(s)
- Dates of procedure(s)

9. STUDY ASSESSMENTS AND PROCEDURES

Refer to the SOA ([Section 1.3](#)) for the timing of all study assessments.

- Participants must provide written informed consent before any Screening tests or assessments are performed.
- No protocol waivers or exemptions will be allowed for eligibility criteria. Assessments performed outside of their defined windows will be handled as protocol deviations.
- Immediate safety concerns should be discussed with the MM or designee immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed in timely manner to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes as specified in the protocol and performed within the timeframe defined in the protocol.
- All protocol assessments are to be recorded on the participant's source documentation.

9.1. INFORMED CONSENT

The Investigator will obtain and document the ICF for each participant screened for this study. All participants will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures. The participant's medical record should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the Investigator's designated Institutional Review Board (IRB)/Ethics Committee (EC) and by the Sponsor. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

9.2. MEDICAL AND MEDICATION HISTORY

Relevant and clinically significant medical and social history will be collected after signing the informed consent and will include all medications taken during the Screening Period through the EOS Visit. History will include tobacco, alcohol, and caffeine use, and any history of alcohol or substance (drug/solvent) abuse. Information regarding concomitant medications, recent blood donations, illnesses, and participation in other investigational drug studies will also be recorded.

9.2.1. PAH History

A complete participant history of PAH, including diagnosis date, associated illness and diseases, and medications will be collected by chart review and participant interview.

9.3. ASSESSMENTS TO EXCLUDE CHRONIC PULMONARY THROMBOEMBOLIC DISEASE

9.3.1. Ventilation-Perfusion Lung Scan

A V/Q lung scan or other local standard of care diagnostics evaluation will be completed only if not available at the time of or after PAH diagnosis as indicated in the Schedule of Assessments ([Section 1.3](#)).

9.3.2. Computed Tomography

A CT angiogram can be used in place of a V/Q lung scan if the participant does not have a history of venous thromboembolic disease. A high-resolution CT scan should be performed if TLC or FVC during Screening is between 60% and 70%; a high-resolution CT chest scan is preferred but if not available at the clinical site, a CT chest scan is acceptable.

9.3.3. Selective Pulmonary Angiography

A selective pulmonary angiography will be performed if a V/Q lung scan is unavailable, and the participant has a history of venous thromboembolic disease as indicated in the Schedule of Assessments ([Section 1.3](#)). The selective pulmonary angiography will also be performed if the V/Q scan shows anything other than "normal" or "low-probability" of chronic thromboembolic

disease. In cases where selective pulmonary angiography is unable to be performed, the local standard of care to rule out chronic pulmonary thromboembolic disease is allowed.

9.4. PULMONARY FUNCTION TEST

PFTs will be completed only if a test is not available within 180 days prior to the Screening Visit as indicated in the Schedule of Assessments ([Section 1.3](#)). PFTs will be conducted at the Screening to assess FEV1, FVC, and TLC. TLC should be performed using a direct measurement of TLC (e.g., whole body plethysmography preferred) for calculating the TLC % predicted.

9.5. PREGNANCY TEST

WOCBP must have a negative serum hCG pregnancy test at Screening and a negative serum or urine hCG pregnancy test at all other study visits as indicated in the Schedule of Assessments ([Section 1.3](#)) and as clinically indicated. If urine test is positive, confirmatory serum test is required, and dosing should be withheld until the serum test is negative.

WOCBP and male participants with a partner of childbearing potential must agree to use at least 1 highly effective birth control method during the study and for at least 8 weeks after the last dose of IMP. See [Appendix 6](#) for detailed contraceptive guidelines.

9.6. WORLD HEALTH ORGANIZATION / NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION ASSESSMENT

PAH will be classified according to a system originally developed for heart failure by the NYHA and then modified by the WHO for participants with PAH ([Galie et al., 2013](#)). The severity of PAH will be graded according to the functional status of the participant and assessed as indicated in the Schedule of Assessments ([Section 1.3](#)). The grades range from FC I, where the participant's disease does not affect their day-to-day activities, to FC IV, where participants are severely functionally impaired, even at rest (see [Appendix 4](#)).

The same Investigator or designee should complete the WHO/NYHA FC evaluation at the participant's first visit and for the duration of the study when possible.

9.7. CLINICAL WORSENING

The Investigator will evaluate the participant for potential clinical worsening throughout the study. If clinical worsening is suspected, an echocardiogram must be performed (see [Section 9.11](#)) and additional clinical evaluations may be required to make a final determination as to whether clinical worsening has been met. Clinical worsening for the purpose of this study is defined as:

- Death **or**,
- Non-elective hospitalization lasting at least 24 hours for the treatment of clinical conditions directly related to worsening PAH and/or right heart failure inclusive of lung transplant, heart/lung transplant, or atrial septostomy; **or**,

- Initiation of rescue therapy with an approved PAH therapy, including IV inotropes, or the need to increase the dose of infusion prostacyclin by more than 15% from baseline; **or**,
- Disease progression, defined as occurrence of both events listed below:
 - A decrease in 6MWD by $\geq 15\%$ from baseline directly related to the PAH progression (e.g., other co-morbidities ruled out) and confirmed by two 6-minute walk tests (6MWTs) at least 4 hours apart, but no more than 1 week ([Section 9.12.2](#) and [Appendix 5](#)), **and**
 - Increase (worsening) in WHO/NYHA FC from baseline.

In cases of clinical worsening, the Investigator must assess carefully if the deterioration of the participant's condition (e.g., worsening FC) is related to the underlying PAH or can be explained by an alternative cause (e.g., transient infection, musculoskeletal disease, surgical or medical intervention other than PAH related). Only persistent clinical deteriorations caused by the underlying PAH and confirmed as per the above criteria, will be considered clinical worsening for purposes of this study.

The clinical worsening events will be reviewed by the MM or designee. The clinical worsening event eCRF should be completed.

Participants who meet the criteria for clinical worsening and have initiated rescue PAH therapy, including an increase in the dose of infusion prostacyclin by more than 15%, must discontinue IMP treatment.

Participants who meet the criteria for clinical worsening but have not initiated rescue PAH therapy, including an increase in the dose of infusion prostacyclin by more than 15%, may remain on IMP treatment. The participants should remain in the study unless the Investigator or designee thinks that it is not clinically warranted or it is not in the participant's best interest.

Should the participant discontinue IMP treatment and/or the study, the participant must complete EOT/ET and EOS procedures as applicable ([Section 1.3](#)). Note: Participants who discontinue the Treatment Period prematurely due to a clinical worsening event are not eligible for study extension participation.

9.8. PHYSICAL EXAMINATION

Full physical examinations will be performed by a study-delegated registered physician at Screening as indicated in the SOA ([Section 1.3](#)). A symptom-directed physical examination will be conducted at all other study visits.

The physical examination will include assessment of the following: general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. Any abnormal findings during the physical examination for conditions that were present prior to informed consent should be recorded in the medical history eCRF. Any abnormal findings during the physical examination that develop or worsen after informed consent that meet the definition

of an AE (i.e., induce clinical signs or symptoms, are considered clinically significant, or require therapy) must be reported in the AE eCRF.

