Efficacy and safety of riociguat (MK-4836) in incipient pulmonary vascular disease as an indicator for early pulmonary arterial hypertension
Double-blind, randomized, multicenter, multinational, placebo-controlled phase IIa study

Clinical Trial Code: ESRA

EudraCT No.: 2021-001633-40

EU CT No.: 2023-509695-42-00

NCT Number: NCT05339087

Version: 1.7; 15.01.2025

CLINICAL STUDY PROTOCOL

Efficacy and safety of riociguat (MK-4836) in incipient pulmonary vascular disease as an indicator for early pulmonary arterial hypertension

Double-blind, randomized, multicenter, multinational, placebo-controlled phase IIa study

ESRA

Local Project ID: 2020-01RCT

Supplier's Protocol No. (MSD): MK-4836-004

Clinical Trial Code:	*ESRA*
EudraCT No.:	2021-001633-40
EU CT No.:	2023-509695-42-00
Clinical Phase:	IIa
Version:	1.7; 15.01.2025

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1 Clinical study protocol synopsis

Protocol title:	Efficacy and safety of riociguat (MK-4836) in incipient pulmonary vascular disease as an indicator for early pulmonary arterial hypertension Double-blind, randomized, multicenter, multinational, placebo-controlled phase IIa study
Acronym	ESRA
Phase:	Phase IIa
Regulatory obligations:	Pharmaceutical study under the applicable Pharmaceutical Drug Law; requires IRB approval / EC vote.
Study location:	Coordinating center: Heidelberg, Germany Other centers: London, Zurich, Graz, Linz, Lille, Naples, Dresden
No. of study sites:	8
Principal investigator:	Prof. Dr. Ekkehard Grünig Thoraxklinik Heidelberg gGmbH at Heidelberg University Hospital Center for pulmonary hypertension Röntgenstraße 1 69126 Heidelber , German Phon [redacted] Fax: [redacted] Mail: [redacted]
Study type:	Randomized, controlled, clinical trial
Study design:	Investigator-Initiated-Trial (IIT) This is a randomized (1:1), double-blind, placebo-controlled, multicenter, multinational study investigating the effect of riociguat (MK-4836) in patients with early pulmonary vascular disease, defined as either a) mean pulmonary arterial pressure (mPAP) ≥25 mmHg with pulmonary vascular resistance (PVR) ≥2 to <3 WU and pulmonary arterial wedge pressure (PAWP) ≤15 mmHg or b) mPAP 21-<25 mmHg with PVR ≥2 WU, and PAWP ≤15 mmHg associated with connective tissue disease (CTD) or as idiopathic/heritable form. Patients in group b will likely represent the greatest proportion of trial participants based on epidemiological data and trial objectives.

The primary efficacy endpoint in this study is the change in PVR from baseline to 24 weeks.

Patients who stop the study or discontinue medication prematurely will be asked to continue with the study and participate in study assessments and visits until the last follow-up as per protocol. Subjects will be taking three doses daily with each dose taken 6 to 8 hours apart. In the case of side effects (e.g. symptomatic hypotension), down-titration by 0.5 mg three times daily (tid) is allowed.

Interventions

After the pre-treatment phase, eligible subjects will be randomized at Visit 1 in a 1:1 ratio to the following 2 treatment groups:

- riociguat (MK-4836) 1.0-2.5 mg group (titration between 1.0 mg and 2.5 mg tid according to individual tolerability)

- placebo group (placebo tid, sham-titration according to individual tolerability).

Estimated Study duration

The study consists of a pre-treatment phase of up to 28 days followed by a 24-week treatment phase. The treatment phase is divided into an 8-week titration phase, followed by a 16-week main study phase

Background

Chronic pulmonary arterial hypertension (PAH) is associated with impaired exercise capacity, quality of life (QoL) and right ventricular function.(Galiè et al. 2016) The disease is characterized by an increase of pulmonary vascular resistance (PVR) and pulmonary arterial pressure, leading to right heart insufficiency.(Galiè et al. 2016, Grünig et al. 2010) Riociguat is a soluble guanylate cyclase stimulator and the first drug that has been approved for the treatment of both PAH and chronic thromboembolic pulmonary hypertension (CTEPH).(Ghofrani et al. 2013) The 12-week PATENT-1 study showed a significant improvement of the primary endpoint 6-minute walking distance (6MWD) and of secondary endpoints such as PVR, N-terminal pro brain natriuretic peptide (NT-proBNP) levels, World Health Organization functional class (WHO-FC), time to clinical worsening and Borg dyspnea score.(Ghofrani et al. 2013) An exploratory analysis of the first 12 weeks of the long-term extension study (PATENT-2) showed further significant improvement of 6MWD in the 215 PAH-patients receiving up to 2.5 mg of riociguat three times daily (tid).(Rubin et al. 2015) In CTEPH-patients the 12-week CHEST-1 study revealed a statistically significant improvement of 6MWD (primary end-point) and in PVR, NT-proBNP serum values, and in WHO-FC (secondary endpoints).(Ghofrani et al. 2013) Further studies investigating the effect of riociguat in an uncontrolled design were the early access study (EAS) in patients with CTEPH (McLaughlin et al.

