Macitentan / ACT-064992

Portopulmonary hypertension

AC-055-404

PORTICO

A randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group study to assess the safety and efficacy of macitentan in patients with portopulmonary hypertension

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Treatment name / number

Macitentan / ACT-064992

Indication

Portopulmonary hypertension

Protocol number, study acronym, study title

AC-055-404, PORTICO: A randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group study to assess the safety and efficacy of macitentan in patients with portopulmonary hypertension

I approve the design of this study.

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INVESTIGATOR SIGNATURE PAGE

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I agree to the terms and conditions relating to this study as defined in this protocol, the electronic Case Report Form (CRF), and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the wellbeing of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an Institutional Review Board or Independent Ethics Committee (IRB/IEC) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IRB/IEC and ensure approval by regulatory authorities (if applicable) have been obtained before the implementation of changes described in the amendment. I will allow direct access to source documents and study facilities to sponsor representative(s), particularly monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IRB/IEC representative. I will ensure that the study treatment(s) supplied by the sponsor are being used only as described in this protocol. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

	Country	**Site number**	**Town**	**Date**	**Signature**
Site Principal Investigator					

This center is performing the: ☐ Pharmacokinetic substudy ☐ Hepatic vein catheterization

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6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under plasma concentration-time curves
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to time t
AUC_{τ}	Area under the plasma concentration-time curve during one dosing interval
BDI	Borg Dyspnea index
BLQ	Below limit of qualification
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CI	Cardiac index
C_{max}	Maximum plasma concentration
CO	Cardiac output
CRA	Clinical Research Associate
eCRF	electronic Case Report Form
CRO	Contract Research Organization
CV	Coefficient of Variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DoA	Delegation of Authority
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid

EMA	European Medicines Agency
EOMT	End of macitentan treatment
EOS	End of Study
EOT-DB	End of Treatment (double-blind)
EOT-OL	End of Treatment (open-label)
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ET-1	Endothelin-1
ET_A	Endothelin receptor A
ET_B	Endothelin receptor B
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
HIV	Human immunodeficiency virus
HR	Heart rate
HVC	Hepatic vein catheterization
HVPG	Hepatic venous pressure gradient
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILSDRB	Independent Liver Safety Data Review Board
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intrauterine device
i.v.	Intravenous
IxRS	Interactive Voice/Web Response System
LDH	Lactate dehydrogenase

LFT	Liver function test
LOQ	Limit of quantification
LVEDP	Left ventricular end diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-stage Liver Disease
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
MTS	Macitentan Treatment Set
NT-proBNP	N-terminal pro-hormone brain natriuretic peptide
OLT	Orthotopic liver transplantation
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PDE5i	Phosphodiesterase type 5 inhibitor
PH	Pulmonary hypertension
PK	Pharmacokinetic
PoPH	Portopulmonary hypertension
PPS	Per-protocol Set
PT-INR	Prothrombin time and International Normalized Ratio
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
s.c.	Subcutaneous
SD	Standard deviation
sGC	Soluble guanylate cyclase (stimulator, riociguat)
SIV	Site initiation visit
SOC	System organ class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
SVO_2	Venous oxygen saturation
TIPS	Transjugular intrahepatic portosystemic shunt

t_{max}	Time to reach maximum plasma concentration
TPR	Total pulmonary resistance
ULN	Upper limit of the normal range
WHO	World Health Organization
WU	Wood Units

PROTOCOL SYNOPSIS AC-055-404

TITLE	A randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group study to assess the safety and efficacy of macitentan in patients with portopulmonary hypertension
ACRONYM	**PORTICO** **POR**topulmonary hypertension **T**reatment w**I**th ma**C**itentan – a rand**O**mized clinical trial
OBJECTIVES	**Primary objective** • To evaluate the effect of macitentan on pulmonary vascular resistance (PVR) as compared to placebo in patients with portopulmonary hypertension (PoPH). **Secondary objectives** • To evaluate the effect of macitentan as compared to placebo on cardio-pulmonary hemodynamics, hepatic portal vein pressure, disease severity, and exercise capacity in patients with PoPH. • To evaluate the safety and tolerability of macitentan as compared to placebo in patients with PoPH. • To evaluate the pharmacokinetics (PK) of macitentan and its active metabolite ACT-132577 in patients with PoPH (PK substudy).
DESIGN	Randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group study.
PERIODS	The study comprises a 28-day Screening period, followed by a 12-week double-blind treatment period. All subjects completing the double-blind treatment period as scheduled will have the opportunity to enter a 12-week open-label treatment period with macitentan. A 30-day Safety follow up period follows discontinuation of study treatment (double-blind or open-label) before the End of Study (EOS) for a subject can occur.
PLANNED DURATION	Approximately 18 months from first subject, first visit to last subject, last visit.
SITE(S) / COUNTRY(IES)	45 sites in 7 countries (planned): BRA, CZE, DEU, ESP, FRA, GBR, USA.

SUBJECTS / GROUPS	84 subjects in 2 groups; 42 subjects per group (randomized 1:1). Randomization will be stratified by region (Europe/North America/Latin America) and by use of background pulmonary arterial hypertension (PAH)-specific therapy (yes/no).
INCLUSION CRITERIA	1) Signed informed consent prior to any study-mandated procedure 2) Male or female ≥ 18 years of age with symptomatic PoPH: • Documented diagnosis of portal hypertension • PAH by right heart catheterization at screening: – Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg – Pulmonary artery wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg 3) PVR ≥ 4 Wood Units (WU) or ≥ 320 dyn.s.cm^{-5} at screening[1] 4) 6-minute walk distance (6MWD) ≥ 50 m at screening 5) Women of childbearing potential must: a) Have a negative serum pregnancy test during screening and a negative urine pregnancy test on Day 1, *and* b) Agree to use reliable methods of contraception from screening up to 30 days after study treatment discontinuation, *and* c) Agree to perform monthly pregnancy tests up to 30 days after study treatment discontinuation.
EXCLUSION CRITERIA	1. PAH due to any other condition than portal hypertension 2. Severe hepatic impairment, as defined by Child-Pugh Class C liver disease or Model for End-stage Liver Disease (MELD) score ≥ 19 3. Unstable liver disease (in the opinion of the investigator) 4. History of transjugular intrahepatic portosystemic shunt (TIPS) within 6 months prior to randomization 5. Documented severe obstructive or restrictive lung disease (in the opinion of the investigator)

[1] Cardiac output measured by thermodilution technique only.

	6. Documented pulmonary veno-occlusive disease 7. Systolic blood pressure (SBP) < 90 mmHg at Screening 8. Body weight < 40 kg at Screening 9. Patients undergoing dialysis 10. Initiation of diuretics or beta blockers within 1 week prior to baseline right heart catheterization (RHC) **or** patients on oral diuretics or beta blockers in whom the dose has not been stable for at least 1 week prior to baseline RHC 11. Hemoglobin < 100 g/L at Screening 12. Serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥ 3 × the upper limit of the normal range (ULN) at Screening 13. Bilirubin ≥ 3 mg/dL at Screening 14. Grades 2, 3, or 4 hepatic encephalopathy 15. History of liver transplantation 16. Documented hepatocellular carcinoma 17. Documented schistosomiasis infection 18. Gastrointestinal bleeding or esophageal variceal bleeding < 3 months prior to randomization 19. Recently started (< 3 months prior to randomization) or planned cardio-pulmonary rehabilitation program based on exercise 20. Treatment with calcium channel blockers, endothelin receptor antagonists (ERA), intravenous/subcutaneous (i.v./s.c.) or oral prostanoids within 3 months prior to randomization 21. Initiation, change in dose or discontinuation of phosphodiesterase type 5 inhibitors (PDE5i), or soluble guanylate cyclase stimulator within 3 months prior to randomization 22. Treatment with interferon within 3 months prior to randomization 23. Treatment with any investigational drug within 3 months prior to randomization 24. Treatment with strong cytochrome P450 (CYP) 3A4 inducers (e.g., carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and

	St. John's wort) within 4 weeks prior to randomization 25. Treatment with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, boceprevir, telaprevir, saquinavir, lopinavir, fosamprenavir, darunavir, tipranavir, atazanavir, nelfinavir, amprenavir, indinavir, and paritaprevir) within 4 weeks prior to randomization 26. Known hypersensitivity to macitentan or its excipients or drugs of the same class 27. Pregnancy, breastfeeding, or intention to become pregnant during the study 28. Known concomitant life-threatening disease with a life expectancy of < 6 months 29. Any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of results 30. Suspected or known current drug or alcohol abuse.
STUDY TREATMENTS	**Investigational treatment** Macitentan film-coated tablet 10 mg once daily. **Comparator and/or placebo** During the double-blind treatment period: Matching placebo tablet once daily.
CONCOMITANT THERAPY	**Allowed concomitant therapy** Oral PDE5i, inhaled prostacyclin analogues, soluble guanylate cyclase (sGC) stimulator are allowed if present for at least 3 months prior to randomization at a stable dose (which must remain unchanged during the double-blind treatment period unless the patient experiences worsening of PAH). Treatment with oral diuretics is allowed if ongoing at a stable dose for at least 1 week prior to baseline right heart catheterization; the dose may be optimized during the treatment period. Beta blockers are allowed if present for at least 1 week prior to baseline right heart catheterization at a stable dose (which should remain unchanged during the study). If discontinuation of beta blockers occurs during the study the patient should

	complete the study as scheduled. During the open-label period, i.v. and s.c. prostanoid therapy (e.g., epoprostenol, treprostinil) is permitted at any time. The following antiviral hepatitis C medications are permitted: simeprevir, sofosbuvir, daclatasvir, ombitasvir, dasabuvir, ledipasvir, etravirine, raltegravir, maraviroc, and ribavirin. **Forbidden concomitant medication** • ERAs (e.g., bosentan, ambrisentan) • During the double-blind period, i.v./s.c. and oral prostanoid therapy (e.g., epoprostenol, treprostinil) is forbidden • Calcium channel blockers • Strong CYP3A4 inducers (e.g., carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's wort) • Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, lopinavir, fosamprenavir, darunavir, tipranavir, atazanavir, nelfinavir, amprenavir, indinavir, boceprevir, telaprevir, paritaprevir and saquinavir) • Treatment with interferon • Any other investigational drug.
ENDPOINTS	***Double-blind treatment period*** *(Baseline is the last assessment prior to initiation of double-blind treatment).* **Primary efficacy endpoint** Relative change from Baseline to Week 12 in PVR. **Secondary efficacy endpoints** • Change from Baseline to Week 12 in mean right atrial pressure (mRAP), mPAP, cardiac index (CI), total pulmonary resistance (TPR), and mixed venous oxygen saturation (SVO_2), all measured at rest • Change from Baseline to Week 12 in 6MWD • Change from Baseline to Week 12 in WHO functional class • Change from Baseline to Week 12 in NT-proBNP. **Other efficacy endpoints** • Change from Baseline to Week 12 in hepatic venous pressure gradient (HVPG)

	• Change from Baseline to Week 12 in Borg dyspnea index. ***Macitentan treatment period (all patients receiving macitentan in either double-blind or open-label treatment periods).*** *(Macitentan Baseline is the last assessment prior to initiation of macitentan treatment).* • Change from macitentan Baseline to each time point in WHO functional class • Change from macitentan Baseline to each time point in NT-proBNP • Change from macitentan Baseline to each time point in 6MWD • Change from macitentan Baseline to each time point in Borg dyspnea index. **Safety endpoints** ***Double-blind treatment period*** *(Treatment-emergent is defined as from first intake of study treatment until to end of double-blind treatment + 30 days or start of open-label treatment, whichever occurs first).* • Treatment-emergent deaths • Treatment-emergent adverse events (AEs) • Treatment-emergent AEs leading to premature discontinuation of double-blind study treatment • Treatment-emergent serious adverse events (SAEs) • Proportion of patients with treatment-emergent ALT and/or AST abnormality (≥ 3, ≥ 5, and ≥ 8 × ULN) • Proportion of patients with treatment-emergent ALT and/or AST abnormality (≥ 3 × ULN) associated with total bilirubin ≥ 2 × ULN (and increased as compared to baseline) • Proportion of patients with treatment-emergent hemoglobin abnormality (< 100 g/L, and < 80 g/L) • Treatment-emergent marked lab abnormalities • Change from Baseline to End of Treatment (double-blind) (EOT-DB) in vital signs • Change from Baseline to EOT-DB in laboratory variables • Change from Baseline to EOT-DB in Child-Pugh

	classification • Change from Baseline to EOT-DB in MELD Score. ***Macitentan treatment period (all patients receiving macitentan in either double-blind or open-label treatment periods)*** *Macitentan treatment-emergent is defined as from first intake of macitentan up to EOS (i.e., 30 days after discontinuation of macitentan treatment). End of macitentan treatment (EOMT) is defined as EOT-DB or End of Treatment (open-label) (EOT-OL), whichever comes last. Macitentan Baseline is defined as last assessment prior to first intake of macitentan.* • Macitentan treatment-emergent deaths • Macitentan treatment-emergent AEs • Macitentan treatment-emergent AEs leading to premature discontinuation of macitentan treatment • Macitentan treatment-emergent SAEs • Proportion of patients with macitentan treatment-emergent ALT and/or AST abnormality (≥ 3, ≥ 5, and ≥ 8 × ULN) up to EOMT • Proportion of patients with macitentan treatment-emergent ALT and/or AST abnormality (≥ 3 ULN) associated with total bilirubin ≥ 2 × ULN (and increased as compared to baseline) up to EOMT • Proportion of patients with macitentan treatment-emergent hemoglobin abnormality (< 100 g/L, and < 80 g/L) up to EOMT • Macitentan treatment-emergent marked lab abnormalities up to EOMT • Change from macitentan Baseline to EOMT in vital signs • Change from macitentan Baseline to EOMT in laboratory variables • Change from macitentan Baseline to EOMT in Child-Pugh classification • Change from macitentan Baseline to EOMT in MELD Score.
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	***Double-blind treatment period*** • **Analysis sets** The Full Analysis Set (FAS) includes all randomized patients

	who received at least one dose of study treatment and who have a baseline value for the primary endpoint (PVR). The Per-Protocol Set (PPS) comprises all patients included in the FAS without major protocol deviations that affect the main analysis of the primary efficacy variable. The Safety Set includes all patients who received at least one dose of study treatment. The PK set comprises all patients from the FAS who did not deviate from the protocol in a way that might affect the evaluation of the PK endpoints. • **Primary endpoint** The primary endpoint is the relative change from baseline to Week 12 in PVR. • **Statistical hypotheses** The null hypothesis is that the treatment difference (macitentan minus placebo) in mean relative change from baseline to Week 12 in PVR is greater than or equal to zero. The alternative hypothesis is that the treatment difference in mean relative change from baseline in PVR is less than zero. • **Type-I and -II errors and power** The type I error (α) is set to 0.025 (one-sided), the type II error is set to 0.10 and the power to 90%. • **Sample size calculation** An integrated analysis of two bosentan studies, BENEFIT (AC-052-366) and EARLY (AC-052-364), and the hemodynamic substudy of SERAPHIN (AC-055-302) suggested that the treatment group difference is expected to be around −0.31 on log scale (95% confidence interval: −0.38, −0.23) and that the within group standard deviation is around 0.41 on log scale. Under these assumptions, 76 evaluable patients will be needed for 90% power (38 patients per group). Accounting for 10% non-evaluable patients, approximately 84 patients will need to be randomized. • **Primary analysis** The primary analysis will be performed on the FAS. The Week 12 versus baseline ratio in PVR will be log transformed (base e) and analyzed using an Analysis of

	Covariance (ANCOVA) with factors for treatment group, region and background PAH-specific therapy and a covariate for baseline log PVR. The treatment group difference in mean change from baseline (on log scale) and its 95% confidence interval will be estimated based on the model. The Geometric Mean Ratio (GMR, macitentan versus placebo) and its 95% confidence interval will be obtained by exponentiation. The null hypothesis will be rejected if the entire 95% confidence interval is below one. The treatment effect will be expressed as (GMR-1) × 100%, where a negative value indicates a reduction of PVR in the macitentan group as compared to the placebo group. If PVR cannot be calculated due to missing PAWP but mPAP and cardiac output (CO) are available for the same visit, PAWP will be imputed. Post-baseline PVR values obtained earlier than Week 12 will be carried forward. For patients where no post-baseline PVR measurement is available, data will be imputed. **Secondary analyses** Secondary efficacy variables will be analyzed for the FAS at α=0.025 (one-sided) using 95% confidence intervals. No correction for multiple testing will be applied for these analyses. • **Safety endpoints** Safety data will be summarized using descriptive statistics. Safety analyses will be performed on the Safety Set. • **Interim analysis** No interim analysis is planned. ***Macitentan treatment period*** • **Analysis sets** The Macitentan Treated Set (MTS) consists of all patients who received at least one dose of macitentan in the double-blind period or open-label period. • **Statistical hypotheses** No formal hypothesis testing will be performed. Efficacy and safety data will be summarized using descriptive statistics.
STUDY COMMITTEES	A Steering Committee will help design the study, provide guidance on the study conduct evaluation of the results, and

	support study publications. An Independent Liver Safety Data Review Board (ILSDRB, an external expert committee of hepatologists) will provide ongoing assessment and advice regarding serious hepatic adverse events of special interest that require further evaluation during the study as per ILSDRB charter.
SUB-STUDIES	**PK substudy** This substudy is planned during the open-label treatment period and described under the same protocol. It will be conducted in participating centers. In these centers, all patients continuing in the open-label treatment period will be offered to participate in the substudy. At least 20 patients eligible for the open-label treatment period will be enrolled. The plasma PK variables will be derived by non-compartmental analysis of the plasma concentration-time profiles. Peak maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve during one dosing interval (AUC_t) values are assumed to be log-normally distributed. PK endpoints are for both macitentan and ACT-132577: • The area under the plasma concentration-time curve during one dosing interval (AUC_t). • Maximum plasma concentration (C_{max}) during a dosing interval. • The time to reach maximum plasma concentration (t_{max}) during a dosing interval.