9.9. VITAL SIGNS

Vital sign measurements will include height and weight, systolic and diastolic blood pressure, heart rate, respirations, pulse oximetry [SpO₂] and body temperature (oral or tympanic). When possible, the same method of body temperature measurement should be used throughout. When possible, vital signs will be recorded using consistent methods between participants. Vital signs will be collected as indicated in the SOA ([Section 1.3](#)). Blood pressure must be taken before each KER-012 or Placebo administration.

The participant should be in supine position for a period of 5 minutes before the vital signs are taken. Vital sign measurements should be taken first if they coincide with the timing of a required blood draw. Ideally, the participant should not have smoked or had any caffeine within the 30 minutes prior to the BP determinations.

If a participant shows systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg, 3 measurements (≥ 5 minutes apart) should be performed to yield a mean value. All 3 values should be reported in the eCRF.

9.10. 12-LEAD ELECTROCARDIOGRAM

A 12-lead ECG will be performed at Screening. Subsequent ECG testing will be performed according to the SOA ([Section 1.3](#)) and will be transmitted centrally but reviewed locally by the Investigator. The Investigator (or a qualified designee at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Clinically significant abnormal findings will be reported as AEs.

The ECG will be performed after the participant has rested comfortably in the supine position for ≥ 5 minutes and prior to dosing of IMP. On visits when the 6MWT is performed, the ECG should be performed first.

The following parameters will be assessed: RR, PR, QRS, QT, QTcF and QTcB.

9.11. ECHOCARDIOGRAM

An echocardiogram must be performed at baseline (Visit 1) and subsequently according to the SOA ([Section 1.3](#)) and per local standards. An echocardiogram must be performed anytime a participant meets the protocol definition of clinical worsening ([Section 9.7](#)). Echocardiograms will be collected and stored in a central repository.

The Investigator (or a qualified designee at the study site) will interpret the echocardiogram for clinical significance. Clinically significant abnormal echocardiogram findings must be reported as AEs. If a Pericardial effusion is found (see [Section 6.3](#) and [Appendix A1-10](#)), further parameters must be collected in the Electronic Data Capture system.

The echocardiogram should be performed after the participant has rested comfortably in the supine position for ≥ 5 minutes and prior to dosing of IMP. On visits when the 6MWT is performed, the echocardiogram should be performed first.

The echocardiogram parameters that will be collected include but are not limited to:

- Machine manufacturer
- Size of inferior vena cava (IVC)
- IVC collapsibility ($< 50\%$, 50% , $> 50\%$) with respect to inspiration
- Estimated systolic pulmonary artery pressure (mmHg), if available
- Tricuspid annular plane systolic excursion (TAPSE) (mm), if available
- Right ventricular fractional area change, if available
- Right ventricular end-systolic area, if available
- Right ventricular end-diastolic area, if available.
- Tricuspid valve velocity (m/s), if available
- Left ventricular ejection fraction (normal, mild, moderate, severely reduced and numeric EF %)
- Left atrial enlargement
- Left atrial volume index (mL/m^2), if available
- Right atrial enlargement
- Right atrial volume index (mL/m^2), if available,
- Right ventricular size (mm), function, hypertrophy, and thickness (mm) (in end diastole)

The echocardiogram parameters that will be collected if a Pericardial effusion (see [Appendix A1-10](#)) is found during any echocardiogram, in addition to those described above, include but are not limited to:

- Size of effusion (mm) at end diastole
- Presence during cardiac cycle (systole or full cardiac cycle)
- Location of effusion (anterior, posterior, apical, inferior lateral, above right atrium, circumferential)
- Quality of effusion (presence of loculations, presence of fibrin)
- Collapsibility of cardiac chambers in diastole (right atrium, right ventricle, left atrium, left ventricle).
- Blood pressure and heart rate at time of echocardiogram
- Mitral inflow variation (%), if available

9.12. EFFICACY ASSESSMENTS

9.12.1. Right Heart Catheterization (RHC)

Pulmonary vascular resistance (PVR) will be measured by RHC and will be obtained according to the SOA ([Section 1.3](#)). RHC will be performed as per the RHC Manual and will assess hemodynamic parameters defined within the RHC Manual. All collected data will be centrally reviewed.

If performed on the same day, RHC should take place after other assessments (i.e., 6MWT, HRQoL) have been completed. A participant will not receive more than 3 RHC assessments during the study.

At the time of crossing over from the Treatment Period to the Extension Period (Week 24), RHC should be performed prior to the Week 24 (Visit 12) IMP administration.

RHC should be performed if a participant terminates from the study early, if clinically appropriate. RHC should be performed at the EOT/ET Visit at the time of their discontinuation or within 10 days of the EOT/ET Visit.

Participants who are re-screened for this study and have had RHC performed as per the RHC Manual within 60 days of re-screening at the same institution and who meet study entry requirements are not required to have a repeat screening RHC.

9.12.2. 6-Minute Walk Test

Six-minute walk distance (6MWD) will be measured by the 6MWT (See [Appendix 5](#)) during the Screening Period and at multiple time-points throughout the study as per the SOA ([Section 1.3](#)). During Screening, the 6MWT is to be performed twice at least 4 hours and no more than 1 week apart; the distance results must be within 15% of each other, based on the longer distance. If the difference between the first and second tests is > 15%, the test may be repeated once more, provided that the repeat test is within 1 week of the previous test. If the difference between the distances remains > 15%, the participant will be considered a screen failure. 6MWT may also be done twice based on criteria outlined for clinical worsening ([Section 9.7](#)). If occurring on the same day, 6MWT should be performed before RHC and before study drug administration on dosing days.

9.12.3. Actigraphy

Evaluation of actigraphy ([Ulrich, Fischler, Speich, & Bloch, 2013](#)) in participants receiving KER-012 is an exploratory endpoint of this study. The aim is to explore novel digital measurements that can provide more meaningful endpoints for the participant population. Participants will be monitored for physical activity using a wrist-worn monitoring device. The device will be provided by the Sponsor and contains a Conformité Européenne (CE) mark. The actigraphy device training and dispensation should occur at the time of signing of the ICF during the Screening Visit. Participants should begin wearing the actigraphy device immediately after training and throughout the Screening Period, for a minimum of 14 days, to establish appropriate

habits and baseline, and then will continue to wear it through the study. Participants who screen fail and are not randomized will discontinue actigraphy at the time of screen failure and return the device per the site's staff instructions.

Actigraphy measurements will be based on raw data collected and include outputs such as (but not limited to): steps, wear/not wear time (for compliance), sedentary, light, moderate, vigorous, very vigorous physical activity, etc. The actigraphy kit includes a Class II (Food and Drug Administration) medical grade triaxial accelerometer designed to continuously monitor the body's movements during daily activity and sleep. These kits will be dispensed by the sites to the participants along with training on how and when to wear, charge, and comply with the study design. Detailed instructions on how to use the device will be provided in the Actigraphy site and participant guides.

9.12.4. Risk Stratification Measures

Risk stratifications of participants receiving KER-012 will be assessed to evaluate the proportion of participants that achieve improvement. Assessments will include ESC/ERC risk category ([Marc Humbert et al., 2022](#)), REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) Lite 2 ([Benza et al., 2021](#)), and COMPERA 2.0 ([Hoeper et al., 2022](#)).