2017) and PATENT plus in PAH.(Galiè et al. 2015) Recently, two retrospective studies of patients who participated in the phase III studies PATENT, CHEST, PATENT plus as well as the Phase II study and early access study in German centers have shown that riociguat treatment (1.0-2.5 mg tid) was associated with a significant reduction of right ventricular (RV) and right atrial (RA) area after 3, 6 and 12 months compared to baseline.(Marra et al. 2015, Marra et al. 2018) RA area significantly decreased after 12 months and RV systolic function assessed with tricuspid annular plane systolic excursion (TAPSE) improved during riociguat therapy.(Marra et al. 2015, Marra et al. 2018)
Early diagnosis of systemic sclerosis associated PAH (SSc-APAH) is of utmost importance, since it leads to significant improvement of survival rates through the implementation of PAH-targeted therapies.(Humbert et al. 2011)

In order to enhance early diagnosis of patients with pulmonary vascular disease, a new hemodynamic definition of PAH was proposed at the 6th World Symposium of PH (Simonneau et al. 2019), which lowered the cut-off for mPAP from ≥25 mmHg (as stated in the actual PH guidelines, Galiè et al. 2016) to >20 mmHg in combination with pulmonary arterial wedge pressure (PAWP) ≤15mmHg and PVR ≥3 Wood Units (WU). The change in the hemodynamic definition of pre-capillary PH represents a step towards the upper limit of physiological hemodynamic thresholds as shown in a systemic review of Kovacs et al. (Kovacs et al. 2009) including 1187 healthy subjects presenting with an upper limit of normal for mPAP of 20.6 mmHg (mean + 2 standard deviations). Subsequent studies performed mainly in SSc patients reported that patients with mildly elevated mPAP (21-24 mmHg) had reduced exercise capacity, impaired QoL, decreased RV output reserve, abnormal pulmonary arterial compliance (PAC) and survival.(Valerio et al. 2013, Coghlan et al. 2018, Nagel et al. 2019) Recent data from cohorts in a US-PH-center (Jaafar et al. 2019), and from SSc-patients cohorts in Zurich and Heidelberg (Xanthouli et al. 2020) have shown that the new PAH definition will most likely prevent an early PAH-diagnosis due to a too highly chosen threshold for PVR ≥3 WU.(Jaafar et al. 2019, Xanthouli et al. 2020) Patients with PVR ≥ 2 WU already had an early pulmonary vascular disease with reduced 6MWD, right heart function, PAC and survival.(Xanthouli et al. 2020) Data on early treatment of patients with early PAH with mildly elevated pulmonary arterial pressures is still scarce.

A recent double-blind-randomized controlled trial (EDITA) testing the effect of ambrisentan, an endothelin receptor antagonist, on mean pulmonary arterial pressure (primary endpoint) among SSc-patients with mildly elevated mPAP and/or exercise PH, without significant left heart or lung disease, failed to change the primary endpoint, however, showed

an improvement of PVR as secondary endpoint (Pan et al. 2019), which may be of prognostic relevance in this patient cohort. Further research in this field is needed.

As PVR has a prognostic significance among patients with SSc-APAH, may be an indicator of early pulmonary vascular disease and previous studies proved the positive effects of riociguat on right heart size and PVR (secondary endpoint in phase III studies), PVR was chosen as primary endpoint of the current study.

The aim of this study is to investigate the effect of riociguat (MK-4836) on PVR, clinical parameters, safety and tolerability in patients with early pulmonary vascular disease.

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with systemic sclerosis: the impact of the new definition of pulmonary arterial hypertension. Ann Rheum Dis. 2020;79(3):370-378.

Materials & Supplies

Investigator-Initiated-Trial (IIT)
Riociguat (MK-4836) and placebo will be supplied by MSD SHARP&DOHME GmbH Germany.

Trial population

Adult male and female patients with CTD or idiopathic/heritable early pulmonary vascular disease.

Both an elevated mean pulmonary arterial pressure >20 mmHg and an increase of PVR >2 WU have been shown to be above the upper limit of normal and are associated with development of manifest PAH and impaired survival in CTD. As a placebo-controlled study would seem unethical in patients, who are in clear indication of targeted treatment, patients with manifest PAH according to the current definition may not be included in this study (combination of both mPAP ≥25 mmHg and PVR ≥3 WU and PAWP ≤15 mmHg).

Patients with early pulmonary vascular disease, indicated by either
a) mPAP ≥25 mmHg with PVR ≥2 to <3 WU and PAWP ≤15 mmHg or
b) mPAP 21-<25 mmHg with PVR ≥2 WU and PAWP ≤15 mmHg (see Group I / Nice Clinical Classification of Pulmonary Hypertension) (acc. to Simonneau et al. 2019) may therefore be included into this study.
Both a) and b) represent one phenotype with early pulmonary vascular disease/pathology. Patients in group b will be mainly enrolled as long as patients in group a are not defined as having pulmonary arterial hypertension according to European pulmonary hypertension guidelines.

Aims and Objectives

The aim of this 24 weeks randomized, controlled study is to investigate the effect of riociguat (MK-4836) treatment on hemodynamics, clinical parameters, safety and tolerability in patients with early pulmonary vascular disease, defined as stated above.

Primary objective

1) To investigate the effect of riociguat (MK-4836) treatment on pulmonary vascular resistance, defined as change from baseline to 24 weeks of treatment.

Secondary objectives

2) To investigate, whether treatment with riociguat (MK-4836) may improve further hemodynamic and clinical parameters, defined as change from baseline to 24 weeks of treatment.
3) To assess safety and tolerability of riociguat (MK-4836) treatment

