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Clinical Study Protocol
Study AV-101-003

Clinical Study Protocol Title:	IMPAHCT-FUL: A Long-Term Extension, Multi-Center Safety Study of AV-101 in Subjects With Pulmonary Arterial Hypertension (PAH) Who Have Completed Study AV-101-002
Study Number:	AV-101-003
Aerovate Therapeutics Compound Number:	AV-101
Short Title:	**I**nhaled I**m**atinib **P**ulmonary **A**rterial **H**ypertension **C**linical **T**rial – **F**ollow **U**p **L**ong Term Extension (IMPAHCT-FUL)
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Protocol Synopsis

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Protocol Title: IMPAHCT-FUL: A Long-Term Extension, Multi-Center Safety Study of AV-101 in Subjects With Pulmonary Arterial Hypertension (PAH) Who Have Completed Study AV-101-002

Short Title: Inhaled I**m**atinib **P**ulmonary **A**rterial **H**ypertension **C**linical **T**rial – **F**ollow **U**p **L**ong Term Extension (IMPAHCT-FUL).

Rationale:

Clinical efficacy of oral imatinib mesylate in the treatment of PAH was observed in Functional Class II-IV patients in the Phase 3 IMPRES trial, in which the primary endpoint, six minute walk distance (6MWD), as well as secondary endpoints measuring pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), cardiac output (CO), and N-Terminal Prohormone-B Natriuretic Peptide (NT-proBNP) all showed statistically significant and therapeutically relevant improvements on top of the maximal standard of care (Hoeper et al., 2013). However, oral imatinib was not well tolerated and further clinical development was halted.

Given the demonstrated clinical efficacy of oral imatinib in PAH, Aerovate is developing a dry powder inhaled imatinib, AV-101, to target the delivery of imatinib to the diseased organ, the lungs. Inhaled administration of AV-101 is expected to provide rapid local exposure of respiratory tissue to imatinib with a lower dose and lower systemic exposure compared to Gleevec® oral tablets. Aerovate expects that inhaled AV-101 administration will result in a more favorable benefit/risk profile than that observed with oral Gleevec administration. Therefore, subjects who successfully complete the 24-week placebo-controlled trial (AV-101-002) will be offered the opportunity to continue into this long-term extension (LTE) study.

Overview and Objectives:

The primary objective of the study is to establish the long-term safety of AV-101. The long-term effects of AV-101 on efficacy measures (e.g., 6MWD, NT-proBNP, cardiac echo) will also be assessed.

Overall Design:

Study AV-101-003 is a long-term extension (LTE) follow up study where recruitment of subjects will continue as the parent study (AV-101-002) progresses from Phase 2b to Phase 3. Subjects who were on placebo in Phase 2b and the Intermediate Part of the study who enroll in the LTE study will be re-randomized to one of the 3 active AV-101 doses until such time as the optimal dose has been selected. Once the optimal dose of AV-101 has been selected, all subjects will be transitioned

to the optimal dose while they continue in the LTE, and subjects completing the Intermediate Part or parent study Phase 3 will enroll into the LTE study at the optimal dose.

Subjects enrolling into the LTE study will be closely followed for the first 24 weeks given that those who transition from placebo will be receiving AV-101 for the first time (See Schedule of Assessments Table 1). Study visits will be every 3 months after completing the first 24-week period. Investigators and subjects will remain blinded to the randomization in the parent study until the optimal dose has been selected for the Phase 3 part in AV-101-002.

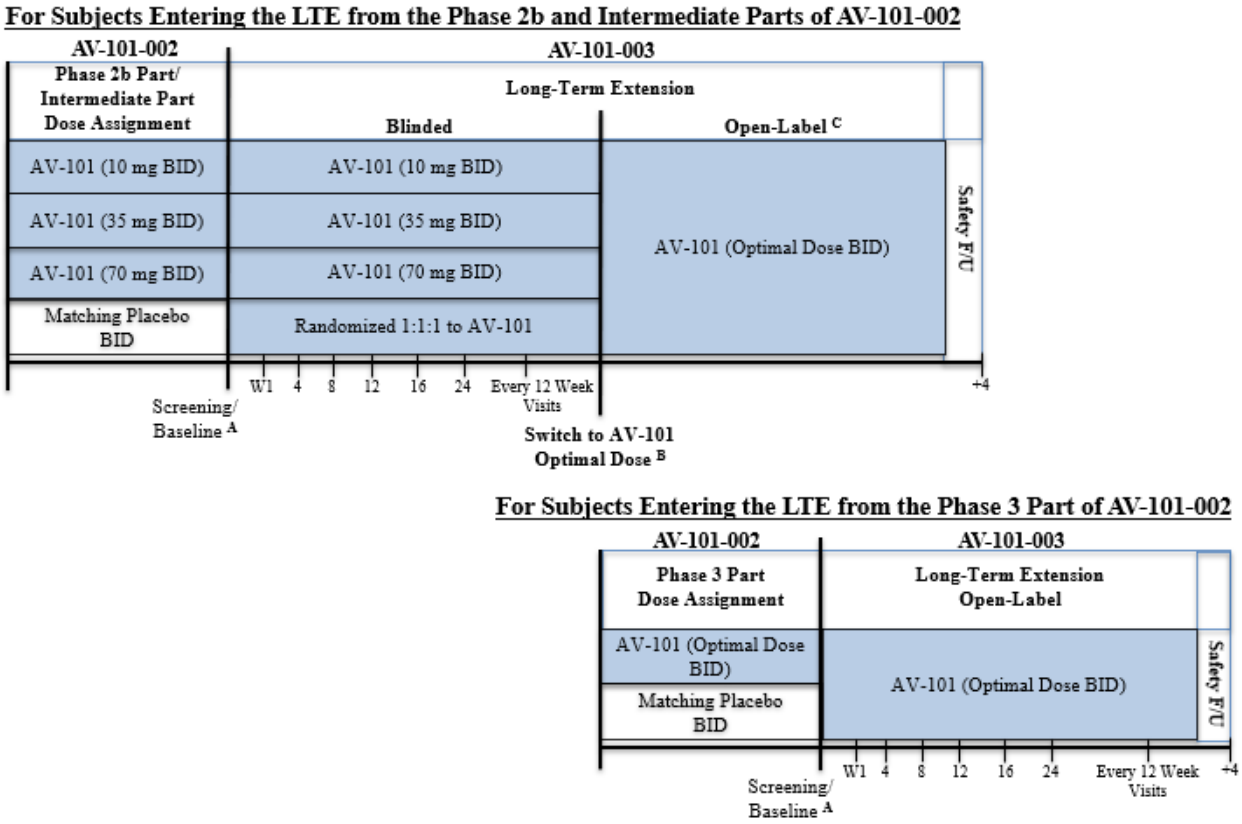
Number of Study Sites: Approximately 140 sites globally

Number of Subjects: Up to approximately 462 subjects

Involvement of Special Committee(s): There will be an independent data safety monitoring board (DSMB) to oversee the safety and welfare of study subjects (Section 3.3).

Figure 1 Study Design of AV-101-003

Figure 1 presents the design schematic of this study.



A. Screening/Baseline Visit and procedures for the LTE will be conducted at the Week 24 Visit for AV-101-002.
B. Once the optimal dose is selected for the parent Phase 3 Part of AV-101-002, subjects who enter the LTE from the Phase 2b Part and the Intermediate Part of AV-101-002 will be transitioned to the optimal dose.
C. Once the AV-101 optimal dose has been selected, the LTE will no longer be blinded. Subjects enrolled during the Intermediate Part of AV-101-002 that enter the LTE study after the optimal dose is selected will be assigned to that dose upon completion of the Week 24 Visit for AV-101-002.

Target Population: Patients with Group 1 PAH who have successfully completed study AV-101-002.

Duration of Study Drug Treatment: The LTE study will continue until 31 December 2025 or until the Sponsor stops the study.

Diagnosis and Main Eligibility Criteria: For a complete list of study inclusion and exclusion criteria, please refer to Section 4.1 and 4.2.

Key Inclusion Criteria:

To be eligible, a participant is required to be or have:

- Consented to participate in the LTE and has successfully completed the placebo-controlled 24-week Study AV-101-002.
- Female subjects of childbearing potential who have agreed to continue to use a highly effective form of contraception during the LTE and for at least 30 days after completing or discontinuing study treatment (highly effective forms of contraception are described in Section 7.8).

Key Exclusion Criteria:

Subjects meeting any of the following criteria:

- The Investigator believes that it would not be in the best interest of the subject to be included in the LTE e.g., for clinical or social reasons.
- Subjects who were not compliant with study medication in AV-101-002 as assessed by the Investigator.
- Applicable for France only: Persons referred to in Article L1122-2 of the French Public Health Code:
  - Person deprived of liberty by a judicial or administrative decision
  - Person under psychiatric care
  - Person admitted to a health or social institution for purposes other than research
  - Person who is the subject of a legal protection measure (tutelage, guardianship, safeguard of justice)
  - Person unable to express consent and who is not subject to a legal protection measure

Study Procedures/Frequency:

Subjects will be followed by the Investigator according to clinical practice, with formal (per protocol) assessments conducted at the Screening/Baseline and at other protocol Clinic Visits. Study visits will occur at Screening/Baseline, Weeks 1, 4, 8, 12, 16 and 24. After the Week 24 visit subjects will return to the clinic every 12 weeks for study assessments. There will be a 4-week follow up by telephone after the subject's End of Treatment (EOT) Visit.

If a subject withdraws consent, they should return for an ED Visit within 14 days following the last dose and they should have a Safety Follow-Up (FU) Visit 4 weeks after the ED Visit. Subjects will then be contacted for Vital Status every 24 weeks after the Safety Follow Up Visit by telephone until study completion.

Assessments that will be done at each visit can be found in the Schedule of Assessments (Table 1).

Test Product, Dose, and Mode of Administration:

Capsules of AV-101 inserted into a dry powder inhaler device for administration to subjects' lungs by inhalation.

Subjects entering the LTE study from the Phase 2b and Intermediate Parts of AV-101-002: Capsule strength: 5 mg, 17.5 mg, or 35 mg AV-101. Administered Doses (2 capsules): 10 mg, 35 mg, or 70 mg AV-101, BID.

Subjects entering the LTE study from the Phase 3 Part of AV-101-002: AV-101 optimal dose, BID

If a subject down titrated the dose of AV-101 in Study AV-101-002 and successfully completed 24 weeks of treatment, the subject should begin the LTE study with 2 capsules BID. If the subject did not tolerate the 2 capsules, they may down titrate to one capsule in the LTE. At the time of the optimal dose selection and transition to the optimal dose in subjects who have down titrated in the LTE, the Investigator should decide whether it is clinically appropriate to transition these subjects given the tolerability history and optimal dose selection (Investigators will be unblinded to the treatment dose at this time). Down titration after subjects have switched to the optimal dose will be permitted.

Statistical Methods:

Summary analyses for this study will be performed periodically to generate safety and effectiveness data for regulatory submissions and for review by the Data Safety Monitoring Board (DSMB). Efficacy measures reported in the parent AV-101-002 study will also be collected in the LTE but only for subjects being treated with the open-label optimal AV-101 dose once it is identified. These efficacy measures will be labeled effectiveness measures for LTE reporting.

Safety and effectiveness data will be summarized by AV-101 treatment groups and all subjects combined at cumulative 24-week intervals. Levels in longitudinal continuous, categorical, and time-to-events data will be presented by time-intervals. LTE intervals will be divided into before and after optimal dose treatment. Continuous data will be summarized using the following descriptive statistics: number of observations, mean, standard deviation, standard error, median, minimum, and maximum. Categorical data will be summarized using frequencies and percentages. Changes from baseline will be calculated as the later value minus the baseline value. Baseline will be defined for all endpoints as the time of starting treatment with AV-101 in the parent study (AV-101-002) or baseline LTE. Baseline for subjects previously randomized to placebo will have their baseline defined at Week 24 of the parent study.

Trends or patterns over time in safety and effectiveness measures will be presented graphically, and in repeated measures models applicable to categorical or continuous data. Time-to-event analysis will be performed using Kaplan-Meier procedures as well as a time-to-event model with time-independent and time-varying covariates.

Study Endpoints

- Safety and tolerability of AV-101
- Survival
- Change from baseline in the 6MWD
- Change from baseline in NT-proBNP
- Time to Clinical Worsening events
- Achievement of the multi-component improvement parameters
    - Percent of subjects who achieve the multi-component parameters by visit
    - Time to achieving the multi-component improvement parameters
- Change in WHO Functional Class status
- Change from baseline in REVEAL Lite 2.0 risk score
- Change from baseline in QoL (emPHasis-10) Questionnaire score
- Change from baseline in Transthoracic Echo parameters of right ventricular (RV) function
- Change from baseline in hemodynamics (in subjects who have RHC measures)

Clinical Worsening Events will be defined as:

- Death (all causes)
- Hospitalization for worsening PAH
- Initiation of parenteral prostanoids
- ≥ 15% decline from baseline in 6MWD accompanied with continued or worsening WHO FC III or IV symptoms. The decline in 6MWD must be confirmed with a repeat test on a different day within 2 weeks. (Baseline is defined by the randomization visit in Study AV-101-002 for those on AV-101 and the Week 24 visit for those on placebo in Study AV-101-002).

Clinical Improvement from baseline will be assessed by the proportion of subjects achieving all 3 of the following components at 6 month intervals:

- WHO FC improvement or maintenance of WHO FC II status
- NT-proBNP ≥ 30% improvement or < 300 pg/ml
- 6MWD ≥ 30-meter improvement

The change from baseline in the REVEAL Lite 2.0 risk score (Benza, 2020) at 6 month intervals classified as low, intermediate, or high risk will be assessed using the following variables to derive the risk score:

- Estimated Glomerular Filtration Rate (eGFR) in ml/min/1.73 m^2 or renal insufficiency if GFR is unavailable
- WHO FC

- Systolic blood pressure and heart rate
- 6MWD
- NT-proBNP

Transthoracic Echocardiogram will be assessed and evaluated at 6 month intervals.

Safety and tolerability of AV-101 will be assessed using the following:

- Adverse Events
- Pulmonary Function Tests at 24-week intervals (Spirometry including FEV_1 and FVC, peripheral oxygen saturations and DLCO [Diffusing Capacity of the Lungs for Carbon Monoxide])
- Safety Laboratory Tests at Weeks 4 and 12, and at 12-week intervals thereafter (including chemistry and complete blood count)

Adverse events will be collected throughout the study period.

Safety data analyses

The independent DSMB will monitor safety at regular intervals throughout the Phase 2b/3 study as well as during the LTE study. Details regarding the members, meeting frequency and stopping rules will be specified in the DSMB charter.

Blinding and unblinding considerations

The study will remain blinded until the optimal dose from Study AV-101-002 has been identified. In the event of a medical emergency, the Investigator will be able to receive the treatment assignment, if required to provide optimal care of the subject. Instructions for Emergency Unblinding can be found in the IWRS Manual. See also Section 7.6 Procedures for Breaking the Treatment Code.

Compliance

The study will be conducted within the guidelines of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) as well as appropriate regulatory requirement(s).