9.12.5. Health-Related Quality of Life

An exploratory endpoint of this study is to evaluate quality of life in participants receiving KER-012 plus background PAH therapy. Two HRQoL questionnaires will be used: Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) ([McCollister et al., 2016](#)) and the emPHasis-10 ([Yorke et al., 2014](#)). These questionnaires should be given to the participant and completed during their main Screening Visit and at other times specified in the SOA ([Section 1.3](#)). If occurring on the same day, HRQoL assessments should be performed prior to other assessments. The participant should not be sent home with the questionnaires to complete and return later.

All questionnaires should be provided in the participant's local language at the beginning of the study visit before any interaction with the study Investigator, including procedures, treatments, and receipt of any test results, to avoid bias to the participant's response to the study questionnaires. Participants should be given sufficient space and time to complete all study questionnaires at each visit and should be encouraged to complete any missing responses. Assistance can be provided, if necessary, but without leading the participant or suggesting specific response options.

9.13. CLINICAL LABORATORY TESTS

See the SOA ([Section 1.3](#)) for timing and frequency and [Appendix 3](#) for the list of clinical laboratory tests to be performed.

The Investigator or designee must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered abnormal clinically significant during participation in the study or 8 weeks after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or designee.

All protocol-required laboratory assessments, as defined in [Appendix 3](#), must be conducted in accordance with the Laboratory Manual and the SOA ([Section 1.3](#)).

9.13.1. Serology

HIV antibody, hepatitis B antigen (HBsAg), hepatitis B core antibody, and hepatitis C virus (HCV antibody with reflex HCV qPCR) screening tests will be performed at Screening only.

9.13.2. Urinalysis

See the SOA ([Section 1.3](#)) for timing and frequency and [Appendix 3](#) for the full list of Urinalysis parameters for clinical laboratory tests to be performed.

9.13.3. Sample Collection Storage and Shipping

Blood samples for hematology, coagulation parameters, serum chemistry, HIV and hepatitis screens, and serum hCG will be collected according to the Laboratory Manual provided by the local or central laboratory and according to the schedule presented in the SOA ([Section 1.3](#)).

9.14. PHARMACOKINETIC ASSESSMENTS

Population PK blood samples will be collected for measurement of serum concentrations of KER-012 as specified in the SOA ([Section 1.3](#)). Instructions for the collection and handling of biological samples will be provided in a Laboratory Manual. The actual date and time (24-hour clock time) of PK sample collection will be recorded for each sample.

Samples collected for analyses of KER-012 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information may unblind the study therefore will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.15. BIOMARKER ASSESSMENTS

Blood samples will be collected to evaluate the PD of KER-012 according to the SOA ([Section 1.3](#)). Blood will be collected for assessment of the following biomarkers:

- BSAP
- Connective tissue growth factor

- Galectin
- NT-proBNP
- Osteopontin
- Other biomarkers may be evaluated as determined by additional data

If required on dosing days, samples should be obtained within 1 hour prior to KER-012 administration.

The details of PAH-related biomarkers and PK/PD analysis will be described in detail in a separate analysis plan. Refer to the Study Procedures Manual for additional details of sample collection, storage, and analysis of biomarkers.

9.16. ANTI-DRUG ANTIBODY

Serum will be assayed by a central laboratory via an enzyme-linked immunosorbent assay method for the presence of antibodies directed against KER-012. ADA information may potentially unblind the study therefore will not be reported to investigative sites or blinded personnel until the study has been unblinded. ADA will be routinely reviewed by the DMC who will provide recommendation for action in specific cases of safety concerns.

9.17. GENETIC TESTING (OPTIONAL)

For participants who opt-in to genetic testing, a genetic sample will be taken to assess the mutation status and allele frequency of *BMPR2*, activin A receptor-like type 1 (*ACVRL1*), caveolin 1 (*CAV1*), eukaryotic translation initiation factor 2 alpha kinase 4 (*EIF2AK4*), endoglin (*ENG*), potassium voltage-gated channel subfamily A member 5 (*KCNA5*), and potassium channel subfamily K member 3 (*KCNK3*) at Screening. Because genetic mutations in *BMPR2* are associated with PAH, this testing may provide insight into the genetic basis of PAH and potential response to KER-012. Participants who do not wish to opt-in to the optional assessments may still participate in the main clinical study.

If a participant who has consented to participate in optional analyses withdraws from the study for any reason other than “lost to follow-up,” the participant will be given the following options regarding the analysis sample, if the sample has already been collected:

- The sample will be maintained per the participant’s original consent
- The participant’s consent may be withdrawn and any remaining sample will be destroyed.

If a participant withdraws consent from the optional assessments and/or requests sample destruction, the Investigator must document the request and inform the Sponsor. The Sponsor will only keep data that are collected or generated up to the point at which consent to use the sample is withdrawn by the participant. Withdrawal of consent from optional analyses does not affect consent to participate in the main clinical study.

9.18. PROTEOMICS, METABOLOMICS AND TRANSCRIPTOMICS

The exploratory analysis using a multiomics approach comparing treatment responses over the course of the study may provide important insights into the pathology of PAH, treatment response and effect of treatment, and IMP mechanism of action. These system-wide assessments may include additional proteomics, metabolomics, and transcriptomics related to disease under study.

Blood samples will be collected at baseline, the Week 24 Visit and/or the EOT/ET Visit. Blood will be collected for exploratory analysis. Complete instructions regarding the processing, packaging, and shipping of samples will be provided in a separate Laboratory Manual. Samples for these analyses will be coded in a manner that allows them to be matched to a study site and/or a participant number but will not carry personal identifiers that could be traced to a specific individual.

Samples may be banked for optional future exploratory analysis and omics testing (see [Appendix A2-5](#) for addition details). However, if it is determined that a sample is not needed, the samples may be destroyed earlier. In some cases, the samples may never be utilized; for example, if there are not an adequate number of samples to perform the analysis.

9.19. UNSCHEDULED VISITS

Should it become necessary to repeat a study assessment (e.g., ECGs or vital signs), the results of the repeat assessment should be entered as an additional unscheduled visit in the eCRF.

Refer to the eCRF completion guidelines for detailed instructions related to eCRF data entry.

9.20. HOME VISITS

Visit 2 (Day 5), Visit 4 (Day 22), Visit 8 (Day 95), and Visit 11 (Day 155) PK, clinical laboratory, and/or biomarker assessments and ADA may be collected by a home visit blood draw as indicated in the SOA ([Section 1.3](#)).

10. STATISTICAL CONSIDERATIONS

10.1. STATISTICAL HYPOTHESIS

10.1.1. Primary Hypothesis

The null hypothesis is that the pooled KER-012 treatment group will have no difference in change from baseline in PVR at Week 24 compared to Placebo. The alternative hypothesis is that the pooled KER-012 treatment group will be different in change from baseline PVR at Week 24 compared to Placebo.

10.1.2. Key Secondary Hypothesis

The null hypothesis is that the pooled KER-012 treatment group will have no difference in change from baseline in 6MWD at Week 24 compared to Placebo. The alternative hypothesis is that the pooled KER-012 treatment group will be different in change from baseline 6MWD at Week 24 compared to Placebo.