Investigational Medicinal Product(s) (IMPs)	**IMP: Test treatment** Riociguat (MK-4836): 1 mg, 1.5 mg, 2 mg and 2.5 mg tid will start at 1.0 mg tid in the beginning of the study. Dosage will be individually up-titrated up to a maximum dosage of 2.5mg tid after 8 weeks according to systemic blood pressure, the physician's and the patient's estimation. Study medication will be taken orally with or without food. Subjects will be taking three doses daily with each dose taken 6 to 8 hours apart. In the case of side effects (e.g. symptomatic hypotension), down-titration by 0.5 mg tid is allowed. **IMP: Placebo** Placebo tablets with the same treatment regimen (tid) as the verum therapy will be provided. Treatment effect will be controlled at each study visit and the sham dose will be adapted.
Sample size	N= 70 (35 patients randomized in each group) If the true treatment effect is at least a 30±34.5% reduction of PVR (effect size is 0.87), a sample size of 29 patients/group (total 58 patients) achieves a statistical power of 90.2% to reject the null hypothesis, according to the two-sample student's t-test, with a type I error of 0.05 (two-sided). With the sample size of 70 patients and a dropout of 15% (valid sample size n=58), we achieve a 90.2% power, if the means of PVR differ by at least 30% and both groups have an equal standard deviation of 34.5%. A sample of 70 patients (35 patients in each group), allocated in a 1:1 ratio, will therefore be included. The primary endpoint will be analyzed by an analysis of covariance (ANCOVA) with baseline values as covariates, which has a power advantage over the student's t-test, achieving a statistical power of 90.2% or more. If the preconditions for ANCOVA are not met, a student's t-test assuming unequal variances (Welch-test) will be performed.

Statistical methods	Data will be pseudonymized and checked for plausibility. After database closure, data will be analyzed. All data will be listed and trial summary tables will be provided with means, medians, variances and respective confidence intervals and with frequency tables. Baseline parameters will be described and compared between study arms and study centers. The primary endpoint, change of PVR, will be compared by ANCOVA of the differences (baseline value to 24 weeks) between the two groups with the baseline value as covariate. Data will be primarily analyzed in the modified intention-to-treat analysis set. As sensitivity analysis, multiple imputation will be performed and analyzed for the primary endpoint. Secondary and exploratory parameters at baseline and during follow-up will be compared between groups comparing the difference between baseline and follow-up visits. Data will be displayed by means and standard deviations, medians and variances with respective 95% confidence intervals.
Indication	Clinical phenotype patients with early pulmonary vascular disease, indicated by either a) mPAP ≥25 mmHg with PVR ≥2 to <3 WU and PAWP ≤15 mmHg or b) mPAP 21-<25 mmHg with PVR ≥2 WU and PAWP ≤15 mmHg. I27.0 Primary pulmonary hypertension (PAH) M34.- Systemic sclerosis M35.- Other systemic involvement of connective tissue MedDRA (V. 12.0) Systemic Sclerosis ID 10042953, Level 4 Connective tissue disorders (excl. congenital) ID 10010761, Level 4 Pulmonary Hypertension ID 10037400, Level 4
Efficacy and safety variables	**Efficacy Variables** **The primary efficacy variable** is the change of PVR from baseline to 24 weeks. **Secondary efficacy endpoints** will be tested hierarchically: • change of cardiac index at rest (baseline to 24 weeks) • change of total pulmonary resistance (baseline to 24 weeks) • change of diffusion capacity of the lung (baseline to 24 weeks) Exercise capacity • change of 6-minute walking distance (baseline to 24 weeks)

Symptoms and quality of life

- change of WHO functional class (baseline to 24 weeks)
- change in QoL (SF-36, physical summation score; baseline value to 24 weeks)

The following parameters will be assessed in every patient according to the visits schedule and analyzed as **exploratory variables**. Exploratory endpoints will be analyzed as change from baseline to 12 and 24 weeks as available per assessment schedule.

QoL assessed by the SF-36 questionnaire

- mental summation score as well as the 8 sub scores

WHO functional class

Lung function and lung diffusing capacity

- FEV1 (forced expiratory volume in 1 second), TLC (total lung capacity), DLCO (diffusing capacity of the lung)

Echocardiography

- systolic pulmonary arterial pressure (sPAP, mmHg), right ventricular area (RV-area, cm^2), and right atrial area (RA-area, cm^2), tricuspid annular plane systolic excursion (TAPSE), left ventricular eccentricity index (LV-EI), RV-pump function and LV-pump function (LV-EF, %).

Analyses of blood samples
Venous blood will be analyzed to determine:

- NT-pro BNP

Blood for blood gas analyses

- oxygen partial pressure, carbon dioxide partial pressure, oxygen saturation of the blood (SpO_2), pH values, bicarbonates, base excess

Pulmonary hemodynamics by right heart catheterization

- sPAP, mPAP, diastolic pulmonary artery pressure (dPAP), pulmonary artery wedge pressure (PAWP), right atrial pressure (RAP), cardiac output and ejection fraction (CO), central venous saturation, via blood gas analysis from pulmonary artery (SvO_2)

Clinical worsening will be defined as time to first event out of:

- worsening of WHO functional class
- deterioration of 6MWD >15% compared to baseline

- need of initiation of targeted PAH treatment
- hospitalization due to worsening of right heart function
- all cause death or lung-transplantation
- atrial septostomy

Safety variables

Laboratory, electrocardiogram (ECG), vital signs, assessment of adverse events and serious adverse events will serve as safety parameters.