Table 1 Visit and assessment schedule

PERIODS	Name	SCREENING	DOUBLE-BLIND TREATMENT			OPEN-LABEL TREATMENT			FOLLOW-UP
	Duration	28 days	12 weeks			12 weeks			30 days
VISITS	Number	1	2	3/4	5	6/7	8	*U1, U2…*	
	Name	Screening	Random-ization	Visits 3/4	EOT-DB[1]	Visits 6/7	EOT-OL[1]	*Unscheduled visit* [2]	EOS[3]
	Time	Day −28	Day 1	Weeks 4/8 (± 4 days)	Week 12 (± 4 days)	Weeks 16/20 (± 4 days)	Week 24 (± 4 days)	*Any day between Day 1 and Week 24*	EOT-DB/OL + 30–33 days
Informed consent		X							
Medical history		X							
Demographics		X							
Concomitant therapy		X	X	X	X	X	X	X	
Physical examination[4]		X	X	X	X	X	X	X	
Vital signs		X			X		X	X	
Height[5] and weight		X			X		X		
Laboratory tests[6]		X[7]	X	X	X	X	X	X	
Serum pregnancy test		X	X[8]	X	X	X	X	X	X[15]
Child-Pugh assessment and/or MELD Score		X			X		X		
Right heart catheterization[9]		X			X				
Hepatic vein catheterization[10]		X			X[11]				
6MWT & BDI		X	X	X	X	X	X	X	
WHO functional class		X	X	X	X	X	X	X	
NT-proBNP			X		X		X	X	
PK substudy						X[12]			
Study drug dispensing/ return[13]			X	X	X	X	X		
Adverse Events[14]		X	X	X	X	X	X	X	X
Serious Adverse Events[14]		X	X	X	X	X	X	X	X

6MWT = 6-minute walk test; AE = adverse event; BDI = borg dyspnea index; CRF = case report form; EOT-DB = end of treatment (double-blind); EOT-OL = end of treatment (open-label); EOS = end of study; HVC = hepatic vein catheterization; MELD = Model for End-stage Liver disease; PK = pharmacokinetics; PT-INR = prothrombin time and international normalized ratio; RHC = right heart catheterization; SAE = serious adverse event; WHO = World Health Organization.

[1] If subject does not reach Week 12 (Visit 5) or does not enter into open-label phase, EOT-DB visit must be performed including RHC, followed by EOS after 30 days. If a subject enters open-label phase, but does not reach Week 24 (Visit 8), EOT-OL visit must be performed but without RHC, followed by EOS after 30 days.
[2] Unscheduled visits may be performed at any time during the study and may include all or some of the indicated assessments, based on the judgment of the investigator.
[3] Visit may be performed by phone.
[4] Data not collected in the CRF; abnormal findings to be recorded as Adverse Events.
[5] Height recorded at Screening only.
[6] Includes hematology, general blood chemistry, liver functions tests, serum bile acids, PT-INR. To be performed monthly during study conduct.
[7] Eligibility to be assessed using Screening laboratory data only
[8] Urine dipstick pregnancy test to be performed in addition to serum.
[9] Cardiac output to be measured using thermodilution technique only.
[10] HVC is not required at sites that do not perform the procedure routinely.
[11] To be performed on or within 7 days prior to EOT-DB (if previously performed at Baseline).
[12] Separate PK substudy Informed Consent Form to be completed prior to any substudy procedure. Can be performed at any time point on or between Visits 6 and 7.
[13] Scheduled study treatment dispensing/return procedures may be adapted according to the site practice.
[14] All AEs and SAEs that occur after signing the Informed Consent Form and up to 30 days after study treatment discontinuation must be reported.
[15] Urine dipstick test.

PROTOCOL

1 BACKGROUND

1.1 Indication

Portopulmonary hypertension (PoPH) is defined as pulmonary arterial hypertension (PAH) associated with portal hypertension with or without underlying hepatic disease. PoPH belongs to Group I (PAH) of the WHO classification of pulmonary hypertension (PH) [Simmoneau 2013]. Diagnosis of PoPH is based on pulmonary hemodynamic criteria for PAH obtained via right heart catheterization (RHC), including mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg at rest, mean pulmonary artery wedge pressure (PAWP) $\leq$ 15 mmHg, within the context of portal hypertension: portal vein pressure > 10 mmHg or hepatic venous pressure gradient (HVPG) > 5 mmHg.

The pathogenesis of PoPH is not fully understood. The development of PoPH appears to be independent of the cause and severity of portal hypertension, but rather as a consequence of the portal hypertension itself in genetically predisposed patients [Cartin-Ceba 2014]. Although the pulmonary vascular changes in PoPH are indistinguishable from those of other forms of PAH, the pathological processes that lead to such changes are not completely understood. It is likely that a combination of aberrant vasoactive and angiogenic signaling due to portal hypertension coupled with a hyperdynamic circulatory state resulting in disruption of the normal hepatopulmonary circulation, increased vascular shear/mechanical stress in the lung vasculature, and thus the pathogenic changes observed in PoPH [Al-Naamani 2013].

On average, PAH is diagnosed 4 to 7 years after the diagnosis of portal hypertension [Halank 2006]. The most common presenting symptom of PoPH is dyspnea on exertion. Other nonspecific symptoms include syncope, chest pain, fatigue, light-headedness, orthopnea, and edema. However, patients often present no specific symptoms indicative of PAH, and PoPH is most commonly diagnosed during evaluation for liver transplantation.

1.2 Epidemiology and natural history

Although PoPH is an uncommon complication of portal hypertension, it accounts for a sizeable percentage of patients with PAH. Recent registries estimate the prevalence of PoPH to be approximately 5–10% of all PAH patients [Humbert 2006, Krowka 2012]. Similarly, the prevalence of PoPH is described to be 5–8.5% amongst all portal hypertension patients undergoing evaluation for liver transplantation in the three largest registries reported to date [Ramsay 1997, Colle 2003, Krowka 2006]. The mean age at presentation of PoPH is during the fifth decade of life (49 ± 13 years). No differences in prevalence between men and woman are observed [Golbin 2007].

The prognosis for patients with PoPH is poor. Historically, 5-year survival outcome was less than 10% [Robalino 1991] but in the modern era with PAH-specific pharmacological intervention available, survival outcomes had improved in the US to 40% at 5 years but still with a 4-fold risk of death versus idiopathic PAH [Benza 2010]. In France, survival outcomes at 5 years were reported to be comparable to that of idiopathic PAH at 68% [Le Pavec 2008]. Causes of death reflect the existence of two serious illnesses: advanced liver disease and PAH with right heart failure [Safdar 2012].

1.3 Current management

The European Respiratory Society (ERS) Task Force on Pulmonary-Hepatic Vascular Disorders [Rodriguez-Roisin 2004] outlines PoPH treatment options as including: intravenous (i.v.) prostacyclin (epoprostenol), prostacyclin analogs (inhaled iloprost), and endothelin receptor antagonists ([ERA]s bosentan). In the intervening time, clinical experience with other newly approved PAH medications, including the phosphodiesterase type 5 inhibitor (PDE5i) sildenafil [Reichenberger 2006, Gough 2009, Hemnes 2009, Hollatz 2012], inhaled and i.v. treprostinil (prostacyclin analog) [Reichenberger 2006, Hollatz 2012, Sakai 2009], and the ERA ambrisentan [Cartin-Ceba 2011, Halank 2011, Condliffe 2014], has been reported suggesting beneficial effects of vasodilator therapy in PoPH. This clinical experience is limited mainly to single-center, open-label studies.

As a whole, clinical experience with ERAs has been favorable in terms of efficacy and safety, as reported in the literature. Studies with bosentan both as a monotherapy [Hoeper 2005, Hoeper 2007] and in combination with sildenafil [Savale 2013] reported improvements in hemodynamic and exercise capacity. As with clinical studies of bosentan in PAH, treatment was discontinued in a proportion of patients after transient elevation in liver transaminases was detected. In constrast, in the three studies reported to date on ambrisentan use in PoPH, no drug-related liver safety events were reported. No randomized clinical trial has been undertaken specifically in PoPH, leaving a paucity of data to demonstrate efficacy or safety of any PAH medication in PoPH. The PATENT-1 study of riociguat in PAH (a soluble guanylate cyclase [sGC] stimulator) showed improvement in the primary endpoint of change in 6-minute walk test (6MWT); however, no data on the subgroup of 13 PoPH patients were reported [Ghofrani 2013].

Orthotopic liver transplantation (OLT) is indicated in advanced liver disease, including portal hypertension, but is contra-indicated in patients who are compromised in terms of their cardiopulmonary hemodynamics, including PoPH. The ERS Task Force [Rodriguez-Roisin 2004] provides an algorithm for PoPH indicating patients with mild (mPAP < 35mmHg) disease as eligible for OLT; patients with moderate (mPAP $\geq$ 35–45 mmHg) disease should receive pulmonary vasodilator therapy prior to OLT to try to stabilize cardiopulmonary hemodynamics (i.e., lower both mPAP and pulmonary vascular resistance [PVR]); and for patients with severe (mPAP $>$ 45 mmHg) disease,

OLT is contraindicated but chronic vasodilator therapy to manage PAH should be considered.

1.4 Endothelin-1 and pulmonary hypertension

Endothelin-1 (ET-1), a 21 amino acid peptide, is one of the most potent vasoconstrictors and mitogens for smooth muscle cells, and contributes to increased vascular tone and proliferation in pulmonary vasculopathy [Galiè 2004].

There are 2 distinct receptors for ET-1: endothelin receptor A (ET_A) and endothelin receptor B (ET_B). The 2 receptors have unique binding locations and affinities for the endothelin peptide [Benigni 1995, Massaki 1998]. The ET_A receptors are expressed on pulmonary vascular smooth muscle cells, whereas ET_B receptors are present both on pulmonary vascular cells and on smooth muscle cells.

When activated, the ET_A receptors located in pulmonary vascular smooth muscle cells mediate a potent vasoconstrictive response, and ET_B receptors on endothelial cells mediate vasodilatation via increased production of nitric oxide and prostacyclin [Hirata 1993, de Nucci 1988]. ET-1 is also known to be a potent mitogen, with the ability to induce cell proliferation in vascular smooth muscle cells. It has been shown that both the ET_A and ET_B receptors mediate the mitogenic action of ET-1 [Clarke 1989, Chua 1992, Davie 2002, Sugawara 1996].

Laboratory and clinical investigations have clearly shown that ET-1 is overexpressed in several forms of pulmonary vascular disease. ET-1 is likely a major player in the vasodilator and vasoconstrictor imbalance, as well as in the abnormal pulmonary vascular remodeling present in the development and progression of PH of various etiologies [Stewart 1991, Giaid 1993].

1.5 Macitentan

Macitentan 10 mg (Opsumit®) is approved in the US, Europe, Australia, Canada, Israel, Mexico, and Switzerland for the treatment of PAH.

1.5.1 Nonclinical results

Macitentan is an orally active, non-peptide, potent dual ET_A and ET_B. Macitentan shows dose-dependent efficacy in nonclinical models of hypertension and PH, and is approximately 10 times more potent than bosentan (Tracleer®). In nonclinical safety studies, no effects on normal physiological functions or electrocardiogram variables, including cardiac repolarization, were observed – with the exception of a decrease in arterial blood pressure (BP) observed in a cardiovascular study in dogs. Macitentan has no genotoxic potential. In the pivotal 26-week and 39-week toxicity studies, the exposures in animals found at the no-observed-adverse-effect levels were above the anticipated clinical exposures and provided a margin of safety for studies in humans. A

study conducted in hairless rats showed that macitentan is not phototoxic *in vivo*. Macitentan does not bind relevantly to melanin. Reproductive toxicity studies showed that macitentan is teratogenic without affecting male or female fertility. Teratogenicity is considered to be an ERA class effect.

More detailed information on macitentan can be found in the Investigator's Brochure (IB) [Macitentan IB].

1.5.2 Clinical information

1.5.2.1 Phase 1 studies

During the Phase 1 program, more than 200 healthy subjects and about 30 patients (with renal and hepatic impairment) were treated with macitentan. Macitentan was well tolerated in all studies. The most frequently reported adverse event (AE) was headache. No clear dose relationship could be discerned for any AE. Eight cases of asymptomatic increases in aminotransferases were observed in the Phase 1 program (6 received macitentan, 2 received placebo). Of these increases, 3 (all 3 subjects received macitentan) were > 3 × the upper limit of the normal range (ULN), and none exceeded 4 × ULN. All cases resolved within 14 days of observation.

The potential for a mutual drug-drug interaction between macitentan and sildenafil was studied in a randomized, crossover study. The pharmacokinetic (PK) profile of macitentan and its metabolite ACT-132577 (the only pharmacologically active metabolite circulating in plasma) was not affected by sildenafil treatment. In addition, although treatment with macitentan resulted in increased maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve during one dosing interval (AUC_{τ}) values, the PK profile of N-desmethyl sildenafil was not affected. No dose adjustment of either compound is required when given concomitantly.

Concomitant treatment with cyclosporine was well tolerated, and did not have any clinically relevant effect on the exposure to macitentan or its metabolites ACT-132577 and ACT-373898 at steady-state.

Minor differences in the PK parameters of macitentan and ACT-132577 were noted between healthy subjects and those with severe renal impairment. However, marked differences in the PK parameters of the pharmacologically inactive metabolite, ACT-373898, were noted between healthy subjects and those with severe renal impairment. The safety profile of macitentan was similar in healthy subjects and those with severe renal impairment.

More detailed information on macitentan can be found in the IB [Macitentan IB].

1.5.2.1.1 Hepatic impairment

The effects of mild, moderate or severe hepatic impairment due to liver cirrhosis on the PK of a single oral dose of 10 mg macitentan were studied in a dedicated Phase 1 study. No correlation between the severity of hepatic impairment and the mean plasma concentrations of macitentan, ACT-132577, and ACT-373898 were apparent. Minor differences between PK parameters of macitentan, ACT-132577, and ACT-373898 were observed between healthy subjects and subjects with mild, moderate, and severe liver impairment. These differences were not considered to be clinically relevant, therefore no dose adjustments are required. There was no correlation between laboratory components of Child-Pugh score and area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$), area under the plasma concentration-time curve from time zero to time t (AUC_{0-t}), C_{max}, and $t_{½}$. No relevant differences in macitentan and ACT-132577 protein binding were observed between subjects with mild, moderate, or severe hepatic impairment and healthy subjects. A reduction in the extent of plasma protein binding of the inactive minor metabolite, ACT-373898, was observed, and the extent of the decrease correlated with the severity of hepatic impairment. This is not expected to be clinically relevant and is not expected to influence clinical outcome.

Only one subject with hepatic impairment experienced elevations in liver function tests (LFTs) that were considered by the investigator as clinically significant. The increases in alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma-glutamyl transferase (GGT) observed in this subject were also reported as AEs. Total bilirubin remained within the normal range. Other clinical chemistry findings were unremarkable.

More detailed information on macitentan Phase 1 studies can be found in the IB [Macitentan IB].

1.5.2.2 Phase 2 studies

A Phase 2 dose-finding study was conducted over 8 weeks in 379 patients with mild to moderate essential hypertension. Four doses of macitentan (0.3 mg, 1 mg, 3 mg, and 10 mg) and enalapril (20 mg) once daily were evaluated versus placebo. The primary efficacy endpoint of change from baseline to Week 8 in mean sitting diastolic blood pressure at trough (i.e., 24 h post-dose) was met. Macitentan was well tolerated across all 4 dose levels. The overall frequency of AEs was similar to that observed in the placebo group. The numbers of patients with at least one serious adverse event (SAE) were equally distributed across groups. There were no deaths.

Five cases of increased liver enzymes > 3 × ULN occurred in the macitentan groups, without obvious dose relationship (one, two, one, and one in the 0.3 mg, 1 mg, 3 mg, and 10 mg dose groups, respectively). In 3 cases, there were other plausible reasons for increased liver enzymes (pancreatic cancer, surgery with general anesthesia, and concomitant antibiotic therapy, respectively). Most of the episodes of liver enzyme

elevations resolved without sequelae within 2–3 weeks of observation. An episode of liver enzyme increase in a patient with pancreatic cancer resolved 48 days after surgery for pancreatic cancer.

A double-blind, randomized, placebo-controlled, multi-center, parallel group Phase 2 study to evaluate the efficacy and safety of a 10 mg dose of macitentan in 178 patients with idiopathic pulmonary fibrosis did not meet the primary endpoint (change in forced vital capacity). Overall, 10 mg macitentan was well tolerated with a similar safety profile in both treatment groups. The incidence of treatment-emergent AEs was similar in both groups. Dyspnea, peripheral edema, anemia, pneumonia and nausea occurred at a higher incidence in patients on macitentan than on placebo.

An equal proportion of patients in the 2 treatment groups experienced SAEs or died during the study. The most frequently reported SAEs and causes of death were all consequences of the underlying disease. Seven patients treated with macitentan had a decrease in hemoglobin levels to ≤ 10 g/dL at some point during the study and the overall incidence of elevations in liver aminotransferases > 3 × ULN was similar to placebo (3.4% in the macitentan group versus 5.1% in the placebo group).

More detailed information on this macitentan Phase 2 study can be found in the IB [Macitentan IB].

1.5.2.3 Phase 3 study in patients with pulmonary arterial hypertension

Efficacy in patients with WHO functional class II-IV PAH was demonstrated with the long-term outcomes SERAPHIN study. The trial demonstrated that macitentan 10 mg reduces the risk of morbidity or mortality in patients with symptomatic PAH, with a hazard ratio versus placebo of 0.547, 97.5% confidence interval 0.392–0.762, $p < 0.0001$. This represents a risk reduction of 45% [Pulido 2013].

Treatment with macitentan was well tolerated. The number of AEs reported and patients discontinuing treatment due to AEs was similar across all groups. The overall incidence of elevations in liver aminotransferases was similar to placebo (4.5%, 3.6%, and 3.4% incidence of ALT or AST > 3 × ULN in the placebo, macitentan 3 mg, and macitentan 10 mg groups, respectively). In addition, no differences were observed between macitentan and placebo on fluid retention (edema). A decrease in hemoglobin – reported as an AE – was observed more frequently on macitentan than placebo, with no difference in treatment discontinuation between groups.

More detailed information on the Phase 3 study in PAH can be found in the IB [Macitentan IB].

1.5.2.4 Summary of potential risks and risk management

Nonclinical studies with macitentan did not identify important risks of likely relevance to humans except for teratogenicity, a class effect of ERAs. The protocol, therefore, includes stringent requirements for pregnancy testing and reliable methods of contraception for female patients of childbearing potential.

In a Phase 1 study of macitentan in patients with chronic hepatic impairment, one patient being treated with macitentan experienced clinically relevant ALT/AST elevations although bilirubin remained in the normal range. In three placebo-controlled studies, a higher percentage of patients treated with macitentan 10 mg had ALT > 3 × ULN compared to placebo. Although an independent review of all data by the Independent Liver Safety Data Review Board (ILSDRB) concluded that there is no definite hepatotoxicity signal, precaution has been taken in this study to exclude subjects with severe hepatic impairment, as described in the Opsumit® prescribing information, or unstable liver disease due to the poor prognosis. Therefore, subjects with a Child-Pugh class C grading or Model for End-stage Liver Disease (MELD) score of ≥ 19 are excluded, as well as those with gastrointestinal or esophageal variceal bleeding within 3 months or transjugular intrahepatic portosystemic shunt (TIPS) within 6 months of randomization, or in the opinion of the investigator the subject is too unstable to enter the study. In addition, subjects must not meet the exclusion criteria of ALT/AST ≥ 3 × ULN and total bilirubin ≥ 3 mg/dL. The inclusion of patients with moderate hepatic impairment is considered justified in this study due to the unaltered PK profile of macitentan between mild, moderate or severe hepatic impairment in the Phase 1 study described above, as well as a fixed rule for discontinuation of study drug in the event of liver aminotransferase elevations. Monthly LFTs are mandatory throughout the study and recommended up to 30 days after study treatment discontinuation. Hepatic encephalopathy is frequent in patients with severe hepatic impairment and can lead to varying degrees of reversible dementia. In order to ensure subjects are fully able to give informed consent, hepatic encephalopathy of Grade 2 and higher has been excluded.