10.2. 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 $200 \text{ dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$ decrease between pooled KER-012 treatment arm and Placebo with a common standard deviation of $300 \text{ dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$, a premature discontinuation rate of 10%, and with 1-sided alpha of 0.10.

10.3. STATISTICAL AND ANALYTICAL PLANS

Data will be summarized using descriptive statistics (mean, median, standard deviation [SD], minimum, and maximum) or frequency counts and percentages, as appropriate to the type of data. Confidence intervals may be presented.

Baseline will be defined as the last assessment on or prior to first dose of IMP for all safety and efficacy analyses.

As of Protocol Amendment Version 6.0, treatment of all participants assigned to Arm 2 (3.0 mg/kg) and Arm 3 (4.5 mg/kg), along with participants assigned to Arm 4 (placebo) who have crossed over to 3.0 mg/kg, will be halted.

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.

10.4. ANALYSIS SETS

10.4.1. Safety Population

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

10.4.2. Efficacy Population

The Full Analysis Set (FAS) is defined as all randomized participants who received at least 1 dose of IMP. Participants will be analyzed according to the treatment to which they were randomized.

10.4.3. PK Population

The PK Population is defined as all randomized participants who received at least 1 dose of KER-012 and who had at least 1 evaluable PK parameter.

10.4.4. Immunogenicity Population

The immunogenicity population will include all randomized participants who receive at least 1 dose of IMP and have at least 1 post-treatment immunogenicity assessment.

10.5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All demographic and baseline disease characteristics will be summarized for the Safety and Efficacy Populations. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

10.6. EFFICACY ANALYSIS

The primary endpoint of change from baseline in PVR at Week 24 will be analyzed using either parametric or non-parametric methods consistent with the statistical assumptions required to support the analyses. In the primary analysis of the primary estimand, analysis of covariance or aligned-rank stratified Wilcoxon test (based on assessment of skewness) ([Hodges & Lehmann, 1962](#); [Mehrotra, Lu, & Li, 2010](#)) will be used to compare the pooled KER-012 and Placebo treatment arms, with the baseline PVR value as the covariate or randomization stratification factor as strata. Missing data from participants for reasons other than clinical worsening will be imputed using a standard multiple imputation approach. For participants who die, the worst-rank score will be used to impute the missing data. For participants who experience a clinical worsening event (other than death), the next worst-rank score will be used to impute the missing data ([Lachin, 1999](#)).

Analysis of the key secondary endpoint of change from baseline in 6MWD at Week 24 will be conducted in a similar manner as the primary analysis of the primary endpoint.

A fixed sequence approach will be used to control the overall Type I error rate for the primary and key secondary endpoints in the following order at 1-sided alpha of 0.10. Only if the previous comparison is significant, will the next comparison be performed.

- Change from baseline in PVR at Week 24: pooled KER-012 plus background PAH therapy vs Placebo plus background PAH therapy
- Change from baseline in 6MWD at Week 24: pooled KER-012 plus background PAH therapy vs Placebo plus background PAH therapy.

10.7. PHARMACOKINETIC ENDPOINT ANALYSES

The PK analysis will use the PK analysis set. Blood samples will be collected prior to dosing and at specified times following dosing as described in [Section 1.3](#) for the determination of serum concentrations of KER-012.

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). A population PK data analysis will be reported separately that will outline the detailed approach to data handling, model development, diagnostics, final model evaluation techniques, results, and conclusions.

Additional PK/PD analysis may be conducted as deemed appropriate.

10.8. SAFETY ANALYSIS

Safety analyses will be carried out using the Safety Population. All safety assessments will be summarized using descriptive statistics. All safety analyses will be based on observed data only, and no missing values will be imputed. Safety will be evaluated based on AEs, clinical laboratory parameters, vital signs, ECGs, and ADA. Reported AE terms will be coded using the MedDRA and summarized by Preferred Term (PT) and System Organ Class categories. The number and percentage of participants with TEAEs, TESAEs, treatment-related TEAEs, treatment-related TESAEs, and TEAEs leading to treatment discontinuation will be summarized by treatment arm. The observed value and change from baseline in clinical laboratory, ECGs, vital signs, and incidence of ADA will be summarized by treatment arm. The number and percentage of participants who meet the potentially clinically significant criteria will be summarized by treatment arm.

10.9. INTERIM ANALYSIS

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; hence, this amendment will not incur any potential operational bias for the analysis results.

An unblinded interim analysis (IA) may be conducted to assess the benefit-risk of KER-012 in participants with PAH as the study continues, as outlined in the IA plan.

11. APPENDICES

APPENDIX 1. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, ADVERSE EVENTS OF INTEREST, AND ADVERSE EVENTS OF SPECIAL INTEREST

A1-1. DEFINITION OF ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a clinical study participant, which does not necessarily have a causal relationship with the administered IMP treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory and other investigational finding), symptom, or disease temporally associated with the use of the IMP, whether or not it is related to the IMP. This includes an exacerbation of preexisting conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated day-to-day fluctuations of preexisting conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Abnormal laboratory and other abnormal investigational findings (e.g., physical exam, ECG) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are otherwise considered clinically significant by the Investigator. AEs will be coded using the MedDRA.

A1-2. DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is any untoward medical occurrence that:

- Results in death
- Is life threatening (i.e., the participant was at immediate risk of death from the event as it occurred; it does not refer to an event which hypothetically might have caused death had it been more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event:

Medical and scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be life threatening or result in death or hospitalization but may jeopardize the participant and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse.

A1-3. SEVERITY OF ADVERSE EVENTS

The Investigator must assess severity (intensity) for each AE and SAE reported during the study according to the NCI CTCAE version 5.0 or higher, wherever possible. The following score should be utilized to assign each AE/SAE to 1 of the following categories if the NCI CTCAE criteria do not apply:

- | | |
|-----------------------------|--|
| Grade 1 (mild): | Asymptomatic or mild; only seen clinically or diagnostically; no treatment required. An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. |
| Grade 2 (moderate): | Requires minor, topical, or noninvasive treatment; age-appropriate instrumental activities of daily living are limited. An event that causes sufficient discomfort and interferes with normal everyday activities. |
| Grade 3 (severe): | Medically significant but not immediately life-threatening; may result in hospitalization or prolonged hospital stay; disabling. An event that prevents normal everyday activities. NOTE: An AE that is assessed as severe should not be confused with an SAE (Appendix A1-2). Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. |
| Grade 4 (life threatening): | Life-threatening; urgent treatment is required. |
| Grade 5 (fatal): | Death associated with the AE/SAE. |

A1-4. RELATIONSHIP OF ADVERSE EVENTS TO INVESTIGATIONAL MEDICINAL PRODUCT

The Investigator is obligated to assess the relationship between the administration of the IMP and the occurrence of each AE/SAE. Factors for the assessment of causal relationship include, but are not limited to, temporal relationship between the AE and the administration of the IMP, known side effects of the IMP, medical history, concomitant therapy, course of the underlying disease and pertinent study procedures.

The causal relationship of the AE to the IMP or study procedures should be assessed by the Investigator (or medically qualified delegate) using the following classifications:

Not Related	In the Investigator's opinion, a causal relationship of the AE to IMP administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation of the observed event.
Related	In the Investigator's opinion, there is a reasonable possibility that the administration of the IMP caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IMP and the AE.