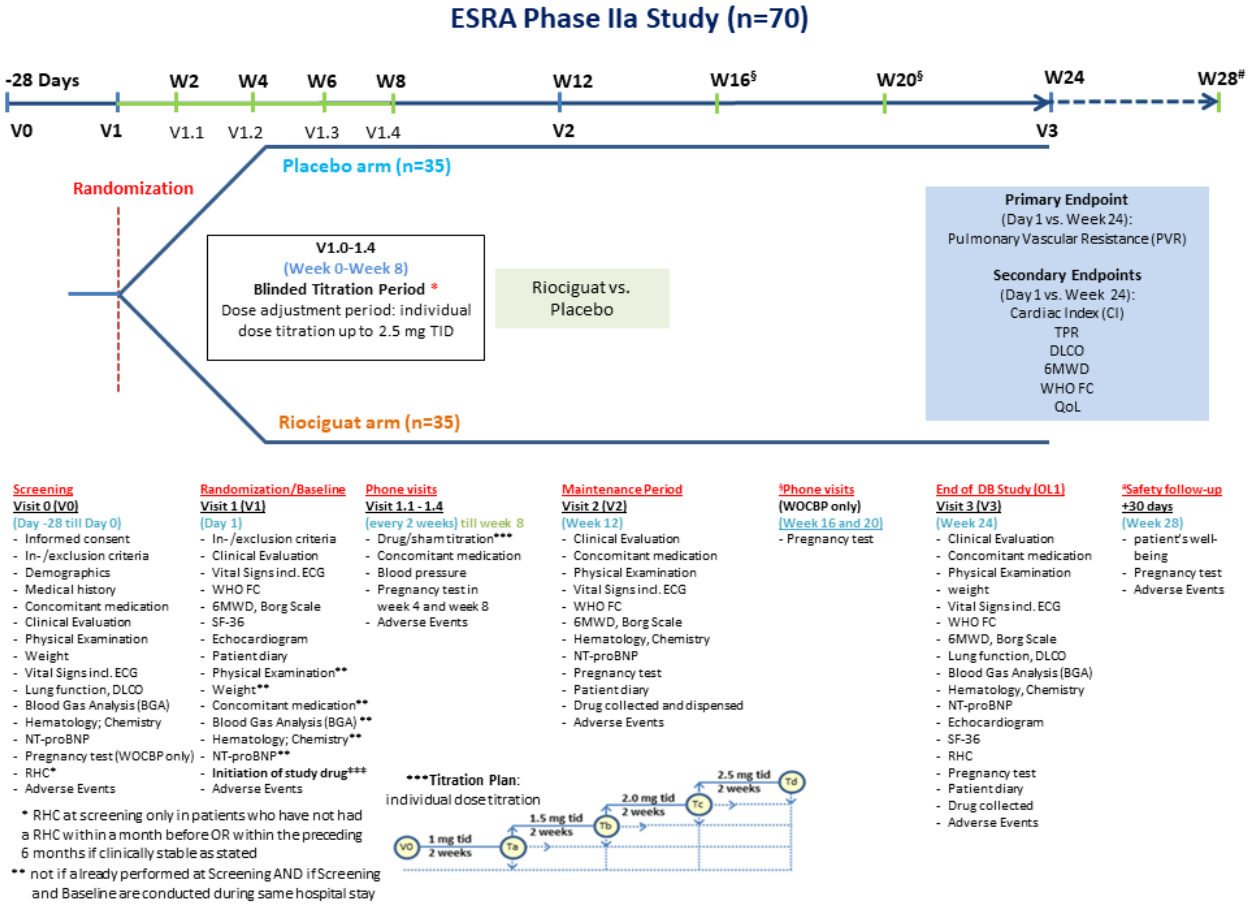
Patients with a serious adverse event occurring during the study treatment will be followed by the study team until the serious adverse event will have resolved to the pre-study level and/or will have been addressed according to best clinical practice. Patients withdrawing from the study prematurely will have a final physical examination.

If a patient withdraws from study treatment and agrees to stay in the study, study related examinations will be performed and data will be obtained according to protocol.

Course of the study	**Screening phase (Day -28 till Day 0):** Eligible patients will be asked to participate upon written informed consent. In case of agreement medical history will be taken and they will undergo screening examinations, according to the table of assessments as described in Section "8.1 Overview of visits and assessments". Right heart catheterization (RHC) at Screening will not be performed in patients with a RHC not older than 1 month at screening or not older than 6 months if the patient had no signs of clinical changes defined as change of 6MWD >10%, WHO-FC change or >30% change in NT-proBNP. RHC must have been measured in the participating center under standardized conditions. **Baseline / Visit 1 (day 1)** Baseline visit will be performed according to the table of assessments as described in Section "8.1 Overview of visits and assessments". Eligibility will be checked again and patients will be randomized. Study drug will be supplied after the patient has received information on titration and study drug intake. **Titration phase / V 1.1 till 1.4 (week 2, 4, 6, 8)** Riociguat (MK-4836) dose will be individually adjusted in accordance with the in-label titration regimen. Dose adjustment will be performed every two weeks by phone taking the systemic blood pressure of the patient, the subjects and physicians' subjective estimation and occurrence of adverse reactions into account. At week 8 the maintenance dose will be established and furtherly continued for the rest of the study. **Interim Visit / Visit 2 (week 12)** At the interim visit in week 12 assessments from screening /baseline will be repeated (except RHC and medical history) as described in Section "8.1 Overview of visits and assessments". Unused study drug will be collected and medication for the remaining 12 weeks at maintenance dose will be supplied. **Termination visit / Visit 3 (week 24)** At this visit in week 24 assessments will be conducted as described in Section "8.1 Overview of visits and assessments". **Follow-up / Visit 4 (30 days after last study drug intake)** Phone call 30±14 days after last study drug intake to assess adverse events and record a final pregnancy test (WOCBP only).
Excluded medication:	Pirfenidon; nintedanib, prednisolone >10 mg/day, PAH specific treatment

Pre-treatment period:	N/A
Duration of observation	Up to 28 days screening period, 24 weeks double-blind, controlled study phase, + 30 days follow-up
Follow-up period	**30 days after week 24 visit** each patient performs a follow-up visit via phone. Clinical follow-up of all SAEs until they have been resolved or improved if possible.
Clinic visits	Double-blind: Screening visit, baseline visit, week 12 and week 24 Additional titration visits every two weeks via phone in the double-blind study phase (week 2, 4, 6, 8), and phone follow-up 30 days after last study drug intake.
Dosing regimen	Individual adjustment during the 8 weeks titration period according to the in-label titration regimen
Route of administration	Oral riociguat (MK-4836) or respective placebo
Endpoints **Primary**	All endpoints will be compared riociguat (MK-4836) vs. placebo: Pulmonary vascular resistance, change from baseline to 24 weeks
Secondary	Endpoints will be analyzed as change / difference • baseline to 24 weeks riociguat (MK-4836) vs. placebo • if available according to visit schedule, exploratory endpoints will also be presented as changes from baseline to 12 weeks. For list of parameters see caption on efficacy and safety variables