Table 1 Schedule of Assessments

Study Procedure*	Screening / Baseline[1]	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20†	Week 24	Every 12 Week Visits	Early Discontinuation or End of Treatment [2]	Safety Follow Up[3]	Vital Status Follow Up[10]
Study Day	**1**	**7 ± 1**	**29 ± 2**	**57 ± 2**	**85 ± 2**	**113 ± 2**	**141 ± 2**	**169 ± 2**	**Every 85 ± 2 thereafter**		**+30d ± 2**	**Every 169 ± 2**
Visit Type	**Clinic**	**Phone**	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Phone**
Written Informed Consent	X											
Medical History	X											
Physical Examination[4]	X		X		X			X	X	X		
Vitals & Weight[5]	X		X		X			X	X	X		
Chemistry & Hematology	X		X		X			X	X	X		
NT-proBNP	X		X		X			X	X	X		
Pregnancy Test[6]	X		X	X	X	X	X	X	X	X		
12-Lead ECG	X		X					X		X		
Resting Transthoracic Echocardiography	X							X	X[7]	X		
Quality of Life Questionnaire	X				X			X	X	X		
6MWT	X		X		X			X	X	X		
Borg Dyspnea Index	X		X		X			X	X	X		
Randomization[8]	X											
Drug Dispensing	X		X		X			X	X			
IMP return/ Compliance			X		X			X	X	X		
WHO Functional Class	X		X		X			X	X	X		
Spirometry Test and Oxygen Saturation[9]	X		X		X			X	X[7]	X		
DLCO	X							X	X[7]	X		

Study Procedure*	Screening / Baseline[1]	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20†	Week 24	Every 12 Week Visits	Early Discontinuation or End of Treatment [2]	Safety Follow Up[3]	Vital Status Follow Up[10]
Study Day	**1**	**7 ± 1**	**29 ± 2**	**57 ± 2**	**85 ± 2**	**113 ± 2**	**141 ± 2**	**169 ± 2**	**Every 85 ± 2 thereafter**		**+30d ± 2**	**Every 169 ± 2**
Visit Type	**Clinic**	**Phone**	**Clinic**	**Phone**	**Clinic**	**Phone**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Phone**
REVEAL Lite 2 Risk Score	X				X			X	X	X		
Concomitant Medications	X	X	X	X	X	X		X	X	X	X	
Clinical Worsening		X	X	X	X	X		X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Vital Status		X	X	X	X	X		X	X	X	X	X

** Unscheduled visits may occur at any time during the study with the assessments to be performed according to the Investigator's judgment. Unscheduled visits may also be necessary for study drug dispensing following temporary withdrawal as described in Sections 6.7 and 7.7.*

† *Week 20 phone visit is only for females of childbearing potential as the main purpose is to provide a reminder to perform home pregnancy testing.*

1. Screening assessments may be performed at the AV-101-002 Week 24 Visit. Study treatment re-randomization shall occur after all AV-101-002 Week 24 procedures are completed for subjects previously randomized to placebo, if LTE participation starts prior to identifying the optimal dose. All LTE participants will be treated with the optimal dose once that dose is identified, unless participants have been down titrated.
2. Subjects discontinuing study treatment must return to the site within 14 days for safety assessments; if this assessment does not correspond with a scheduled study visit, then an Early Discontinuation (ED) Visit will be performed. If the subject is unwilling or unable to come into the clinic for the ED or the End of Treatment Visit, then this visit with as many assessments as possible can be conducted by telephone.
3. The Safety Follow-Up Visit will be performed 30 days (± 2 days) after the ED Visit.
4. A focused physical examination (PE) will be performed at Baseline and clinic post-baseline visits.
5. Height will be recorded at the Screening Visit using the measurement taken from AV-101-002.
6. Urine pregnancy test for females of childbearing potential only. Additionally, home urine pregnancy testing is required every 4 weeks between study visits. When home pregnancy testing is required, a telephone call to the subject is required to confirm the test date, result of the test, lot number, and expiration date of the test (see Section 7.8). NOTE: Follicle Stimulating Hormone (FSH) test may be performed at Screening, per Investigator's discretion to confirm post-menopausal state. A reminder to perform home pregnancy testing is given during phone visits at Weeks 8, 16 and 20.
7. Resting Transthoracic Echocardiography, PFT's and DLCO to be performed every 24 weeks following Week 24 Visit.
8. Randomization or study drug allocation will be performed by IWRS.
9. Testing includes FEV_1, FVC, and peripheral oxygen saturations.
10. Vital Status will be collected every 24 weeks after the Safety Follow Up Visit by telephone until study completion.

1 Introduction

Aerovate Therapeutics Inc. (Aerovate) is developing AV-101 (imatinib powder for inhalation) for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) in adults with WHO Functional Class II–IV symptoms as a disease modifying drug to improve exercise capacity and delay disease progression. AV-101 is a drug-device combination product designed to deliver imatinib directly to respiratory tissues.

1.1 Background

Data from the REVEAL registry demonstrate that, from the time of diagnostic right heart catheterization and even with treatment, patients with PAH had 1-, 3-, 5-, and 7-year survival rates of 85%, 68%, 57%, and 49%, respectively (McGoon and Miller, 2012). This reflects the serious nature of the disease and the need for alternative PAH treatments with new mechanisms of action that directly target the proliferative nature of the vasculopathy, with the ultimate goal being to halt or reverse disease progression.

Clinical efficacy of oral imatinib mesylate in the treatment of PAH was observed in Functional Class II-IV patients in the Phase 3 IMPRES trial, in which the primary endpoint, six minute walk distance (6MWD), as well as secondary endpoints measuring pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), cardiac output (CO), and N-Terminal Prohormone-B Natriuretic Peptide (NT-proBNP) all showed statistically significant and therapeutically relevant improvements on top of the maximal standard of care (Hoeper et al., 2013). However, oral imatinib was not well tolerated and further clinical development was halted.

At therapeutic concentrations, imatinib is an inhibitor of the Abelson murine leukemia viral oncogene homolog (ABL), Colony Stimulating Factor 1 Receptor (CSF1R), KIT Proto-Oncogene Receptor Tyrosine Kinase (cKIT), Discoidin Domain Receptor (DDR), Lymphocyte-Specific Protein Tyrosine Kinase (LCK) and Platelet-derived growth factor receptor (PDGFR) kinases (Davis et al., 2011). Signaling through each of these kinases has been implicated in histopathologic remodeling in PAH including PDGFR mediated proliferation and apoptotic resistance of vascular smooth muscle and endothelial cells, KIT expression directly in the vasculature and its influence on precursor cells, fibrotic signaling and recovery mediated by DDR and ABL, as well as immune dysregulation via LCK, CSF1R and KIT (Schermuly et al., 2005; Montani 2011; Rojo et al., 2019; Leitinger et al., 2014; and Rossy et al., 2012). Due to its anti-proliferative effects, imatinib has the potential to be a disease-modifying therapy for PAH.

Given the demonstrated clinical efficacy of oral imatinib in PAH, Aerovate is developing a dry powder inhaled imatinib, AV-101, to target the delivery of imatinib to the diseased organ, the lungs. Inhaled administration of AV-101 is expected to provide rapid local exposure of respiratory tissue to imatinib with a lower dose and lower systemic exposure compared to Gleevec® oral tablets. Aerovate expects that inhaled AV-101 administration will result in a more favorable benefit/risk profile than that observed with oral Gleevec administration. Therefore, subjects who successfully complete the 24-week placebo-controlled trial (AV-101-002) will be offered the opportunity to continue into this long-term extension (LTE) study.

1.2 Risk/Benefit Assessment

1.2.1 Known Potential Risks

The clinical program for AV-101 is designed to assess the safety (local and systemic) and efficacy of AV-101 in the treatment of patients with PAH. A Phase 1 Single Ascending Dose (SAD)/ Multiple Ascending Dose (MAD) study (Study AV-101-001) in healthy volunteers has been completed. Doses ranged from 1 mg to 90 mg in the SAD study and 10 mg to 90 mg BID for 7 days in the MAD study. This study also included a cohort of patients administered a single dose of Gleevec 400 mg oral tablets. This study established that the systemic exposure to imatinib following the inhaled administration of AV-101 is lower than the predicted steady state systemic exposure of oral imatinib.

AV-101 ranging from 1 mg to 90 mg was well tolerated in the Phase 1 SAD/MAD study. There were no clinically important changes in vital signs, pulmonary function tests including pulse oximetry, and ECG measures. There were no serious adverse events (SAE) reported and most of the adverse events were mild in severity (See Investigators' Brochure). One subject discontinued in the MAD 90 mg group due to vomiting on Day1, which was mild in severity and assigned as treatment related by the Investigator. Exposure of multiple doses of AV-101 in the MAD study was compared to the exposure after an oral dose of imatinib (400 mg). The maximum dose of AV-101 (90 mg BID) was demonstrated to be well within the exposure of oral imatinib.

The Sponsor has conducted two 28-day GLP inhalation toxicity studies in rats and Non-Human Primates (NHP), as well as a 6-month toxicity study in NHPs, with full histopathology of standard tissues to support local and systemic safety of AV-101. Two 7-day dose range finding inhalation toxicity studies in rats and NHPs as well as a 4-day intratracheal and oral administration comparative study in rats and a single-dose multi-route comparative pharmacokinetics study in rats have also been conducted. Inhalation exposures in both the rat and NHP studies exceeded the proposed clinical doses. There were no apparent adverse clinical observations or effects on hematology, clinical chemistry, or organ weights in either rats or NHPs.

[redacted]

[redacted]

The systemic safety of imatinib mesylate is well documented, and the specific risks associated with chronic oral exposure to imatinib mesylate have been characterized as described in the Gleevec prescribing information (Gleevec product labeling). The most frequently reported adverse reactions with oral imatinib (greater than or equal to 20%) that were more frequent than placebo are diarrhea, fatigue, nausea, periorbital edema, reduction in hemoglobin, peripheral edema, rash and vomiting. Other known potential risks of imatinib reported in the Gleevec labeling, particularly for patients with comorbidities and risk factors, include edema and severe fluid retention, cytopenia, severe congestive heart failure and left ventricular dysfunction, severe hepatotoxicity, Grade 3/4 hemorrhage, gastrointestinal perforations, cardiogenic shock/left ventricular dysfunction, bullous dermatologic reactions, hypothyroidism, fetal harm when administered to a pregnant woman, growth retardation occurring in children and pre-adolescents, reports of motor vehicle accidents, and renal toxicity (Novartis Pharmaceuticals Corporation, 2022).

The safety profile of AV-101 is expected to be broadly consistent with that known for oral imatinib. However, inhaled AV-101 will be dosed at absolute levels lower than Gleevec and delivered directly to the lungs, reducing systemic exposure to imatinib. In published studies of oral imatinib mesylate, including 229 PAH patients who received imatinib 200 – 400 mg/day from 6 months to 204 weeks, similar AE profiles to those reported for Gleevec were observed. Subdural hematoma (SDH) occurred during imatinib treatment in 10 PAH patients in the published studies. Of the 10 patients, 1 died of SDH, 8 recovered, and 1 died of an unrelated cause. The exact relationship between oral imatinib mesylate treatment and SDH complications is unclear, but all patients who experienced SDH were on concomitant anticoagulation therapy. Imatinib is a competitive inhibitor of CYP3A4 and CYP2C9 enzymes that metabolize warfarin, which may result in increased plasma concentrations of these compounds and an increased risk of developing SDH. Anticoagulant use is disallowed in the AV-101-02 and AV-101-003 studies. Investigators are required to evaluate subjects for the presence of any signs or symptoms suggestive of intracranial bleeding such as: headache, confusion, vomiting, slurred speech etc.

In addition:

AV-101 must not be administered to pregnant or nursing women.

Additional details can be found in the Investigators' Brochure.

1.2.2 Known Potential Benefits

Oral imatinib mesylate (400 mg) has been shown to positively benefit hemodynamics and exercisability in patients with PAH. Therefore, there is the potential that AV-101 could benefit participants in this study including improvements in symptoms, exercisability, and quality of life, in addition to the benefit of medical evaluation throughout the study. Participation in this study may help generate future benefits for patients experiencing PAH.

1.2.3 Assessment of Risk/Benefit

The doses of AV-101 used in this study are well below the oral dose of imatinib mesylate (400 mg) which was poorly tolerated in a previous study in patients with PAH. The doses of AV-101 delivered directly to the lung are much lower than 400 mg and are expected to be well tolerated; however, there is the potential that AV-101 could still cause side effects leading to intolerability in some subjects. The safety and tolerability of AV-101 demonstrated in the Phase 1 study and the non-clinical toxicology studies, and the establishment of a safety review committee all contribute to risk mitigation and to the safe initiation and conduct of this study.

1.2.3.1 COVID-19: Risk Mitigation/Benefit Assessment

The Sponsor will continually assess whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to study subjects, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

1. PAH continues to be a condition associated with a high morbidity and mortality despite advances in treatment strategies over the past 25 years.

2. Despite such treatments, the prognosis for patients with PAH remains poor (see Section 1.1). There is a clear need for new treatments to target the underlying pathophysiology of PAH.

3. Imatinib is an inhibitor of several protein kinases implicated in the pathophysiology of pulmonary hypertension. Treatment with oral imatinib resulted in improved hemodynamics and exercise capacity in a controlled trial (Imatinib in Pulmonary Arterial Hypertension, a Randomized Efficacy Study [IMPRES]), among PAH patients inadequately responsive to 2 to 3 PAH-specific therapies.

4. Based on the current knowledge, this compound has the potential to become an additional treatment option for patients with PAH and has the potential to at least partially to correct the pathology of the disease.

5. There are no data or biological reason to suspect that imatinib would have any negative effect on immune response or interfere with potential SARS-CoV-2 vaccine inoculation and subjects will be allowed to receive vaccinations for SARS-CoV-2 or booster shots if required during the trial.

6. The IMPAHCT-FUL trial has been designed to minimize any unnecessary potential viral exposure by allowing some of the study visits to be conducted remotely (see Section 6.7).

7. Additionally, given the heterogeneity of disease course in individuals infected with COVID-19, should a subject become infected during the trial and is symptomatic and hospitalized, study drug administration will be temporarily discontinued keeping the subject's safety as the only priority (see Section 6.7).

Benefit-Risk Conclusion

PAH is a serious condition with high morbidity and mortality despite the advances made in treatment strategies and therapies. There is an underlying and important unmet medical need to develop therapies for these patients who ultimately may need a lung transplant.

In light of the current COVID-19 pandemic, and with the mitigation and safety monitoring procedures to be followed, it can be concluded that this study can proceed for the benefit of patients with PAH (see Section 6.7).

1.3 Scientific Rationale for Study Design

Study AV-101-003 is a LTE study for subjects having successfully completed study AV-101-002. The objective of this extension study is to allow for continuation of treatment and to evaluate the long-term safety of AV-101.

Use of Background PAH Therapy:

Subjects will be allowed to use any background licensed PAH therapies as clinically indicated; however, inhaled prostacyclins will not be allowed.

Use of Placebo:

There will be no placebo in the LTE study.

1.4 Justification for Dose Selection

Benefit/Risk Assessment:

The doses administered in the Phase 2b and Intermediate Parts of Study AV-101-002 are 10 mg, 35 mg, and 70 mg BID. In the LTE study, subjects will continue on the same active dose and placebo subjects will be re-randomized to one of these active doses until such time as the optimal dose has been selected from the Phase 2b data based upon efficacy, safety, and tolerability. Once the optimal dose has been selected, subjects in the LTE will be transitioned to the optimal dose. Subjects on the optimal dose or placebo in the Phase 3 Part of AV-101-002 will continue in the LTE at the optimal dose.

2 Objectives and Endpoints

2.1 Study Objectives

The objective of the study is to establish the long-term safety and tolerability of AV-101. The long-term effects on survival as well as clinical and quality of life measures over time will also be assessed.

2.2 Study Endpoints

- Safety and tolerability of AV-101
- Survival
- Change from baseline in the 6MWD
- Change from baseline in NT-proBNP
- Time to Clinical Worsening events
- Achievement of the multi-component improvement parameters
    - Percent of subjects who achieve the multi-component parameters by visit
    - Time to achieving the multi-component improvement parameters
- Change in WHO Functional Class status
- Change from baseline in REVEAL Lite 2.0 risk score
- Change from baseline in QoL (emPHasis-10) Questionnaire score
- Change from baseline in Transthoracic Echo parameters of right ventricular (RV) function
- Change from baseline in hemodynamics (in subjects who have RHC measures)

Endpoint Evaluation:

Clinical Worsening Events will be defined as:

- Death (all causes)
- Hospitalization for worsening PAH
- Initiation of parenteral prostanoids
- ≥ 15% decline from baseline in 6MWD accompanied with continued or worsening WHO FC III or IV symptoms. The decline in 6MWD must be confirmed with a repeat test on a different day within 2 weeks. (Baseline is defined by the randomization visit in Study AV-101-002 for those on AV-101 and the Week 24 visit for those on placebo in Study AV-101-002).