Macitentan treatment was associated with a dose-related reduction in hemoglobin levels. Therefore, patients with hemoglobin < 100 g/L are excluded from the study. Furthermore, hemoglobin levels are monitored monthly throughout the study.

Due to the vasodilator effect of macitentan, effects on BP might occur. In patients with normal BP at baseline, there was a slightly higher incidence of AEs denoting hypotension with macitentan than with placebo. Thus, patients with systolic blood pressure (SBP) < 90 mmHg are excluded from this study.

1.6 Purpose and rationale of the study

Although PoPH is included in the WHO Group I Pulmonary Hypertension spectrum of diseases (PAH) according to the updated guidelines for clinical classification of PH [Simmoneau 2013], no targeted PAH therapy has to date demonstrated efficacy in this patient population in a randomized, controlled clinical trial. PoPH patients have been excluded from protocols in PAH due to the potential for altered drug metabolism as a consequence of the underlying hepatic disease. However, as PoPH is essentially pre-capillary PH, these patients are managed on a day-to-day basis with commercially available PAH medications including ERAs. Use of these pulmonary vasodilators has been mostly based on evidence from single-center, open-label experience.

In the Phase 3 AC-055-302/SERAPHIN study, macitentan demonstrated efficacy in PAH by improving long-term clinical outcomes, functional status and exercise capacity. In addition, incidences of ALT/AST elevations > 3 × ULN were similar to placebo. Phase 1 data in chronic hepatic impairment showed no clinically relevant change in the PK of macitentan and its metabolites in varying grades of liver disease severity [Macitentan IB].

Therefore, it is believed that macitentan could be an efficacious treatment for PoPH with a safety and tolerability profile unaffected by the underlying hepatic disease.

The aim of this study is to investigate the efficacy of macitentan on cardiopulmonary hemodynamics as well as the safety and tolerability in patients with PoPH in a randomized, placebo- controlled study setting.

2 STUDY OBJECTIVES

2.1 Primary objective

- To evaluate the effect of macitentan on PVR as compared to placebo in patients with PoPH.

2.2 Secondary objectives

- To evaluate the effect of macitentan as compared to placebo on cardio-pulmonary hemodynamics, hepatic portal vein pressure, disease severity, and exercise capacity in patients with PoPH.
- To evaluate the safety and tolerability of macitentan in patients with PoPH
- To evaluate the PK of macitentan and its active metabolite ACT-132577 in patients with PoPH (PK substudy).

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This study is designed as a randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group Phase 4 study assessing the efficacy and safety of macitentan in PoPH.

Approximately 84 adult subjects with PoPH will be randomized (1:1) to receive either macitentan 10 mg, or matching placebo, once daily orally. Subject allocation to treatment groups will be stratified by background PAH therapy receipt (yes/no) to ensure balance within this subgroup. Stratification by region of enrollment will also be performed as the number of enrolled subjects per center is expected to be low and variation in total subject numbers will exist on a country-to-country level. Attrition rate is expected to be 10%, leaving 76 evaluable patients at Week 12.

Subjects must have confirmed diagnosis of PoPH with a PVR of ≥ 4 Wood Units (WU) (≥ 320 dyn.s.cm-5) at enrollment but not have severe hepatic impairment (defined as Child-Pugh Class C or MELD score ≥ 19). Subjects must have 6-minute walk distance (6MWD) ≥ 50 m at enrollment but may be in any WHO functional class.

The study will be conducted in approximately 45 sites in 7 countries. Randomization will proceed until the required number of subjects has been reached. It will be competitive across participating sites. Actelion may wish to replace sites with no subject enrollment.

The study consists of the following study periods:

Screening Period commences from signature of the Informed Consent Form (ICF) and ends with subject randomization (up to 28 days after signed informed consent).

Double-Blind Treatment Period starts immediately after randomization with the first dose of double-blind study treatment at the end of Visit 2 (Day 1 of study) and ends with End of Treatment (double-blind) (EOT-DB) on the day of the last dose of double-blind study treatment (scheduled Day 84, Week 12, or earlier in case of premature discontinuation of double-blind study treatment).

Open-Label Treatment Period starts immediately after EOT-DB (for patients who reach Week 12 of double-blind study treatment) with the first dose of open-label study treatment at the end of Visit 5 and ends with End of Treatment (open-label) (EOT-OL) on the day of the last dose of open-label study treatment (scheduled Day 168, Week 24, or earlier in case of premature discontinuation of open-label study treatment).

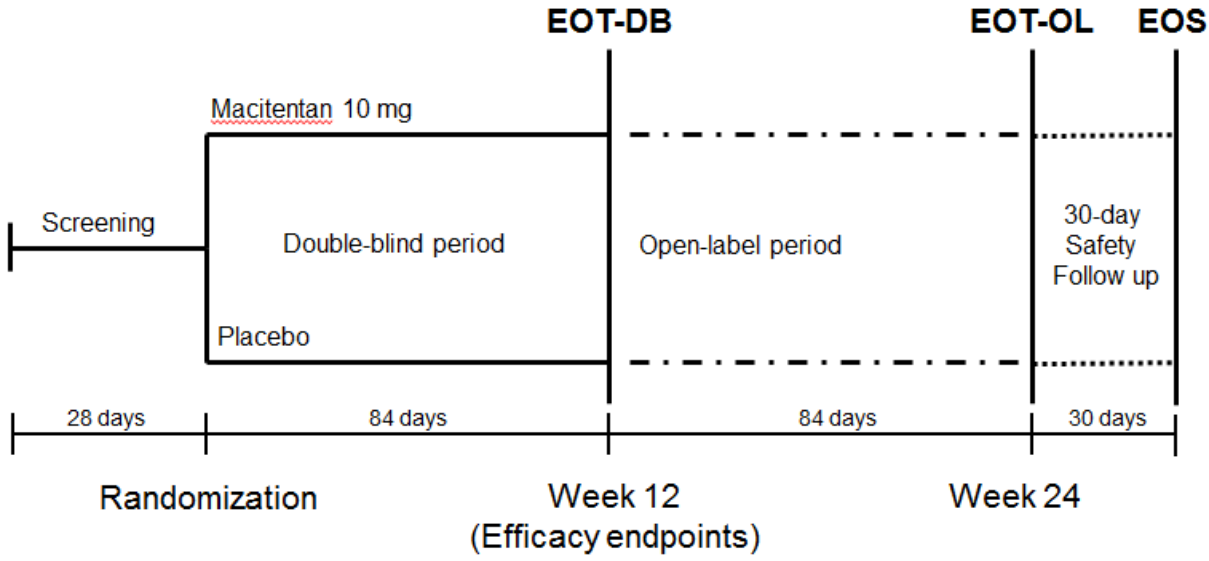
Safety Follow-up Period starts immediately after the last dose of study treatment (double-blind study treatment or open-label study treatment) and ends with the End of Study (EOS) 30 to 33 days after the last dose of study treatment.

EOS must occur in any patient discontinuing either double-blind or open-label study treatment prematurely and having completed the Safety follow-up period.

Study Duration

Subject participation in the study will be maximum 33 weeks (up to 28 days Screening + 24 weeks' treatment + 30 days safety follow up). The overall study design is depicted in Figure 1.

Figure 1 Study design



EOT-DB = end of treatment (double-blind); EOT-OL = end of treatment (open-label); EOS = end of study.

3.2 Study design rationale

A placebo-controlled trial conducted in a randomized, double-blind fashion provides the most definite and rigorous method of evaluating the efficacy and safety of a medical treatment.

The present study aims at assessing whether macitentan improves hemodynamic variables and whether this improvement translates into symptomatic and clinical improvement in PoPH subjects. Subjects will receive macitentan or placebo for 12 weeks followed by 12 weeks of open-label macitentan treatment and then a 30-day safety follow-up.

The 12-week double-blind treatment period is selected because it is considered to be adequate to observe the anticipated treatment effect on the primary endpoint of change in PVR, but short enough to minimize risk of randomization to placebo. The risk of bias

introduction from patients initiating add-on therapy is deemed relatively low in this timeframe and the number of missing assessments due to premature study discontinuation is also expected to be minimized. Additionally, in studies involving hemodynamics and exercise capacity, variability and placebo effect are of sufficient magnitude to justify the inclusion of a placebo control group [Wright 2009]. Risk of exposure to placebo is also minimized by permitting into the study subjects already receiving stable background oral PDE5i, sGC stimulator, or inhaled prostanoid PAH therapy. Once in the open-label period patients may also receive i.v. or subcutaneous (s.c.) prostanoid PAH-therapy at the investigator's discretion.

Treatment with ERAs has been associated with increased incidence of edema, anemia and/or decreased hemoglobin as well as LFT abnormalities. From 3 placebo-controlled studies with macitentan, no significant imbalance in LFT elevations was observed across macitentan treatment groups (any dose) and placebo. However, due to underlying liver disease in PoPH, liver safety events are likely to occur in this population and a placebo arm is the only way to show quantitatively whether there is a likely association of liver abnormalities with the use of the study treatment.

The 12-week open-label treatment period is intended to offer all patients the opportunity to receive active study treatment and allows time for organizing appropriate treatment after the study. In addition, the open-label phase is being used to perform a substudy in a minimum of 20 participating subjects in order to obtain information on the PK of macitentan in PoPH.

3.3 Study Committees

A Steering Committee has been appointed by Actelion to design the protocol, oversee the conduct of the study, evaluate the results and support publications. The committee is governed by a steering committee charter.

An Independent Liver Safety Data Review Board (ILSDRB, an external expert committee of hepatologists) provides ongoing assessment and advice regarding serious hepatic adverse events of special interest that require further evaluation during the study (as per ILSDRB charter).

4 SUBJECT POPULATION

4.1 Subject population description

Subjects enrolled will be male or female aged 18 years and over with a confirmed diagnosis of symptomatic PoPH and a baseline PVR of ≥ 4 WU (≥ 320 dyn.s.cm^{-5}), in any WHO functional class and capable of performing a 6MWT. Subjects may be PAH-treatment naïve or receiving background PDE5i, sGC stimulators, or inhaled

prostanoid therapy. Subjects must not have severe hepatic impairment, as defined by Child-Pugh class C liver disease or a MELD score ≥ 19.

A minimum of 84 subjects will be enrolled. An assumed attrition rate of 10% will leave 76 evaluable patients at Week 12 for the primary analysis.

4.2 Rationale for the selection of the study population

The primary objective of the study is to demonstrate a reduction in PVR versus baseline with macitentan treatment as compared to placebo. A subset of PoPH patients with elevated PVR (≥ 4 WU or 320 dyn.s.cm^{-5}) has been selected to improve the chance of observing the planned placebo-corrected reduction of 27% from baseline. No restriction on WHO functional class and a minimum 6MWD of ≥ 50 m will permit patients with severely symptomatic PH to be enrolled, as macitentan is expected to show a treatment effect on PVR in these patients as well.

As PoPH is managed clinically with PAH-targeted therapy, subjects receiving concomitant background PDE5i, sGC stimulators, or inhaled prostacyclin therapy at a stable dose may be enrolled. This is also to mitigate the risk of exposure to placebo during the study. Subjects receiving strong vasodilator therapy at baseline (i.v. or s.c. prostanoids) are excluded.

Subjects with severe hepatic impairment (defined here as Child-Pugh C or MELD score ≥ 19) are not permitted to be enrolled due to their poor prognosis, as are those whose liver disease is unstable in the opinion of the investigator. Such patients have an increased risk of premature discontinuation, transplantation or death during the double-blind phase of the study which would impact the study's ability to achieve its primary objective. Other indicators of severe liver disease and/or poor prognosis include gastrointestinal and esophageal variceal bleeding, as well as total serum bilirubin ≥ 3 mg/dL.

As there is limited data on macitentan in pediatric PAH, subjects under the age of 18 years are excluded.

4.3 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled. It is not permitted to waive any of the criteria for any subject:

1. Signed informed consent prior to any study-mandated procedure
2. Male or female ≥ 18 years of age with symptomatic PoPH:
    - Documented diagnosis of portal hypertension

- PAH by right heart catheterization at screening:
  - mPAP ≥ 25 mmHg
  - PAWP or left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg

3. PVR ≥ 4 WU or ≥ 320 dyn.s.cm^{-5} at screening[2]
4. 6MWD ≥ 50 m at screening
5. Women of childbearing potential must:
   - Have a negative serum pregnancy test during screening and a negative urine pregnancy test on prior to randomization on Day 1, *and*
   - Agree to use reliable methods of contraception [see Section 4.5] from screening up to 30 days after study treatment discontinuation, *and*
   - Agree to perform monthly pregnancy tests up to 30 days after study treatment discontinuation.

4.4 Exclusion criteria

Subjects must not meet any of the following exclusion criteria. It is not permitted to waive any of the criteria for any subject:

1. PAH due to any other condition than portal hypertension
2. Severe hepatic impairment, as defined by Child-Pugh Class C liver disease or MELD score ≥ 19
3. Unstable liver disease (in the opinion of the investigator)
4. History of TIPS within 6 months prior to randomization
5. Documented severe obstructive or restrictive lung disease (in the opinion of the investigator)
6. Documented pulmonary veno-occlusive disease
7. Systolic blood pressure (SBP) < 90 mmHg at Screening
8. Body weight < 40 kg at Screening
9. Patients undergoing dialysis

[2] Cardiac output measured by thermodilution technique only.

10. Initiation of diuretics or beta blockers within 1 week prior to baseline RHC **or** patients on oral diuretics or beta blockers in whom the dose has not been stable for at least 1 week prior to baseline RHC
11. Hemoglobin < 100 g/L at Screening
12. Serum AST and/or ALT ≥ 3 × ULN at Screening
13. Bilirubin ≥ 3 mg/dL at Screening
14. Grades 2, 3, or 4 hepatic encephalopathy
15. History of liver transplantation
16. Documented hepatocellular carcinoma
17. Documented schistosomiasis infection
18. Gastrointestinal bleeding or esophageal variceal bleeding < 3 months prior to randomization
19. Recently started (< 3 months prior to randomization) or planned cardio-pulmonary rehabilitation program based on exercise
20. Treatment with calcium channel blockers, an endothelin receptor antagonist (ERA), i.v./s.c. or oral prostanoids within 3 months prior to randomization
21. Initiation, change in dose or discontinuation of PDE5i or soluble guanylate cyclase stimulator within 3 months prior to randomization
22. Treatment with interferon within 3 months prior to randomization
23. Treatment with any investigational drug within 3 months prior to randomization
24. Treatment with strong cytochrome P450 (CYP) 3A4 inducers (e.g., carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's wort) within 4 weeks prior to randomization
25. Treatment with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, boceprevir, telaprevir, saquinavir, lopinavir, fosamprenavir, darunavir, tipranavir, atazanavir, nelfinavir, amprenavir, indinavir, and paritaprevir) within 4 weeks prior to randomization
26. Known hypersensitivity to macitentan or its excipients or drugs of the same class
27. Pregnancy, breastfeeding, or intention to become pregnant during the study
28. Known concomitant life-threatening disease with a life expectancy of < 6 months

29. Any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of results
30. Suspected or known current drug or alcohol abuse.

4.5 Reliable contraception for women of childbearing potential

4.5.1 Definition of woman of childbearing potential

A woman is considered to be of childbearing potential unless she meets at least one of the following criteria:

- Previous bilateral salpingo-oophorectomy or hysterectomy.
- Premature ovarian failure confirmed by a specialist.
- Pre-pubescence, XY genotype, Turner syndrome, uterine agenesis.
- Post-menopausal, defined as 12 consecutive months with no menses without an alternative medical cause (ICH M3 definition).

4.5.2 Europe and Latin America

The use of at least one of the following methods is regarded as reliable contraception:

1. Oral, implantable, transdermal, or injectable hormonal contraceptives or intrauterine devices (IUD), *or*
2. True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the patient, *or*
3. Permanent female sterilization (tubal occlusion/ligation at least 6 weeks prior to screening), *or*
4. Sterilization of the male partner, with documented post-vasectomy confirmation of the absence of sperm in the ejaculate.

Rhythm methods, use of a condom by the male partner alone, use of a female condom or diaphragm alone are not considered acceptable methods of contraception for this study.

4.5.3 North America

The use of one of the following options is regarded as reliable contraception:

Option 1	Option 2	Option 3	Option 4
One method from this list:	**One method from this list:**	**One method from this list:**	**One method from this list:**
Standard intrauterine device (IUD) (Copper T380A IUD) Intrauterine system (LNg 20IUS: progesterone IUS) Progesterone implant Tubal sterilization	Estrogen and progesterone oral contraceptives ("the Pill") Estrogen and progesterone transdermal patch Vaginal ring Progesterone injection	Diaphragm with spermicide Cervical cap with spermicide	Partner's vasectomy
	PLUS one method from this list:	**PLUS one method from this list:**	**PLUS one method from this list:**
	Male condom Diaphragm with spermicide Cervical cap with spermicide	Male condom	Male condom Diaphragm with spermicide Cervical cap with spermicide Estrogen and progesterone oral contraceptives ("the pill") Estrogen and progesterone transdermal patch Vaginal ring Progesterone injection

IUD, intrauterine device; IUS, intrauterine system.

4.6 Medical history

Relevant medical history, as defined below, must be recorded in the electronic Case Report Form (eCRF):

- Chronic medical conditions and new acute medical conditions within the past 6 months (e.g., anemia, hepatitis C infection, HIV infection, obstructive or restrictive lung disease, hypertension, renal disease)
- Complications or symptoms associated with the PAH (e.g., right heart failure, peripheral edema) or portal hypertension (e.g., liver decompensation)
- Cause of portal hypertension (e.g., cirrhosis, hepatitis infection, thrombosis)
- History of TIPS and date of procedure

- History of spontaneous or congenital porto-systemic shunts
- History of esophageal varices or gastrointestinal bleeding, ascites, hepatic encephalopathy (including Grade)
- History of alcoholism and/or drug abuse
- Any previous life-threatening conditions, including date (e.g., myocardial infarction).

5 TREATMENTS

5.1 Study treatment

Study treatment in this study includes double-blind as well as open-label study treatment. Double-blind treatment comprises investigational treatment (i.e., macitentan 10 mg) or matching placebo administered orally once daily. Open-label study treatment consists of open-label macitentan 10 mg and is also administered orally once daily.

5.1.1 Investigational treatment: description and rationale

The investigational treatment is macitentan 10 mg and is administered orally once daily, in accordance with the Opsumit® prescribing information.