Study diagram:



Abbreviations

6MWD	*6-Minute Walking Distance*
AE	*Adverse Event*
ANCOVA	*Analyses of Covariance*
APAH	*Associated Pulmonary Arterial Hypertension*
ATS	*American Thoracic Society*
BGA	*Blood Gas Analysis*
CI	*Cardiac Index*
CO	*Cardiac Output*
CRF	*Case Report Form*
CT	*Computed Tomography*
CTCAE	*Common Terminology Criteria for Adverse Events*
CTEPH	*Chronic thromboembolic pulmonary hypertension*
CV	*Curriculum Vitae*
DBL	*Data Base Lock*
DLCO	*Diffusion limited carbon monoxide*
dPAP	*Diastolic Pulmonary Artery Pressure*

DSUR	*Development Safety Update Report*
EC	*Ethics Committee*
ECG	*Electrocardiogram*
ERS	*European Respiratory Society*
ESC	*European Society of Cardiology*
FEV_1	*Forced expiratory volume in the first second*
FPI	*First Patient In*
FVC	*Forced Vital Capacity*
GCP	*Good Clinical Practice*
HDL	*High Density Lipoprotein*
HIV	*Human Immunodeficiency Virus*
HPAH	*Heritable PAH (Familial PAH)*
ICF	*Informed Consent Form*
ICH	*International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*
IIT	*Investigator Initiated Trial*
IMP	*Investigational Medicinal Product*
INN	*International Nonproprietary Name*
IPAH	*Idiopathic Pulmonary Arterial Hypertension*
IRB	*Institutional Review Board*
ISF	*Investigator Site File*
ISRCTN	*International Standard Randomized Controlled Trial Number*
ITT	*Intention To Treat*
LSI	*Last Subject In*
LSO	*Last Subject Out*
LTOT	*Long-Term Oxygen Therapy*
LV-EI	*Left Ventricular Eccentricity Index*
mPAP	*Mean Pulmonary Artery Pressure*
mRAP	*Mean Right Arterial Pressure*
NCI	*National Cancer Institute*
NT-proBNP	*N-terminal prohormone of brain natriuretic peptide*
NYHA	*New York Heart Association*
O_2	*Oxygen*
PAH	*Pulmonary Arterial Hypertension*
PAP	*Pulmonary Arterial Pressure*
PAWP	*Pulmonary Artery Wedge Pressure*
PH	*Pulmonary Hypertension*
pO2	*Partial Pressure of Oxygen*
PVR	*Pulmonary Vascular Resistance*
QoL	*Quality of Life*
RA(-area)	*Right Atrial (Area)*
RAP	*Right Atrial Pressure*

RHC	*Right Heart Catheterization*
RV	*Residual Volume*
RV(-area)	*Right Ventricular (Area)*
SAE	*Serious Adverse Event*
SpO_2	*Peripheral Oxygen Saturation*
SC	*Steering Committee*
SF-36	*36-Item Short Form Survey as part of the Medical Outcome Study*
SGPT	*Serum Glutamic-Pyruvate Transaminase, also known as ALAT*
SGOT	*Serum Glutamic-Oxaloacetic Transaminase, also known as ASAT*
sPAP	*Systolic Pulmonary Artery Pressure*
SmPC/SPC	*Summary of Product Characteristics*
SSc	*Systemic Sclerosis*
SSc-APAH	*Systemic Sclerosis Associated PAH*
SUSAR	*Suspected Unexpected Serious Adverse Reaction*
SvO_2	*Venous Oxygen Saturation*
TAPSE	*Tricuspid Annular Plane Systolic Excursion*
TLC	*Total Lung Capacity*
USA	*United States of America*
WHO	*World Health Organization*
WHO-FC	*World Health Organization Functional Class*
WOCBP	*Women of childbearing potential*

2 Introduction

2.1 Scientific Background

Chronic pulmonary arterial hypertension (PAH) is associated with impaired exercise capacity, quality of life (QoL) and right ventricular function.(Galiè et al. 2016) The disease is characterized by an increase of pulmonary vascular resistance and pulmonary arterial pressure, leading to right heart insufficiency.(Galiè et al. 2016, Grünig et al. 2010) Riociguat is a soluble guanylate cyclase stimulator and the first drug that has been approved for the treatment of both PAH and chronic thromboembolic pulmonary hypertension (CTEPH).(Ghofrani et al. 2013) The 12-week PATENT-1 study showed a significant improvement of the primary endpoint 6-minute walking distance (6MWD) and of secondary end-points as PVR, N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels, World Health Organization functional class (WHO-FC), time to clinical worsening and Borg dyspnea score.(Ghofrani et al. 2013) An exploratory analysis of the first 12 weeks of the long-term extension study (PATENT-2) showed further significant improvement of 6MWD in the 215 PAH-patients receiving up to 2.5 mg of riociguat three times daily.(Rubin et al. 2015) In CTEPH-patients the 12-week CHEST-1 study revealed a statistically significant improvement of 6MWD (primary end-point) and in PVR, NT-proBNP serum values,

and in WHO-FC (secondary end points).(Ghofrani et al. 2013) Further studies investigating the effect of riociguat in an uncontrolled design were the early access study (EAS) in patients with CTEPH (McLaughlin et al. 2017) and PATENT plus in PAH.(Galiè et al. 2015) Recently, two retrospective studies of patients who participated in the phase III studies PATENT, CHEST, PATENT plus as well as the Phase II study and early access study in German centers have shown that riociguat treatment (1.0-2.5 mg tid) was associated with a significant reduction of right ventricular (RV) and right atrial (RA) area after 3, 6 and 12 months compared to baseline.(Marra et al. 2015, Marra et al. 2018) RA area significantly decreased after 12 months and RV systolic function assessed with tricuspid annular plane systolic excursion (TAPSE) improved during riociguat therapy.(Marra et al. 2015, Marra et al. 2018)