A1-5. RECORDING OF ADVERSE EVENTS

It is the responsibility of the Investigator to document all AEs that occur during the study. All AEs will be recorded on the appropriate pages of the eCRF from the time of informed consent until study completion/discontinuation for all participants.

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostic reports) relative to the event. All AEs are required to be assessed by the Investigator. The Investigator will record all relevant information regarding an AE/SAE in the eCRF. All details of any treatments initiated due to the AE should also be recorded in the participant's source document and eCRF.

If a participant suffers from the same AE more than once and the participant recovers in between the events, the AEs should be recorded separately. If an AE worsens in severity during the study, a new entry of the event must be made in the eCRF.

The Investigator should make best attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information, and should be noted as 1 comprehensive event. In the absence of a diagnosis, the individual signs/symptoms should be documented as the AE/SAE terms.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the participant was enrolled in the study or before the IMP was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier or later than planned).

NOTE: A procedure is not an AE; the reason for conducting the procedure is the AE. Hospitalization is not an AE; the reason for hospitalization is the AE. Death is not an AE; the cause of death is the AE (an exception is sudden death of unknown cause, which is an AE).

Each case of COVID-19 infection, including asymptomatic infections and/or COVID-19-related medical conditions, should be recorded as an AE in the eCRF and appropriately assessed for severity (intensity) and for seriousness. If available, Investigators are encouraged to provide

additional information on the confirmatory test, anti-COVID-19 vaccination, treatment received for COVID-19 infection, and actions taken with the IMP due to COVID-19 infection events.

When recording a death on an eCRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept.

The following data should be documented for each AE:

- Description of the symptom event
- Classification of ‘serious’ or ‘not serious’
- Severity
- Date of first occurrence and date of resolution (or change in severity, or marked as ongoing, if applicable)
- Action taken with IMP
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, or death [with date and cause reported]).

After the initial AE or SAE, the Investigator is required to proactively follow each participant.

All AEs/SAEs documented at a previous visit/contact that are designated as ongoing, will be reviewed at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE/SAE.

A1-6. REPORTING OF SERIOUS ADVERSE EVENTS

All SAEs that occur from the time of informed consent until study completion/discontinuation for all participants, whether considered related or unrelated to IMP, will be recorded on the SAE form, and submitted to the CRO at the contact listed below immediately, not later than within 24 hours of obtaining knowledge of the events.

NOTE: Any SAEs and deaths that occur at any time after completion of the study that the Investigator considers to be related to IMP must be reported to the CRO immediately, not later than within 24 hours of obtaining knowledge of the events.

Study Contact for Reporting SAEs:

[REDACTED]
[REDACTED]
[REDACTED]

As the Sponsor has a legal responsibility to notify the appropriate Regulatory Authorities about the safety of a new investigational drug, prompt notification to the Sponsor by the Investigator, or nominee, of an SAE is required.

Any follow-up to an SAE must be completed and submitted within 48 hours of receipt of any new/updated information. Queries will be issued by the Sponsor or designee in the email form and will require a response via email. If a query response requires an entry or an update to the eCRF, then that should be done simultaneously to ensure data continuity.

In addition to reporting the SAE to the Sponsor, the Investigator must also notify the IRB/EC that approved the study, according to their requirements.

Copies of all correspondence relating to the reporting of SAEs should be maintained in the site's study files and will be checked routinely by the study monitor.

If the Sponsor and/or the Investigator consider the SAE to be KER-012 related (i.e., an adverse reaction) and unexpected (suspected unexpected serious adverse reaction [SUSAR]), it will be reported to the IRB/EC, study Investigators, and the appropriate Regulatory Authorities by the Sponsor (or designee) in accordance with the local regulations within the predefined timelines. SUSARs will be submitted electronically to the EudraVigilance database via EVWEB or electronically using the E2B(R3) electronic Individual Case Safety Report form.

A1-7. REPORTING OF PREGNANCY

Pregnancies and suspected pregnancies (elevated hCG or positive pregnancy test in a WOCBP regardless of disease state) occurring while the participant is on the IMP or within 8 weeks of the participant's last dose of the IMP are considered immediately reportable events. The IMP is to be discontinued immediately. Pregnancy information should be completed in the Pregnancy Report Form and faxed or emailed to the safety mailbox provided by the CRO ([Appendix A1-6](#)) immediately within 24 hours of site awareness of the pregnancy or suspected pregnancy. Pregnancies in female partners of male participants should also be reported and will be followed in the same manner. The female partner will be consented before any personal and pregnancy data are collected. The pregnancy must be followed through the final pregnancy outcome; under special circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post-delivery. Any premature termination of the pregnancy will be reported as an AE. Abnormal pregnancy outcomes (e.g., spontaneous abortion [includes miscarriage and missed abortion], fetal death, stillbirth, congenital anomalies, ectopic pregnancy, neonatal death) are considered SAEs. Any neonatal death that occurs within 1 month of birth should be reported, without regard to causality, as an SAE. Any infant death that is assessed as related to the in-utero exposure to KER-012 should be reported as an SAE.

A1-8. OVERDOSE

An overdose, accidental or intentional, which is not associated with an AE should be reported as a protocol deviation and details captured in dosing eCRF.

In the event of overdose, the participant should be monitored for signs and symptoms as appropriate, and the AEs should be reported if overdose is associated with clinical signs and symptoms. In case of overdose-associated AEs, participants should receive supportive measures as necessary. Actual treatment should depend on the severity of the clinical situation and the treating physician's judgment.

A1-9. ADVERSE EVENTS OF INTEREST

For purposes of this protocol, the following adverse events will be considered as AEs:

- **ISR**

An ISR, for the purposes of this protocol, is a reaction developing at the site of an injection of the IMP. The IMP may require multiple injection sites, therefore ISR will be assessed, and signs and symptoms will be recorded for each injection site on the appropriate eCRF. One comprehensive event will be reported for IMP administration per visit on AE eCRF based on signs and symptoms, unless different injection sites presented by different signs and symptoms. In addition to information collected for AEs ([Appendix A1-5](#)), the following information will be collected for ISR:

- Location (by quadrant)
- Primary, most prevalent sign/symptom, onset time from injection
- Secondary signs/symptoms, onset time from injection
- For signs and symptoms impacting skin (i.e., erythema, rash, ulceration) affected size (e.g., 2x4 cm).

A1-10. ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESIs) are considered important parameters to be monitored in order to assess the overall safety of the PAH population and therefore be added for safety monitoring in the KER-012 clinical trial. For further information, refer to the current KER-012 Investigator's Brochure.

AESIs are selected non-serious and serious AEs that must be recorded in the electronic data capture (EDC) system immediately, within a maximum of 24 hours after becoming aware of the event. For the time period beginning when the ICF is signed through 8 weeks (56 days $\pm$ 5 days) after administration of the last dose of KER-012/Placebo or the start of alternative (off-study) treatment for PAH, whichever is earlier, any AESI, or follow up to an AESI, whether related to study drug or not, must be recorded. If the EDC system is not available, please report any AESI immediately, within a maximum of 24 hours after becoming aware of the event, using the AESI Questionnaire along with the AE/SAE form provided.