5.1.2 Matching placebo: description and rationale

Matching placebo is administered orally and also once daily. Rationale for the use of a placebo arm is provided in Section 3.1.

5.1.3 Study treatment administration

The first administration of study treatment will take place at site during the randomization visit (Visit 2), and only after successful completion of the ICF procedure and all screening/randomization assessments. **At all subsequent visits (apart from PK substudy), study treatment must only be taken after all study procedures have been performed.**

At home, one tablet (macitentan 10 mg or matching placebo) must be taken orally every morning irrespective of food intake. If a dose is missed, take the next dose at the next scheduled time point (i.e., do not take one tablet in the evening and then one table the next morning). Two tablets must never be taken on the same day.

5.1.4 Treatment assignment

Eligible subjects will be randomized in a 1:1 ratio to either macitentan 10 mg or matching placebo. Treatment allocation will be stratified based on receipt of background PAH therapy (Yes/No) and by region (Europe/North America/Latin America).

At Visit 1 (Screening), all screened subjects will be assigned a study-specific subject number by the Interactive Voice/Web Response System (IxRS) provider. Note: In case of re-screening, the original number will also be used the second time.

At Visit 2 (Randomization), after having confirmed the eligibility of the subject and prior to the start of study treatment, the investigator/delegate will contact the IxRS to randomize the subject. The IxRS will assign a randomization number to the subject, and assign the treatment bottle number which matches the treatment arm assigned by the randomization list to the randomization number. The bottle with this unique number will then be dispensed to the subject and the first dose administered.

The randomization list is generated by an independent Contract Research Organization (CRO) [redacted] using SAS version 9.3, and kept strictly confidential.

5.1.5 Blinding

The first part of this study will be performed in a double-blind fashion. The investigator and study staff, the subjects, the monitors, Actelion and CRO staff involved in the conduct of the study will remain blinded to the treatment until study closure.

Although the second part of the study will be performed in an open-label manner, all subjects and study-related staff will remain blinded as to the patient's original randomization group.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and accessible only to authorized persons who are not involved in the conduct of the study.

The investigational treatment and its matching placebo are indistinguishable and all subject kits will be packaged in the same way.

5.1.6 Unblinding

5.1.6.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure in accordance with Actelion Standard Operating Procedures (SOPs).

5.1.6.2 Unblinding for SUSARs

When a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, Actelion Global Drug Safety will request the unblinding of the treatment assignment. The randomization code will not be communicated to the site staff or to the Actelion study team; unblinded SUSAR information will be anonymized and provided to Actelion Global Drug Safety, respective health authorities and IRBs/IECs only. SUSARs will be reported to investigators in a blinded fashion.

5.1.6.3 Emergency procedure for unblinding

The investigator, study staff and sponsor staff must remain blinded to the subject's treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. The occurrence of OLT during the double-blind treatment period could constitute such an event. In this case, the investigator can receive the unblinded randomization code for study treatment allocation through the IxRS. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended code break with Actelion.

The occurrence of any code break during the study must be clearly justified and explained by the investigator. In all cases, Actelion must be informed as soon as possible before or after the code break.

The circumstances leading to the code break must be documented in the subject's site file and eCRF.

Refer to the IxRS manual for complete information regarding the IxRS procedures for randomization, study treatment assignment, and unblinding.

5.1.7 Study treatment supply

Actelion will supply all study treatments to the site according to the local regulations. Manufacture, labeling, packaging and supply of study treatments will be conducted according to Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) and any local or national regulatory requirements.

All treatment supplies are to be used only in accordance with this protocol, and not for any other purpose.

5.1.7.1 Study treatment packaging and labeling

5.1.7.1.1 Study treatment packaging

Study treatment is provided as tablets and supplied in childproof bottles containing 36 tablets.

5.1.7.1.2 Study treatment labeling

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located. Each medication bottle has a label with a tear-off part specifying the study protocol number, the packaging batch number, and the bottle number. When the study treatment is given to the subject, this tear-off part must be removed and attached to the Study Treatment Dispensing Log.

5.1.7.2 Study treatment distribution and storage

Treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the medication labels. The investigator is responsible for the safe and proper handling and storage at the investigational site.

5.1.7.2.1 Study treatment distribution

The study centers will be supplied with study treatment according to the centers' needs, depending on the rate of subject enrollment. Each center will have an individual stock of study treatment, which will be re-supplied continuously as soon as a predefined minimum level of study treatment has been reached.

5.1.7.2.2 Study treatment storage

Study treatment must be kept in a locked room or a locked cupboard in a restricted access room, which can be accessed only by the pharmacist, the investigator, or another duly designated person as specified on the delegation of authority (DoA) form.

The subject must be educated on the proper study treatment storage conditions at home.

The study treatment must be stored below 30 °C (86 °F) and must be protected from moisture. Unopened, sealed study medication bottles may be stored in refrigerators (above +2 °C [36 °F]). Storage below +2 °C / 36 °F (e.g., in the freezer) is not permitted. Opened bottles must not be stored in the refrigerator.

A temperature log must be maintained and temperature control should occur at least on a weekly basis at the site. Actelion will provide a temperature log; however, the use of the log is not mandatory if the site has an acceptable means of recording the temperature. Any temperature recording system routinely used at site is acceptable as long as all required information is included and certification of calibration is provided. If the temperature is captured electronically, a print-out should be made available to the CRA during each on-site visit for filing in the Investigator Site File (ISF).

In case a deviation from the defined temperature range is identified by the study center, the deviation must be reported to the CRA, preferably in writing and with supporting documentation (e.g., copy of the temperature log showing data for all excursion days). The CRA should immediately contact Actelion for further advice. The affected study treatment will not be used (e.g., it will be segregated physically at the study center) until confirmation from Actelion is obtained that its use is safe. In case the temperature deviation is outside of the acceptable limit, the study treatment is kept segregated at the study center and returned to Actelion following internal study treatment return processes. New study treatment supplies will be provided to the study center.

Temperature deviations correspondence must be kept in the ISF.

5.1.7.3 Study treatment dispensing

Study treatment can only be dispensed upon written prescription by an authorized study physician listed on the DoA form.

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Subjects are asked to return all used, partially used and unused study treatment bottles at each visit. The protocol-mandated study treatment dispensing/return procedures may not be altered without prior written approval from Actelion. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

Once a subject has been randomized and study treatment assigned, the corresponding bottle must not be used for another subject. If a subject has been dispensed a bottle in error (one that has not been allocated yet to another subject), the IxRS helpdesk must immediately be contacted.

At the time study treatment is distributed, the subject should be educated on the proper storage conditions at home [see Section 5.1.7.2.2].

5.1.7.4 Study treatment return and destruction

The site must record the amount of study treatment received, dispensed, used, lost and returned during the study.

On an ongoing basis and/or on termination of the study, the monitor will collect used and unused subject kits, which will be sent to the warehouse, where Actelion or a deputy will check treatment reconciliation. In certain circumstances, used and unused treatment containers may be destroyed at the site once treatment accountability is finalized and has been checked by the CRA, and written permission for destruction has been obtained from Actelion.

5.1.8 Compliance with study treatment

Study treatment accountability must be performed by the study staff on the day of the visit and before providing further study treatment, in order to ensure that the subject is compliant with study requirements. Study treatment accountability is recorded in the eCRF and checked by the monitor during site visits and at the end of the study. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

Prior to each new dispensation, the visit compliance must be evaluated by the site staff, based on study treatment accountability, as per formula below:

Compliance = [(number of tablets provided to subject - number of tablets returned) / Total number of Tablets that should have been taken during the period] × 100

The site staff should discuss any compliance issue with the subject and re-educate him/her on correct administration of study treatment. Details of such discussion must be documented in the subject's file.

If the compliance with study treatment intake is < 80% or > 120%, permanent discontinuation of study treatment may be considered after consultation with Actelion.

5.1.9 Study treatment dose adjustments and interruptions

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruption of study treatment are described in Section 5.1.11.

If study treatment intake is interrupted by the subject for any reason, she/he must immediately inform the investigator.

Interruptions of study treatment should be kept as short as possible. If treatment is stopped for more than 14 days, reintroduction is not permitted and treatment must be permanently discontinued [see Section 5.1.11].

Study treatment dose errors/interruptions must be recorded in the eCRF.

5.1.10 Premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator or Actelion.

A subject has the right to prematurely discontinue study treatment at any time by withdrawal from treatment only or by withdrawal from treatment and any further participation in the study.

The investigator should discontinue study treatment for a given subject if, on balance, he/she believes that continued administration would be contrary to the best interests of the subject.

Premature discontinuation of study treatment may also result from a decision by Actelion, e.g., in case of premature termination or suspension of the study [see Section 9.3].

Study treatment may be discontinued in response to an AE, lack of efficacy (including disease progression, treatment failure, worsening of patient condition), a protocol deviation (including eligibility failure, non-compliance with study requirements, such as non-compliance with study treatment intake or visit attendance), or if the subject is lost to follow-up. Study-specific criteria for discontinuation of study treatment are described in Section 5.1.11.

The main reason and whether discontinuation of study treatment is the decision of the subject, the investigator or Actelion must be documented in the eCRF.

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study and will be followed up until EOS or 30 days after study treatment discontinuation, provided that the subject's consent for this limited participation in the study has not been withdrawn.

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. Subjects who die or are lost to follow-up are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study is described in Sections 9.2 and 9.4, respectively.

5.1.11 Study-specific criteria for interruption / premature discontinuation of study treatment

A) Pregnancy

If a female subject becomes pregnant while on study treatment, study treatment must be discontinued immediately, and a Pregnancy Form must be completed [see Section 10.3].

B) Liver aminotransferases abnormalities

Interruption of study treatment
Study treatment must be interrupted in the following cases:

- Asymptomatic increase in aminotransferases (i.e., ALT and/or AST) ≥ 3 and $< 8 \times$ ULN.

In such a case, perform a re-test of aminotransferases (ALT and AST), total and direct bilirubin, and alkaline phosphatase within one week. If AST and/or ALT elevation is confirmed, continue to monitor aminotransferases, total and direct bilirubin, and alkaline phosphatase levels weekly until values return to pre-treatment levels or within normal ranges. If the aminotransferase values return to pre-treatment levels or within normal ranges, reintroduction of study treatment can be considered. Interruptions must be for less than 2 consecutive weeks; longer interruptions must lead to permanent discontinuation of study treatment.

Reintroduction of study treatment after treatment interruption should only be considered if the potential benefits of treatment with macitentan outweigh the potential risks and when liver aminotransferase values are within pre-treatment levels or within normal ranges. The advice of a hepatologist is recommended.

Liver aminotransferase levels must then be checked within 3 days after reintroduction, then again after a further 2 weeks and thereafter according to the recommendations above (i.e., at monthly intervals).

Permanent discontinuation of study treatment
Study treatment must be stopped and its reintroduction is not to be considered in the following cases:

- Aminotransferases ≥ 8 × ULN
- Aminotransferases ≥ 3 × ULN and associated with new or worsening clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu like syndrome (arthralgia, myalgia, fever)
- Aminotransferases ≥ 3 × ULN associated with total bilirubin ≥ 2 × ULN and increased as compared to baseline

In such cases, aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must be monitored weekly after study treatment discontinuation until values return to pre-treatment levels or within normal ranges.

Other diagnoses (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus,) and/or etiologies (e.g., acetaminophen-related liver toxicity) should be considered and ruled out by performing the appropriate tests.

All liver aminotransferases abnormalities leading to study treatment interruption or discontinuation must be recorded as AEs [see Section 10].

An ILSDRB (an external expert committee of hepatologists) provides ongoing assessment and advice regarding any hepatic events that require further evaluation during the study.

C) Hemoglobin abnormalities

In case of hemoglobin decrease from baseline* of > 20 g/L, a retest must be performed within 10 days, with additional laboratory evaluations that may include, but are not limited to, any of the following:

- Red blood cell cellular indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), peripheral blood smear, reticulocyte count, iron status (iron level, serum ferritin, total iron binding capacity, transferrin saturation), lactate dehydrogenase, indirect bilirubin.

Study treatment should be temporarily interrupted if clinically mandated based on the investigator's judgment, or in any of the following situations:

- A decrease in hemoglobin to < 80 g/L (< 4.9 mmol/L),
- A decrease in hemoglobin from baseline* of > 50 g/L,
- The need for transfusion.

Reintroduction of study treatment may be considered if hemoglobin recovery, defined as a return of hemoglobin above the lower limit of the normal range or if it returns to a value close to that at baseline.

Interruption of study treatment must not last longer than 2 consecutive weeks; longer interruption must lead to permanent discontinuation of study treatment.

*Baseline hemoglobin: last value obtained prior to first intake of double-blind study treatment.

D) Child-Pugh classification or MELD Score worsening

If a subject is assessed as being Child-Pugh class C of liver disease or MELD Score ≥ 19 at EOT-DB then study treatment must be permanently discontinued and the 30-day Safety follow-up is to be performed. The subject must not initiate open-label treatment.

E) Start of a PAH specific therapy / strong CYP3A inducer / investigational drug

Double-blind study treatment must be permanently discontinued if escalation of PAH-specific therapy is required (e.g., other ERAs, i.v./s.c. prostanoids), strong CYP3A4 inducers and/or any other investigational treatments are started during the double-blind treatment period.

Open-label study treatment must only be discontinued in the open-label period if an ERA, strong CYP3A4 inducer, and/or any other investigational treatments is started. I.v./s.c. prostanoids are permitted in the open-label period at the investigator's discretion.

F) Orthotopic Liver transplantation

If a subject undergoes OLT during the double-blind treatment phase, they must stop all study treatment at the earliest convenience and undergo EOS after 30 days' safety follow up.

If a subject undergoes OLT during the open-label treatment phase, continued treatment with OL study medication is permitted until Week 24 (EOT-OL), after which the 30 days' safety follow up should be performed.

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to the start of study (i.e., date of informed consent).

A concomitant therapy is any treatment that is either initiated or ongoing during Screening, after Randomization, or up to 30 days after the end of study treatment.

5.2.2 Reporting of previous/concomitant therapy in the CRF

Any previous treatment for PAH / right heart failure (including diuretics) and/or portal hypertension (including beta blockers, hepatitis C medications) that has been discontinued within 3 months prior to randomization must be recorded in the eCRF. Generic name, route, start/end date of administration (as well as whether it was ongoing at start of study treatment and/or EOS) and dose will be collected. Any change in dose or route of administration will be captured on the log by completing a new line.

All medications (including dietary supplements, traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) taken between Screening visit and EOS are to be recorded on the concomitant medications page of the eCRF. Generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, and indication will be recorded in the eCRF.

Hormonal contraceptives will be recorded on the contraception page of the eCRF.

5.2.3 Allowed concomitant therapy

Oral PDE5i, inhaled prostacyclin analogues, soluble guanylate cyclase (sGC) stimulator are allowed if present for at least 3 months prior to randomization at a stable dose (which must remain unchanged during the double-blind treatment period unless the patient experiences worsening of PAH).

Treatment with oral diuretics is allowed if ongoing at a stable dose for at least 1 week prior to baseline right heart catheterization; the dose may be optimized during the treatment period.

Beta blockers are allowed if present for at least 1 week prior to baseline right heart catheterization at a stable dose (which should remain unchanged during the study). If discontinuation of beta blockers occurs during the study the patient should complete the study as scheduled.

During the open-label period, i.v. and s.c. prostanoid therapy (e.g., epoprostenol, treprostinil) is permitted at any time.

The following antiviral hepatitis C medications are permitted: simeprevir, sofosbuvir, daclatasvir, ombitasvir, dasabuvir, ledipasvir, etravirine, raltegravir, maraviroc, and ribavirin.

5.2.4 Forbidden concomitant therapy

- ERAs (e.g., bosentan, ambrisentan)
- During the double-blind period, i.v./s.c. and oral prostanoid therapy (e.g., epoprostenol, treprostinil) is forbidden
- Calcium channel blockers
- Strong CYP3A4 inducers (e.g., carbamazepine, rifampin, rifampicin, rifabutin, rifapentin, phenobarbital, phenytoin, and St. John's wort)
- Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir, lopinavir, fosamprenavir, darunavir, tipranavir, atazanavir, nelfinavir, amprenavir, indinavir, boceprevir, telaprevir, paritaprevir, and saquinavir)
- Treatment with interferon
- Any other investigational drug.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Double-blind treatment period

Baseline is the last assessment prior to initiation of double-blind treatment.

6.1.1.1 Primary efficacy endpoint

The primary efficacy endpoint is relative change from baseline to Week 12 in PVR.

A geometric mean in the active group showing a reduction of at least 20% in PVR when compared to the placebo geometric mean is considered clinically relevant in this patient population.

6.1.1.2 Secondary efficacy endpoints

- Change from Baseline to Week 12 in mean right atrial pressure (mRAP), mPAP, cardiac index (CI), total pulmonary resistance (TPR), and mixed venous oxygen saturation (SVO_2), all measured at rest
- Change from Baseline to Week 12 in 6MWD
- Change from Baseline to Week 12 in WHO functional class
- Change from Baseline to Week 12 in NT-proBNP.

6.1.1.3 Other efficacy endpoints

- Change from Baseline to Week 12 in hepatic venous pressure gradient (HVPG)
- Change from Baseline to Week 12 in Borg dyspnea index.

6.1.2 Macitentan-treatment period

Macitentan Baseline is the last assessment prior to initiation of macitentan treatment (i.e., double-blind baseline for subjects randomized to receive blinded macitentan 10 mg, or Week 12/EOT-DB for subjects assigned to placebo during the double-blind treatment period).

- Change from macitentan Baseline to each time point in WHO functional class
- Change from macitentan Baseline to each time point in NT-proBNP
- Change from macitentan Baseline to each time point in 6-minute walk distance (6MWD)
- Change from macitentan Baseline to each time point in Borg dyspnea index.

6.2 Safety endpoints

6.2.1 Double-blind treatment period

For the double-blind treatment period, treatment-emergent is defined as from first intake of study treatment until end of double-blind treatment + 30 days, or initiation of open-label treatment, whichever occurs first).

- Treatment-emergent deaths
- Treatment-emergent AEs
- Treatment-emergent AEs leading to premature discontinuation of double-blind study treatment
- Treatment-emergent SAEs
- Proportion of patients with treatment-emergent ALT and/or AST abnormality (≥ 3, ≥ 5, and $\geq 8 \times$ ULN)
- Proportion of patients with treatment-emergent ALT and/or AST abnormality ($\geq 3 \times$ ULN) associated with total bilirubin $\geq 2 \times$ ULN (and increased as compared to baseline) up to EOT-DB

- Proportion of patients with treatment-emergent hemoglobin abnormality (< 100 g/L, and < 80 g/L)
- Treatment-emergent marked lab abnormalities
- Change from Baseline to EOT-DB in vital signs
- Change from Baseline to EOT-DB in laboratory variables
- Change from Baseline to EOT-DB in MELD score
- Change from Baseline to EOT-DB in Child-Pugh classification.