Clinical Improvement will be assessed by the proportion of subjects achieving all 3 of following components at 6 month intervals:

- WHO FC improvement or maintenance of WHO FC II status
- NT-proBNP ≥ 30% improvement or < 300 pg/ml
- 6MWD ≥ 30-meter improvement

The change in the REVEAL Lite 2.0 risk score (Benza 2020) at 6 month intervals assessed as either low, intermediate or high risk and will be assessed using the following variables to derive the risk score:

- Estimated Glomerular Filtration Rate (eGFR) in ml/min/1.73 m2 or renal insufficiency if eGFR is unavailable
- WHO FC
- Systolic blood pressure and heart rate
- 6MWD
- NT-proBNP

Transthoracic Echocardiogram will include the following parameters and will be evaluated at 6 month intervals:

- Right Ventricular (RV) myocardial strain
- Tricuspid annular systolic velocity (TA S')
- Tricuspid annular peak systolic excursion (TAPSE)
- RV fractional area change (RVFAC)
- RV ejection fraction (RVEF)
- Tricuspid regurgitant jet velocity (TRJV) to calculate pulmonary artery systolic pressure (PASP)
- RV/PA Coupling (TAPSE/PASP)

Safety and tolerability of AV-101 will be assessed using the following:

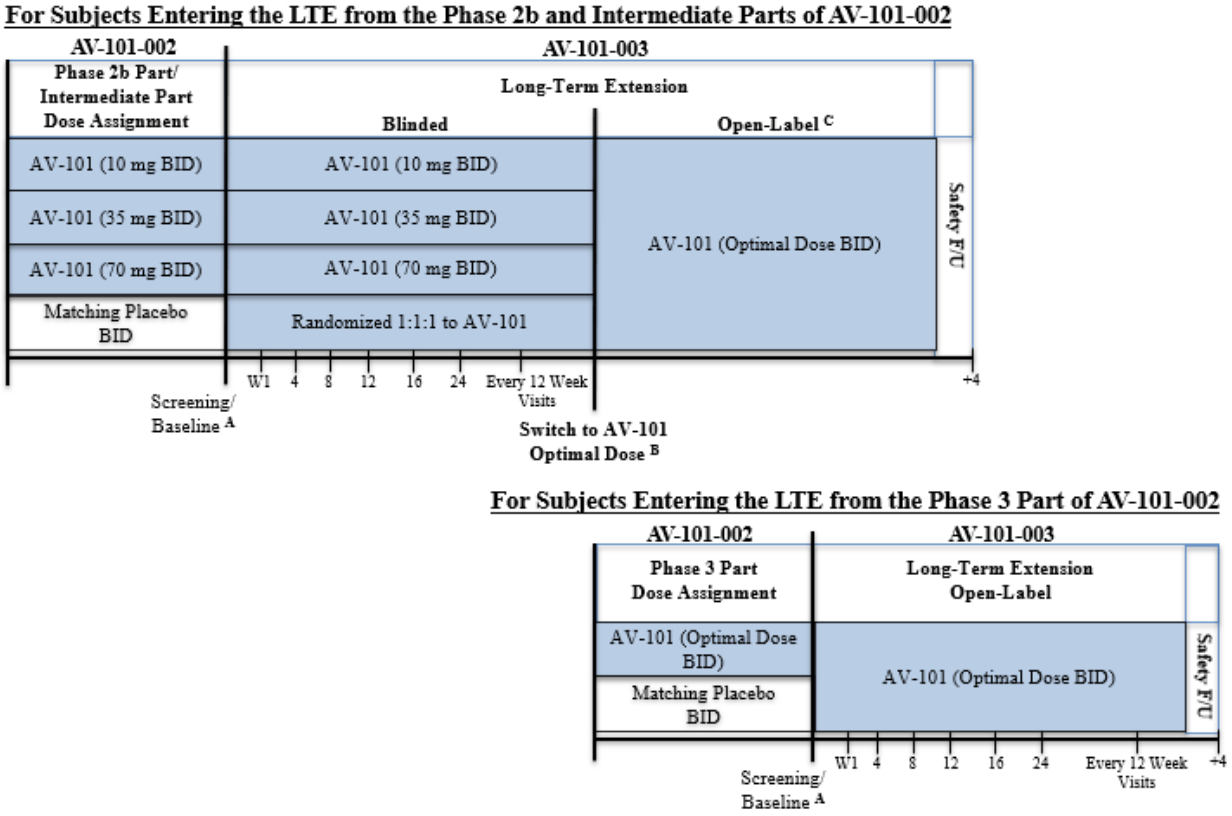
- Adverse Events
- Pulmonary Function Tests at 24-week intervals (Spirometry including FEV_1 and FVC, peripheral oxygen saturations and DLCO [Diffusing Capacity of the Lungs for Carbon Monoxide])
- Safety Laboratory Tests at Weeks 4 and 12, and at 12-week intervals thereafter (including chemistry and complete blood count)

Adverse events will be collected throughout the study period. The DSMB will review the safety data throughout the trial.

3 Study Design

3.1 Overall Design

Figure 1: Study Design of Study AV-101-003



A. Screening/Baseline Visit and procedures for the LTE will be conducted at the Week 24 Visit for AV-101-002.
B. Once the optimal dose is selected for the parent Phase 3 Part of AV-101-002, subjects who enter the LTE from the Phase 2b Part and the Intermediate Part of AV-101-002 will be transitioned to the optimal dose.
C. Once the AV-101 optimal dose has been selected, the LTE will no longer be blinded. Subjects enrolled during the Intermediate Part of AV-101-002 that enter the LTE study after the optimal dose is selected will be assigned to that dose upon completion of the Week 24 Visit for AV-101-002.

The doses administered in the Phase 2b and Intermediate parts of Study AV-101-002 are 10 mg, 35 mg, and 70 mg BID. In the LTE study subjects will continue on these doses and placebo subjects will be re-randomized to one of these active doses until such time as the optimal dose has been selected from the Phase 2b data based upon efficacy, safety, and tolerability. Once the optimal dose has been selected subjects in the LTE will be transitioned to the optimal dose. Subjects enrolled during the Intermediate Part of AV-101-002 that enter the LTE study after the optimal dose is selected will be assigned to that dose upon completion of the Week 24 Visit for AV-101-002. Subjects on the optimal dose or placebo in the Phase 3 Part of AV-101-002 will continue in the LTE at the optimal dose.

The schedule of activities and visit frequency will be similar to the parent study (AV-101-002) for the first 24 weeks of the LTE (Table 1). Thereafter, the interval between study visits will be increased to every 3 months. In the LTE study the quality-of-life instrument used will be the emPHasis-10 questionnaire. Investigators are encouraged to collect RHC hemodynamics in subjects who have in their opinion normalization or near normalization of hemodynamics on the transthoracic echo.

In a small cohort of subjects treated with oral imatinib for PAH, a responder analysis showed that the treatment duration for a complete hemodynamic response was approximately 3 years (Speich, 2015). Therefore, the LTE study will continue until 31 December 2025 or until the Sponsor stops the study.

3.2 End of Study Definition

A subject has completed the study if he/she has completed all study assessments, including the last visit or the last scheduled procedure shown in the Schedule of Assessments (Table 1). See Section 9.2.6 for details on study and sites closures.

3.3 Data Safety Monitoring Board

A DSMB will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of the analysis plan for DSMB review is described in the charter, which is available upon request.

4 Study Population

The eligibility criteria in Sections 4.1 (Inclusion Criteria) and 4.2 (Exclusion Criteria) are designed to enroll only subjects who completed AV-101-002. All relevant medical and nonmedical conditions as well as tolerance to AV-101 should be taken into consideration when deciding whether a subject is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the subject's routine medical care, including Week 24 assessments from AV-101-002 which will serve as baseline for this study, the Investigator will confirm that the subject has provided written informed consent, as indicated in Section 9.1.3.

4.1 Inclusion Criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Subjects who have consented to participate.
2. Subjects who have successfully completed the placebo-controlled 24-week study AV-101-002 without a treatment-limiting toxicity resulting in discontinuation of study drug.
3. Female subjects of childbearing potential who have agreed to continue to use a highly effective form of contraception during the LTE and for at least 30 days after completing or discontinuing study treatment (highly effective forms of contraception are described in Section 7.8).

4.2 Exclusion Criteria

Subjects that are or have the following exclusion criteria at the Screening Visit or during the Screening Period are not eligible for the study:

1. Subjects for whom the investigator believes that it would not be in the best interest of the subject to be included in the LTE e.g., for clinical or social reasons.
2. Subjects who were not compliant with study medication in AV-101-002 as assessed by the Investigator.
3. Clinically relevant history or current psychological abnormality (including alcohol abuse), psychiatric or neurological illness or autonomic neuropathy, which in the opinion of the Investigator could jeopardize or would compromise the subject's ability to participate in the trial.
4. Recent major surgical intervention which in the opinion of the Investigator would compromise the subject's ability to participate in the trial.
5. Pregnant or breast-feeding females

6. Applicable for France only: Persons referred to in Article L1122-2 of the French Public Health Code:
   - Person deprived of liberty by a judicial or administrative decision
   - Person under psychiatric care
   - Person admitted to a health or social institution for purposes other than research
   - Person who is the subject of a legal protection measure (tutelage, guardianship, safeguard of justice)
   - Person unable to express consent and who is not subject to a legal protection measure

5 Treatment

5.1 Investigational Medicinal Product (IMP)

AV-101 will be supplied as white, opaque capsules containing imatinib dry powder in three capsule strengths of 5, 17.5, and 35 mg. When the optimal dose has been identified from the Phase 2b Part of the parent study, sites will be supplied with capsule strengths appropriate for the optimal dose.

Capsules of AV-101 will be inserted into the AV-101 dry powder inhaler (AV-101 DPI; also known as CDA-Haler, manufactured by Emphasys) for administration to the subjects' lungs via inhalation.

5.2 Device Information

The AV-101 DPI device is a single capsule-use, reusable dry powder inhaler. A capsule is placed into the chamber of the inhaler prior to each use. Once actuated, the powder is delivered to the participant's lungs in conjunction with an inspiratory maneuver.

5.3 Packaging and Labeling

The investigational product and devices will be supplied as kits containing a four (4) week supply. Each package will contain four (4) AV-101 DPI devices and four (4) 30 cc HDPE bottles of study drug. Each bottle will contain 32 capsules of study medication. Each bottle and kit will be labeled with a unique-identifier and bar-code and will be dispensed by the Investigative Site/Site Pharmacy at each site in accordance with participant randomization.

5.4 Study Drug Administration

The investigational product should be administered according to the Instructions For Use (IFU), which will be provided to the study subjects. Each dose will require 2 capsules and each dose will be administered once in the morning and once in the evening, approximately 10-12 hours apart, and ideally within 30 minutes of food.

A single bottle should be used for one week before opening a second bottle, and the bottle cap must be replaced after removing the capsules. A new DPI must be used with every new bottle of capsules. A single capsule will be placed in the AV-101 DPI with each use. Upon completion of

the inhalation maneuver, the empty capsule is removed from the device and discarded. The process is repeated to receive the full dose. The device should be cleaned after each dose per the IFU.

5.5 Down Titration

If a subject down titrated the dose of AV-101 in Study AV-101-002 and successfully completed 24 weeks of treatment, the subject should begin the LTE study with 2 capsules BID at the assigned dose i.e., either re-randomized if coming from placebo or continuing on the randomized dose but at two capsules BID if on active. If the subject does not tolerate the 2 capsules, they may down titrate to one capsule in the LTE. At the time of optimal dose selection and the transition to the optimal dose in subjects who have down titrated in the LTE, the investigator should decide whether it is clinically appropriate to transition these subjects to the optimal dose given the tolerability history and optimal dose selection (Investigators will be unblinded to treatment dose at this time). E.g., if a subject in the 10 mg dose group has to down titrate to one capsule (5 mg) then it is likely inappropriate to transition the subject to 70 mg if that is the chosen optimal dose for Phase 3 and LTE; however, this decision should be based on the Investigator's opinion. Down titration to one capsule BID after being switched to the optimal dose in the LTE will be permitted.

If a subject develops intolerable adverse events during the study, a down titration from two capsules to one capsule will be allowed. The Investigator should conduct an Unscheduled telephone or video visit with the subject to discuss and decide whether down titration to a lower dose is warranted. Careful consideration should be made whether to down titrate or not, and the decision to down titrate should be made when the alternative would be to withdraw study treatment due to drug intolerability. The Investigator should capture any adverse or clinical worsening events, and in cases where the Investigator agrees that down titration is appropriate, the CRO Medical Monitor should be notified as soon as possible. Subjects will not be allowed to up-titrate after having down titrated.

If it is determined by the Investigator that down titration is warranted, the subject will be instructed to take only 1 capsule BID from the assigned study drug bottles. The date and reason for down titration must be recorded in the subject's source documents and in the eCRF.

Down titration is also required if an ECG reveals, for a subject, a QTc interval that exceeds 500 msec, or a QTc progression of ≥ 60 msec (see Section 5.9.2).

5.6 Randomization, Blinding, and Measures to Minimize Bias

An interactive web-based randomization system (IWRS) will be used to randomize a previously placebo-treated subject to study drug assignment in the period prior to identification of the optimal dose. Subjects randomized to active treatments in the parent study will remain in their previously assigned active treatment until the optimal dose is identified.

Once a previously placebo treated subject meets the eligibility criteria and is enrolled, the subject will be randomly assigned to a unique randomization number that is associated with the treatment assignment per the randomization list. The subject identification in the parent and LTE trials will remain the same. In addition, the IWRS will allocate study drug to subjects according to the Schedule of Assessments (Table 1).

Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

5.7 Study Drug Preparation, Handling, Storage, and Accountability

Acquisition

The investigational product will be supplied to the clinical site directly from a depot or warehouse as required.

Storage

The kits should be stored in a dry place between 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).

Handling

Packaged clinical kits must be handled and stored as units.

Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study drug, the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Only subjects enrolled in the study may receive study drug and only authorized site staff may supply it.
- Study drug accountability records at the study site will include the following:
    - Confirmation of receipt, in good condition and in the defined temperature range
    - The dose each subject used during the study
    - The disposition (including return, if applicable) of any unused study drug
    - Dates, quantities, study drug number, expiry dates, and the subject numbers
- The Investigator site will maintain records, which adequately document that subjects were provided the dose specified in this protocol, all study drug provided was fully reconciled, and all study drug and device complaints have been documented.
- Unused study drug must not be discarded or used for any purpose other than the present study prior to accountability being performed by the Study Monitor. No study drug or inhaler that is dispensed to a subject may be re-dispensed to a different subject.
- Used and unused devices should be returned by the subject to the site unless otherwise indicated per local policy.

- A Study Monitor will periodically collect the study drug accountability forms.
- Further guidance and information for the final disposition of unused study drug, and study relevant forms such as those to report study drug and device deficiencies, complaints, and incidents are provided in the Pharmacy Manual.

Device and Study Drug Disposal (if applicable):

Devices will be disposed of according to the Pharmacy Manual.

Destruction of used and unused study drug should be performed at the site if allowed by local law only after Sponsor/designee authorization. If that is not possible, the Sponsor/designee will be responsible.

5.8 Study Drug Compliance

Dosing will be done by the subject or subject's caregiver at home throughout the study. Prior to discharge from each scheduled site visit, subjects will be given sufficient study drug for at-home dosing until the next scheduled visit.

Subjects will be instructed to return all unused study drug including the kits at each clinic visit, in order to allow the assessment of compliance with the study treatment. See Section 5.3 for details on how study drug will be packaged. Subjects will be instructed to return all used and unused devices unless otherwise indicated per local policy.

Compliance will be determined based on the amount of unused drug returned. Acceptable compliance for the study is defined as ≥ 80% of planned study drug administration.

Consequences of noncompliance will lead to retraining and/or discontinuation of study drug as described in Section 6.8. In case of overdose see Section 7.9.

5.9 Prior and Concomitant Therapy

Record in the eCRF all prior (therapy taken withing 30 days of the Screening/Baseline Visit) and concomitant therapies (e.g., medicines or nondrug interactions) used from the time the subject signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information (according to the eCRF completion guidelines).

Record in the eCRF information regarding vaccination against SARS-CoV-2 (including any booster vaccination), for any subject that has received the vaccine at any time prior to Screening. See Section 6.7 regarding considerations for SARS-CoV-2 and variants. Contact the CRO Medical Monitor for any questions on concomitant or prior therapy.

5.9.1 Permitted Medicines

Any medications that are considered necessary to protect subject welfare and will not interfere with the study medication may be given at the Investigator's discretion.

Permitted medications are any medications that are required by the subject during the course of the study, and which are not specifically prohibited by the protocol. Any such medications prescribed or used must be recorded in the eCRF.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug (according to the eCRF completion guidelines). Of note, any newly prescribed or changes to diuretic therapy (dose, frequency, etc.) should be captured in the eCRF.

5.9.1.1 Permitted PAH Medicines

The addition of a new PAH therapy(ies) must be documented in the eCRF as well as in the concomitant therapy section. At this time there is no drug interaction data with AV-101 and inhaled prostacyclins and so any inhaled prostacyclin should not be used while taking AV-101 in the LTE study.

5.9.2 Prohibited Medicines

The following treatments are not permitted during the study:

- Inhaled prostacyclin therapies
- Warfarin (or any vitamin K antagonists), DOACs or dual antiplatelet therapy

Use of any of the above nonpermitted medicines and therapies require IMP discontinuation (see Section 6.8) (anti-platelet monotherapy with e.g. aspirin or clopidogrel is allowed).

The use of strong CYP3A4 inhibitors may increase the systemic exposure to imatinib. Likewise, strong CYP3A4 inducers may decrease the exposure of imatinib. It is unknown what contribution of systemically circulating AV-101 will contribute to potential efficacy or adverse events and so alternatives to strong CYP3A4 inhibitors or inducers should be considered.

High doses of oral imatinib are known to have the potential to prolong the QTc interval on the ECG. Drugs that are known to increase the QT interval should be used with caution. For a list of such drugs please refer to https://crediblemeds.org. In the event that a subject develops an absolute prolongation of the QTc interval to a value > 500 msec, or develops a change from baseline in the QTc interval of ≥ 60 msecs, the subject should undergo a dose reduction. If a subject has already undergone a dose reduction for other reasons, then they should discontinue study drug. The subject should return for an unscheduled visit after two weeks of dose reduction and the ECG should be repeated. If there is a shortening of the QTc interval to < 500 msec, or the change from baseline is

now < 60 msec, the subject should remain on the reduced dose. If there is no change in the QTc interval after reducing the dose then the subject should be discontinued from study drug.

6 Study Assessments and Procedures

Before subjects commence any study-specific activities or procedures, including Week 24 assessments from AV-101-002 which will serve as baseline for this study, the Sponsor requires a copy of the study site's written Independent Ethics Committee/Institutional Review Board (IEC/IRB) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable. Each subject must sign and date the ICF before participating in study-specific activities. If an unexpected circumstance occurs that would prohibit the subject from entering the study at Week 24 on AV-101-002, this may be discussed with the CRO Medical Monitor and/or Sponsor.