AESIs for this trial include the following:

- Pericardial effusion

For the purpose of this protocol, an AESI of Pericardial effusion includes, but is not limited to, the following PTs: Pericardial effusion, Pericardial effusion malignant, Cardiac tamponade, and Pericardial drainage. In addition to the AE/SAE Form, an AESI Questionnaire will be used to capture additional information, including, but not limited to:

- Prior history of Pericardial effusion
- Prior medical history that may increase the potential of developing Pericardial effusion
- Prior or concomitant medications that may be associated with Pericardial effusion
- Description of the Pericardial effusion such as size, rapidity of development, distribution, and composition
- Signs or symptoms consistent with clinical worsening

APPENDIX 2. REGULATORY, ETHICAL, AND STUDY OVERSIGHT

This study will be conducted in accordance with the Protocol; ICH E6: GCP: Consolidated Guidance (R2-Integrated Addendum) March 2018; Declaration of Helsinki World Medical Association Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, as it may be amended; applicable data protection laws and regulations; and all laws, rules, and regulations applicable to the study or KER-012 in jurisdictions in which the Investigator conducts the study.

A2-1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE APPROVAL

The protocol will be submitted for approval to the appropriate IRB/EC. Prior to initiation of the study, the Investigator must provide the Sponsor or CRO with a copy of the written IRB/EC approval of the protocol and study ICF before the study may begin at the investigative site(s).

This approval letter will identify the study ICF by date and the study protocol by protocol number, title, and date and/or version number. The Investigators will receive all the documentation needed for submitting the present protocol to the IRB/EC. The composition of the IRB/EC will also be provided to the Sponsor or CRO. If approval is suspended or terminated by the IRB/EC, the Investigator will notify the Sponsor or CRO immediately.

It is the responsibility of the Investigator to report study progress to the IRB/EC as required. The Investigator at the study site or his/her nominee will be responsible for reporting SAEs to the IRB/EC as soon as possible, and in accordance with the guidelines of the IRB/EC.

A2-2. REGULATORY APPROVAL

Relevant study documentation will be submitted to the Regulatory Authorities of the participating country, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

The Investigator will ensure that this study is conducted in full compliance with the protocol, the Declaration of Helsinki, the ICH GCP guidelines, Regulation (EU) No. 536/2014, and all other applicable local laws and regulations. Compliance with these standards provides assurance that the rights, safety, and wellbeing of participants are protected.

In agreeing to the provisions of the protocol, these responsibilities are accepted by the Investigator.

A2-3. ETHICAL CONDUCT OF THE STUDY

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, ICH GCP guidelines, Regulation (EU) No. 536/2014, and the applicable national and local laws and regulatory requirements.

A2-4. PARTICIPATION INFORMATION AND CONSENT

The process of obtaining informed consent must be in accordance with applicable regulatory requirements and must adhere to ICH GCP guidelines.

The Investigator is responsible for ensuring that no participant undergoes any study-related examination or activity before that participant has given written informed consent to participate in the study.

The Investigator or designated personnel will inform the participant of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The participant should be given every opportunity to ask for clarification of any points they do not understand and, if necessary, ask for more information. At the end of the discussion, the participant will be given ample time to consider participation in the study. Participants will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file. A signed and dated copy of the participant ICF will be provided to the participant or their authorized representative.

- Sites in Germany: see [Appendix A7-1.2](#)

It should be emphasized that the participant may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the participant is otherwise entitled. Participants who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, a new ICF will be approved by the IRB/EC (and Regulatory Authorities, if required). The study participants will be informed about this new information, and re-consent will be obtained.

A2-5. FUTURE USE OF STORED SPECIMENS AND DATA

Blood and urine samples may be stored and used for future research to develop methods, assays, prognostics, and/or companion diagnostics related to PAH, bone disorders, and muscle disorders and/or to further understand the mechanism of action or safety of KER-012.

Samples may be stored for a maximum of 10 years following the last participant's last visit. The collection, labeling, storage, and shipment of samples will be detailed in the Laboratory Manual.

A2-6. ACCESS TO SOURCE DOCUMENTS

In compliance with local regulations and ICH GCP guidelines, it is required that the Investigator and institution permit the Sponsor and authorized representatives of the Sponsor, the regulatory agency(s), and the IRB/EC direct access to review the participant's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform the participant and obtain their consent to permit named representatives to have access to his/her study-related records without violating the confidentiality of the participant.

A2-7. PROTOCOL AMENDMENTS

No changes (amendments) to the protocol may be implemented without prior approval from the Sponsor and the appropriate IRB/EC, except where necessary to eliminate an immediate hazard to participants, or when the change involves only logistical or administrative aspects of the study. If a protocol amendment requires changes to the Information Sheet and Consent Form (ICF), the revised ICF, prepared by the Investigator, must be approved by the IRB/EC.

A2-8. PROTOCOL DEVIATIONS

It is the Investigator's responsibility to ensure that staff and participants follow the protocol and to address any issues that could lead to deviation. Prospective protocol waivers will not be granted.

If any issue arises relating to the safety of study participants and requires a deviation from the protocol, the Investigator may immediately make such a deviation. If there is a need for such a deviation, the Investigator or designee must notify the Sponsor and the responsible IRB/EC of the facts and circumstance causing the deviation as soon as is reasonably practical, but in any event no later than 5 working days after the change is implemented. The nature and reasons for the protocol deviation will be recorded in the protocol deviation log.

The Sponsor may not reimburse the Investigator for cases in which the study procedures and evaluations are conducted in a way that results in major protocol deviations, such as enrollment of ineligible participants or serious deviations resulting in the removal of a participant's data from the analysis.

A2-9. QUALITY ASSURANCE AND QUALITY CONTROL

A2-9.1. AUDIT AND INSPECTION

Study centers and study documentation may be subject to quality assurance audit(s) during the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by Regulatory Authorities at their discretion, during or after completion of the study.

A2-9.2. MONITORING

Data for each participant will be recorded on an eCRF. Data collection must be completed for each participant who signs an ICF and is administered IMP.

In accordance with the ICH GCP guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the monitor will review regulatory documentation, eCRFs, source documentation, and IMP storage, preparation, and accountability. The eCRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents.

The Investigator must permit the monitor, the IRB/EC, the Sponsor's internal auditors, and representatives from Regulatory Authorities' direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs. Some monitoring visits may be conducted remotely if applicable in accordance with the study COVID-19 Mitigation Plan and current local restrictions.

The Investigator must ensure that the monitor is allowed to review all source documents pertinent to study participants and must cooperate with the monitor to ensure that any problems noted during the study are resolved. The Investigator must maintain a comprehensive and centralized filing system of all study related documentation that is suitable for monitoring by the Sponsor or its designated monitors and by quality assurance auditors or representatives of Regulatory Authorities.

A2-9.3. DATA MANAGEMENT PROCEDURES

The Sponsor or its designee will provide eCRF Completion Guidelines for eCRF data entry. Study-specific data management procedures will be maintained in the Data Management Plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

The Investigator or designee should enter data into the eCRF in a timely manner after the participant visit. The eCRFs and any supporting documents should be available for retrieval at any given time. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and all required reports.