Marked laboratory abnormalities are defined in Actelion internal guidelines as detailed in Appendix 6.

6.2.2 Macitentan-treatment period safety endpoints

Macitentan treatment-emergent is defined as from first intake of macitentan up to EOS (i.e., 30 days after discontinuation of macitentan treatment). End of macitentan treatment (EOMT) is defined as EOT-DB or EOT-OL, whichever comes last. Macitentan baseline is defined as last assessment prior to first intake of macitentan.

- Macitentan treatment-emergent deaths
- Macitentan treatment-emergent AEs
- Macitentan treatment-emergent AEs leading to premature discontinuation of macitentan treatment
- Macitentan treatment-emergent SAEs
- Proportion of patients with macitentan treatment-emergent ALT and/or AST abnormality (≥ 3, ≥ 5, and ≥ 8 × ULN) up to EOMT
- Proportion of patients with macitentan treatment-emergent ALT and/or AST abnormality (≥ 3 ULN) associated with total bilirubin ≥ 2 × ULN (and increased as compared to baseline) up to EOMT
- Proportion of patients with macitentan treatment-emergent hemoglobin abnormality (< 100 g/L, and < 80 g/L) up to EOMT
- Macitentan treatment-emergent marked lab abnormalities up to EOMT
- Change from macitentan Baseline to EOMT in vital signs
- Change from macitentan Baseline to EOMT in laboratory variables
- Change from macitentan Baseline to EOMT in Child-Pugh classification
- Change from macitentan Baseline to EOMT in MELD Score.

6.3 Pharmacokinetic endpoints

A PK substudy will be performed in consenting patients at any time on or between Visit 6 / Week 16 and Visit 7 / Week 20 (open-label period). Recruitment into the substudy will be stopped only after a minimum of 20 subjects have provided sufficient plasma samples of good quality to allow evaluation of the PK profile of macitentan in PoPH. Please see Appendix 1 for a detailed description of procedures.

7 STUDY ASSESSMENTS

All study assessments are performed by a qualified study staff member: medical, nursing, or specialist technical staff, and are recorded in the eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF. When applicable, the assessments should be performed in the following order:

- Blood sampling
- Physical examination
- WHO functional class
- 6-minute walk test
- Borg dyspnea index
- Right heart/hepatic vein catheterization at rest

If the principal investigator delegates any study procedure/assessment for a subject, e.g., RHC, blood sampling etc., to an external facility, he/she should inform Actelion to whom these tasks are delegated. The set-up and oversight will be agreed upon with Actelion. The supervision of any external facilities remains under the responsibility of the principal investigator.

Calibration certificates for the following devices used to perform study assessments must be available prior to the randomization of the first subject:

- Temperature measurement devices for study medication storage area and freezer,
- Right heart/hepatic catheterization equipment,
- Scale for measuring body weight.

7.1 Screening/baseline assessments

Date of informed consent, baseline demographics (sex, age, race, ethnicity, body weight, height) as well as a reason for why a woman is not considered to be of childbearing potential (if applicable) are to be recorded in the eCRF at Visit 1/Screening only after informed consent has been signed.

Complete, clinically relevant medical history (previous and ongoing at randomization) as described in Section 4.6 and liver disease characteristics:

- Date and mode of portal hypertension diagnosis (liver biopsy, hepatic vein catheterization, ultrasound, presence of esophageal varices, ascites, history of TIPS, other
- Cause of portal hypertension: Intrahepatic (autoimmune hepatitis, alcohol cirrhosis, hepatitis B cirrhosis, hepatitis C cirrhosis, nonalcoholic steatohepatitis, primary

biliary cirrhosis); pre-hepatic (portal vein thrombosis/clots, congenital); post-hepatic (hepatic vein thrombosis, inferior vena cava thrombosis); other

- Child-Pugh class and/or MELD Score are also to be assessed and documented in the eCRF at Visit 1/Screening.

PAH disease characteristics such as 6MWT, Borg dyspnea index, WHO functional class, as well as vital signs, body mass index, and ongoing medications are to be documented in the eCRF at Visit 1/Screening.

Right heart and hepatic vein catheterization data are to be collected in the eCRF at Visit 1/Screening. Hepatic vein catheterization is not a required procedure for study entry but should be collected where possible. Reason for Screen failure, if applicable, must also be given in the eCRF at Visit 1/Screening.

At Visit 2/Randomization, WHO functional class, 6MWT, Borg dyspnea index, and ongoing medications are to be collected in the eCRF. Any SAEs occurring during Screening relating to study-mandated procedures are to be documented in the eCRF.

A physical examination of the subject should be performed at both Visit 1/Screening and Visit 2/Randomization. Data are not collected in the eCRF though abnormal findings are to be recorded as AEs. Serum laboratory and pregnancy testing should be performed at Visit 1/Screening and repeated at Visit 2/Randomization (urine pregnancy test required in addition at Visit 2 prior to randomization [see Section 4.3]), whereas blood sampling for baseline NT-proBNP should only be performed at Visit 2/Randomization. Laboratory data are only collected in the eCRF for local lab assessments [see Section 7.3.5]. Only laboratory data from Visit 1/Screening are to be considered for subject eligibility. Vital signs are to be assessed and documented in the eCRF at Visit 1/Screening.

AEs and SAEs occurring during the Screening and Randomization Visit phase are to be documented in the eCRF.

7.2 Efficacy assessments

7.2.1 Hemodynamic measurements – Right heart catheterization

Invasive cardiac hemodynamic variables are measured according to the Actelion RHC guidelines (see the PORTICO catheterization handbook) at Baseline and Week 12, or at permanent discontinuation of double-blind study treatment if prior to Week 12 (at the investigator's discretion).

A maximum of 2 RHC are performed during the study duration. Catheterizations should be performed according to the Actelion guidelines and the thermodilution technique should be used to measure cardiac output (CO).

The following variables are to be measured and collected in the eCRF: Heart rate (HR), PAWP or LVEDP (if PAWP is not available), mRAP, systolic/diastolic/mean PAP, CO, SVO_2. Non-invasive SBP and diastolic blood pressure (DBP) are collected and entered into the eCRF. PVR will be calculated locally and entered into the eCRF at Visit 1/Screening.

The following hemodynamic variables will be calculated by Actelion for analysis purposes [see Section 11.2 and the PORTICO catheterization handbook for formulae]: PVR, TPR, CI.

RHC reports, including traces, must be signed by the person performing the procedure, or by the principal investigator and filed at site in the subject's file.

7.2.2 Hemodynamic measurements – Hepatic vein catheterization

HVPG, an estimate of portal pressure, is measured by hepatic vein catheterization (HVC) at Baseline and Week 12, or at permanent discontinuation of double-blind study treatment if prior to Week 12 (at the investigator's discretion).

HVPG should be measured at the same time as RHC variables where possible, but within 1 week prior to EOT-DB if the procedure cannot be performed on the same day. HVC is not required at sites that do not perform the procedure routinely.

HVPG measurements will be done after at least 4 hours of fasting, at rest, in the supine position, under local anesthesia and mild sedation. A catheter introducer will be placed into the right jugular vein (or femoral) by the Seldinger technique. It will be used to advance a balloon-tipped catheter into the main right hepatic vein for repeated measurements of wedged (occluded) and free hepatic venous pressures. Intravascular pressures will be measured using highly sensitive pressure transducers, calibrated before each measurement. HVPG will be calculated as the difference between wedged and free hepatic venous pressures. Measurements will be performed at least as duplicates and repeated until, ideally, the 2 consecutive reliable measurements do not differ by more than 1 mmHg. The mean of these two measurements will be considered final. It is up to the investigator, according to his best clinical judgment, to identify the reliable value in case that this requirement is not fulfilled. Only the final value will be recorded in the CRF.

HVC reports must be signed by the person performing the procedure, or by the principal investigator. Corresponding HVC documents must be filed at site in the subject's file.

7.2.3 WHO functional class

WHO functional class is evaluated at Screening, Baseline/Randomization, and then every Visit until EOT-DB or EOT-OL, whichever comes last [see Appendix 5 for more details on performing the assessment].

7.2.4 6-minute walk test

The 6MWT [ATS Statement 2002] is evaluated at Screening, Baseline/Randomization, and then every Visit until EOT-DB or EOT-OL, whichever comes last. It is a test which measures the distance walked by the subject in six minutes.

Detailed guidelines on the correct execution of this test, the "Actelion guidelines for 6MWT", can be found in the Appendix 3. It is important that for each individual subject the 6MWT is conducted under the same conditions throughout the study (e.g., same location, same tester, same time of day, with or without nasal oxygen therapy [and with same flow rate as Baseline]).

7.2.5 Borg dyspnea index

The Borg dyspnea index is evaluated after each 6MWT. It rates dyspnea on a scale from 0 to 10 [see Appendix 4 for more details on performing the assessment].

7.2.6 Serum NT-proBNP

A blood sample will be drawn at Baseline/Randomization (Visit 2), EOT-DB, and EOT-OL for the analysis of serum NT-proBNP.

Serum NT-proBNP samples will be shipped to the central laboratory on dry ice as soon as possible after blood sample has been drawn or stored frozen at −20 °[−4 °F] ± 2 °C [± 3.6 °F] until the shipment can occur. A temperature log must be maintained and temperature control should occur at least on a weekly basis. NT-proBNP samples will be processed through the central laboratory and the results will be sent electronically to Actelion on an ongoing basis. Further details regarding blood sampling procedures, collection and shipment of biomarker samples are described in the central laboratory manual.

7.3 Safety assessments

The definitions, reporting and follow-up of AEs, SAEs [and pregnancies] are described in Section 10.

7.3.1 Vital signs

Vital signs (BP, pulse rate) will be measured at Screening (Visit 1), EOT-DB, and EOT-OL, and entered in the eCRF. BP (systolic and diastolic) and pulse rate will be measured in a supine or sitting position after the subject has rested for at least 5 minutes. The right or left arm may be used. The same position and arm should be used throughout the trial for an individual subject. When applicable, vital signs should be measured before the 6MWT.

7.3.2 Weight and height

Height and weight are measured at Visit 1/Screening and entered into the eCRF. Weight is measured again at EOT-DB.

7.3.3 Physical examination

Physical examination (i.e., inspection, percussion, palpation and auscultation) is to be performed during the course of the study. If an abnormality is found it should be specified in the eCRF, describing the signs related to the abnormality (e.g., systolic murmur) and not the diagnosis (e.g., mitral valve insufficiency). Clinically relevant findings (other than those related to PoPH) that are present at study start (i.e., signing of informed consent) must be recorded on the Medical History CRF page. Physical examination findings made after study start, which meet the definition of an AE [Section 10.1.1] must be recorded by the investigator on the AE page of the CRF.

7.3.4 Child-Pugh classification and/or MELD Score assessment

Assessment of liver disease severity using the Child-Pugh classification and/or MELD Score [see Appendix 2 for definitions] is to be performed at Screening/Visit 1, EOT-DB, and EOT-OL and entered into the eCRF. Serum laboratory analyses used for calculating either assessment must be performed using study lab kits but local labs may also be used in parallel and data entered into the eCRF. An ultrasound scan of the abdomen should be performed for assessing the Child-Pugh class. Data must be complete for Screening purposes.

In case a patient has progressed to Child-Pugh C or MELD Score ≥ 19 at Week 12, open-label medication must not be started. Serum laboratory analyses used for calculating either assessment must be performed using study lab kits but local labs may also be used in parallel and data entered into the eCRF. EOS must be completed after a 30-day Safety follow-up period.

7.3.5 Laboratory assessments

7.3.5.1 Type of laboratory

A central laboratory ([redacted]) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Central laboratory data will be automatically transferred from the central laboratory database to Actelion's clinical database.

Eligibility of subjects in Screening may be determined using local laboratory tests as long as the central laboratory kit is used in parallel. Similarly, at Week 12 (EOT-DB), laboratory assessments for calculating the MELD Score and/or Child-Pugh classification

may be performed using local laboratory testing if a central laboratory kit is used in parallel.

All local laboratory data must be entered into the clinical database via dedicated eCRF pages. The investigator/delegate will provide Actelion with the name, professional degree, and *curriculum vitae* of the director of the local laboratory, a copy of the laboratory's certification, and the normal ranges for each laboratory test that is evaluated in the study. These laboratory references must be updated whenever necessary.

Under specific circumstances (e.g., if the patient lives far from the site and cannot return every month), laboratory samples may be collected at a laboratory close to where the patient lives (satellite laboratory), and sent to the central laboratory for analysis. In such a case, the satellite laboratory must be provided with the central laboratory sampling kits. Shipment of the samples will be organized by the satellite laboratory. If this process is implemented, the satellite laboratory must be identified prior to enrollment of the patient in the study. The supervision of the satellite laboratory remains under the responsibility of the principal investigator.

In exceptional cases (e.g., patient is hospitalized in a different hospital from the study center due to a medical emergency, missing laboratory values) the local laboratory results (with the corresponding normal ranges) will be entered into the clinical database via dedicated CRF pages.

In case a central laboratory sample is lost or cannot be analyzed for any reason, the investigator will collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time-window and these test results are available.

Central laboratory reports will be sent to the investigator. In case of specific (pre-defined) laboratory abnormalities, the central laboratory will alert Actelion and the concerned site. Alert flags that will trigger such notifications are displayed in Appendix 7.

All laboratory reports must be signed and dated by the principal investigator or delegate within 3 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are known at the time of informed consent signature must be recorded on the medical history page of the CRF. Any clinically relevant laboratory abnormalities detected after informed consent signature must be reported as an AE or SAE as appropriate [see Section 10], and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant. Further laboratory analyses must be performed as indicated and according to the judgment of the investigator.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual.

7.3.5.2 Laboratory tests

The total amount of blood collected during the study will not exceed 200 mL:

1. At Visit 1/Screening approximately 15 mL of blood will be collected
2. At Visit 2/Randomization, EOT-DB and EOT-OL approximately 25 mL of blood will be collected
3. At Visits 3 and 4 approximately 15 mL of blood will be collected
4. At Visits 6 and 7 approximately 15 mL of blood will be collected
5. At the PK substudy (optional), approximately 24 mL will be collected.

Hematology

Hematology tests will be performed at every Visit (1–8) and include:

- Hemoglobin, hematocrit
- Erythrocyte count (reticulocyte count)
- Leukocyte count with differential counts
- Platelet count.

Rules for study treatment interruption in case of hemoglobin abnormalities are provided in Section 5.1.11.

Clinical chemistry

- Aminotransferases (AST/ALT), alkaline phosphatase, total and direct bilirubin
- GGT
- Bile acids
- Creatinine, blood urea nitrogen (BUN)
- Uric acid
- Lactate dehydrogenase (LDH), cholesterol, triglycerides
- Glucose
- Sodium, potassium, calcium, chloride
- Albumin, protein.

Rules for study treatment interruption in case of liver enzymes abnormalities are provided in Section 5.1.11.

Coagulation tests

- Prothrombin time and International Normalized Ratio (PT-INR).

Pregnancy test

A serum pregnancy test for women of childbearing potential will be performed monthly from Visits 1 to 8 and if pregnancy is suspected during the study. At Visit 2 and at the end of the 30-day Safety follow up, a urine dipstick pregnancy test is to be performed.

8 SCHEDULE OF VISITS

Table 1 provides a summary of all visits and assessments described in the following sections.

To ensure compliance, at each visit the study personnel must remind women of childbearing potential to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.

It is permitted to re-screen subjects once, if the reason for non-eligibility was transient (e.g., abnormal laboratory test, insufficient wash-out period of a forbidden medication, etc.), provided that documented authorization has been received from Actelion. Only screening assessments that will be older than 28 days at the time of randomization need to be repeated at the time of re-screening.

8.1 Screening Period

8.1.1 Screening (Visit 1)

All Screening assessments must be performed within 28 days prior to Randomization. Historical data for Baseline RHC and HVC may be entered into the eCRF if the procedure was performed within 28 days of Randomization and per the requirements described in Sections 7.2.1 and 7.2.2. Screening commences with signature of the ICF and ends with subject randomization (up to 28 days after signed informed consent).

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate face to face explanation of the objectives, methods, and potential hazards of the study. The subjects who agree to participate in the study must sign the ICF prior to any study-related assessment or procedure. Screening and Randomization cannot occur on the same day.

Visit 1 includes:

- Subject information leaflet and consent form signature

- Obtain subject number from IxRS
- Recording of demographics, medical history, cause of portal hypertension, date and method of portal hypertension diagnosis, date of PoPH diagnosis
- Physical examination
- Complete laboratory tests, including serum pregnancy test for women of childbearing potential
- Child-Pugh and/or MELD score assessment
- Recording of previous and concomitant medications
- Recording of methods of contraception (for females of childbearing potential only) and initiation of protocol-compliant contraception if applicable. The reason why a female is not considered to be of childbearing potential will also be collected in the eCRF
- Measurement of vital signs, height and body weight
- WHO functional class
- 6MWT and Borg dyspnea index
- RHC and HVC
- Recording of AEs and SAEs.

The investigator will check all the inclusion/exclusion criteria and decide on the subject's eligibility for the study. HVC is not required at sites that do not perform the procedure routinely. Only laboratory data from Visit 1/Screening are to be considered for subject eligibility. Eligibility of subjects may be determined using local laboratory tests as long as the central laboratory kit is used in parallel and the results entered into the eCRF. It must be verifiable in the source documents that the subject met each of the inclusion criteria and none of the exclusion criteria. If the subject is not randomized, the reason for screening failure is to be documented in the eCRF.

8.2 Double-blind treatment period

8.2.1 Randomization (Visit 2)

Visit 2 corresponds to the start of the treatment period (Day 1 of the study) for subjects that are eligible after all Screening assessments have been performed. It must take place within 28 days after start of Screening. However, Screening and Randomization cannot take place on the same day.

Visit 2 includes:

- Recording of changes in concomitant medications
- Assessment of methods of contraception (for females of childbearing potential only)
- Physical examination
- WHO functional class

- 6MWT and Borg dyspnea index
- Complete laboratory tests, including serum & urine pregnancy test for women of childbearing potential [see Section 4.3]
- Blood sample for serum NT-proBNP
- Recording of AEs/SAEs:
  - All AEs occurring after study treatment initiation are to be reported in the eCRF
  - All SAEs occurring after signing of the ICF are to be reported in the eCRF and on an SAE form.

Laboratory values from Visit 2/Randomization are not to be considered for subject eligibility. After completion of all Screening and Randomization assessments and confirmation of eligibility (i.e., verification of all entry criteria) by the investigator:

- Randomization via IxRS to obtain Randomization and study treatment bottle number
- Dispensing of 1 bottle of study treatment [see Section 5.1.7.3]

8.2.2 Week 4 (Visit 3)

Visit 3 is scheduled 4 weeks (± 4 days) after Randomization.