The Week 24 end of study visit of the parent study (AV-101-002) also represents the baseline visit for the LTE study (AV-101-003). The following assessments will be conducted/collected during the baseline visit of the LTE and at selected time points specified in the Schedule of Assessments (Table 1). Additional procedures deemed necessary as part of standard of care may be performed at the discretion of the Investigator. All missed visits and any performed procedures that are not protocol-specified activities must be documented in the subject's medical record and the appropriate eCRF. General considerations for study visits include, but are not limited to the following:

- No protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the CRO Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct (see Section 6.7.1 for COVID-19 considerations).
- The Investigator will obtain written informed consent before the end of study visit for study AV-101-002 and as specified in Section 9.1.3(Informed Consent Process). Upon the subject's agreement, their primary health care provider should be informed about the subject's enrollment in the study.
- Order of Procedures:
    - Health-related QoL assessments should be performed prior to all other study procedures.
    - Vital signs should be collected prior to blood draws. Blood samples for NT-proBNP levels should be collected prior to the 6MWT.
    - All other study assessments should also be performed, according to the Schedule of Assessments (Table 1).
- **Unscheduled visits:** may occur at any time during the study with the assessments to be performed according to the Investigator's judgment. Unscheduled visits may also be necessary for study drug dispensing following temporary withdrawal as described in Sections 6.7 and 7.7.

6.1 Screening/Baseline Visit

The appropriate baseline assessments for the LTE (Table 1 Schedule of Assessments) will be collected at the end of study visit (Week 24) for AV-101-002. Depending on outcome for analysis, baseline values reported during the parent trial may be used especially among subjects randomized to active treatment groups. Following Day 1 in the LTE, all subjects will have a telephone visit at Week 1 (7 days) for safety follow up.

Safety

- Review prior (within the past 30 days) and current concomitant medications and therapies
- Record AEs

Randomization

Subjects who were on placebo and entering the LTE from the Phase 2b and Intermediate Parts of Study AV-101-002 will be centrally randomized via an IWRS.

6.2 Post-Screening/Baseline Visits

Assessments to be performed for each visit are outlined in the Schedule of Assessments (Table 1). At each of the clinic visits where study drug dispensing is required, site staff will contact the IWRS to obtain the appropriate kit numbers and the specified kit(s) will be dispensed.

6.2.1 Telephone Visits

Telephone Contacts are required at Week 1, Week 8, Week 16 and Safety FU. AE, Concomitant Medications, Clinical Worsening and Vital Status (when required) must be assessed. For women of childbearing potential, a reminder to perform home pregnancy testing is also provided during the telephone visits including an additional call at Week 20. In addition, Investigators are required to evaluate subjects for the presence of any signs or symptoms suggestive of intracranial bleeding such as: headache, confusion, vomiting, slurred speech, etc.

6.2.2 Early Discontinuation Visit

Criteria for discontinuation are provided in Section 6.8. Subjects discontinuing study treatment must return to the site within 14 days for safety assessments. If this assessment does not correspond with a scheduled study visit, then an Early Discontinuation (ED) Visit will be performed.

Should a subject withdraw consent to be followed, they should return for an ED Visit within 14 days following the last dose and will have a Safety FU 4 weeks after the ED Visit. As many of these assessments as possible should be conducted.

If the subject is unwilling or unable to come into the clinic for the ED Visit, then this visit with as many assessments as possible can be conducted by telephone.

6.2.3 End of Treatment Visit

In a small cohort of subjects treated with oral imatinib for PAH, a responder analysis showed that the treatment duration for a complete hemodynamic response was approximately 3 years (Speich, 2015). Therefore, the LTE study will continue until 31 December 2025 or until the Sponsor stops the study.

Subjects may be able to receive expanded access supply of AV-101 should it be approved by regulatory authorities and available commercially in other countries or regions of the world. If AV-101 is not approved by either the FDA or EMA, then expanded access supply will be considered on a case-by-case basis.

6.2.4 Safety Follow Up Period

After the last dose of the IMP, subjects will be required to enter a 30-day Safety Follow Up Period.

Subjects who complete an ED Visit are also required to complete the 30-day Safety Follow Up Period.

Subjects will be contacted 30 days (± 2 days) after the ED Visit to review adverse events and concomitant medications. Ongoing AEs will be followed as outlined in Section 7.4. Subjects will then be contacted for Vital Status every 24 weeks after the Safety Follow Up Visit by telephone until study completion.

6.3 Demographic and Other Baseline Characteristics

Demographic data such as year of birth, self-reported race (Note: in France race is not recorded) and ethnic origin, gender, weight, (BMI will be automatically calculated in the eCRF), will be assessed at baseline. Information about previous and concomitant medications will also be recorded.

PAH is a rare disease, and this study is the first evaluation of the long-term safety of AV-101 in patients with PAH. Race and ethnicity are collected, where permitted, to support the understanding if potential ethnic differences exist in exposure and/or response to the investigational product among different ethnic groups.

Complete medical and disease history will be recorded. All ongoing conditions and relevant/significant medical history (including cardiovascular history, all major hospitalizations and surgeries) will be recorded at the baseline visit in the parent study. Should there be significant changes in medical and disease history upon entry into the LTE, these changes will be recorded. Symptoms related to PAH and/or the underlying etiology of the disease need not be listed on the medical history form; however, worsening of any symptoms during the course of this study must be captured as an AE.

Other baseline measurements such as physical examination, safety laboratory parameters, ECG, and vital signs will be recorded in the eCRF.

6.4 Effectiveness Assessments and Procedures

Assessments for the effectiveness endpoints will be evaluated based on the visits specified in the Schedule of Assessments (Table 1).

6.5 Safety Assessments and Other Study Procedures

Safety will be assessed by physical examinations, vital signs, ECGs, clinical laboratory tests, pulmonary function (spirometry) tests and evaluation of AE/SAEs.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the study, starting from the time of the subject's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject (Section 7.1).

Adverse events of special interests (AESI) are peripheral edema, periorbital edema, facial edema, nausea, vomiting, diarrhea, anemia, subdural hematoma, pneumonia, upper and lower respiratory tract infection, oral candidiasis, severe cough, and wheezing. These are clinically important events seen with oral imatinib, and/or other events important with respect to inhaled medications.

Given the occurrence of subdural hematomas in the IMPRES study, Investigators should be alert and routinely question subjects as to any symptoms suggestive of intracranial bleeds including headache, confusion, vomiting, slurred speech, etc. If such signs and/or symptoms are present, then appropriate further investigations should be undertaken.

6.5.1 Physical Examinations

Investigators should pay special attention to clinical signs related to previous serious illnesses.

At Screening/Baseline and all post-baseline clinic visits, a focused physical examination will be performed, and will include assessments of the skin, HEENT, thorax/lungs, abdomen, and cardiovascular, musculoskeletal and neurological systems, as well as any new subject complaints or changes from baseline.

Any clinically significant findings collected prior to the LTE study consent will be documented as medical history. Any new or worsening abnormal physical examination findings collected after the LTE consent that are considered clinically significant by the Investigator should be reported as AEs and recorded in the AE eCRF if the finding meets the definition of an AE.

6.5.2 Vital Signs

Vital sign measurements (BP, pulse rate, temperature, respiratory rate), weight and height will be collected prior to any other study-related procedures, at the visits specified in Table 1.

- Temperature, pulse rate, respiratory rate

- Blood pressure and pulse measurements will be assessed with the subject seated with a completely automated device. Manual sphygmomanometer can be used only if an automated device is not available.
    - Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones)
- Vital signs are to be taken before blood collection for laboratory tests.
- Height will be recorded at the Screening/Baseline Visit using the measurement value taken from AV-101-002. Body weight will be measured with a balance beam scale, if possible.

6.5.3 Resting Electrocardiogram (ECG)

Digital 12-lead ECGs for all subjects will be recorded at the site using an appropriate ECG machine.

- A standard, single, digital 12-lead ECG will be obtained as outlined in the Schedule of Assessments after the subject has been resting in the supine position for 5 minutes using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc intervals.

All digital ECGs will be documented by recording date and time of collection. All ECG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject. The Investigator will judge the overall interpretation as normal or abnormal. Clinical significance and the reason for the abnormality will be recorded in the source documents and in the eCRF. Abnormal values will not be recorded as AEs unless they are a clinically significant change and/or the reason for discontinuation of the study drug due to AEs or are SAEs.

If an ECG result reveals a QTc interval that exceeds 500 msec, or a QTc progression of ≥ 60 msecs from baseline, the subject must follow the instructions for down titration of investigational product per Section 5.5 (Also see Section 5.9.2).

6.5.4 Right Heart Catheterization (RHC)

If during the LTE study the Investigator believes that a subject has normalized, or near normalized, their hemodynamics then a RHC, if clinically appropriate, is encouraged to confirm this. RHC parameters should be collected using the same methods that were used for the subject in AV-101-002. All PAH medications, chronic medications, and study drug should be taken as prescribed on the day of the RHC. The date of the RHC and the hemodynamic data should be entered into the eCRF.

6.5.4.1 Parameters measured during the RHC

6.5.4.1.1 Heart rate

Heart rate should be determined at the time of the cardiac output measure by thermodilution. Heart rate should be measured in duplicate until 2 consecutive values, measured during cardiac output assessment, do not differ by more than 10%. The last value should be recorded in the eCRF.

6.5.4.1.2 Cardiac Output by the Thermodilution method

Thermodilution is the preferred protocol recommended method for the measurement of CO. If the Fick method is used, then the VO2 must be measured and not estimated. At least 3 determinations that are within 10% variability of one another must be measured. Measurements must be repeated until this reliability is met. The mean cardiac output will be defined as the average of these 3 measurements and used for the calculation of PVR. The mean value will be recorded on the eCRF.

If the mean cardiac output is auto-generated, Investigators must ensure that the measures used to calculate the mean are within the 10% variability and are available to be recorded on the eCRF. The last value will be recorded on the eCRF.

6.5.4.1.3 Systemic arterial pressure (systolic, diastolic, and mean):

Systemic arterial pressures should be taken just prior to entry of the catheter and should be measured in duplicate until 2 consecutive values do not differ by more than 10%. The last value should be recorded on the eCRF.

6.5.4.1.4 PAP (systolic, diastolic, and mean)

Pulmonary arterial pressures should be measured at end expiration and should be measured in duplicate or until 2 consecutive values do not differ by more than 10%. The last value will be recorded on the eCRF.

Mean PAP (mPAP) is derived in the electronic data capture (EDC) system per the following equation:

$$mPAP = ([\text{diastolic PAP} \times 2] + \text{systolic PAP}) \div 3$$

6.5.4.1.5 Mean right atrial pressure (mRAP)

Mean RAP should be measured in duplicate and the mean value calculated and recorded on the eCRF.

6.5.4.1.6 Pulmonary Capillary Wedge Pressure (PCWP) or Left Ventricular End Diastolic Pressure (LVEDP)

The PCWP or LVEDP should be recorded as the mean of 3 measurements at end-expiration. It is strongly preferred that the same assessment (PCWP or LVEDP) be performed for both RHC

assessments. In situations where this is not possible, the Investigator should provide an explanation in the eCRF.

The following additional recommendations from the 5th World Symposium working group on definitions and diagnosis of pulmonary hypertension (Hoeper 2013b) should be considered:

- Zero the pressure transducer at the midthoracic line in a supine patient halfway between the anterior sternum and the bed surface. This represents the level of the left atrium.
- The balloon should be inflated in the right atrium from where the catheter should be advanced until it reaches the PCWP position. Repeated deflations and inflations of the catheter should be avoided because this has been associated with ruptures of pulmonary arteries (PAs).

6.5.4.1.7 Mixed venous oxygen saturation (SVO2):

Blood gas from a pulmonary artery mixed venous blood sample should be measured in duplicate or until 2 consecutive values do not differ by more than 3%. The last value should be recorded on the eCRF.

6.5.4.1.8 Calculated parameters

- PVR (dynes•sec/cm^5) = [(mPAP – PCWP) ÷ mean cardiac output] x 80 or; [(mPAP – LVEDP) ÷ mean cardiac output] x 80
- CI = CO ÷ BSA
- SV = CO ÷ HR
- Body Surface area (BSA; m^2) = 0.007184 x $weight^{0.425}$ x $height^{0.725}$ where weight is in kg and height is in cm.

6.5.5 Resting Transthoracic Echocardiogram (ECHO)

Instructions for the collection and transmittal of ECHOs to the core laboratory will be provided in a separate study-specific imaging manual. Images will be digitized and stored to an optical disk for subsequent analysis.

A core imaging laboratory will collect all echocardiographic data and provide centralized blinded adjudication safety and efficacy assessments, including those listed as secondary endpoints of right ventricular function. The following parameters will be assessed: tricuspid annular peak systolic excursion (TAPSE), right ventricular myocardial strain, tricuspid annular systolic velocity (TA S'), right ventricular fractional area change (RVFAC), RV/PA coupling (TAPSE/PASP) and tricuspid regurgitant jet velocity (TRJV). The study-specific imaging manual will contain a complete list of the required parameters.

The Investigator will review the ECHOs for any clinically significant abnormalities to ensure subject safety. Abnormal changes in ECHO findings from baseline that are considered clinically

significant by the Investigator should be reported as AEs and recorded in the AE eCRF page if the finding meets the definition of an AE.

A core imaging laboratory will conduct a central analysis of the echocardiographic data.

6.5.6 Clinical Laboratory Assessments

Blood samples will be collected and sent for testing at the Central Laboratory. Refer to Table 2 for the required clinical laboratory tests and to the Schedule of Assessments for the time points. Specific instructions for processing, labeling, and shipping samples will be provided in a Central Laboratory Manual. Urine pregnancy test kits are provided for women who require testing. Urine pregnancy tests are performed locally during clinic visits and home testing.

- All samples should be clearly identified.
- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or as required by local regulations.
- The tests will be performed by the central laboratory unless otherwise noted.
- The Investigator must review each laboratory report, document their review, and record any clinically relevant changes occurring during the study in the source documents and in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- Non-fasting blood samples are acceptable for this study.
- Repeat laboratory testing may be required during the study for various reasons, e.g., loss of sample en-route to the Central Laboratory. Any testing which is required to be repeated should be reevaluated as soon as possible after the designated visit.

6.5.6.1 Clinical Safety and Screening Evaluations

Table 2 Laboratory Assessment Parameters

Laboratory Assessments	Parameters		
Hematology	Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count	RBC Indices: MCV MCH %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Total bilirubin Bilirubin-direct (only if total bilirubin is outside the normal range)	Calcium Serum creatinine (eGFR will be calculated from serum creatinine using the CKD-EPI equation)	Glucose Potassium Sodium Total protein Uric acid
Other Tests	The FSH test may be performed at Screening, per Investigator's discretion to confirm post-menopausal state. For women of childbearing potential, urine pregnancy testing is performed at each study visit, and home pregnancy testing is required every 4 weeks, from randomization, between study visits.		

6.6 Other Assessments

6.6.1 NT-proBNP

NT-proBNP is a biological marker which is known to be released in response to changes in pressure inside the heart. Storage and analyses of samples will be handled according to the study Lab Manual.

6.6.2 Study Questionnaire (emPHasis-10)

In the LTE study the quality-of-life instrument used will be the emPHasis-10 questionnaire. The emPHasis-10 is a short 10 question questionnaire used to assess the health-related quality of life (HRQoL) in patients with pulmonary hypertension (PH). Each question uses a 6-point semantic scale (0 – 5) for a maximum score of 50.

Please refer to Appendix 2 for the sample study questionnaire.

6.6.3 6-Minute Walk Test and Borg Dyspnea Scale

6.6.3.1 6-Minute Walk Test (6MWT)

The 6MWT will be conducted according to the European Respiratory Society/American Thoracic Society technical standard for field walking tests [in accordance with local standard operating procedures], and following guidelines established by Holland et. Al. (2014). Please see Appendix 3 for guidance based on Holland et al.

6.6.3.2 Borg Dyspnea Scale

Subject perception of breathlessness after exertion will be reported using the Borg CR Scale® (CR10). The BDI score will be assessed immediately following completion of the 6MWT. Please refer to Appendix 4 for guidelines on conducting the BDI.

6.6.4 WHO Functional Class

WHO FC will be assessed at all study visits.

Class Description

Class I: 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: Pulmonary hypertension resulting in slight limitation of physical activity. Subject is comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class III: Pulmonary hypertension resulting in marked limitation of physical activity. Subject is comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class IV: Pulmonary hypertension with inability to carry out physical activity without symptoms. Subject manifests signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

The Investigator will complete the WHO Functional Class assessment. Every effort should be made to have the same Investigator or medically qualified designee assess the subject at each study visit.