Early diagnosis of systemic sclerosis associated pulmonary arterial hypertension (SSc-APAH) is of utmost importance, since it leads to significant improvement of survival rates through the implementation of PAH-targeted therapies.(Humbert et al. 2011)

Therefore, a new hemodynamic definition of PAH was proposed at the 6th World Symposium of PH (Simonneau et al. 2019), which lowered the cut-off for mean pulmonary arterial pressure (mPAP) from ≥25 mmHg (as stated in the actual PH guidelines, Galiè et al. 2016) to >20 mmHg in combination with pulmonary arterial wedge pressure (PAWP) ≤15mmHg and PVR ≥3 Wood Units (WU). The change in the hemodynamic definition of pre-capillary PH represents a step towards the upper limit of physiological hemodynamic thresholds as shown in a systemic review of Kovacs et al. (Kovacs et al. 2009) including 1187 healthy subjects presenting with an upper limit of normal for mPAP of 20.6mmHg (mean + 2 standard deviations). Subsequent studies performed mainly in SSc patients reported that patients with mildly elevated mPAP (21-24 mmHg) had reduced exercise capacity, impaired QoL, decreased RV output reserve, abnormal pulmonary arterial compliance (PAC) and survival.(Valerio et al. 2013, Coghlan et al. 2018, Nagel et al. 2019) Recent data from cohorts in a US-PH-center (Jaafar et al. 2019), and from SSc-patients cohorts in Zurich and Heidelberg (Xanthouli et al. 2020) have shown, that the new PAH-definition will most likely prevent from an early PAH-diagnosis due to a too high threshold for PVR ≥3WU.(Jaafar et al. 2019, Xanthouli et al. 2020) Patients with PVR > 2 WU already had an early pulmonary vascular disease with reduced 6MWD, right heart function, PAC and survival (Xanthouli et al. 2020). Data on early treatment of patients with early PAH with mildly elevated pulmonary arterial pressures is still scarce.

A recent double-blind-randomized controlled trial (EDITA) testing the effect of ambrisentan, an endothelin receptor antagonist, on mean pulmonary arterial pressure (primary endpoint) among

SSc-patients with mildly elevated mPAP and/or exercise PH, without significant left heart or lung disease, failed to change the primary endpoint, however, showed an improvement of PVR as secondary endpoint (Pan et al. 2019), which may be of prognostic relevance in this patient cohort. Further research in this field is needed.

As PVR has a prognostic significance among patients with SSc-APAH and previous studies proved the positive effects of riociguat on right heart size and PVR (secondary endpoint in phase III studies), PVR was chosen as primary endpoint of the current study.

The aim of this study is to investigate the effect of riociguat (MK-4836) on PVR, clinical parameters, safety and tolerability in patients with early pulmonary vascular disease.

2.2 Trial Rationale/ Justification

The aim of this 24 weeks randomized, controlled multicenter, multinational study is to investigate the effect of riociguat (MK-4836) treatment on pulmonary vascular resistance in patients with early pulmonary vascular disease, indicated by either a) mPAP ≥25 mmHg with PVR ≥2 to <3 WU and PAWP ≤15 mmHg or b) mPAP 21-<25 mmHg with PVR ≥2 WU and PAWP ≤15 mmHg.

2.3 Study Committees

The following study committees will be established, each governed by a separate charter:

- **Independent Steering Committee (SC)** - to advise on the study protocol, oversee the conduct of the study, contribute to interpretation of the results, and support publications.

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

3 Trial Objectives and Endpoints

3.1 Primary Objective and Primary Endpoint

1) To investigate the effect of treatment with riociguat (MK-4836) in patients with early pulmonary vascular disease, defined as either a) mean pulmonary arterial pressure (mPAP) ≥25 mmHg with pulmonary vascular resistance (PVR) ≥2 to <3 WU and pulmonary arterial wedge pressure (PAWP) ≤15 mmHg or b) mPAP 21-<25 mmHg with PVR ≥2 WU, and PAWP ≤15 mmHg associated with connective tissue disease (CTD) or as idiopathic/heritable form.

3.2 Secondary Objectives

1) To investigate, whether treatment with riociguat (MK-4836) may improve further hemodynamic and clinical parameters in patients with early pulmonary vascular disease, defined as stated above.

2) To assess safety and tolerability of riociguat (MK-4836) treatment in patients with early pulmonary vascular disease, defined as stated above.

Secondary efficacy endpoints will be tested hierarchically:

- change of cardiac index at rest (baseline to 24 weeks)
- change of total pulmonary resistance (baseline to 24 weeks)
- change of diffusion capacity of the lung (baseline to 24 weeks)
- change of 6-minute walking distance (baseline to 24 weeks)
- change of WHO functional class (baseline to 24 weeks)
- change in QoL (SF-36, physical summation score; baseline to 24 weeks)

Exploratory endpoints

The following parameters will be assessed in every patient according to the visits schedule and analyzed as **exploratory variables**. Secondary endpoints will be analyzed as change from baseline to 12 and to 24 weeks as exploratory variables if available according to assessment schedule.