Visit 3 includes:

- Recording of changes in concomitant medications
- Assessment of methods of contraception (for females of childbearing potential only)
- Physical examination
- WHO functional class
- 6MWT and Borg dyspnea index
- Complete laboratory tests, including serum pregnancy test for women of childbearing potential [see Section 4.3]
- Recording of AEs and SAEs
- Study medication return and dispensing of a new bottle.

8.2.3 Week 8 (Visit 4)

Visit 4 is scheduled 8 weeks (± 4 days) after Randomization.

Visit 4 includes:

- Recording of changes in concomitant medications
- Assessment of methods of contraception (for females of childbearing potential only)
- Physical examination
- WHO functional class
- 6MWT and Borg dyspnea index

- Complete laboratory tests, including serum pregnancy test for women of childbearing potential [see Section 4.3]
- Recording of AEs and SAEs
- Study medication return and dispensing of a new bottle.

8.2.4 EOT-DB (scheduled Visit 5)

EOT-DB is scheduled 12 weeks (± 4 days) after Randomization, or earlier in case of premature discontinuation of double-blind study treatment.

EOT-DB includes:

- Recording of changes in concomitant medications
- Assessment of methods of contraception (for females of childbearing potential only)
- Physical examination
- Measurement of vital signs and body weight
- WHO functional class
- 6MWT and Borg dyspnea index
- RHC and HVC
- Complete laboratory tests, including serum pregnancy test for women of childbearing potential [see Section 4.3]
- Child-Pugh and/or MELD score assessment
- Blood sample for serum NT-proBNP
- Recording of AEs and SAEs
- Study medication return and dispensing of open-label medication.

Once EOT-DB has been performed, subjects should continue the study in the open-label treatment period.

8.3 Open-label treatment period

8.3.1 Week 16 (Visit 6)

Visit 6 is scheduled 16 weeks (± 4 days) after Randomization.

Visit 6 includes:

- PK substudy, if applicable [see Appendix 1]
- Recording of changes in concomitant medications
- Assessment of methods of contraception (for females of childbearing potential only)
- Physical examination
- WHO functional class
- 6MWT and Borg dyspnea index

- Complete laboratory tests, including serum pregnancy test for women of childbearing potential [see Section 4.3]
- Recording of AEs and SAEs
- Study medication return and dispensing of a new bottle.

8.3.2 Week 20 (Visit 7)

Visit 7 is scheduled 20 weeks (± 4 days) after Randomization.

Visit 7 includes:

- PK substudy, if applicable [see Appendix 1]
- Recording of changes in concomitant medications
- Assessment of methods of contraception (for females of childbearing potential only)
- Physical examination
- WHO functional class
- 6MWT and Borg dyspnea index
- Complete laboratory tests, including serum pregnancy test for women of childbearing potential [see Section 4.3]
- Recording of AEs and SAEs
- Study medication return and dispensing of a new bottle.

8.3.3 EOT-OL (scheduled Visit 8)

EOT-OL is scheduled 24 weeks (± 4 days) after Randomization, or earlier in case of premature discontinuation of open-label study treatment.

EOT-OL includes:

- Recording of changes in concomitant medications
- Assessment of methods of contraception (for females of childbearing potential only)
- Physical examination
- Measurement of vital signs
- WHO functional class
- 6MWT and Borg dyspnea index
- Complete laboratory tests, including serum pregnancy test for women of childbearing potential [see Section 4.3]
- Child-Pugh and/or MELD score assessment
- Blood sample for serum NT-proBNP
- Recording of AEs and SAEs
- Study medication return.

8.4 EOS

After permanent study treatment discontinuation (double-blind OR open-label), all subjects will enter a 30-day Safety follow-up period.

EOS is scheduled 24 weeks + 30 to 33 days after randomization. It must be performed at least 30 days after study treatment discontinuation (double-blind OR open-label) and may be performed by telephone.

EOS includes:

- Urine pregnancy test
- Recording of AEs with onset up to 24 hours after study treatment discontinuation
- SAEs with onset up to 30 days after study treatment discontinuation.

9 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

9.1 Study completion

For an individual subject the study is only considered completed once EOT-DB or EOT-OL has been performed and the 30-day Safety follow up is complete (EOS).

The study is considered complete when all subjects have performed the 30-day Safety follow up (EOS).

9.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study, die or are lost to follow-up for any other reason. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, they believe that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion for any reason, including premature termination or suspension of the study [see Section 9.3].

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual fail. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, email address, person to be contacted in case the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject, document all attempts and enter the loss of follow-up information into the eCRF. The following methods must be used: at least three documented telephone calls on different days must be placed to the last available telephone number and one registered letter must be sent by post to the last available home

address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., site staff visit to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

If premature withdrawal occurs for any reason, the reason for premature withdrawal from the study, along with who made the decision (subject, investigator or Actelion) must be recorded in the eCRF.

If for whatever reason (except death or loss-to-follow-up) a subject was withdrawn from the study, the investigator should make efforts to conduct a last visit/contact to assess the safety and well-being of the subject, collect unused study treatment and discuss follow-up medical care. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 9.4.

9.3 Premature termination or suspension of the study

Actelion reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If a study is suspended or prematurely terminated, Actelion will promptly inform the investigators, the IRBs/IECs and Health Authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator in agreement with Actelion must promptly inform all enrolled subjects, and ensure their appropriate treatment and follow-up, as described in Section 9.4. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates a study without prior agreement from Actelion, the investigator must promptly inform Actelion and the IRB/IEC, and provide both with a detailed written explanation of the termination or suspension.

If the IRB/IEC suspends or terminates its approval/favorable opinion of a study, the investigator must promptly notify Actelion and provide a detailed written explanation of the termination or suspension.

Any suspension or premature termination of the study must be discussed with the Steering Committee.

9.4 Medical care of subjects after study completion/ withdrawal from study

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s)/medical care is necessary and available according to local regulations.

After premature study withdrawal, the investigator must remind the subject that he/she must not use any other investigational treatment in the 30 days following study treatment discontinuation. Female subjects of childbearing potential need to be reminded of the requirement to continue using a reliable method of contraception until 30 days after intake of the last dose of study treatment.

10 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

10.1 Adverse events

10.1.1 Definitions of adverse events

An AE is any adverse change, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease that occurs in a subject during the course of the study, whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment initiation until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the

course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

Overdose, misuse and abuse of the study treatment should be reported as an AE and, in addition, study treatment errors must be documented in the study treatment log of the CRF.

10.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the CRF.

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

The three categories of intensity are defined as follows:

- **Mild**

The event may be noticeable to the subject. It does not influence daily activities, and usually does not require intervention.

- **Moderate**

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort, and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 10.3.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

10.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by an investigator who is a qualified physician.

10.1.4 Adverse events associated to study design or protocol mandated procedures

An AE is defined as related to study design or protocol mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease.

10.1.5 Reporting of adverse events

All AEs occurring after study start (i.e., signing of informed consent) and up to 30 days after study treatment discontinuation must be recorded on specific AE pages of the CRF.

10.1.6 Follow-up of adverse events

AEs still ongoing more than 30 days after study treatment discontinuation must be followed up until they are no longer considered clinically relevant.

10.2 Serious adverse events

10.2.1 Definitions of serious adverse events

10.2.1.1 Serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalization, or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did

not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

10.2.1.2 Serious adverse events associated with the study design or protocol mandated procedures

An SAE is defined as related to study design or protocol mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease or a complication of an invasive procedure that is specifically required by the protocol.

10.2.2 Reporting of serious adverse events

10.2.2.1 During screening period

All SAEs that occur after study start (i.e., signing of informed consent) must be reported (whether considered associated or not associated to study design or study-mandated procedures).

These SAEs must be reported on an SAE form and also in the CRF.

10.2.2.2 During treatment period

All SAEs, regardless of investigator-attributed causal relationship, must be reported.

These SAEs must be reported on an SAE form (except if waived [see Section 10.2.5]) and also on the AE pages in the eCRF.

10.2.2.3 During 30-day follow-up period

All SAEs, regardless of investigator-attributed causal relationship, which occur up to 30 days after study treatment discontinuation must be reported on AE pages in the eCRF and on an SAE form (except if waived [see Section 10.2.5]).

10.2.3 Follow-up of serious adverse events

SAEs still ongoing at the EOS visit must be followed up until resolution or stabilization, or until the event outcome is provided, e.g., death.

10.2.4 After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to the Actelion drug safety department within 24 hours of the investigator's knowledge of the event, **only** if considered causally related to previous exposure to the study treatment by the investigator.

10.2.5 Reporting procedures

All SAEs must be reported by the investigator to the Actelion drug safety department within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be faxed to the Actelion drug safety department (contact details are provided on the SAE form). The investigator must complete the SAE form in English, and must assess the causal relationship of the event to study treatment.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Actelion drug safety department may contact the investigator to obtain further information.

If the subject is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

The reference safety document to assess expectedness of a suspect serious adverse reaction and the need for expedited reporting by the sponsor to Health Authorities, ECs/IRBs and investigators is the reference safety information section of the IB [Macitentan IB].

10.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

10.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during the study including during the 1 month following study treatment discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Actelion Pregnancy form, which is faxed to the Actelion drug safety department (see contact details provided on the Actelion Pregnancy form), and on an AE page in the eCRF.

10.3.2 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the Actelion drug safety department.

Any AE associated with the pregnancy occurring during the follow-up period after study treatment discontinuation must be reported on separate AE pages in the CRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 10.3.1.

10.4 Study safety monitoring

Clinical study safety information (AEs, SAEs, laboratory values, vital signs, and project-specific labs/examinations as required) is monitored and reviewed on a continuous basis by the Actelion Clinical team (in charge of ensuring subjects' safety as well as data quality) by periodically monitoring clinical studies activities from protocol conception to database closure.

11 STATISTICAL METHODS

All statistical analyses will be conducted by Actelion or by designated Contract Research Organizations supervised by Actelion.

A Statistical Analysis Plan (SAP) will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

11.1 Analysis Sets

11.1.1 Screened Analysis Set

This analysis set includes all patients who were screened and received a screening number.

11.1.2 Full Analysis Set

The Full Analysis Set (FAS) includes all randomized patients who received at least one dose of study treatment in the double-blind treatment period and have a baseline value for the primary endpoint (PVR).

11.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) comprises all patients included in the FAS without major protocol deviations that might affect the main analysis of the primary efficacy variable. The reasons for excluding patients for the PPS will be fully defined and documented in the SAP.

11.1.4 Safety Set

The Safety Set includes all patients who received at least one dose of study treatment in the double-blind treatment period.

11.1.5 Other analysis sets

The Macitentan Treated Set (MTS) consists of all patients who received at least one dose of macitentan in the double-blind or open-label treatment period.

The PK set comprises all patients from the FAS who did not deviate from the protocol in a way that might affect the evaluation of the PK endpoints.

11.1.6 Usage of the analysis sets

The primary efficacy analysis will be performed on the FAS based on treatment as randomized. Secondary and exploratory efficacy analyses will also be performed on the FAS.

Safety analyses related to the double-blind treatment period will be performed on the Safety Set based on treatment as received.

Summaries of efficacy and safety data obtained in all subjects who received macitentan (regardless of the treatment period) will be performed on the MTS.

Subject listings will be based on the Safety Set, unless otherwise specified. Subject disposition will be described for the Screened Analysis Set.

Analysis of PK in the PK substudy will be performed on the PK Set.

11.2 Variables

11.2.1 Primary efficacy variable

The primary efficacy variable is the relative change from baseline to Week 12 in PVR.

PVR [dyn·s·cm-5] is calculated as (mPAP − PAWP) / CO × 80 (also refer to the PORTICO catheterization handbook). The relative change from baseline is equal to the ratio of Week 12 to baseline PVR, minus one. The ratio of Week 12 to baseline PVR will be the variable used in the analyses.

11.2.2 Secondary efficacy variables

Secondary efficacy variables are changes from baseline to Week 12 in:

- mRAP [mmHg]
- mPAP [mmHg]
- CI [L/min/m^2], calculated as CO / body surface area (BSA) where
  BSA [m^2]= 0.007184 × $weight^{0.425}$ [kg] × $height^{0.725}$ [cm]
- TPR [dyn·s·cm^{-5}], calculated as mPAP / CO.
- SVO_2 [%]
- WHO functional class [I–IV]
- 6MWD [m]
- NT-proBNP [pmol/L]

11.2.3 Other efficacy variables

11.2.3.1 Double-blind treatment period

For all patients, changes from baseline to Week 12 in:

- HVPG [mmHg]
- Borg dyspnea index (range 6–20)

11.2.3.2 Macitentan treatment period

For patients who received macitentan in the double-blind or open-label treatment period, changes from macitentan Baseline to each time point for the following variables:

- WHO functional class
- 6MWD
- NT-proBNP
- Borg dyspnea index

Macitentan baseline is defined as last assessment prior to macitentan initiation, i.e., for patients who received macitentan already in the double-blind period baseline is the start of double-blind macitentan and for patients who received macitentan only in the open-label period baseline is Week 12.

11.2.4 Safety variables

11.2.4.1 Double-blind treatment period

Treatment-emergent is defined as from first intake of study treatment until to end of double-blind treatment + 30 days or start of open-label treatment, whichever occurs first. For all patients, safety variables include:

- Treatment-emergent AEs up to EOT-DB
- Treatment-emergent deaths up to EOT-DB
- Treatment-emergent SAEs up to EOT-DB
- AEs leading to premature discontinuation of study treatment up to EOT-DB
- Occurrence of LFT (ALT or AST) abnormalities up to EOT-DB, classified as:
    - $\geq 3 \times$ ULN;
    - $\geq 3 \times$ ULN and $< 5 \times$ ULN;
    - $\geq 5 \times$ ULN and $< 8 \times$ ULN;
    - $\geq 8 \times$ ULN.
- Occurrence of hemoglobin abnormalities up to EOT-DB, classified as:
    - $<$ 80 g/L;
    - $\geq$ 80 g/L and $<$ 100 g/L.
- Occurrence of ALT and/or AST abnormality $\geq 3 \times$ ULN associated with total bilirubin $\geq 2 \times$ ULN (and increased as compared to baseline) up to EOT-DB
- Treatment-emergent marked laboratory abnormalities up to EOT-DB

- Change from baseline to EOT-DB in vital signs
- Change from baseline to EOT-DB in laboratory variables
- Change from baseline to EOT-DB in Child-Pugh classification
- Change from baseline to EOT-DB in MELD score

11.2.4.2 Macitentan treatment period

For patients who received macitentan in the double-blind or open-label treatment period the same safety variables as in the Section 11.2.4.1 will be considered with macitentan treatment emergent instead of treatment emergent, and EOMT instead of EOT-DB.

11.2.5 Other variables

Variables associated with the PK substudy are described in Appendix 1.

11.3 Description of statistical analyses

11.3.1 Overall testing strategy

The overall type I error is $\alpha = 0.025$ (one-sided). The type II error is set to 0.10 and the power to 90%.

11.3.2 Analysis of the primary efficacy variable(s)

11.3.2.1 Hypotheses and statistical model

The null hypothesis is:

The treatment difference (macitentan minus placebo) in mean relative change from baseline to Week 12 in PVR is greater than or equal to zero or, equivalently, the geometric mean ratio (macitentan versus placebo) of the ratios of Week 12 to baseline PVR is greater than or equal to one.

The alternative hypothesis is:

The treatment difference in mean relative change from baseline in PVR is less than zero or, equivalently, the geometric mean ratio is less than one.

11.3.2.2 Handling of missing data

If PVR cannot be calculated due to missing PAWP but mPAP and CO are available for the same visit, one the following will be applied:

1. If PAWP is missing both at baseline and post-baseline, the treatment group medians will be imputed (based on the FAS).
2. If PAWP is missing either at baseline or post-baseline, the patient's available PAWP will be imputed.

This imputation is based on the clinical assumption that macitentan does not affect PAWP.

Baseline: Patients without a baseline PVR measurement will be excluded from the analyses.

Post-baseline: In patients with a post-baseline PVR measurement obtained before Week 12, the post-baseline PVR measurement will be carried forward. For patients where no post-baseline PVR measurement is available, data will be imputed. Imputation rules will be specified in the SAP.

11.3.2.3 Main analysis

The primary analysis will be performed on the FAS.

PVR will be summarized by time point and treatment group using descriptive statistics as well as geometric means and Coefficients of Variation (CVs). The ratio of Week 12 to baseline PVR will be summarized similarly.

The ratio of Week 12 to baseline PVR will be log-transformed (base e) and analyzed using an Analysis of Covariance (ANCOVA) with factors for treatment group (macitentan versus placebo), background PAH-specific therapy at baseline, region and a covariate for baseline log PVR. The treatment group difference (on log scale) and its 95% confidence interval will be estimated based on the model. The geometric mean ratio (macitentan versus placebo) and its 95% confidence interval will be obtained by exponentiation. The null hypothesis will be rejected if the entire 95% confidence interval is below one.

The log transformation for PVR is justified by the fact that ratios versus baseline follow a normal distribution more closely after a log transformation. In addition, mean absolute changes from baseline on log scale can be translated into (geometric) mean ratios by exponentiation.

The treatment effect will be expressed as (Geometric Mean Ratio [GMR]-1) × 100%, where a negative value indicates a reduction of PVR in the macitentan group as compared to the placebo group.

11.3.2.4 Supportive/sensitivity analyses

A sensitivity analysis will be performed on the FAS where, for patients with a post-baseline PVR measurement obtained before Week 12, a model-based imputation will be used for the log-transformed PVR:

- log PVR [at Week 12] = log PVR [at week t<12] + (12-t) × *slope* where

- *slope* is the expected change from baseline in log PVR based on the main analysis model, restricted to patients who had their post-baseline PVR measurement at Week 12.

Another sensitivity analysis will be performed on the PP set that will (at least) be restricted to completers, i.e., patients with a Week 12 PVR measurement taken at Week 12.

Additional sensitivity analyses may be specified in the SAP.

11.3.2.5 Subgroup analyses

A subgroup analysis for the primary endpoint will be performed for patients with versus without PAH-specific therapy at baseline using the ANCOVA model specified in Section 11.3.2.3, but without the factor for PAH-specific therapy.

Another subgroup analysis will be performed by region using the ANCOVA model without the factor for region.

Additional subgroup analyses will be specified in the SAP. Interactions between treatment and subgroups will be explored.

11.3.3 Analysis of the secondary efficacy variable(s)

Secondary efficacy analyses will be performed on the FAS at $\alpha = 0.025$ (one-sided) using 95% confidence intervals. No correction for multiple testing will be applied for these analyses.

Changes from baseline to Week 12 in pressure-volume variables (mRAP, mPAP, CI, TPR) and SVO_2 will be summarized and analyzed as described in Section 11.3.2.3, but without the log-transformation.