6.6.5 Clinical Worsening

Clinical worsening events will be defined as:

- Death (all causes)

- Hospitalization for worsening PAH
- Initiation of parenteral prostanoids
- ≥ 15% decline from baseline in 6MWD accompanied with continued or worsening WHO FC III or IV symptoms. The decline in 6MWD must be confirmed with a repeat test on a different day within 2 weeks. (Baseline is defined by the randomization visit in Study AV-101-002 for those on AV-101 and the Week 24 visit for those on placebo in Study AV-101-002).

6.6.6 Clinical Improvement

Clinical improvement will be assessed by the proportion of subjects achieving all 3 of the following components at 6 month intervals:

- WHO FC improvement or maintenance of WHO FC II status
- NT-proBNP ≥ 30% improvement or < 300 pg/ml
- 6MWD ≥ 30-meter improvement

6.6.7 REVEAL Lite 2 Risk Score

The change in the REVEAL Lite 2 risk score (Benza 2020) at 6 month intervals classified as low, intermediate, or high risk will be assessed using the following variables to derive the risk score:

- Estimated Glomerular Filtration Rate (eGFR) in ml/min/1.73m^2 or renal insufficiency if eGFR unavailable
- WHO FC
- Systolic Blood Pressure and heart rate
- 6MWD
- NT-proBNP

Table 3 Variables Included in the REVEAL Lite 2 Risk Calculator

Parameter	REVEAL Lite 2 Variable	Score
Renal Insufficiency	eGFR < 60 mL/min/1.73 m^2 or defined by clinical judgment if eGFR is not available	+1
NYHA or WHO FC	FC I	-1
	FC III	+1
	FC IV	+2
Vital Signs	Systolic Blood Pressure < 110 mm Hg	+1
	Heart Rate > 96 bpm	+1
6MWD	≥ 440 m	-2
	320 m to < 440 m	-1
	< 165 m	+1
BNP/NT-proBNP	NT-proBNP < 300 pg/mL	-2
	NT-proBNP ≥1100 pg/mL	+2
TOTAL SCORE	*Sum of the above scores +6*	+6

The total REVEAL Lite 2 risk score will be used to determine the risk category in the following manner:

- Low Risk = REVEAL Lite 2 risk score 1 – 5
- Intermediate Risk = REVEAL Lite 2 risk score 6 – 7
- High Risk = REVEAL Lite 2 risk score ≥ 8

6.7 Considerations for Coronavirus Outbreaks

To ensure the safety of trial participants in IMPAHCT-FUL, new processes or modifications to protocol assessments may be put in place to reduce the risks associated with the coronavirus pandemic.

The Coronavirus pandemic may impose difficulties with study conduct which may inhibit the subject's ability to attend in-clinic study visits. In cases of such limitations, it is the Investigator's responsibility to ensure the safety of study subjects which should include phone or video contact to assess the subject's well-being including any adverse events, collection of study samples and clinical data as best as possible, and direct shipment of study drug to study subjects if necessary. In these situations, conduct of study procedures may occur outside of the clinical site (i.e., at a subject's home) by site personnel, or by trained but non-study personnel. Documentation of these cases and the site's management of the subjects should be recorded in the Investigator study files.

6.7.1 Considerations for COVID-19 and Study Subjects

If a subject becomes positive for SARS-CoV-2 during the study and is symptomatic and hospitalized (severe disease), the study drug should be temporarily withdrawn. Subjects who are asymptomatic or with mild symptoms (at home) do not need to withdraw study drug unless the severity changes and they are hospitalized. In the case of severe disease (hospitalization), study drug may be restarted after 20 days from the onset of symptoms and at least 24 hours without fever (CDC guidance 12 March 2021 – "When you can be around others"). If the CDC guidance should change, then the current available guidance should be followed. As much as possible, subjects should be followed as per the study schedule.

Vaccination or booster shots for SARS-CoV-2 and variants will be allowed during the study. Timing and type of vaccination should be clearly recorded in the eCRF as well as any subsequent AEs and their relation to the vaccination.

6.8 Discontinuation of Study Drug and Subject Discontinuation/ Withdrawal

6.8.1 Discontinuation of Study Drug

At the time of early study drug discontinuation subjects may elect to (1) discontinue from the study and agree to telephone contacts per the visit schedule, or (2) discontinue from the study, and withdraw consent to be contacted in the future for further collection of study-related data.

For subjects who withdraw from or are withdrawn from taking the study drug, every attempt should be made to follow the subject for long term outcomes. However, if a subject withdraws consent to be contacted, they must complete the Early Discontinuation (ED) Visit within 14 days of AV-101 discontinuation, and then the Safety Follow-Up visits as described in Section 6.2.2 and 6.2.4.

For subjects who are lost to follow-up, or who died, Safety Follow-up Visits may not be possible. In any case, the appropriate eCRF section must be completed.

The subject must be discontinued from taking study drug in the event of any of the following:
Examples:

- Enrollment despite violation of an inclusion or exclusion criterion which, in the Investigator's and/or Sponsor's opinion, makes discontinuation of the subject necessary.
- Occurrence of an AE/SAE that makes discontinuation of study drug desired or considered necessary by the Investigator and/or the subject.
- Participation in any other interventional study during the duration of this study for which the Investigator considers discontinuation of the AV-101 necessary.
- Occurrence of pregnancy (for further details in case of pregnancy, refer to Section 7.8).
- If disease activity is considered unacceptably high and treatment escalation beyond permitted medication changes (Section 5.9.1) is warranted in the view of the Investigator.

- Anaphylaxis, anaphylactoid, or other severe or life-threatening hypersensitivity reactions, based on the Investigator judgement.
- Use of a nonpermitted medicine, as defined in Section 5.9.2. This should first be confirmed with the CRO Medical Monitor before discontinuation of the study drug.
- Noncompliance, judged as significant by the Investigator or Sponsor including noncompliance to the required study considerations, as defined in Section 5.8.
- Surgery considered by the Investigator or Sponsor to be major (see Section 4.2).
- Occurrence of any other clinical condition for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee.

The Schedule of Assessments specifies the data to collect at study drug discontinuation and follow-up, and any additional evaluations that need to be completed.

6.8.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time, at his/her own request (i.e., withdrawal of consent). However, withdrawal of consent from trial participation should be rare and unusual. Because of this, the Investigator must be involved in the discussions with the subject regarding a withdrawal of consent. Investigator or designee should make reasonable effort to obtain explanation for subject withdrawal and ask about the occurrence of any AEs.

- The subject may be withdrawn by the Investigator due to participation in another clinical study.
- The subject may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- The Schedule of Assessments specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.
- A subject is considered withdrawn from the study due to death.
- A subject must be withdrawn from the study in the event the subject is lost to follow-up.

When a subject must be withdrawn from the study, the Investigator or designee will inform the CRO Medical Monitor immediately, who will then inform the Sponsor's medically responsible individual.

If there is a medical reason for withdrawal from the study, the subject will remain under the supervision of the Investigator until satisfactory health has returned or the subject's health has stabilized. The Investigator will inform the subject's primary health care provider as applicable and as agreed by the subject if the subject withdraws from the study, in order to ensure the subject receives the appropriate follow up and care.

6.9 Lost to Follow-Up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain if the subject wants to or should continue in the study.
- Before a subject is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the subject:
    1. where possible, make 3 telephone calls, AND
    2. if necessary, send a certified letter (or an equivalent local method) to the subject's last known mailing address.

  All contact attempts should be documented in the subject's medical record.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and deemed "lost to follow-up". Under this circumstance, and in order to obtain information on the vital status (if the subject is alive or deceased), the site may contact the subject's family provided appropriate consent has been obtained.

6.10 Medical Care of Subjects after End of Study

In the event that the subject has withdrawn/discontinued early from the study, standard of care treatment for the subject's PAH should be administered by their attending physician.

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for patients with PAH.

7 Adverse Event/Device Deficiency Handling and Reporting

7.1 Adverse Event Definition and Assessment

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its OUTCOME.

Adverse Events of Special Interest

Adverse events of special interests (AESI) are peripheral edema, periorbital edema, facial edema, nausea, vomiting, diarrhea, anemia, subdural hematoma, pneumonia, upper and lower respiratory tract infection, oral candidiasis, severe cough, and wheezing. These are clinically important events seen with oral imatinib, and/or other events important with respect to inhaled medications.

Adverse Device Effect

Adverse device effect (ADE) is an AE related to the use of an investigational medical device. This includes an AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Device Deficiency

Device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, or use errors, and inadequate labeling. All device deficiencies must be reported to the Sponsor/CRO, regardless of whether they lead to an adverse event, per instructions and on the required Product Quality Complaint Form found in the study Pharmacy Manual. If the device deficiency results in an AE, report the AE as directed in Section 7.5.

7.1.1 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regards to the following categories:

1) Seriousness

A serious adverse event (SAE) or reaction is defined as any untoward medical occurrence that, at any dose, has any of the following consequences:

- Results in death
- Is life-threatening (This means the subject is at risk of death at the time of the event. It does not mean that the event hypothetically might have caused a death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent one of the above outcomes.

The seriousness criteria for a device SAE are slightly different from the seriousness criteria for a drug and include the following:

- Death
- Serious deterioration in the health of the subject, that resulted in any of the following:
    - Life-threatening illness or injury
    - Permanent impairment of a body structure or body function
    - Hospitalization or prolongation of hospitalization
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function
    - Chronic Disease
- Fetal distress, fetal death, or a congenital physical or mental impairment or birth defect

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

2) Severity

The severity of an AE is made by the Investigator based on his or her clinical experience and familiarity with the literature. Grade refers to the severity of the AE. The Common Terminology Criteria for Adverse Events (CTCAE) V5 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4 Life-threatening consequences; urgent intervention indicated

Grade 5 Death related to an AE, Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study drug discontinuation or are considered otherwise medically important by the Investigator. Laboratory abnormalities that require medical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased alanine aminotransferase) must be reported as the AE rather than the abnormal value itself.

The severity of abnormal laboratory values should be evaluated according to the CTCAE and recorded per the Qualitative Toxicity Scale, as follows:

Mild: CTCAE Grade 1

Moderate: CTCAE Grade 2

Severe: CTCAE Grade 3 and 4

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

See Section 7.7 for additional details on how to manage AEs associated with abnormal laboratory findings.

3) Causality

The Investigator will establish the causality of the AE or ADE to the experimental treatment. The Investigator will use clinical judgement and should consider the participant's history, most recent physical examination findings, and concomitant medications when assessing causality. For the purpose of clinical study AE reporting, AEs or ADEs should be classified as "Not Related" or "Related" to study treatment or to the device, respectively.

> **Not Related:** There is no reasonable temporal or causal relationship between the study drug, device, or procedure and the event. A reasonable alternative explanation must be available.

Related: There is a reasonable possibility of a temporal and causal relationship between the study drug, device, or procedure and the event.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and should be reported in medical history and are not to be considered AEs.

Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions) are not to be considered as AEs.

7.2 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent/date of first signature of first informed consent) and continues until the last Safety FU per Table 1.

- After informed consent, but prior to initiation of study drug, all SAEs, but only those non-serious AEs related to protocol-mandated procedures should be collected. All AEs that are not related to study procedures should be recorded as worsening medical history.
- Following initiation of study medication, all AEs should be collected, regardless of cause or relationship.
- Events will be summarized on the basis of the date of onset for the event.

A treatment-emergent AE will be defined as any AE that begins on or after the date and time of first dose of study drug through 30 days after last dose of study drug.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (i.e., signs the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported in the eCRF database and to the CRO as instructed. This also includes any SAEs resulting from protocol-associated procedures performed from screening onwards.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study drug, regardless of causality, should also be reported. Any SAE assessed as

related to study drug must be recorded and reported to the CRO, whenever it occurs, irrespective of the time elapsed since the last administration of study drug.

Investigators are not obligated to actively seek SAEs after the end of the protocol-defined follow-up period; however, if the Investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug (AV-101), he/she should promptly document and report the event to the CRO. Such an SAE occurring after the end of the study should be reported to the Sponsor.

The method of recording AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Section 7.5.

7.3 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable change in the subject's condition will be recorded as an AE, regardless of if it is reported by the subject or observed by the Investigator. In addition, Investigators are required to evaluate subjects for the presence of any signs or symptoms suggestive of intracranial bleeding such as: headache, confusion, vomiting, slurred speech, etc.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs and device deficiencies must be additionally documented and reported using the appropriate Report Form as specified in Section 7.5.

7.4 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed for their outcome continuously throughout the study, as specified in Section 7.2 (Time Period and Frequency for Collecting AE and SAE Information). All AEs should be followed up until resolution if possible. If by the last day in the study (including the 30-day period after last administration of study drug) the AE has not resolved, then the AE will be followed up until the Investigator, the CRO Medical Monitor and/or the Sponsor determine that the subject's condition is stable. However, the CRO Medical Monitor and/or the Sponsor may request that certain AEs be followed until resolution.

All SAEs ongoing at the last Safety FU Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.5 Investigator Requirements and Instructions for Reporting Adverse Events, Serious Adverse Events, Adverse Events of Special Interest and Device Deficiencies

Recording and Follow-Up of AEs

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study drug administration time), its severity, its causal relationship with the study drug and study device, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the study drug or study device, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF completion guidelines to be provided by the CRO or Sponsor.

Reporting Serious Adverse Events, Adverse Events of Special Interest and Device Deficiencies

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the CRO utilizing the Safety Event Report Form. All SAE reports should be transmitted using the Safety Event Report Form, which must be completed by the Investigator following specific completion instructions to be provided by the CRO or Sponsor.

Additional documents must be provided by the Investigator, if available, only if requested by the CRO/Sponsor or its designee (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the SAE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the CRO/Sponsor or designee and (as applicable) to allow the CRO/Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the drug safety department which may contact the Investigator directly via email or via the responsible CRO Medical Monitor to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a nonserious AESI, the Investigator will complete the AE eCRF in the same manner as other AEs. Serious AESIs must be reported in an expedited manner within 24 hours of awareness as an SAE as outlined above.

Device Deficiency

In the event of an AE associated with device deficiency, the Investigator will complete the AE eCRF noting relatedness to the device. Serious AEs or ADEs as a result of device deficiency must be reported in an expedited manner within 24 hours of awareness of an SAE as outlined above. In addition, the device deficiency must be reported to the Sponsor/CRO on the Product Quality Complaint Form found in the study Pharmacy Manual.

7.6 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor/designee will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study subjects to the IEC/IRB that approved the study.

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the study, or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs (and ADE's) that are both serious and unexpected/unanticipated and considered to be related to the administered product (SUSARs/USADEs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. A USADE is a serious adverse device effect, which by its nature, incidence,

severity, or outcome has not been identified in the current version of the Investigators' Brochure. All USADE's follow the same reporting requirements as for SUSARs.

Device Deficiency

Investigator should assess all device deficiencies for SADE (serious adverse device effect) potential. For investigational devices, reportable events include any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Procedures for Breaking the Treatment Codes

If the Investigator decides that unblinding is warranted in cases of a medical emergency where knowledge of randomization group is required, the Sponsor/CRO must be notified within 24 hours after unblinding. The Investigator must provide the CRO the reason for unblinding without revealing the study drug, except to the CRO's designated drug safety representative, as appropriate. The date of and reason for unblinding must be recorded in the source documents. Contact information for unblinding in an emergency is given on the subject emergency card provided to each subject, as noted in Section 9.2.1 (Emergency Medical Support).

Treatment code unblinding is performed in the IWRS. After logging into the IWRS, the Investigator must indicate the action for "unblinding by the site". The investigator must enter the site number, subject number, and subject's year of birth. The instructions are also found in the "Blinded Site User, Blinded Investigator, Blinded Coordinator, Blinded Monitor User Guide" for the Cenduit IWRS.

In the event that the IWRS is inaccessible, the Investigator should call the Cenduit Global Helpdesk which is available 24 hours, 365 days a year. Live translation is available. The Global Helpdesk numbers are:

Toll-Free United States and Canada: 1-877-253-3080

Universal Free EU: 00-800-1012-1960

Direct-Dial United States and Canada: 1-610-871-0150

Direct-Dial United Kingdom: +44 140 334 2316

The Cenduit IWRS User Guide additionally provides an international telephone list for specific countries. The Sponsor (or delegate) will submit any Suspected Unexpected Serious Adverse Reactions (SUSAR) reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

If emergency unblinding is required for an AE/SAE/SADE, causality assessments should be documented for the AE/SAE/SADE prior to unblinding.

7.7 Management of Adverse Events Associated with Abnormal Laboratory Findings

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 5 and as outlined below.

Grades 1 (Mild) and 2 (Moderate) Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the Investigator.

Grades 3 (Severe) Laboratory Abnormality or Clinical Event

Study drug may be continued if the event is considered to be not related to study drug.

For clinical event or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2.

If a laboratory abnormality recurs to ≥ Grade 3 following re-starting of study drug and is considered related to study drug and medically important by Investigator and/or Sponsor/designee, then the study drug should be permanently discontinued, and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered not related to study drug may not require permanent discontinuation.