A2-9.4. DATA PROTECTION

The Sponsor as Data Controller ensures that all its processing activities involving personal data performed in the scope of this study are compliant with, but not limited to, the requirements set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments, the

Health Insurance Portability and Accountability Act (HIPAA), and any additional applicable national laws on Data Protection.

To comply with the applicable laws and regulations on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and processed personal data, the Sponsor has implemented and maintains the following measures:

- Restriction and monitoring of physical access to the Sponsor's office a to employees, personnel, consultants, and approved visitors.
- Ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical study.
- Implementing the pseudonymization and encryption of personal data, as appropriate.
- Implementing cybersecurity measures designed to protect the ongoing confidentiality, integrity and availability of processing systems and services.
- Implementing network, application, database security by means of firewalls and antivirus/anti-malware.
- Means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident.
- Logging of security events/incidents in information systems.
- Implementing procedures that cover reporting, analysis, monitoring, and resolution of security incidents.
- Ensuring that the Sponsor's information systems, computers and software involved in the performance of the services provided in the Study are backed up.
- A process for regularly testing, assessing, and evaluating the effectiveness of the Sponsor's technical and organizational measures for ensuring the security of the processing.
- Implementing procedures to capture within reasonable time-manner any personal data breach occurred.
- Implementing policies and practices for securing destruction of paper documents containing personal data.

The Sponsor will ensure the technical and organizational security measures described above are periodically reviewed and updated to take into account any material evolution on technological developments. The Sponsor may apply additional specific statutory requirements, where applicable in the national laws, and will implement the necessary security measures even if they are not expressly listed above.

In addition to the above-mentioned technical and organizational measures, the Sponsor will make sure that appropriate and suitable safeguards are used, including by entering into standard contractual clauses issued by the European Commission, as may be replaced from time to time,

with its subcontractors, as applicable, to address any risks to the protection of personal information.

Except for the activities in the scope of the site monitoring, the name of the participant will neither be asked for, nor recorded by the Sponsor. An identification number will be allocated to each participant registered in the IRT system. This number will identify the participant and will be included on all eCRFs, and corresponding material and data associated with the subject.

Monitors acting on behalf of the Sponsor will have access to fully identifiable information only in the scope of the site monitoring visits, and only for the source data verification mandatory under clinical trial framework, including the ICH GCP obligations applicable to the conduct of the Study. Staff involved in the performance of this task are bound by any additional stricter confidentiality clauses imposed upon them, as compared to other staff members.

The Sponsor has put in place a policy that governs responding to and reporting of any data breach that occurs at the Sponsor's or its sub-contractor's facilities and premises, as required by applicable law or regulation. In case of the occurrence of any data breach, the Sponsor will immediately apply relevant measures from its policy to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach. Any data breach that is likely to result in a high risk to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority within 72 hours of the Sponsor becoming aware of the data breach. In addition, in the event of a data breach that is likely to result in a high risk to the rights and freedoms of data subjects, such data subjects will be informed by the Sponsor (via clinical study site) without undue delay.

A2-9.5. BUSINESS CONTINUITY PLAN

The protocol includes the following adaptations to minimize risk while prioritizing the overall well-being and best interests of all involved in the study. This protocol was written considering the impact of COVID-19 and other situations beyond the participant's and site's control, should they occur, such as states of emergency, natural disasters, public health mandates, etc., which may affect the conduct and execution of Study KER-012-A201. These situations are referred to hereafter as "catastrophic situations(s)." With these priorities in mind, the protocol design will still permit assessment of safety and efficacy of KER-012.

- Study visits, when applicable, can be conducted as home visits.
- Some monitoring activities may take place remotely or with a modified schedule.

In addition to the above items included in the protocol, ongoing risk assessments and monitoring of the COVID-19 situation or other circumstances will be conducted by the Sponsor with input from the Investigator at both a site and country level. These ongoing assessments include changes to any of the following:

- Potential impact on study participants
- Potential impact on study site staff

- Potential impact on Sponsor/CRO staff conducting site monitoring and central review of data

If visits proceed at the site during a catastrophic situation such as COVID-19, Investigators should follow their institutional and locally accepted clinical and governmental recommendations to ensure the safety of study participants while at the site. In the case of the COVID-19 pandemic, this may include, but is not limited to the site is safe to enter, participant temperature screening, maintaining safe distances between the study participant and the site staff, sterilization or disinfection of the common areas and study equipment (e.g., thermometers, ECG, etc.), and efficiently managing the time spent at the site. Deviations from the protocol because of COVID-19 or other unforeseen circumstances will be captured the same way as all other protocol deviations with the addition of being categorized as due to COVID-19 or other unforeseen circumstances, as appropriate.

In the European Union, in any emergency or pandemic situation, except COVID-19, all procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment to the competent authority for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

Other mitigation plans, as appropriate, may be instituted.

A2-10. RECORD RETENTION

The Investigator will maintain all study records according to ICH GCP guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Study Agreement. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility, and the Sponsor will be notified.

A2-11. PUBLICATIONS

Any and all scientific, commercial, and technical information disclosed orally, visually, or in writing by Keros in this protocol or elsewhere will be considered the confidential and proprietary property of Keros (the “Confidential Information”). The Investigator shall hold the Confidential Information in confidence and shall not disclose the Confidential Information to any third party except to such of the Investigator’s employees and staff as have been made aware that the Confidential Information is confidential, who are bound to treat it as such, and to whom disclosure is necessary to evaluate the Confidential Information. The Investigator shall not use the Confidential Information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study. The Investigator shall not use or exploit the Confidential Information for the benefit of another without the prior written consent of Keros.

The Investigator agrees that Keros is and shall remain the exclusive owner of the Confidential Information and all patent, copyright, trade secret, trademark, and other intellectual property

rights therein. No license or conveyance of any such rights to the Investigator is granted or implied herein.

The Investigator understands that the information developed from this clinical study will be used by Keros in connection with the development of KER-012 and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, and government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide Keros with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between Keros and the Investigator and/or the Investigator's institution.

APPENDIX 3. CLINICAL LABORATORY PARAMETERS

The tests listed below will be performed by the central laboratory at the time points specified in the SOA ([Section 1.3](#)).

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

Chemistry	Hematology	Urinalysis
Albumin (ALB) Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) Calcium Magnesium Phosphorous Chloride Carbon dioxide Creatinine C-reactive protein (CRP) eGFR (calculated CKD-EPI) Glucose Lactate dehydrogenase (LDH) Potassium Sodium Total bilirubin Total protein Creatinine kinase	Red blood cells (RBC) Hemoglobin (Hgb) Hematocrit (Hct) Red blood cell indices Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Red cell distribution width (RDW) White blood cells (WBC) White blood cell differential (absolute and %) Platelet count Reticulocyte Panel: Reticulocyte count % Reticulocyte count-absolute	Appearance Specific gravity pH Protein Glucose Ketones Urobilinogen Bilirubin Albumin ¹ Urea Creatinine Blood Protein/creatinine ratio (calculated) Albumin/creatinine ratio (calculated) ¹ Urine pregnancy test ²
Biomarkers	Serology	Coagulation ³
Bone specific alkaline phosphatase (BSAP) Connective tissue growth factor (CTGF) Galectin N-terminal pro hormone B-type natriuretic peptide (NT-proBNP) Osteopontin	Hepatitis B surface antigen Hepatitis B core antibody Hepatitis C virus (HCV antibody with reflex HCV qPCR) Human immunodeficiency virus Serum pregnancy test	Prothrombin time (PT) Activated partial thromboplastin time (aPTT) International normalized ratio (INR)

Abbreviations: eGFR= estimated glomerular filtration rate.