WHO functional class will be summarized by time point and treatment group using frequency tables. Changes from baseline in WHO functional class will be dichotomized as worsening (i.e., change > 0) versus no change or improvement (i.e., change ≤ 0). Worsening will be analyzed using a logistic regression model with covariates for treatment group, background PAH-specific therapy at baseline and region.

6MWD will be summarized by time point and treatment group using descriptive statistics. Change from baseline to each time point will be summarized similarly. Change from baseline in 6MWD will be analyzed using a repeated measurements model with factors for treatment group, time point, treatment by time interaction, background PAH-specific therapy at baseline and region, and covariates for baseline 6MWD and WHO functional class. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject. NT-proBNP will be summarized by time point and treatment group using descriptive statistics as well as

geometric means and CVs. The ratio of Week 12 to baseline NT-proBNP will be summarized similarly. The ratio versus baseline in NT-proBNP will be log-transformed and analyzed using an ANCOVA with covariates for treatment group, background PAH-specific therapy at baseline, region and baseline log NT-proBNP.

11.3.4 Analysis of the other efficacy variables

Changes from baseline to Week 12 in HPVG and Borg dyspnea index (related to the double-blind treatment period) will be summarized by treatment group in the FAS using descriptive statistics.

Changes from macitentan baseline to each time point in WHO functional class, 6MWD, NT-proBNP and Borg dyspnea index (related to the macitentan treatment period) will be summarized for the MTS using descriptive statistics.

11.3.5 Analysis of the safety variables

The safety analyses described below will be performed on the Safety Set for data from the double-blind treatment period. For these analyses the (double-blind) treatment-emergent period is defined from start of double-blind treatment up to the start of open-label treatment or 30 days after double-blind treatment discontinuation, whichever occurs first.

The safety analyses will also be performed on the MTS for data from the macitentan treatment period. For these analyses, macitentan treatment-emergent is defined as from first intake of macitentan up to EOS (i.e., 30 days after discontinuation of macitentan treatment). EOMT is defined as EOT-DB or EOT-OL, whichever comes last. Macitentan baseline is defined as last assessment prior to intake macitentan.

All safety data will be listed, with flags for quantitative abnormalities.

11.3.5.1 Adverse events

A treatment-emergent AE is any AE temporally associated with the use of a study treatment. The number and percentage of patients experiencing treatment emergent AEs and SAEs at least once will be tabulated by treatment group and by:

- MedDRA System organ class (SOC) and individual preferred term within each SOC, in descending order of incidence.
- Frequency of patients with events coded with the same preferred term, in descending order of incidence.

Furthermore, treatment-emergent AEs and SAEs will be tabulated as described above by severity and relationship to study treatment.

AEs leading to premature discontinuation of study treatment and death will also be summarized as described above.

Listings will be provided for all reported AEs, including SAEs. In addition, separate listings will be provided for SAEs, for AEs leading to premature discontinuation of study treatment, and for AEs leading to death.

11.3.5.2 Laboratory variables

Descriptive summary statistics by visit and treatment group will be provided for observed values and absolute changes from baseline, in both hematology and blood chemistry laboratory tests. In order to minimize missing data and to allow for unscheduled visits, all recorded assessments up to EOT-DB plus 30 days will be assigned to the most appropriate visit time point according to the best fitting time-window for that assessment.

Actelion internal guidelines will be used for the definitions of marked abnormalities and for the standardization of numeric values obtained from different laboratories and/or using different normal ranges. Standard numeric laboratory variables are transformed to standard units. All laboratory data transferred are taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments.

Marked laboratory abnormalities will be summarized for each laboratory parameter by treatment group providing their incidence and frequency. Absolute values and changes from baseline of laboratory parameter values during the course of the study will be summarized using the usual location and scale summary statistics by treatment group.

Laboratory variables are the following:

- Hematology: hemoglobin, hematocrit, erythrocyte count, leukocyte count with differential counts, platelet count, prothrombin time and coagulation tests (PT-INR).
- Blood chemistry: AST, ALT, alkaline phosphatase, total and direct bilirubin, LDH, creatinine, uric acid, glucose, cholesterol, triglycerides, Sodium, potassium, chloride, calcium, protein, albumin, GGT, bile acids, and BUN.

The number and percentage of patients with LFT abnormalities (classified as in Section 11.2.4) will be tabulated by treatment group.

The number and percentage of patients with hemoglobin abnormalities (classified as in Section 11.2.4) will be tabulated by treatment group.

11.3.5.3 Vital signs and body weight

Blood pressure (i.e., DBP and SBP), HR, and body weight will be summarized for each study visit where recorded using the usual location and scale summary statistics by treatment group for both absolute values and changes from baseline. Patients for whom

no post-baseline value is available are excluded from the analysis of the changes from baseline in the Safety Set.

Changes from baseline in Child-Pugh score and MELD score will be summarized similarly as vital signs.

11.3.6 Analysis of other variables

See Section 4.3.1 of Appendix 1 for analysis of PK variables.

11.4 Interim analyses

No interim analysis is planned for this trial.

11.5 Sample size

11.5.1 Sample size justification

An integrated analysis of two bosentan studies, BENEFIT (AC-052-366) and EARLY (AC-052-364), and the hemodynamic substudy of SERAPHIN (AC-055-302) with macitentan suggested that the treatment group difference on PVR is expected to be around −0.31 on log scale (95% confidence intervals: −0.38, −0.23) and that the within group standard deviation (SD) is around 0.41 on log scale (90% confidence intervals: 0.39, 0.43). Under these assumptions, 76 evaluable patients will be needed for 90% power (38 patients per group). Accounting for 10% non-evaluable patients, approximately 84 patients will need to be randomized.

11.5.2 Sample size sensitivity

Table 2 gives more details about the integrated analysis of PVR. It also shows the ‘best’ and ‘worst’ case sample sizes based on the 95% confidence interval around the treatment effect for each study as well as for the integrated analysis. It appears that the proposed sample size of 84 patients is robust to some deviations from the assumptions given above.

Table 2 Treatment effects (differences on log-scale as well as % reduction versus placebo), variability in integrated analysis of three studies (AC-052-366, AC-052-364 and AC-055-302) and associated sample size for 90% power in the PORTICO study.

Study	Protocol	Treatment Effect		95% CI of Effect		SD	90% CI of SD		Sample Size*	Best Case	Worst Case
EARLY	AC-052-364	−0.26	−23%	−0.41	−0.11	0.50	0.45	0.54	158	64	924
BENEFIT	AC-052-366	−0.25	−22%	−0.35	−0.15	0.32	0.29	0.35	70	36	204
SERAPHIN	AC-055-302	−0.45	−36%	−0.58	−0.32	0.38	0.35	0.43	32	20	64
Overall		−0.31	−27%	−0.39	−0.23	0.41	0.39	0.44	76	48	132
Corrected for Baseline PVR		−0.31	−26%	−0.38	−0.23	0.41	0.39	0.43	76	48	132

*For 90% power and a two-sided alpha of 5%
Best case: based on lower limit of 95% CI for effect
Worst case: based on upper limit of 95% CI for effect
CI = confidence interval; PVR = pulmonary vascular resistance; SD = standard deviation.

12 DATA HANDLING

12.1 Data collection

The investigator/delegate is responsible to ensure the accuracy, completeness, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

CRF data will be captured via electronic data capture (EDC using the Rave system provided by Medidata Solutions, Inc., a web-based tool). The investigator and site staff will be trained to enter and edit the data via a secure network, with secure access features (username, password and identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to 21 CFR Part 11).

Subject Screening and Enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through the IxRS system and eCRF.

For each subject enrolled, regardless of study treatment initiation, a CRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF.

12.2 Maintenance of data confidentiality

The investigator/delegate must ensure that data confidentiality is maintained. On CRFs or other documents submitted to Actelion, subjects must be identified only by number, and never by name or initials, hospital numbers or any other identifier. The investigator/delegate must keep a subject identification code list, at the site, showing the randomization number, the subject's name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to Actelion, and must be kept in strict confidence by the investigator/delegate.

12.3 Database management and quality control

Electronic CRFs will be used for all subjects. The investigator will have access to the site CRF data until the database is locked. Thereafter, they will have read-only access. The CRF must be kept current to reflect subject status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Actelion on an ongoing basis to look for unexpected patterns in data and study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the CRF. All electronic queries visible in the system either require a data correction (when applicable) and/or a response from the investigator/delegate to clarify the queried data directly in the CRF, or simply a data correction in the CRF. The investigator/delegate must, on request, supply Actelion with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of Health Authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database closure.

Laboratory samples will be processed through a central laboratory and the results will be sent electronically to Actelion. PK samples will be processed through a bioanalytical laboratory and the results will be sent electronically to Actelion.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate SOP. After database closure, the investigator will receive the CRF of the subjects of her/his site (including all data changes made) on electronic media or as a paper copy.

13 PROCEDURES AND GOOD CLINICAL PRACTICE

13.1 Ethics and Good Clinical Practice

Actelion and the investigators will ensure that the study is conducted in full compliance with ICH-GCP Guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research is conducted.

13.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as Subject Information Leaflet used to obtain informed consent) to an IRB or IEC. Approval from the committee must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol after receipt of the approval must also be submitted as amendments by the investigator to the IRB/IEC in accordance with local procedures and regulations [see Section 13.6].

A list of members participating in the IRB/IEC meetings must be provided, including the names, qualifications and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation. If a study staff member was present during a meeting, it must be clear that this person did not vote.

13.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP guidelines and local regulations from each individual participating in this study and/or legal representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

The ICF will be provided in the country local language(s).

Site staff authorized to participate to the consent process and/or to obtain consent from the subject and/or legal representative will be listed on Actelion Delegation of Authority form. A study physician must always be involved in the consent process.

The subject and/or legal representative must sign, personally date and time (if appropriate) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF must also be signed, personally dated and timed (if appropriate) by the authorized site staff listed on Actelion Delegation of Authority form.

A copy of the signed and dated ICF is given to the subject and/or legal representative; the original is filed in the site documentation.

The informed consent process must be fully documented in the subject's medical records, including study reference, subject number, date/time (if applicable) when the subject was first introduced to Actelion clinical study, date/time (if applicable) of consent, who participated in the consent discussion, who consented the subject and any additional person present during the consent process (e.g., subject family member), copy of the signed ICF given to the subject / legal representative.

In the case that the site would like to recruit a subject who would be considered as vulnerable (e.g., subject cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure subject rights are respected and the consent obtained is legally valid. Actelion, the regulatory authorities (if applicable) and the IRB/IEC must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IRB/IEC, according to procedures and before subjects are recruited.

13.4 Compensation to subjects and investigators

Actelion provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

13.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the approved version of the protocol and must not implement any deviation/change from the protocol, except when the change involves only logistical or administrative aspects (e.g., change in telephone number), or in case it would be necessary to eliminate an immediate hazard to the subject.

If a protocol deviation occurs, the investigator/delegate will inform Actelion or its representative, in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. IRB/IEC and regulatory authorities must be informed, according to their requirements, but no later than 15 calendar days after the event.

13.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. A protocol amendment must be submitted to IRB/IEC, and regulatory authorities, according to their requirements.

13.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring and available when needed.

These records are to be classified into two different categories of documents: investigator's file, and subject clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with Actelion's requirements (e.g., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and Actelion to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from Actelion. Should the investigator wish to assign the study records to another party, or move them to another location, Actelion must be notified in advance.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the monitor has been provided personal and restricted access to study subjects only, to verify consistency between electronic source data and the CRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the monitor could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the monitor. The print-outs must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies having the same information as the original subject's data. The printouts will be considered as the official clinical study records.

In order to verify that the process the site uses to prepare certified copies is reliable, the monitor must be able to observe this process and confirm that the comparison of the

source documents and the certified copy did not reveal inconsistencies. The monitor does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per Actelion's instructions. If it were not possible for the monitor to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study. The printouts should be filed either with the subject medical records or with the subject's CRF.

13.8 Monitoring

Prior to study start, a site initiation visit (SIV) will be performed after the required essential study documents are approved by Actelion. The study treatment will be shipped to the site upon approval of the required essential documents.

The principal investigator must ensure that all site personnel involved in the study will be present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the initiation visit.

The SIV must be completed before the site can start the screening of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the principal investigator and filed in the ISF.

During the study, the monitor will contact and visit the investigational site regularly, and on request must be permitted to have access to trial facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered in the CRFs and other protocol-related documents. Actelion monitoring standards require full verification that informed consent has been provided, and verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety and tolerability endpoints. Additional checks of the consistency of the source data with the CRFs will be performed according to the study-specific monitoring plan. The frequency of the monitoring visits will be based on subject recruitment rate and critical data collection times.

The principal investigator must ensure that the CRF is completed after a subject's visit to the site, and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the monitor. The required site personnel must be available during monitoring visits and allow adequate time to meet with the monitor to discuss study related issues.

The investigator agrees to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized

or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site and when there are no more active subjects and after all study data have been accepted by medical review and all follow-up issues have been resolved. In case a site does not enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of Actelion.

13.9 Investigator site file

Each site will be provided with an ISF prior to the initiation visit. It will contain all the essential documents that are required to always be up-to-date and filed at site as per ICH GCP section 8.

The ISF will include a table of content listing the essential documents. All study related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the monitor regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH GCP as well as instructions from Actelion. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the principal investigator must inform Actelion immediately.

If the principal investigator changes, or if the site relocates, the monitor must be notified as soon as possible.

13.10 Audit

Actelion's Global Quality Management representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to Actelion's requirements (e.g., SOPs) will also be verified. Prior to initiating this audit, the investigator will be contacted by Actelion to arrange a time for the audit.

The investigator and staff must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

13.11 Inspections

Health Authorities and/or IRB/IEC may also wish to conduct an inspection of Actelion's clinical study (during the study or after its completion).

Should an inspection be requested by a Health Authority and/or IRB/IEC, the investigator must inform Actelion immediately, (usually via the CRA), that such a request has been made.

The investigator and staff must cooperate with inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

13.12 Reporting of study results and publication

Study results will be documented in a clinical study report that will be signed by Actelion representatives and the coordinating investigator (or principal investigator for single-center studies).

The coordinating investigator and the Steering Committee, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion prior to publication.

Actelion will post results from its clinical studies on Actelion's Clinical Trial Register, and on external/national registries, as required by law.

Actelion's Policy on Disclosure of Clinical Research Information can be found at: http://www.actelion.com/documents/corporate/policies-charters/policy-scientific-publications.pdf

In accordance with the Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before publication in a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Journal Editors (ICMJE) criteria, and be based on:

- substantial contributions to: the conception or design of the study, or the acquisition, analysis or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of Actelion, and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to Actelion for review at least 30 days prior to submission for publication or presentation. Upon review, Actelion may provide comments, and may also request alterations and/or

deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

Actelion's Policy on Scientific Publications can be found at:
http://www.actelion.com/documents/corporate/policies-charters/policy-scientific-publications.pdf

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15 APPENDICES

Appendix 1 PORTICO PK substudy

1 STUDY OBJECTIVES

This substudy aims to assess the pharmacokinetics (PK) of macitentan and its metabolite ACT-132577 in patients with portopulmonary hypertension from the PORTICO study.

2 INVESTIGATIONAL PLAN

2.1 Overall study design and plan

This PORTICO PK substudy is a prospective, multicenter, open-label, single-arm study including at least 20 patients that are on steady-state treatment with macitentan in the open-label period of the AC-055-404/PORTICO study. The substudy will be conducted in consenting patients from all centers who agree to participate and in all regions.

The study will consist of the following periods:

- Screening period:

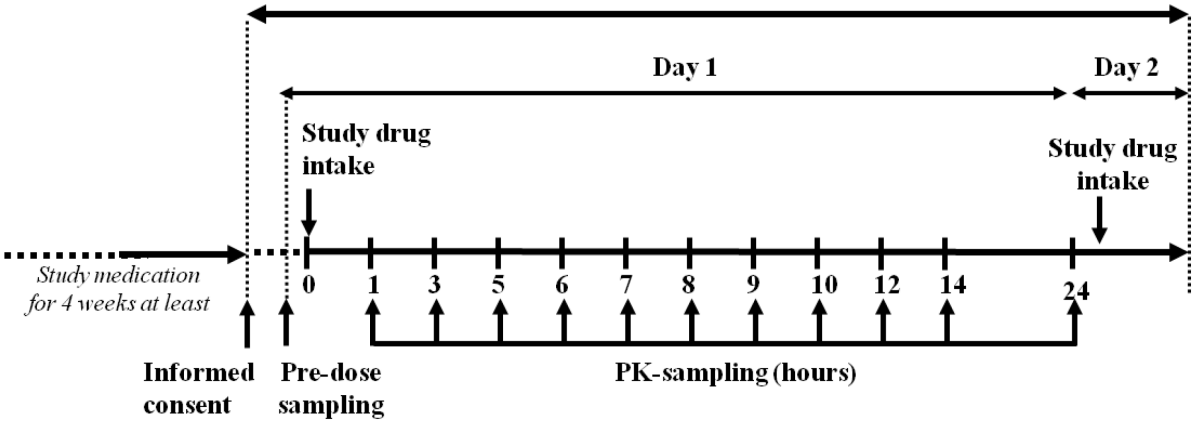
A Screening visit will be scheduled within 28 days before enrollment into the PK substudy. At this visit the study will be discussed with the patient and the Informed Consent Form will be signed.

- PK assessments period:

PK assessments will be performed after open-label study treatment for the AC-055-404/PORTICO study has been taken for at least 4 weeks. The substudy may be performed on or at any time between the scheduled Visit 6 and Visit 7 of the OL treatment period. The PORTICO PK substudy will consist of two visits (Day 1 and Day 2). On the first study day of the PORTICO PK substudy (Day 1), eligibility will be checked before start of assessments. Following the check, a pre-dose blood sample will be drawn (preferably before 10.00 am).

On Day 1, the study treatment, one 10 mg tablet of macitentan, will be taken directly after the morning pre-dose blood sample. Following this, the patient will be considered enrolled into the PORTICO PK substudy. Blood samples for PK will then be drawn at specified time points after study treatment administration over a 24-hour time period as presented in Figure 2. In order to ensure timely blood sampling, patients may be offered an overnight stay at the clinic or sampling may be performed local to the patient's home. The last PK blood sample will be drawn 24 hours after study treatment intake on Day 1. Study treatment intake on Day 2 must only occur after this last blood draw, which concludes the PORTICO PK substudy.

Figure 2 PK substudy design



2.2 Study population

2.2.1 Patient population

The patient population will consist of patients who are participating in the open-label period of the AC-055-404/PORTICO study and have received the open-label study treatment (10 mg of macitentan, once daily oral dose) for at least 4 weeks.

2.2.2 Inclusion criteria

- Signed Informed Consent Form prior to initiation of any study-mandated procedure.
- Patients participating in the open-label period of the AC-055-404/PORTICO study and having received the open-label study treatment for at least 4 weeks.
- Pre-dose PK blood sampling done prior to study medication on Day 1.