Grades 4 (Severe) Laboratory Abnormality or Clinical Event

For clinical event or Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug and medically important by the Investigator and/or Sponsor/designee, study drug should be permanently discontinued, and the subject managed according to local clinical practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered not related to the study drug.

All subjects experiencing AEs must be monitored until symptoms subside and any abnormal laboratory values have resolved, returned to baseline levels, is considered irreversible, or have a reasonable explanation for the changes observed.

7.8 Pregnancy and Contraception

It is not known whether treatment with AV-101 may cause injury or harm to an unborn child if taken during pregnancy, or if it may cause harm to a breastfeeding infant. For this reason, pregnant or breastfeeding women are not allowed to take part in the study. It is important that women avoid

getting pregnant during the study. Therefore, all women of childbearing potential taking part in the study must use a highly effective form of contraception for at least 28 days prior to when they will receive the first dose of study drug, and for at least 30 days after completing or discontinuing study treatment. All hormonal contraceptive methods used must be associated with inhibition of ovulation. Abstinence is acceptable only as true abstinence: when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.*

At the Baseline Visit, all women capable of having children will have a pregnancy test (Urine test). Women capable of having children include all women except those whose menstrual periods have not occurred for more than 1 year after menopause (change of life or postmenopausal), or those who have had sterilization surgery (tubal ligation or a complete hysterectomy and/or removal of both ovaries). Postmenopausal is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range at the Screening Visit may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

In addition to pregnancy testing performed at study visits, all women of childbearing potential are provided home urine pregnancy tests to be performed every 4 weeks from the date of randomization. The tests are performed at home during the months for which a study visit does not occur. If the 4-week interval falls on a visit date, then testing is to be performed during the study visit. Women must be instructed to immediately report a positive test result to the Study Investigator.

The subject must be contacted when the test is due, and the following recorded:
In source documentation:

- Test date
- Test result
- Lot number of the test
- Expiration date of the test

In the eCRF:

- Test date
- Test result

The results are to be documented in the eCRF and in the patient file in a timely manner. It is not acceptable to obtain the result only at the next scheduled visit. In the event of pregnancy, a referral to a gynecologist for confirmation of pregnancy must be organized as soon as possible. In addition, the pregnancy must be reported to the sponsor as described in Section 7.8.1, and further consequences in regard to ongoing participation in the study must be discussed with the patient. In the event there are uncertainties about a pregnancy test outcome, the patient should similarly contact the site immediately to discuss further steps e.g. exclusion of pregnancy by serum pregnancy test.

Table 4 contains a list of highly effective forms of contraception. Women who are not capable of bearing children are exempt from contraception requirements.

Table 4 Protocol Defined Highly Effective Forms of Contraception

Single Methods	Combination Methods
Intrauterine Devices (IUDs) Intrauterine hormone-releasing system (IUS) **Progesterone** • Implant • Injection **Tubal Sterilization** **Bilateral oophorectomy** **Bilateral Salpingectomy** **Total hysterectomy** **Vasectomy with Documented Azoospermia 3 months After the Procedure** ***Abstinence** from heterosexual intercourse (lifelong decision or at least 1 year)	**Estrogen and Progesterone** • Combined oral contraceptives • Transdermal patch • Intravaginal ring

7.8.1 Pregnancy Reporting

The Investigator must notify the CRO/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Section 7.5.

Investigators must actively follow-up, document and report on the outcome of all pregnancies, even if the subjects are withdrawn from the study.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Pregnancy Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 7.5, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the study, the subject must be discontinued from study drug. The Sponsor/designee must be notified without delay and the subject must be followed as indicated above.

7.9 Treatment of Overdose

For this study, any dose of study drug greater than 4 capsules per day will be considered an overdose, provided it can be confirmed that the subject actually dosed with extra capsules. If a subject is down titrated to one capsule, accidental dosing with two capsules will not be considered an overdose.

Even if it is not associated with an AE or an SAE, any overdose must be recorded in source documents and the appropriate CRF and reported to the Sponsor/CRO in an expedited manner according to the SAE reporting procedure in Section 7.5.

The Sponsor does not recommend specific treatment for an overdose. The effects of an overdose of AV-101 are unknown and there is no known specific treatment in case of overdose. In the event of overdose, subjects should be considered for hospitalization for observation if clinically indicated, and appropriate supportive treatment should be given as needed per the Investigator's clinical judgment.

8 Statistical Considerations

This section presents an overview of the statistical analyses that will be used to meet the study objectives. Details of the statistical analyses will be provided in a statistical analysis plan (SAP).

8.1 Introduction: Study Design and Analysis Overview

The LTE is a longitudinal study of the long-term safety and effectiveness of PAH patients treated with AV-101 at different dose levels until being transitioned to the optimal dose of AV-101 which is selected after the completion of the Phase 2b Part of Study AV-101-002 (referred to as the parent study). About 370 subjects (with a maximum of 462 subjects) are expected to start the LTE. LTE subjects may be grouped into the following treatment groups:

- **Group 1 – Optimal Dose Treatment:** Subjects treated with the optimal dose throughout the parent trial and throughout their LTE participation.
- **Group 2 – Non-Optimal Dose Active Treatment, then Optimal Dose Treatment:** Subjects treated with active doses not selected as the optimal dose, who eventually will be treated with the optimal dose when this dose is selected.
- **Group 3 – Placebo to Non-Optimal Dose, then Optimal Dose Treatment:** Subjects originally assigned to the placebo arm during the parent trial then re-randomized to the two non-optimal active groups. Later, they will receive the optimal dose when it is selected.
- **Group 4 – Placebo to Optimal Dose Treatment:** Subjects originally assigned to the placebo arm during the parent trial then either re-randomized or switched to optimal dose.

Further characteristics of these LTE treatment groups are described in Section 8.3.

Among the comparisons to consider are:

1) LTE levels and trends among subjects always on the optimal dose Group 1 will be compared in order with those of:

    Group 4: Placebo to optimal dose treatment

    Group 3: Placebo to non-optimal dose, then optimal dose treatment

    Group 2: Non-optimal dose active treatment, then optimal dose treatment

2) Levels and trends in LTE safety and effectiveness endpoints for subjects always on the optimal dose (Group 1) will be compared to levels and trends during the parent study among these same subjects. This will be done to document whether the effects of the previous optimal dose on subsequent measures of effectiveness and safety while still undergoing treatment persist, improve, plateau, or dip the longer the duration of the optimal treatment.

3) Trends in continuous LTE effectiveness endpoints will be assessed separately for continuous dose intensity and continuous relative dose intensity.

4) Levels and trends in LTE safety and effectiveness after 24 weeks of optimal dose treatment in each of the four treatment groups will be reported.

Other comparisons will be outlined in the Statistical Analysis Plan.

The association of LTE AV-101 treatment groups with levels and trends in LTE safety will be explored with a continuous AV-101 treatment exposure based on average weekly dose intensity. Planned weekly dose intensity during the parent trial ranges from zero among those who only received placebo treatment, 140 mg/week among those randomized to 10 mg per dose BID, 490 mg/week among those randomized to 35 mg per dose BID and 980 mg/week among those randomized to 70 mg per dose BID. With dose titration, early treatment discontinuation, or missed doses, average dose intensity per week will be calculated by summing up AV-101 with the cumulative sum divided by the duration of treatment in weeks.

Safety and effectiveness endpoints collected while subjects are participating in the parent study will serve as the benchmark for safety and effectiveness endpoints collected during the LTE study. LTE levels of safety and effectiveness endpoints will be presented by LTE treatment groups and LTE visits intervals disaggregated by visits prior to or after subjects are dosed with the optimal dose. These safety and effectiveness levels will be presented using descriptive statistics applicable to continuous or categorical data. Trends or patterns over time in a select set of safety and effectiveness measures will be presented graphically. Continuous data will be summarized using the following descriptive statistics: number of observations, mean, standard deviation, standard error, median, minimum, and maximum. Categorical data will be summarized using frequencies and percentages.

Changes from baseline will be calculated as the later value minus the baseline value. Baseline will be defined for specific endpoints as the time prior to starting active treatment with AV-101 in either the LTE or the parent study. Baseline values for subjects will consist of the baseline values during the parent trial among subjects in the always active treatment groups (optimal dose [Group 1] or non-optimal dose [Group 2]). For subjects who are initially assigned to placebo in the parent

trial, baseline values consist of either Week 24 parent trial values or baseline LTE prior to re-randomization to active treatment.

Trends or patterns over time in safety and effectiveness measures will be presented using repeated measures data analysis methods applicable to categorical or continuous data. Time-to-event analyses will be performed using Cox models with time-independent and time-varying covariates, specifically, extent of AV-101 dose intensity as continuous or categorical variables. For time to event data like overall survival, the starting period is the day prior to the first dose in the parent trial. Kaplan-Meier procedures for time -to-event analysis will also be performed.

For longitudinal continuous variables, the shape of the effectiveness trajectory (trends), repeated measures models over time will be fitted to assess whether the effectiveness measure indicates waxing, waning or remaining persistently over time. During the LTE, visits may be grouped into before or after optimal dose is administered. Levels of the LTE effectiveness endpoints before or after optimal dose treatment during the LTE will be reported.

8.2 Analysis Sets

The following analysis sets will be used to address the specific protocol objectives.

Screened Analysis Set (SAS): The screened analysis set consists of subjects treated at least once in the parent study who signed the informed consent to participate in the LTE study. This is the analysis set for presenting LTE baseline information and the status of subject participation in the LTE study.

Safety (SAF) Analysis Set: The safety analysis set includes all subjects enrolled in the LTE who received at least one dose of treatment during the LTE. This analysis set is the primary analysis set used for all safety summaries.

Full Analysis Set (FAS): The full analysis set includes all subjects enrolled in the LTE who received at least one dose of treatment during the LTE and have at least one post-LTE entry effectiveness measure recorded. This analysis set is the primary analysis set used for all effectiveness analyses.

8.3 Treatment Exposure, Estimated Number of Subjects in Group Comparisons of Interest

LTE-eligible subjects from the Phase 2b and Phase 3 parts of the parent study will complete 24-weeks of treatment as part of that study, additional weeks of treatment under the same active treatment arms as they enter LTE and until they start optimal dosing once this dose is identified at the end of Phase 2b.

LTE-eligible subjects from the Phase 2b and Intermediate Parts of the parent study who are randomized to placebo will be re-randomized in a blinded manner to any of the active treatment dose groups at LTE entry and prior to being treated with the optimal dose at the end of Phase 2b. Depending on the timing of their enrollment and initial treatment in the Intermediate part of the study, treatment duration under the parent study will be at least 24 weeks prior to being treated

with the optimal dose at the end of Phase 3. The actual duration of treatment during the parent study, during the waiting period for the optimal dose and during the LTE, will be reported.

LTE subjects will be treated at different dose levels prior to the optimal dose being identified. In addition, duration of treatment under the parent dose among those in the Phase 2b and Intermediate Parts may vary before the optimal dose is identified at the end of Phase 2b. Thus time-varying treatment exposure is a key characteristic of the combined parent and LTE trials and will be considered in describing levels and trends in safety and effectiveness endpoints recorded during the LTE trial.

The actual number of subjects by LTE treatment groups will be reported. Summary descriptive statistics will be reported for dose intensity and relative dose intensity by LTE treatment groups. Patterns of continuous dose intensity will be described by fitting a polynomial regression with dose intensity as a response variable and weeks in the study as polynomial splines. In addition, levels and patterns of dose intensity (and relative dose intensity) over LTE time intervals will be described.

8.4 Baseline and Demographics and Subject Study Disposition

With exception of the delayed-start analysis, for both the efficacy and safety analyses, baseline will be defined as the time prior to starting active treatment with AV-101 in either the LTE or the parent study. For Groups 1 and 2, since the subjects start receiving active treatment in the parent study, the baseline will be the values prior to first dose during the parent trial. For Groups 3 and 4, the subjects receive placebo in the parent trial and then receive active treatment in the LTE study, thus, the baseline will be the values prior to the first dose in LTE study.

Demographics and baseline data, medical and surgical history will be summarized using the screened analysis set. These demographics and baseline data will be presented by the LTE treatment groups as described in Section 8.1.

Demographic and baseline data will be summarized using summary statistics of mean, standard deviation, median, lower quartile, upper quartile, min and max for continuous variables and number and percentage of subjects in each category.

Subject treatment status and study participation status will be reported for the safety analysis set. Subjects who completed all LTE assessments and early treatment discontinuation and withdrawal from the study including reasons for treatment or study discontinuation will be reported by LTE treatment groups.

8.5 Effectiveness Analyses

Descriptive summary statistics will be reported for each effectiveness endpoint by LTE treatment groups. The FAS will be used as the analysis set. Comparisons of levels in effectiveness endpoints at specific visits (e.g. Week 24 after LTE baseline) among LTE treatment groups will be performed using statistical models applicable to the measurement scale (continuous, categorical, time-to-event). Tests of hypotheses in these models will be performed with two-sided tests at 0.05 significance level, adjusted for multiple comparisons. Effectiveness endpoints among Group 1

subjects will be compared with subjects in Group 4, Group 3, and Group 2. Associated 95% confidence intervals for the difference in outcomes in pairwise treatment comparisons will be presented. Trends in effectiveness endpoints measured over time will be presented graphically by using applicable summary statistics at each time point. If appropriate, statistical tests of the differences in trends may be performed.

8.5.1 Delayed-Start Efficacy Analysis

The delayed-start analysis (Liu-Seifert et al., 2015; Wang et al., 2019) will be performed to evaluate potential disease modifying characteristics of the treatment. Week 24 and Week 48 data will be compared between Group 1 and Group 4. Group 1 (optimal dose treatment) is the early start group and Group 4 (placebo to optimal dose treatment) is the late start group. The analyses will include the following three comparisons:

- At Week 24, the change from baseline of an efficacy variable for Group 1 that achieves statistical significance compared with Group 4
- At Week 48, the change from baseline of an efficacy variable for Group 1 that achieves statistical significance compared with Group 4
- For the change from Week 24 to Week 48 of an efficacy variable, Group 1 is not inferior to Group 4

For continuous efficacy variables such as 6MWD, ANCOVA will be used with baseline 6MWD and randomization stratification factors as covariates. Normality will be examined using the Shapiro-Wilk test. If a normal distribution is rejected, a non-parametric Wilcoxon rank sum test stratified by stratification factors will be used. A multiple imputation method will be used to handle the missing data.

If Week 24 or Week 48 has missing data and subjects are still alive, a standard multiple imputation (MI) will be implemented using a regression model accounting for baseline 6MWD, randomization stratification factors, and if necessary, additional covariates such as demographic variables. For missing 6MWD data due to death, a random sample from the worst 10% change among all subjects will be used.

NT-proBNP is also a continuous variable; therefore, the delayed-start analysis will be performed similar to 6MWD.

The WHO function class improvement is a binary variable; therefore, the delayed-start analysis will be performed by Cochran-Mantel-Haenszel (CMH) test with randomization stratification factors as strata.

8.5.2 Longer Term Analysis for the First Tier of Efficacy Endpoints

1) Overall survival throughout the parent trial and LTE study duration

Kaplan-Meier survival analysis will be performed. The probability of survival will be evaluated at one, three, and five (if there is sufficient follow-up time) years after initial study participation in the parent trial through the completion of the LTE trial.

A Cox regression analysis will be performed with baseline REVEAL Lite 2.0 category score and IPAH/HPAH or Non-IPAH/HPAH category. The hazard ratio and its 95% CI for the pairwise LTE treatment groups will be reported for Group 1 versus Group 4, Group 3, and Group 2 respectively.

2) Change from LTE baseline to post-LTE baseline in continuous effectiveness endpoints

The continuous endpoints measured at multiple timepoints include:

- Change from baseline in NT-proBNP
- Change from baseline in 6MWD
- Change from baseline in REVEAL Lite 2.0 Score
- Change from baseline in QoL emPHasis-10 Questionnaire score
- Change from baseline in Borg dyspnea index

The following analysis described for change from baseline in NT-proBNP will be used for the analysis of the continuous endpoints enumerated above.

The pairwise mean difference in change from LTE baseline among LTE treatment groups will be estimated using a mixed model for repeated measures (MMRM) model where the response is change from LTE baseline in an NT-proBNP at each post-baseline visit for each subject.

The explanatory variables will include:

- Fixed effect factors
    - Visit
    - LTE treatment groups
    - LTE treatment groups by visit interaction
    - IPAH/HPAH or Non-IPAH/HPAH category
- Fixed effect covariates
    - Continuous pre-LTE baseline value
    - Continuous parent trial baseline REVEAL 2.0 score
- Subjects as random effects

Unstructured covariance will be specified. If the fitted model does not converge with unstructured covariance, a simpler covariance will be specified. LSMeans by trial treatment groups and difference in mean change from baseline in NT-proBNP at each visit will be reported. At each post-baseline visit (with focus on Weeks 24, 48 and 72 after LTE entry) the difference in mean change from baseline in NT-proBNP between treatment groups and its 95% CI for the treatment term will be reported. The mean difference in change from LTE baseline between subjects always on the optimal dose will be compared in the following order: 1) always on placebo (Group 4); 2) placebo followed by an active treatment dose (Group 3); 3) always on the non-optimal dose (Group 2). Average treatment effectiveness before and after optimal dose treatment during the LTE will also be presented.