QoL assessed by the SF-36 questionnaire

- mental summation score as well as the 8 sub scores

WHO functional class

Lung function and lung diffusing capacity

- FEV1 (forced expiratory volume in 1 second), TLC (total lung capacity), DLCO (diffusing capacity of the lung)

Echocardiography

- systolic pulmonary arterial pressure (sPAP, mmHg), right ventricular area (RV-area, cm^2), and right atrial area (RA-area, cm^2), tricuspid annular plane systolic excursion (TAPSE), left ventricular eccentricity index (LV-EI), RV-pump function and LV-pump function (LV-EF, %).

Analyses of blood samples
Venous blood will be analyzed to determine:

- NT-pro BNP

Blood for blood gas analyses

- oxygen partial pressure, carbon dioxide partial pressure, oxygen saturation of the blood (SpO_2), pH values, bicarbonates, base excess

Pulmonary hemodynamics by right heart catheterization

- sPAP, mPAP, diastolic pulmonary artery pressure (dPAP), pulmonary artery wedge pressure (PAWP), right atrial pressure (RAP), cardiac output and ejection fraction (CO), central venous saturation, via blood gas analysis from pulmonary artery (SvO_2)

Clinical worsening will be defined as time to first event out of:

- worsening of WHO functional class
- deterioration of 6MWD >15% compared to baseline
- need of initiation of targeted PAH treatment
- hospitalization due to worsening of right heart function
- all cause death or lung-transplantation
- atrial septostomy

Safety variables

Laboratory, electrocardiogram, vital signs, assessment of adverse events and serious adverse events will serve as safety parameters.

Patients with a serious adverse event occurring during the study treatment will be followed by the study team until the serious adverse event will have resolved to the pre-study level and/or will have been addressed according to best clinical practice.

If a patient withdraws from study treatment and agrees to stay in the study, study related examinations will be performed and data will be obtained according to protocol.

4 Trial Design

Investigator-Initiated-Trial (IIT)

This is a prospective, randomized, controlled, parallel-group, double-blind multicenter multinational clinical trial, which investigates the effect of riociguat (MK-4836) in patients with early pulmonary vascular disease, defined as either a) mean pulmonary arterial pressure (mPAP) ≥25 mmHg with pulmonary vascular resistance (PVR) ≥2 to <3 WU and pulmonary arterial wedge pressure (PAWP) ≤15 mmHg or b) mPAP 21-<25 mmHg with PVR ≥2 WU, and PAWP ≤15 mmHg associated with connective tissue disease (CTD) or as idiopathic/heritable form. Patients in group b will be mainly enrolled as long as patients in group a are not defined as having pulmonary arterial hypertension according to European pulmonary hypertension guidelines.

The primary efficacy endpoint in this study is the change in PVR from baseline to 24 weeks. The study consists of a pre-treatment phase of up to 28 days followed by a 24-week treatment phase. The treatment phase is divided into an 8-week titration phase, followed by a 16-week main study phase.

The patients who discontinue medication prematurely will be asked to continue with study assessments and perform study visits as outlined in the protocol. Subjects will be taking three doses daily with each dose taken 6 to 8 hours apart. In the case of side effects (e.g. symptomatic hypotension), down-titration by 0.5 mg tid is allowed. The maintenance dose achieved after 8 weeks should be at least 1.5 mg tid.

Medical examinations comprise of medical history, physical examination, electrocardiogram (ECG), blood gas analyses, lung function tests, DLCO, WHO-FC, 6MWD, quality of life questionnaires, laboratory testing (including NT-proBNP), echocardiography at rest, and right heart catheterization (RHC) according to clinical practice. If patients fulfil the inclusion criteria they will be invited to join the study. The prospective period of data collection will comprise of a 24-week study period and a follow-up phase of about 30±14 days.

After the pre-treatment phase, eligible subjects will be randomized at Visit 1 in a1:1 ratio to the following 2 treatment groups

- Riociguat (MK-4836) 1.0-2.5 mg group (titration between 1.0 mg and 2.5 mg tid based on an individual dose titration scheme)
- placebo group (placebo tid)

5 Trial Duration and Schedule

5.1 Study Phases

- Screening Phase: up to 28 days before treatment start
- Treatment phase: 24 weeks ± 14 days including 8 weeks titration phase and 16 weeks continuation phase.
- Safety Follow-up: patient's well-being will be monitored by phone after 30 ± 14 days after last intake of study drug.

5.2 Trial Duration

The overall duration of the trial is expected to be approximately 4 ½ years. The actual overall duration or recruitment may vary.

Total trial duration: [4 ½ years]

Duration of the double-blind phase: [24 weeks ± 14 days]

Safety follow-up: [30 ± 14 days]

5.3 Recruitment plan

Study sites will be activated to enroll the needed patient number for this study.

Case payments will be provided according to performed visits. Sites will be regularly informed about the screening process.

6 Selection of Subjects

6.1 Number of Subjects

As calculated in section 10.1, 70 subjects will be enrolled in the clinical trial, 35 subjects per treatment group.

6.2 General Criteria for Subjects' Selection

Adult male and female patients with early pulmonary vascular disease will be included.

Both an elevated mean pulmonary arterial pressure >20 mmHg and an increase of PVR >2 WU have been shown to be above the upper limit of normal and are associated with development of manifest PAH and impaired survival in CTD. As a placebo-controlled study would seem unethical in patients, who are in clear indication of targeted treatment, patients with manifest PAH according to the current definition may not be included in this study (combination of both mPAP ≥25 mmHg and PVR ≥3 WU and PAWP ≤15 mmHg).