2.2.3 Exclusion criteria

- Clinical instability during the week prior to enrollment into the substudy.
- Ongoing renal failure or dialysis.
- Arm veins unsuitable for i.v. puncture.

2.2.4 Concomitant medications

All other concomitant medications are allowed, but must be kept stable for at least one week prior to enrollment on Day 1 and during the 24 hours of PK sampling.

2.2.4.1 Prohibited concomitant medications

All prohibited concomitant medications are listed in Section 5.2.4 of the AC-055-404/PORTICO study protocol.

2.3 Study treatment

The study treatment is macitentan, 10 mg provided for the AC-055-404/PORTICO study.

2.3.1 Treatment dose and administration

Patients can only be enrolled if the study treatment for the AC-055-404/PORTICO study was continuously taken for at least 4 weeks during the open-label period. On Day 1 of the PORTICO PK substudy, the study treatment will be taken directly after the pre-dose blood sample. On Day 2 study treatment will be taken after the last (24 h) PK blood sample was drawn. If the study treatment intake during the PK sampling days is performed at the clinic, patients must bring at least two tablets when visiting the site on Day 1. The study treatment intake on Day 1 and Day 2 must be observed by the investigator / study coordinator / phlebotomist and the date and exact times will be recorded in the electronic Case Report Form (eCRF).

2.3.2 Pharmacokinetic and pharmacodynamic endpoints

Plasma PK variables of ACT-132577 and metabolites will be derived by noncompartmental analysis of the plasma concentration-time profiles.

PK endpoints for both macitentan and ACT-132577:

- The area under the plasma concentration-time curve during one dosing interval (AUC_τ).
- Maximum plasma concentration (C_{max}) during a dosing interval.
- The time to reach maximum plasma concentration (t_{max}) during a dosing interval.

2.3.2.1 Calculation of PK endpoints and assumptions

The PK endpoints will be derived as follows:

- The measured individual plasma concentrations of macitentan and its metabolite, ACT-132577 will be used to directly obtain C_{max} and t_{max}.
- AUC_τ will be calculated according to the linear trapezoidal rule using the measured concentration-time values above the limit of quantification (LOQ) during one dosing interval.
- The PK variables will be calculated on the basis of the real (actual) blood sampling time points.

All areas under plasma concentration-time curves (AUC) and C_{max} values are assumed to be log-normally distributed. Depending on the data obtained compartmental models may be used.

2.4 Study assessments

2.4.1 Pharmacokinetic and pharmacodynamic assessments

2.4.1.1 Timing for sampling

If applicable, patients should arrive at the clinic on Day 1 so that the pre-dose sample can be drawn before 10.00 a.m.

For the PK assessment the blood samples must be drawn at the following time points:

Day 1: Immediately before administration of the dose of study treatment in the morning (pre-dose) and 1 h, 3 h, 5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 12 h, and 14 h post-dose.

Day 2: 24 h post-dose.

2.4.1.2 Procedures for sampling

Approximately 2 mL of blood will be collected in tubes containing ethylene diamine K3 tetra-acetic acid via an i.v. catheter placed in an antecubital vein in the arm. The indwelling catheter will be kept patent (e.g. by insertion of a mandrin), which will be changed after each blood sampling. Immediately following collection of the required blood volume, the tubes will be slowly tilted backwards and forwards (no shaking) to bring the anti-coagulant into solution, and immediately cooled on ice.

Within 30 minutes of collection, the tubes will be centrifuged at approximately 1500 × g for 10 minutes at 2–8 °C. When a centrifuge that can be cooled is not available, the blood samples and the bucket of the centrifuge must be cooled on ice prior to centrifugation. Following centrifugation, the plasma will be transferred into one labeled polypropylene tube. All samples will be stored in an upright position at −20 °C. The date and exact actual clock time of each blood sample draw will be entered into the eCRF.

2.4.1.3 Labeling

The tubes and labels for the samples will be provided to the investigator and/or site staff. The labeling will comply with the applicable laws and regulations of the countries in which this substudy is conducted.

2.4.1.4 Bioanalysis

The concentrations of macitentan and its metabolite ACT-132577 in plasma will be determined using a validated liquid chromatography coupled to mass spectrometry method. The foreseen LOQ in plasma for macitentan and ACT-132577 is 1 ng/mL. The concentrations will be calculated by interpolation from the calibration curve. Quality control samples will be analyzed throughout the study. Their measured concentrations will be used to determine between-run and overall precision and accuracy of the analysis.

2.4.1.5 Shipping procedures

The investigator and/or site staff are responsible for shipment of the samples. Samples must be sent from the site to the central laboratory [redacted] using an appropriate courier service at time intervals specified in laboratory guidelines. The central laboratory will organize the shipment of PK plasma samples to [redacted] at Actelion Pharmaceuticals Ltd [redacted] at time intervals agreed with the sponsor. The plasma samples must be temperature controlled, tracked and packed securely with the completed shipment forms in polystyrene-insulated shipping containers together with enough dry ice to last for 48 hours.

2.4.1.6 Total blood volume

The total blood volume to be taken for the PK assessments will be approximately 12 × 2 mL = 24 mL

2.5 Assessment schedule

Figure 2 provides an overview of the chronological sequence of the assessments.

3 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

For a detailed description of the safety definitions and reporting requirements, refer to Section 10 of the AC-055-404/PORTICO protocol.

All AEs occurring from screening period to the 24-hour time point (Day 2) will be reported as AEs in the AC-055-404/PORTICO CRF and will be analyzed and reported in the context of the AC-055-404/PORTICO study.

4 STATISTICAL METHODOLOGY AND ANALYSES

4.1 Statistical Analysis Plan

A SAP will be written and finalized before database closure. The SAP will provide full details of the analyses (including PK), data displays, and algorithms to be used for data derivations.

The SAP will include the definition of major and minor protocol deviations and the link between major protocol deviations and the analysis sets.

Major and minor protocol deviations will be identified by medically trained staff before study closure.

4.2 Analysis sets

The PK analysis will be performed on the PK set.

This analysis set comprises all patients who did not deviate from the protocol in a way that might affect the evaluation of the PK endpoints.

4.3 Pharmacokinetic analysis

4.3.1 Pharmacokinetic statistical analysis and endpoint display

Individual plasma concentration-time data will be listed by patient. The individual and mean plasma concentration-time profiles will be plotted on a linear scale.

The derived PK variables for macitentan and ACT-132577 (AUC_{τ}, C_{max}, and t_{max}) will be listed by patient.

For mean value calculations, all values below the LOQ (below the limit of quantification [BLQ] values) will be set to zero if ≤ 50% of the values at a given time point are BLQ. If > 50% of the values at a given time point are BLQ, no mean value will be calculated. Mean concentration-time profiles will be generated using these criteria.

Plasma concentrations per time point will be summarized using arithmetic mean, minimum, median, maximum, standard deviation (SD), standard error (SE), and two-sided 95% confidence interval of the mean.

AUC_{τ}, C_{max}, t_{max} * will be summarized with arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, CVb in %, and 95% confidence interval of the arithmetic and geometric means.

(* For t_{max} the geometric mean and its 95% confidence interval will not be calculated).

Appendix 2 Child-Pugh, MELD, and hepatic encephalopathy scales in classification of liver disease

1) Child-Pugh Classification

The Child-Pugh classification will be used for assessing the severity of the liver disease according to the following criteria:

Score	Bilirubin (mg/dL)	Albumin (g/dL)	Prothrombin time (sec prolonged)	Ascites (grade)	Encephalopathy (grade)
1	< 2	> 3.5	< 4	Absent	None
2	2–3	2.8–3.5	4–6	Slight	1–2
3	> 3	< 2.8	> 6	Moderate	3–4

Child-Pugh class: A (mild): 5–6; B (moderate): 7–9; C (severe): ≥ 10

2) MELD Score

The MELD score is calculated using the following formula:
MELD Score = 0.957 × Loge(creatinine mg/dL) + 0.378 × Loge(bilirubin mg/dL) + 1.120 × Loge(INR) + 0.6431
Multiply the score by 10 and round to the nearest whole number.

- Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD score calculation. The maximum serum creatinine considered within the MELD score equation is 4.0 mg/dL.
- If subject had dialysis twice within a week prior to the serum creatinine test then the MELD score will be calculated with a serum creatinine value of 4.0 mg/dL.

3) Hepatic encephalopathy grades are defined in the table below.

Grade 0	Normal consciousness, personality, neurological examination, electroencephalogram
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4	Unrousable coma, no personality/behavior, decerebrated, slow 2–3 cps delta activity

Appendix 3 Actelion guidelines for 6MWT

The American Thoracic Society (ATS) published an official statement on the 6-minute walk test (6MWT) in 2002 [ATS Statement 2002]. Only a brief summary of these guidelines is included here.

- The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The use of treadmill is forbidden.
- The walking distance used for the test should be 30 meters (100 feet) in length. This distance should be marked every 3 meters (10 feet). The turnaround point should be marked with a cone. A starting line, which marks the beginning and the end of each 60-meter lap, should be marked on the floor using brightly colored tape. Any deviation from this should be approved in written form by Actelion before implementation.
- The study staff member administering the 6MWT should stand near the starting line during the test and must not walk with the patient! Intermittent rest periods are allowed if the patient can no longer continue. If the patient needs to rest, he/she may pause, lean against the wall or sit and should continue walking whenever he/she feels able. The timer must continue to run. The test can be stopped at any moment in case the patient complains of having chest pain, intolerable dyspnea, leg cramps, or has a pale or ashen appearance.
- The 6MWT is a non-encouraged test. No instructions or encouragement will be given during the test. Eye contact and body language signaling the patient to speed up should be avoided during the test.
- For an individual patient, repeat testing should always be conducted, if possible, by the same tester, at the same location, and preferably at about the same time of the day to minimize variability.

Required equipment:

- Countdown timer (or stop watch)
- Mechanical lap counter
- Two small cones for the turnaround points
- A chair that can be easily moved along the walking course
- Worksheets on a clipboard
- Sphygmomanometer
- Automated electronic defibrillator
- Source of oxygen

Patient preparation

- The patient should wear comfortable clothing and appropriate walking shoes.
- The meals preceding the test should be light, and the patient should not have exercised vigorously within 2 hours of beginning the test.
- The patient should sit at rest for at least 10 minutes before the test starts.
- Patients should receive their usual medication on the day of the test. If the patient is used to taking bronchodilators before a walk, he/she should take them 5–30 minutes before the test.
- For patients receiving continuous 24-hour oxygen therapy, it is recommended that the flow rate remains constant for the duration of the study. However, from one hour prior to and until the completion of the 6MWT, the flow rate must remain constant.

Measurement of the 6MWD/6MWT – Instructions to the patient

The person administering the test will use the following exact dialogue with the patient: "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able to. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation".

(The tester demonstrates the walking and pivots around a cone briskly).

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. I will tell you when 2 minutes, 4 minutes have elapsed. Keep walking when I talk." After these instructions are given to the patient, the person administering the test will then ask:

"Do you have any questions about the test?"

"Please explain what you are going to do."

"Are you ready?"

"Start now, or whenever you are ready."

As soon as the patient starts to walk, the tester will start the timer and write down start time.

The tester will tell the patient the time elapsed by saying:

“You have 4 minutes to go.”

“You have 2 minutes to go.”

When the timer is 15 seconds from completion, the tester says:

“In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you”.

When the timer alarm rings the tester says:

“Stop!”

The tester walks over to the patient, marks the spot where the patient stopped, records the total distance walked in the worksheet and congratulates the patient on good effort.

Appendix 4 Borg dyspnea index

Borg rating	Perceived exertion
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

Appendix 5 WHO functional classification of pulmonary hypertension

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

Appendix 6 Laboratory abnormalities

Laboratory abnormalities according to the most updated version of CTCAE. A marked abnormality is defined based on the following list (SI units).

Parameter	LL	LLL	HH	HHH	HHHH
Hemoglobin (g/L)	< 100	< 80	Increase in (> 20 g/L above ULN) or above baseline if baseline is above ULN	Increase in (> 40 g/L above ULN) or above baseline if baseline is above ULN	
Hematocrit	< 28% for females < 32% for males	< 20%	> 60% in men > 55% in women	> 65%	
Platelet count (10^9 /L)	< 75	< 25	> 600	> 999	
Leucocytes (× 10^9 /L)	< 3.0	< 2.0	> 20.0	> 100.0	
Neutrophils (10^9 /L)	< 1.5	< 1.0	NA	NA	
Eosinophils			> 5.0 × 10e9 or > 5%	NA	
Lymphocyte (10^9 /L)	< 0.8	< 0.5	> 4.0	> 20.0	
AST (U/L)	NA	NA	≥ 3 × ULN	≥ 5 × ULN	≥ 8 × ULN
ALT (U/L)	NA	NA	≥ 3 × ULN	≥ 5 × ULN	≥ 8 × ULN
AP	NA	NA	≥ 2.5 × ULN	≥ 5 × ULN	
Total bilirubin (umol/L)	NA	NA	≥ 2.5 × ULN	≥ 5 × ULN	

Parameter	LL	LLL	HH	HHH	HHHH
INR			≥ 1.5 × ULN or > 1.5 times above baseline if on anticoagulation	≥ 2.5 × ULN or > 2.5 times above baseline if on anticoagulation	
Creatinine (umol/L)	NA	NA	≥ 1.5 × ULN or 1.5 × baseline	≥ 3 × ULN or > 3 × baseline	
Glucose (mmol / L)	< 3.0	< 2.2	> 8.9	> 13.9	
Calcium (mmol/L)	< 2.0	< 1.75	> 2.9	> 3.1	
Sodium (mmol/L)		< 130	> 150	> 155	
Potassium (mmol/L)	< 3.2	< 3.0	> 5.5	> 6.0	
Magnesium (mmol/L)	< 0.5	< 0.4	-	> 1.23	
Uric acid (mmol/L)	-	-	> 0.59	> 0.72	
Albumin (g/L)	< 30	< 20	-	-	
BUN	-	-	≥ 2.5 × ULN	≥ 5 × ULN	

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CTCAE = common terminology criteria for adverse events; LL / HH = marked abnormalities; LLL / HHH / HHHH = alert values; INR = international normalized ratio; NA = not applicable; SI = international system of unit; ULN = upper limit of the normal range.

Appendix 7 Central laboratory alert flags

On top of the flags described below, at a minimum, results above the upper limit or below the lower limit of the reference range for normal subjects will be flagged.

- **Exclusionary Alert Value - At Screening (V1):** The result is outside the study specific defined limit for inclusion in the study.
  - Hemoglobin < 100 g/L
  - AST ≥ 3 × ULN
  - ALT ≥ 3 × ULN
  - Bilirubin ≥ 3 mg/dL
  - Serum pregnancy test positive
- **Total Bilirubin flag Alert Value - All visits except screening (V1):**
  In combination with ALT and/or AST ≥ 3 × ULN
  - Total bilirubin ≥ 2 × ULN

Dependent on previous total bilirubin assessment, stopping study treatment should be considered (i.e., worsening).

- **Interruption or permanent discontinuation of study treatment - All visits except screening (V1):**

Please refer to the study protocol; study treatment must be interrupted [see protocol Section 5.1.11]:

- Asymptomatic increase ALT and/or AST ≥ 3 and < 8 × ULN

Study treatment must be permanently stopped in case of:

- Aminotransferases ≥ 8 × ULN
- Aminotransferases ≥ 3 × ULN and associated with new or worsening clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu like syndrome (arthralgia, myalgia, fever)
- Aminotransferases ≥ 3 × ULN and associated with total bilirubin ≥ 2 × ULN and increased as compared to baseline
- Serum pregnancy test positive
- Hemoglobin < 80 g/L
- Hemoglobin > 50 g/L decrease from baseline

- **Repeat Alert value - All visits after randomization (V2):**
  Repeat testing is needed:
  - AST ≥ 3 × ULN
  - ALT ≥ 3 × ULN
  - Hemoglobin > 20 g/L decrease from baseline

Appendix 8 List of protocol amendments

Document Date	Amendment	Changes
15 JAN 2015	Amendment 1, resulting in Global Protocol Version 2	• Visit window was changed to ± 4 days from ± 7 days to ensure patients had enough study treatment until the next visit. • Reference to hepatic event questionnaire was removed as this form was removed from the eCRF • Daclatasvir was added as permitted Hepatitis C medication following its approval • Analysis of urea was removed as it was not needed in addition to blood urea nitrogen. • NT-proBNP storage/shipping text was further clarified • It was clarified that laboratory assessments to be used for eligibility assessment were those performed at Visit 1 / Screening (not Visit 2 / Randomization). • A urine dipstick pregnancy test was added to the assessments at Visit 2 / Randomization in order to have the result prior to treatment assignment. • It was clarified that HVC was not mandatory • It was clarified that PAH or PoPH medications stopped within 3 months prior to randomization were required to be documented in the eCRF.
9 JUN 2015	Local Amendment, resulting in Local protocol version 2.FRA.A	• An OLE period was added to the study in order to ensure that patients continued receiving study treatment after study completion (i.e., including the OL period)
5 AUG 2015	Local Amendment resulting in Local protocol version 2.GBR.A	• Inclusion was restricted to WHO FC III–IV, in order to enroll only patients for whom the local commissioning guidelines would permit continued macitentan treatment after study completion.
21 APR 2016	Amendment 2, resulting in Global Protocol Version 3 and Local protocol version 3.GBR.A	• It was clarified that local laboratory assessments were allowed in order to simplify eligibility assessment and implementation of the stopping rule (i.e., for calculating MELD score and/or Child-Pugh classification) at Week 12. It was further clarified that the central laboratory kit was required to be used in parallel to the use of local laboratory assessments. • It was clarified that study treatment was allowed to be continued in case of OLT during the OL period of the

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		study, based on medical consideration. • It was allowed to perform the PK substudy closer to the patient's home to ease participation • Certain eligibility criteria were modified based on medical considerations, e.g., exclusion criterion 15: transplant expected within 3 months removed; exclusion 21: CCBs moved to exclusion 20; beta blockers moved to exclusion 10) • The list of allowed and forbidden medications was updated with newly approved antiviral medications • It was clarified that screening started on the day of ICF signature • The definition of the Full Analysis Set was modified to include patients for whom post-baseline PVR was imputed.
21 APR 2016	Local Amendment, resulting in Local protocol version 3.FRA.B	• It was also allowed to perform the PK substudy during the OLE as the requirement to have been on OL treatment for 4 weeks is met during the OLE.

CCB = calcium channel blocker; eCRF = electronic Case Report Form; FC = functional class; HVC = hepatic vein catheterization; ICF = informed consent form; MELD = Model for End-Stage Liver Disease; NT-proBNP = N-terminal pro-brain natriuretic peptide; OL = open-label; OLE = open-label extension; OLT = orthotopic liver transplantation; PAH = pulmonary arterial hypertension; PoPH = portopulmonary hypertension; PK = pharmacokinetic; PVR = pulmonary vascular resistance; WHO = World Health Organization.