Trends in change from baseline (CFB) will initially be assessed graphically. To obtain a measure of trends using MMRM, visits as continuous variables, and visit by LTE treatment groups interactions will be entered into the model. The coefficient for continuous visit associated for each of the LTE treatment groups indicates the linear trend in change from baseline over visit. A non-linear trend in CFB will be tested by entering visit as quadratic or cubic spline of visit in the model.

3) Maintenance or improvement in WHO Functional Class throughout the LTE

At each post-LTE baseline visit, a subject's status with respect to remaining in or decreasing from the same WHO FC will be recorded. At each post-baseline visit, the proportion of subjects who remain or improve on their baseline WHO FC will be reported by treatment groups. A logistic regression model will be fitted where the response at each visit is whether the subject remains in or improves in WHO FC. The explanatory variables consist of LTE treatment groups, visit, LTE treatment groups by visit, IPAH/HPAH or non-IPAH/HPAH category, and continuous LTE baseline REVEAL Lite 2.0 score.

Visits within a subject form a cluster. Estimated proportions by treatment group and visit will be reported. For Week 24 after optimal dose treatment, the log of odds and proportions of subjects who maintain or improve WHO FC and their 95%CI will be reported by treatment groups. Odd ratios (OR) and 95%CI for subjects always on optimal dose (Group 1) relative to those subjects on always on placebo (Group 4) will be reported. OR and 95%CI among subjects always on optimal dose (Group 1) relative to those of subjects on placebo and then active treatment (Group 3) and OR and 95%CI among subjects always on optimal dose (Group 1) relative to those of subjects on non-optimal dose (Group 2) will also be reported.

4) Time to Clinical Worsening

Time to clinical worsening while in the parent trial and LTE will be based on the first occurrence of any of the following events for each subject.

- Death
- Initiation of parenteral prostanoids
- Hospitalization for worsening PAH
- ≥ 15% decline from baseline in 6MWD and accompanied with progression to or continued WHO FC III or IV symptoms

A subject is evaluated for experiencing any of the above components of clinical worsening throughout the parent trial and LTE study period. Time to clinical worsening is the number of days between the earliest occurrence of the clinical worsening component and the date of the first dose in the parent trial. With treatment groups that change over time intervals, event and censoring will be defined within each time interval. A subject who does not experience any of the clinical worsening component throughout a treatment period/interval is censored and is assigned time to worsening status by the end of the interval. Subjects who are lost to follow-up are typically considered censored. Supplemental analyses will be performed where subjects with an unknown clinical worsening event will be considered to

experience the event and the time to clinical worsening status is the last contact with the subject.

The probability of clinical worsening every 24 weeks after the first dose in the parent trial throughout the LTE will be reported, descriptively as well as based on a Cox model for time to clinical worsening while holding covariates at their means.

A Cox model will be fitted to time to clinical worsening with terms for time-varying by treatment dose groups, continuous LTE baseline REVEAL Lite 2.0 score (among those randomized to placebo in Phase 3), continuous parent baseline REVEAL Lite 2.0 score, and IPAH/HPAH or Non-IPAH/HPAH category.

The hazard ratio and its 95% CI for the pairwise treatment dose groups will be reported for:

- Always on the optimal dose (Group 1) versus always on placebo (Group 4)
- Always on the optimal dose (Group 1) versus on placebo followed by an active dose (Group 3)
- Always on the optimal dose (Group 1) versus always on a non-optimal dose (Group 2)

Kaplan-Meier curves by parent trial treatment groups will be generated.

5) Achieving multicomponent clinical improvement will be analyzed as a binary as well as a time to event response throughout the LTE period

a) Binary response throughout LTE period: At each LTE visit, a subject response is set to 1 for achieving multicomponent clinical improvement if he meets all of the following three conditions:
   - FC improvement or maintenance of FC II status
   - NT-proBNP ≥ 30% improvement or < 300 pg/ml
   - 6MWD ≥ 30 meters improvement

   Otherwise, the response value is 0.

A logistic regression model will be fitted to the binary response of achieving multicomponent clinical improvement at each visit. The explanatory variables will include LTE treatment groups categorical visit, LTE treatment groups by visit interaction, continuous LTE baseline REVEAL Lite 2.0 score, continuous parent baseline REVEAL Lite 2.0 score, and IPAH/HPAH or Non-IPAH/HPAH category. The subject's multicomponent clinical improvement status during the parent study may be considered as an explanatory variable. Subjects will be specified as clusters.

b) **Time to Event Response from start to end of the LTE**: Time to achieve multicomponent clinical improvement response is defined as the days since the first

dose that a subject achieves clinical improvement in all 3 components from the start through the end of LTE. The number of days between the date that a subject meets all of the multicomponent improvement parameters and the first LTE dose date is the time to achieving multicomponent improvement. A subject who does not experience multicomponent improvement is censored during the time interval. A subject who is lost to follow-up without recording this multicomponent improvement is censored at the last visit in which the above parameters are recorded. Supplemental analyses will be performed where those lost to follow-up are considered a failure at the time of the lost to follow-up.

The Cox hazard model as described for time to clinical worsening will be implemented for time to multicomponent clinical improvement.

8.5.3 Analysis of Tier 2 Effectiveness Endpoints

- **Change from LTE baseline in echocardiographic parameters at LTE Weeks 24, 48, 72 and 96 including (but not limited to) tricuspid annular peak systolic excursion (TAPSE), right ventricular myocardial strain, tricuspid annular systolic velocity (TA S'), and right ventricular fractional area change (RVFAC):** For each subject, the above echocardiographic parameters will be measured at LTE baseline and Weeks 24, 48, 72, and 96. The mean value and change from baseline at each visit will be summarized descriptively for each treatment group. The mean difference in change from baseline at each visit between subjects always on optimal dose (Group 1) and subjects always on placebo (Group 4) will be summarized and the 95%CI for the difference will be provided. Mean difference and the 95% CI between subjects always on optimal dose (Group 1) and subjects on placebo then active dose (Group 3) will be calculated, followed by taking the difference and the 95% CI between subjects always on optimal dose (Group 1) and subjects on non-optimal dose (Group 2). Mean change from baseline before and after optimal dose treatment during LTE will be presented.

- **Change from baseline in hemodynamics as assessed by RHC in LTE:** For those subjects who have RHC data, change from LTE baseline over time will be summarized for mPAP, PVR, cardiac output and mean right atrial pressure (mRAP), separately, by LTE treatment dose groups. Mean change from baseline before and after optimal dose treatment during the LTE will be presented.

8.6 Safety Analysis

Safety analyses will be conducted using the safety analysis set. The baseline will be defined as prior to the first AV-101 treatment. For Groups 1 and 2, the parent AV-101-002 study baseline will be used. For Groups 3 and 4, the AV-101-003 study baseline will be used and the placebo treatment data from the parent study will not be used. For the analyses of safety parameters, all four groups will be displayed individually. In addition, Groups 1 and 4 will be pooled as the optimal dose treatment group. Groups 2 and 3 will be pooled since they start with the non-optimal dose and then are switched to the optimal dose. An overall pool of all 4 groups will also be presented.

As previously defined, Groups 2 and 3 are treated with the non-optimal dose first and then are converted to the optimal dose. They will be further analyzed based on two treatment intervals. The first interval will start with the first day and end with the last day of the non-optimal AV-101 treatment. The second interval will start with the first day of the optimal AV-101 treatment, and end with the last day of the optimal AV-101 treatment or the data cutoff date for the analysis.

Treatment-emergent AEs (TEAEs), i.e. AEs that start or worsen at the start of AV-101 will be tabulated by system organ class and preferred term. Tables of fatal adverse events, SAEs, treatment-related AEs, and adverse events leading to withdrawal from investigation product will be provided. Subjects who experience more than one event in a given System Organ Class (SOC) and preferred term (PT) will be counted once within that SOC and PT. The total number of events and the number and percentage of subjects with each unique event will be reported.

The latest version of MedDRA will be used to code adverse events and the NCI CTCAE version 5.0 will be used to grade the severity of adverse events and laboratory toxicities.

Tabulations and detailed listings of subjects that experience AEs, AESIs, TEAEs, SAEs and ADEs and unexpected issues with inhaler use will be provided. AE severity and the relationship to AV-101 or the inhaler will also be reported.

For repeated safety events of special interest, incidence density will be compared between treatment arms by fitting a negative binomial model to counts of safety events with total weeks of study participation as an offset variable.

For select safety parameters, descriptive statistics (sample size, mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum) of observed measurements at each visit and of the change from baseline (baseline is defined as the last measurement prior to the first dose of AV-101) to each visit will be presented by visit and by treatment dose groups.

Shift tables for laboratory parameters will be compared among treatment groups by visits. Shift tables may be based on toxicity grading or values classified as low or above normal ranges.

Tabulation and listings of abnormal and/or clinically significant findings/values will be presented for laboratory findings, vital signs, physical examinations, ECG, concomitant medications, concomitant procedures and other safety parameters.

9 Responsibilities

9.1 Investigator Responsibilities

9.1.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2 Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor/designee with sufficient, accurate financial information, as requested, for the Sponsor/designee to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

9.1.3 Informed Consent Process

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

Subjects must be informed that their participation is voluntary.

Subjects or an individual or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, the Health Insurance Portability and Accountability Act (HIPAA) requirements (where applicable) and the IRB/IEC or study center.

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

If the ICF is updated during their participation in the study, subjects must be re-consented to the most current, approved version at the next on-site study visit, unless otherwise indicated by the IRB/IEC. The medical record must include a statement that written informed re-consent was obtained.

A copy of the signed ICF(s) must be provided to the subject.

The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing, and inspection purposes.

Subjects who are rescreened are required to sign a new ICF.

9.1.4 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected.

The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study subject. The file must identify each subject, contain the following demographic and medical information for the subject, and should be as complete as possible:

- Subject's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases

- Prior and concomitant therapies (including changes during the study)
- Study identifier (i.e., the Sponsor's study number) and subject's study number
- Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
- Any medical examinations and clinical findings predefined in the protocol
- All AEs
- Date that the subject left the study, including any reason for early withdrawal from the study or study drug, if applicable

All source data must be filed (e.g., ECHO, RHC report and tracings, ECG recordings, and laboratory results). Each document must clearly identify the subject and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.

Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval. Investigators must notify the Sponsor/designee in advance if source documents are to be moved to another location, such as for archiving.

The definition of what constitutes source data can be found in the eCRF guidelines.

9.1.5 Data Protection

The Sponsor will assign a unique identifier to subjects after obtaining their informed consent. All subject records or datasets transferred to the Sponsor will contain the identifier only; subject names or any identifiable information will not be transferred.

The Sponsor must inform subjects that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain the subjects' confidentiality.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB, institutional policies, or sponsor requirements.

The Investigator will complete the subject registration using the IWRS (Section 5.6). If the subject meets all inclusion criteria and does not meet any of the exclusion criteria, the subject will be randomized by IWRS.

The sponsor will ensure protection of data privacy by adhering to guidelines published by the European Commission, and other national guidelines and regulatory requirements addressing data protection.

9.2 Sponsor Responsibilities

This clinical study is Sponsored by: Aerovate Therapeutics, Inc.

The Coordinating Investigator represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

The study will appear in the following clinical studies registries: ClinicalTrials.gov and EudraCT.

Details of structures and associated procedures will be defined in a separate Integrated Project Management Plan, which will be prepared under the supervision of the Clinical Study Leader.

A DSMB will be formed in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study (see Section 3.3).

The Sponsor will adhere to all applicable laws and regulations for reporting safety data throughout conduct of the AV-101-003 study. The Sponsor will ensure prompt and ongoing communication of safety data through the following processes:

- All SAEs will be reported to the CRO's Drug Safety Department (DSD). When an SAE is received, the CRO DSD will notify the Sponsor within 1 business day. The CRO DSD will process and the Sponsor will review and approve all SAE reports in accordance with internal procedures and the Safety Management Plan. All SAEs meeting the definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR) will be communicated to the study Investigators, ECs/IRBs, and Health Authorities as required in accordance with the CRO's internal procedure(s) and established regulatory timelines.
- When important new safety information is identified, the AV-101 Investigators' Brochure (IB) will be updated promptly and at a minimum on a yearly basis. The updated IB will be submitted to study Investigators within 30 business days of being finalized and in accordance with applicable laws and regulations.
- The impact of important new safety information will be continuously evaluated for the need to revise key study documents including the AV-101-003 protocol, patient information, and the informed consent forms. The Sponsor will make needed revisions to these documents promptly and will provide them to Health Authorities, ECs/IRBs, and study Investigators without delay as required. Note: new safety information requiring an Urgent Safety Measure will follow required procedures and applicable regulatory requirements.

- All protocol deviations (PD), including safety-related deviations, will be recorded and processed according to the CRO's internal procedure(s), including necessary corrective actions for non-compliance. Monthly reviews of aggregate PDs, including safety-related PDs, will be conducted by the CRO, and quarterly reviews will be conducted by the Sponsor and CRO. The evaluation of trends may lead to additional actions including the revision of key study documents and training.

9.2.1 Emergency Medical Support

The Sponsor or designee will provide Emergency Medical Support (EMS) cards to subjects at the time of randomization for use during the study. These provide the means for subjects to identify themselves as participating in a clinical study. These also give health care providers access to any information about a subject's participation in the study that may be needed to help determine the course of medical treatment for the subject. The information on the EMS card may include the process for emergency unblinding (if applicable).

The first point of contact on the EMS card, for all medical emergencies associated with a study subject, will be the clinical study Investigator caring for the subject. Thus, the Investigator's emergency contact information will be included on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

When the Investigator is not available, the EMS card will include provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician (or designated CRO Medical Monitor) to assist with the medical emergency and to provide support for the potential unblinding of the subject concerned.

9.2.2 Clinical Study Insurance and Compensation to Subjects

The Sponsor is responsible for AEs that are associated with this study and cause damage to the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the subject. The Sponsor has purchased insurance coverage to fulfill this responsibility.

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

9.2.3 Clinical Study Report

Clinical study reports will be written by the Sponsor in consultation with the Coordinating Investigator after the completion of the study.

9.2.4 Publication

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission of

the study results for presentation or publication. This allows Aerovate to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by agreement.

Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

9.2.5 Dissemination of Clinical Study Data

After completion of the study, a clinical study report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3, and will be submitted in accordance with local regulations.

Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to the Investigator's employees and staff who have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for 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 understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical Investigators, to the Health Authorities, and to other 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 the Sponsor 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.

9.2.6 Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed. The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include:

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

9.3 Regulatory and Ethical Considerations

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

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

The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigators' Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.

Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study subjects. When applicable, amendments will be submitted to the appropriate Health Authorities.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures
- Notifying the IRB/IEC of unanticipated SAEs or other significant safety findings, as required by IRB/IEC procedures
- Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

9.4 Data Quality Assurance

All subject study data will be recorded on printed or eCRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information in the eCRF.

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

The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at study completion.