¹ Albumin and albumin/creatinine ratio are not required prior to dosing.

² Urine pregnancy tests are performed on site using a urine pregnancy test kit and not part of central lab urinalysis.

³ All participants will have coagulation performed at Screening and baseline. Subsequent evaluations are only performed on participants taking anti-coagulation medication.

Investigators must document their review of each laboratory safety report.

APPENDIX 4. WORLD HEALTH ORGANIZATION FUNCTIONAL CLASSIFICATION (WHO-FC)

(Galie et al., 2013)

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

APPENDIX 5. SIX-MINUTE-WALK TEST

A standardized 6MWT will be performed in accordance with the [A. T. S. Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories \(2002\)](#) and [\(Holland et al. \(2014\)\)](#). The 6MWT should be administered by the same tester at each study site throughout the study, whenever possible. The 6MWT should be performed indoors, along a long, flat, straight (without turns or significant curves), enclosed, well-ventilated area with a hard surface that is seldom traveled. The walking course should be 30 m in length and at least 2-3 m wide. The length of the area should be marked every 3 m. The turnaround points should be marked (e.g., with a cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor (e.g., using brightly colored tape).

Emergency equipment as per local standards should be available at the time/place of the test. The distance walked in 6 minutes (6MWD) will be calculated and recorded to closest meter.

Requirement of acute supportive rescue medication (e.g., oxygen therapy) and any adverse events occurring during the 6MWT will be recorded. If a participant was assessed at baseline with supplemental oxygen, oxygen should be given at same flow rate in all subsequent 6MWT. Intermittent rest periods are allowed if the participant can no longer continue. If the participant needs to rest briefly, they may stand or sit and then begin again when they are sufficiently rested but the clock will continue to run. A participant should use his or her usual walking aids (if needed) during the test (cane, walker, etc.). Same walking aids should be used throughout the study. If circumstances arise that walking aids needs to be used post baseline, such needs should be recorded.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. A chair that can be easily moved along the walking course
3. Lap counter or worksheets on a clipboard
4. A source of oxygen
5. Portable pulse oximeter

PARTICIPANT PREPARATION

6. Comfortable clothing and shoes should be worn.
7. The participant's usual medical regimen should be continued.
8. A light meal is acceptable before early morning or early afternoon tests.
9. Participants should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.

3. The participant should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate.

Instruct the participant as follows:

The staff administering the test will use the following exact dialogue with the participant:

“The aim of this test is to walk as far as possible for 6 minutes. You will walk along this hallway between the markers, as many times as you can in 6 minutes. I will let you know as each minute goes past, and then at 6 minutes I will ask you to stop where you are. Six minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary, but please resume walking as soon as you are able. Remember that the objective is to walk AS FAR AS POSSIBLE for 6 minutes, but don’t run or jog. Do you have any questions?”

Position the participant at the starting line. You should also stand near the starting line during the test. Do not walk with the participant.

The staff administering the test will then start the test by saying the following to the participant:

“Are you ready?”

“Start when I say “GO””

As soon as the participant starts to walk, start the timer.

Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the participant. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the participant the following (in even tones): “You are doing well. You have 5 minutes to go.”

When the timer shows 4 minutes remaining, tell the participant the following: “Keep up the good work. You have 4 minutes to go.”

When the timer shows 3 minutes remaining, tell the participant the following: “You are doing well. You are halfway done.”

When the timer shows 2 minutes remaining, tell the participant the following: “Keep up the good work. You have only 2 minutes left.”

When the timer shows only 1 minute remaining, tell the participant: “You are doing well. You have only 1 minute to go.”

Do not use other words of encouragement (or body language to speed up).

If the participant stops walking during the test and needs a rest, say this: “You can lean against the wall if you would like; then continue walking whenever you feel able.” Do not stop the timer.

If the participant stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), bring the chair over for the participant to sit on, discontinue the walk, and note on the worksheet the distance, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: “In a moment I’m going to tell you to stop. When I do, just stop right where you are, and I will come to you.”

When the timer rings (or buzzes), say this: “Stop!” Walk over to the participant. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

Post-test:

1. Record the number of laps from the counter if not on worksheet.
2. Record the additional distance covered (the number of meters in the final partial lap) using the markers and/or measuring tape.
3. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

APPENDIX 6. CONTRACEPTIVE GUIDANCE

WOCBP and fertile male participants with a partner of childbearing potential must agree to use highly effective contraceptive method(s) while on the IMP (including dose interruptions) and for at least 8 weeks after the last dose of the IMP. A WOCBP is a woman who is considered fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

A male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

WOCBP will undergo a serum pregnancy test at the Screening Visit and the results must be available prior to administration of the first dose of IMP. Thereafter, urine or serum pregnancy tests will be performed as indicated in the SOA ([Section 1.3](#)) and as clinically indicated. If a urine pregnancy test is positive, it will be confirmed by a serum pregnancy test, and dosing should be withheld until lack of pregnancy is confirmed.

The following birth control methods may be considered highly effective (failure rate of less than 1% per year):

- Combined (estrogen and progesterone) hormonal contraception associated with inhibition of ovulation, initiated ≥ 1 month prior to Day 1:
 - Oral
 - Intravaginal
 - Transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation, initiated ≥ 1 month prior to Day 1:
 - Oral
 - Injectable
 - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal ligation or occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the participant and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence.

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the participant's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Institutional Review Board/Independent Ethics Committee (IECs/IRBs). Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Male participants who are sexually active with a female partner of childbearing potential must agree to use condoms and have his female partner(s) use ≥ 1 of the contraceptive measures listed above.

If a contraceptive method listed above is restricted by local regulations/guidelines, then an alternative approved contraception method must be used.

All participants must agree to refrain from donating/freezing germ cells (eggs/sperm) for the duration of the study and for 8 weeks after the last dose of IMP.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, WOCBP must adhere to the contraception requirement (described above) from the signing of the ICF at Screening, through the duration of study treatment and for at least 8 weeks after the last dose of KER-012. If there is any question that a WOCBP will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

APPENDIX 7. COUNTRY-SPECIFIC GUIDELINES

Please reference applicable country-specific adjustments or modifications:

A7-1.1. FRANCE

For sites in France, see country-specific exclusion criteria regarding specific populations per applicable French law (Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1).

EXCLUSION CRITERIA

- Persons under court protection, persons not affiliated to a social security system, protected adults.

A7-1.2. GERMANY

For sites in Germany, the ICF will be provided to the participant only. Authorized representatives are not allowed to receive the ICF.

A7-1.3. ALL COUNTRIES IN THE EUROPEAN UNION

For sites in the European Union, participants should be discontinued from treatment if any of the following criteria are met:

- ALT or AST $\geq 5 \times$ ULN or if elevated at baseline, $\geq 5 \times$ increase from baseline.
- Total bilirubin $\geq 3 \times$ ULN or if elevated at baseline, $\geq 3 \times$ increase from baseline.

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