Study monitors will perform ongoing source data verification to confirm that data in the eCRF are accurate, complete, and verifiable; that the safety and rights of subjects are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

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11 Appendices

Appendix 1 Abbreviations

6MWD/6MWT	Six-minute Walk Distance/Test
ADE	Adverse Device Effect
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
BDI	Borg Dyspnea Index
BID	Twice-daily dosing
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CFB	Change From Baseline
CI	Cardiac Index
CIOMS	Council for International Organizations of Medical Sciences
CO	Cardiac Output
CRF/eCRF	Case Report Form/Electronic Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
DOAC	Direct Oral Anticoagulant Therapy
DPI	Dry Powder Inhaler
DSD	Drug Safety Department
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
ED	Early Discontinuation
EDC	Electronic Data Capture
emPHasis-10	Questionnaire for assessing Health-Related Quality of Life in pulmonary arterial hypertension
EOT	End-of-Treatment
FAS	Full Analysis Set

FC	Functional Class
FEV_1	Forced Expiratory Volume in 1 second
FSH	Follicle Stimulating Hormone
FU	Follow-up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFR/eGFR	Glomerular Filtration Rate/estimated Glomerular Filtration Rate
HDPE	High Density Polyethylene
HEENT	Head, Ears, Eyes, Nose, Throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRQoL	Health-Related Quality of Life
I/HPAH	Idiopathic/Heritable PAH
IB	Investigators' Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Review Committee
IFU	Instructions For Use
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IWRS	Interactive Web-Response System
LTE	Long-Term Extension
LVEDP	Left Ventricular End-Diastolic Pressure
LVEF	Left Ventricle Ejection Fraction
M	Meters
MAD	Multiple Ascending Dose
MMRM	Mixed Model for Repeated Measures
mPAP	Mean Pulmonary Arterial Pressure

mRAP	Mean Right Atrial Pressure
NOAEL	No-Observed-Adverse-Effect-Level
NHP	Non-Human Primates
NT-proBNP	N-Terminal Prohormone-B Natriuretic Peptide
OD	Optimal Dose
OR	Odds Ratio
PAH	Pulmonary Arterial Hypertension
PASP	Pulmonary Artery Systolic Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PD	Protocol Deviation
PE	Physical Exam
PFT	Pulmonary Function Test
PH	Pulmonary Hypertension
PK	Pharmacokinetics
PR	Pulse Rate
PT	Preferred Term
PVR	Pulmonary Vascular Resistance
QoL	Quality of Life
QRS	ECG Measurement for the QRS Complex
QT	ECG Measurement for the time from the start of the Q wave to the end of the T wave
QTc/QTCF	QT Corrected/ QT Corrected by Fridericia's formula
REVEAL Lite 2	Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk calculator; abridged
RHC	Right Heart Catheterization
RR	Respiratory Rate
RV	Right Ventricular
RVFAC	Right Ventricular Fractional Area Change
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAF	Screened Analysis Set
SAP	Statistical Analysis Plan

SAS	Safety Analysis Set
SDH	Subdural Hematoma
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
SVO_2	Mixed Venous Oxygen Saturation
TA S'	Tricuspid Annular Systolic Velocity
TAPSE	Tricuspid Annular Peak Systolic Excursion
TB	Tuberculosis
TRJV	Tricuspid Regurgitant Jet Velocity
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USADE	Unanticipated Serious Adverse Device Effect
VO_2	Oxygen consumption
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

Appendix 2 Sample Quality of Life Questionnaire

Subjects must be able to read and understand the Quality of Life questionnaire. Below is a reference example in English; however, translated questionnaires and instructions will be provided for subjects, as appropriate, and submitted to Independent Ethics Committee/Institutional Review Board (IEC/IRB), if applicable.

emPHasis-10

emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total:

Date:

pha UK pulmonary hypertension association

MANCHESTER 1824 The University of Manchester

Appendix 3 Guidance for 6-Minute Walk Test

The 6-minute walk test will be conducted according to the European Respiratory Society/ American Thoracic Society Technical Standard (Task Force Report ERS/ATS Technical Standard, Holland et al 2014, http://ow.ly/Bq2B9). The test should also be conducted in in accordance with local standard operating procedures.

Please refer to the following guidelines (an excerpt from the ERS/ATS Technical Standard reference above) for conducting the 6-minute walk test.

General

The 6MWT plays a key role in evaluating functional exercise capacity, assessing prognosis and evaluating response to treatment across a wide range of respiratory diseases. Since publication of the previous American Thoracic Society (ATS) statement on the 6MWT in 2002 [1], new information regarding the 6MWT has emerged in a range of areas, including methods of test performance and interpretation. This increased body of knowledge has significant implications for the good conduct of the 6MWT in individuals with chronic respiratory disease, in both research and clinical settings.

The 6MWD is very sensitive to variations in methodology, including use of encouragement, provision of supplemental oxygen, changes in track layout and length, and use of wheeled walkers. These factors should be held constant on repeat testing.

> NOTE: If institutional policies require or subject preference to where a face mask to avoid exposure to pathogens during the Screening walk, then a similar mask should be worn during subsequent 6MWTs.

The 6MWT is a self-paced test of walking capacity. Patients are asked to walk as far as possible in 6 minutes along a flat corridor. The distance is recorded in feet or meter. Standardized instructions and encouragement are given during the test.

Test Equipment

TABLE 3 Equipment required for conduct of field walking tests
At least one chair, positioned at one end of the walking course
A validated scale to measure dyspnea and subjective fatigue
Sphygmomanometer for blood pressure measurement
Pulse oximeter*
Stopwatch
Pre-measured marks along the track/corridor

Access to oxygen and telephone in case of an emergency
An emergency plan
Portable supplemental oxygen if required by patient to perform exercise test
Clipboard with reporting sheet and pen

***Pulse Oximetry data is not required by the protocol but sites should perform this if it is their normal practice.**

Test location and staffing

- The test should be conducted along a quiet course.
- The 6MWT should be performed along a flat, straight course with a hard surface with little pedestrian traffic. It is recommended that the walking course be 30 m (approximately 100 feet) or more in length, to be consistent with the courses on which reference equations have been generated.
- The ends of the course should be marked such that they are easily visible to patients.
- A comfortable temperature is important and air conditioning should be available if needed.
- Testing should be performed in a location where a rapid, appropriate response to an emergency is possible.
- The assessor performing the test should be properly trained.

Patient preparation

- Patients should wear comfortable clothing and appropriate shoes for walking.
- Patients should use their usual walking aids during the test and this should be documented on the assessment form.
- Patients should not have exercised vigorously within 2 hours of beginning the test but should have taken their usual medications.
- All subsequent testing occasions should occur at about the same time of day to minimize intra- day variability, including variability in self-paced tests (6MWT) associated with bronchodilator use.
- A warm-up is not permitted prior to commencing the test, neither is a shortened version of the test.
- If respiratory function tests are to be performed on the same day, this should occur prior to exercise testing, to avoid the confounding effects of exercise on these measures.
- The patients should then rest for at least 15 min before commencing an exercise test.

Use of oxygen

- If a patient is on long-term oxygen therapy, oxygen should be given at their standard flow rate or as directed by a physician or a protocol.
- All tests should be performed using the same oxygen conditions, in order to make a valid comparison between testing occasions.

- If oxygen supplementation is needed during the walks and serial tests are planned, then oxygen should be delivered in the same manner (flow rate and delivery device) for all subsequent walks.
- The type of oxygen delivery device should also be noted on the report: for instance, whether the subject carried liquid oxygen or pushed or pulled an oxygen tank, and whether the delivery was pulsed or continuous.
- Assessors should avoid transportation of the oxygen source where possible; however, if the subject is not able to control/carry/manage their own oxygen cylinder, the assessor should try to walk slightly behind the subject to avoid setting the walking pace.
- It should be clearly documented how the assessor has assisted with the transport of the oxygen, so any subsequent walk tests with the same subject can be performed in the same manner.

Testing protocol for 6MWT

Medications

Patients should be instructed to take all usual medications.

Immediately prior to the test

- Patients should rest in a chair, located near the starting position, before the test starts.
- The assessor should provide standardized instructions (see Table 5), verbally for the test.
- The patient should be positioned at the starting line.
- The timer should be started as soon as the patient starts to walk.

TABLE 5 Standardized verbal instructions for the 6-min walk test

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.
6 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?

Conduct

- The patient should be encouraged every 60 seconds using the standard phrases (Table 6).
- Other words of encouragement and other nonverbal prompts should not be used.
- If the patient stops walking during the test, the timer must not be stopped.
- The patient should be allowed to rest while sitting or standing, as they prefer.
- While the patient is stopped, standardized encouragement should be provided every 30 seconds (Table 6).
- The time that the patient stopped and the time that walking is recommenced should be recorded.

TABLE 6 Standardized encouragement for the 6-min walk test	
1 min	You are doing well. You have 5 minutes to go.
2 min	Keep up the good work. You have 4 minutes to go.
3 min	You are doing well. You are halfway.
4 min	Keep up the good work. You have only 2 minutes left.
5 min	You are doing well. You have only 1 minute to go.
6 min	Please stop where you are.
If the patient stops during the test, every 30 seconds once SpO2 is >85%	Please resume walking whenever you feel able.

Immediately on test cessation

- Patient should be asked to rate their dyspnea and subjective fatigue on the standardized scale.
- In addition, it is important to understand the reason for test termination/limitation, so patients should be asked why they could not walk any further.

Recording performance of the 6MWT

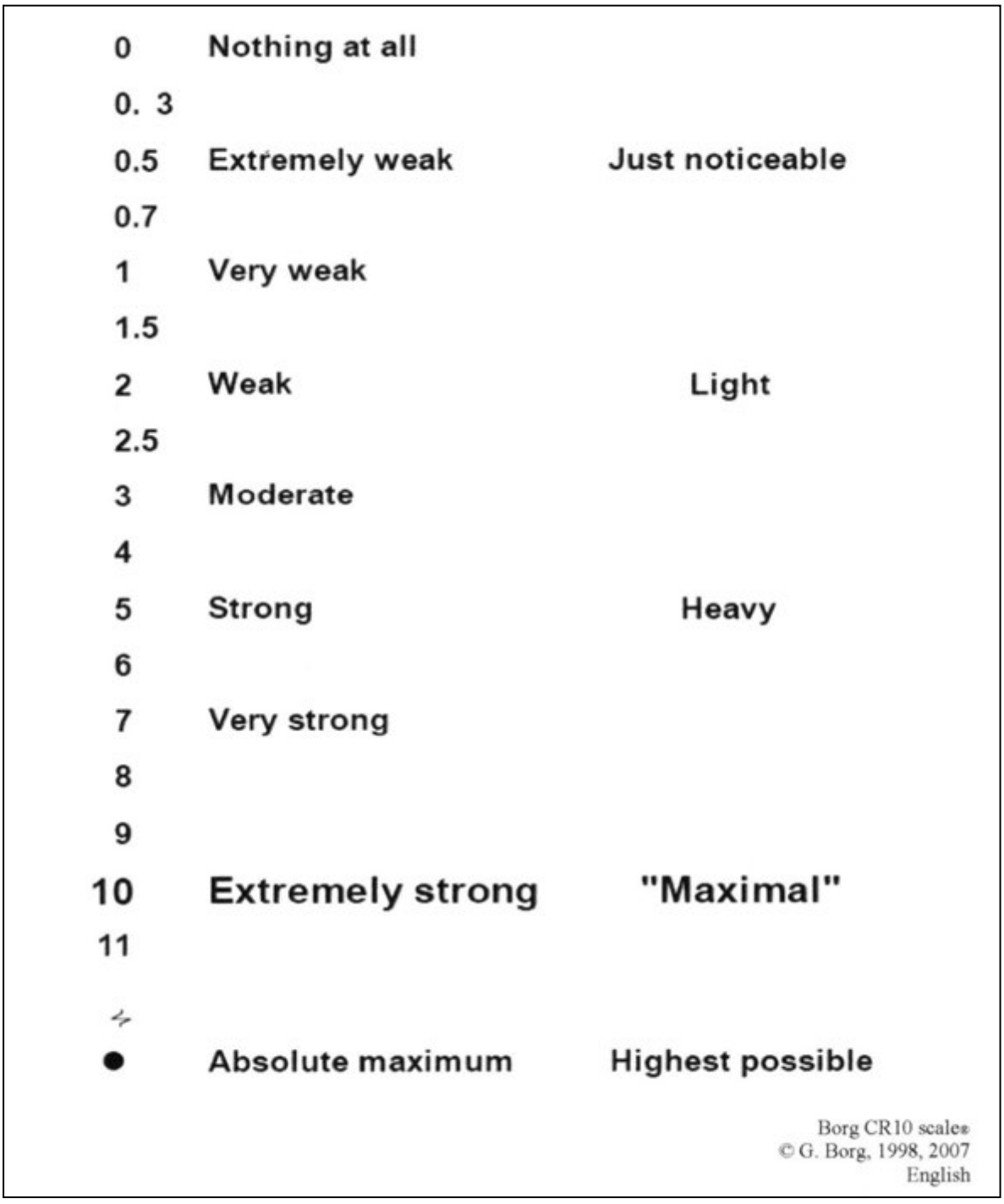
- The primary outcome to be reported is 6MWD.
- The number of laps and any additional distance covered (the number of meters or feet in the final partial lap) should be recorded.
- The total distance walked is calculated, rounding to the nearest meter or foot.
- If the patient stopped during the test, the total time stopped, the number of stops over the 6 min are also reported.

Reference

[1] ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111–117

Appendix 4 Borg Dyspnea Index

The Borg Dyspnea Index score must be assessed immediately following completion of the 6-minute walk test (see Appendix 3). Subjects must be able to read and understand the Borg Dyspnea Index and the associated instructions. Below are reference examples in English; however, a translated index and instructions will be provided for subjects, as appropriate, and submitted Independent Ethics Committee/Institutional Review Board (IEC/IRB), if applicable.



Instruction. Use this rating scale to report how strong your perception is. It can be exertion, pain or something else. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or "Extremely strong", "Maximal" is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is "Very weak", you should say "1", if it is "Moderate", say "3". Note that "Moderate" is "3" and thus weaker than "Medium", "Mean" or "Middle". If the experience is "Strong" or "Heavy" (it feels "Difficult") say "5". Note that "Strong" is about half of "Maximal". If your feeling is "Very strong", choose a number from 6 to 8. If your perception or feeling is stronger than "10", - "Extremely strong", "Maximal" – you can use a larger number, e.g. 12 or still higher (that's why "Absolute maximum" is marked with a dot "•").

It's very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating exertion give a number that corresponds to how hard and strenuous you perceive the work to be. The perception of exertion is mainly felt as strain and fatigue in your muscles and as breathlessness or any aches.

0 "Nothing at all", means that you don't feel any exertion whatsoever, no muscle fatigue, no breathlessness or difficulties breathing.

1 "Very weak" means a very light exertion. As taking a shorter walk at your own pace.

3 "Moderate" is somewhat but not especially hard. It feels good and not difficult to go on.

5 "Strong". The work is hard and tiring, but continuing isn't terribly difficult. The effort and exertion is about half as intense as "Maximal".

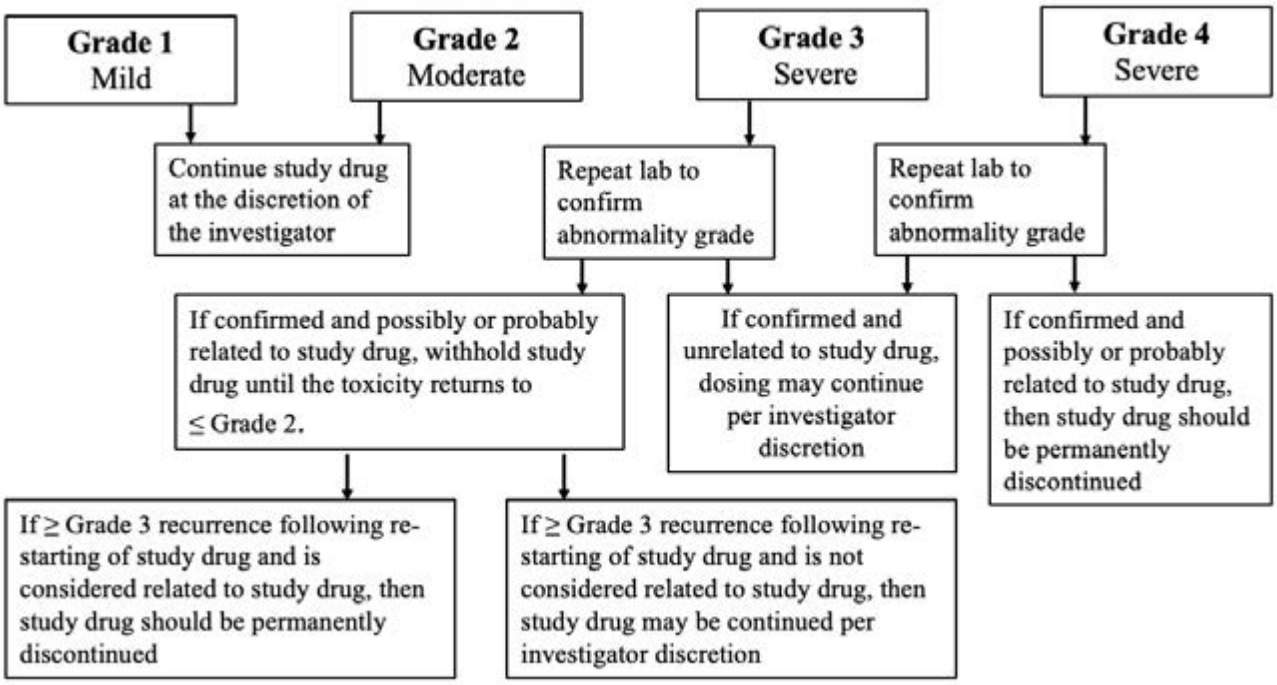
7 "Very strong" is quite strenuous. You can still go on, but you really have to push yourself and you are very tired.

10 "Extremely strong – Maximal" is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.
• Is "Absolute maximum" for example "12" or even more.

Any questions?

Borg CR10 scale®
© G. Borg, 1998, 2007
English

Appendix 5 Management of Abnormal and Medically Important Laboratory Abnormality



Appendix 6 Investigator Signature Page

Study Title:	IMPAHCT-FUL: A Long-Term Extension, Multi-Center Safety Study of AV-101 in Subjects With Pulmonary Arterial Hypertension (PAH) Who Have Completed Study AV-101-002
Clinical Study Protocol Version:	Amendment 2.0

This protocol has been approved by Aerovate Therapeutics, Inc. The following signature documents this approval.

[redacted]

Aerovate Therapeutics, Inc.

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I understand and agree that it contains all necessary details for me and my staff to conduct this study as described.

I am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council for Harmonisation, Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Aerovate Therapeutics, Inc.

Principal Investigator Name (Printed)	Signature
Date	Site Number