It is assumed that for any patient, considered for inclusion, a regular diagnostic workup in accordance with international guidelines (ESC/ERS Guidelines) was performed. Hemodynamics will be assessed by right heart catheterization at the screening visit, up to 1 month prior to screening or up to 6 months prior to screening if the patient had no signs of clinical changes defined as change of 6MWD >10%, WHO-FC change or >30% change in NT-proBNP. RHC must have been measured in the participating center under standardized conditions. For statistical considerations see section 10.

6.3 Inclusion Criteria

1. ≥18 years of age at time of inclusion.
2. Male and female patients with early pulmonary vascular disease, defined as either

   a) mean pulmonary arterial pressure (mPAP) ≥25 mmHg with pulmonary vascular resistance (PVR) ≥2 to <3 WU and pulmonary arterial wedge pressure (PAWP) ≤15 mmHg (group I PAH according to 2022 ERS/ESC guidelines) or

b) mPAP 21-<25 mmHg with PVR ≥2 WU, and PAWP ≤15 mmHg associated with connective tissue disease (CTD) or as idiopathic/heritable form (see Group I / Nice Clinical Classification of Pulmonary Hypertension) (acc. to Simonneau et al. 2019; Humbert et al. 2022). Patients with rheumatoid arthritis or connective tissue disease of any kind, except systemic lupus erythematosus, may also be included. Patients in group b will be mainly enrolled as long as patients in group a are not defined as having pulmonary arterial hypertension according to European pulmonary hypertension guidelines.

3. Treatment naïve patients (with respect to PAH specific medication)
4. Unspecific treatments which may also be used for the treatment of pulmonary hypertension such as oral anticoagulants, diuretics, digitalis, calcium channel blockers or oxygen supplementation are permitted. Permitted are also treatments of the rheumatologic disease. However, these drugs must have been started at least 1 month before right heart catheterization.
5. Right-heart catheterization results must not be older than 1 month at Visit 1 (will be considered as baseline values, the time frame can be prolonged up to 6 months, if the patient has had no signs of clinical changes defined as >20% change of 6MWD, WHO FC, > 30% change in NT-proBNP) and must have been measured in the participating center under standardized conditions (refer to the study specific Swan Ganz catheterization manual). If the respective measurements have not been performed in context with the patient's regular diagnostic work up, they have to be performed as a part of the study during the pre-study phase (after the patient signed the informed consent).
6. Women without childbearing potential defined as postmenopausal women with amenorrhea for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females, women with bilateral tubal ligation, women with bilateral ovariectomy, and women with hysterectomy can be included in the study.
7. Women of childbearing potential can only be included in the study if all of the following applies (listed below):
    a. Negative serum pregnancy test at screening and at study start (visit 1).
    b. Agreement to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation. These tests should be performed by the patient at home.
    c. Agreement to use a highly effective contraception method from screening until at least 30 days after last dose of study medication.

Option 1 or	Option 2 One method from this list	or Option 3	or Option 4
Tubal sterilization (occlusion or ligation of tubes at least 6 weeks prior to Screening)	Oral*, Implantable*, Transdermal*, or Injectable* hormonal contraceptives Intrauterine Devices	Sterilization of the male partner with documented post-vasectomy confirmation of the absence of sperm in the ejaculate **PLUS one method from this list** Oral*, Implantable*, Transdermal*, or Injectable* hormonal contraceptives Intrauterine devices Diaphragm, female condom cervical cap, partner's use of a condom	True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the subject.

* If a hormonal contraceptive is chosen from this group, it must have been taken for at least 28 days prior to study start (visit 1).

8. Patients who are able to understand and follow instructions and who are able to participate in the study for the entire period.
9. Patients must have given their written informed consent to participate in the study after having received adequate previous information and prior to any study-specific procedures.

6.4 Exclusion Criteria

1. Patients with systemic lupus erythematosus.
2. Concomitant PAH-targeted treatment is not allowed during the study. Accordingly, patients scheduled to receive another investigational drug during the course of this study cannot participate (see exclusion criterion 12). Patients already receiving or having received any PAH targeted therapy will therefore not be included into the study. Such treatment may not be discontinued to enable inclusion into the study.
3. Concomitant treatment with phosphodiesterase 5 inhibitors, endothelin receptor antagonists and prostacyclin analogues due to digital ulcers is contraindicated and must not

be taken during the study period. Such drugs must have a washout-phase of 3 days at the time of right heart catheterization at screening. Intravenous treatment with prostacyclin analogues should not be performed within 1 week of right heart catheterization. Any decision to discontinue above-mentioned drugs will be made by the clinicians and the patient at screening, which takes part during the patients' regular routine visit. The discontinuation of above-mentioned drugs will be evaluated by considering the presence or absence of digital ulcers and their frequency of appearance in the patient's medical history.

4. Pulmonary hypertension explained by other cause including group 2, 3, 4 and 5 PH according to the current guidelines.
5. Cardiac comorbidity, defined with three or more of the following conditions: uncontrolled arterial hypertension, diabetes mellitus, body mass index >35, left atrial enlargement >20 cm^2, atrial fibrillation, left ventricular ejection fraction <50%.
6. Pulmonary comorbidity, defined as forced vital capacity (FVC) ≤70; forced expiratory volume in 1 second (FEV1) ≤50%; diffusion capacity of the lung (DLCO) ≤30%.
7. Patients with a medical disorder, condition, or history of such that would impair the patient's ability to participate or complete this study in the opinion of the investigator.
8. Patients with underlying medical disorders with an anticipated life expectancy below 2 years (e.g. active cancer disease with localized and/or metastasized tumor mass).
9. Patients with a history of severe or multiple drug allergies (defined as allergic reactions to three or more structurally unrelated drugs).
10. Patients with hypersensitivity to the investigational drug or any of the excipients.
11. Contraindications according to summary of product characteristics of riociguat (e.g. arterial hypotension with systolic blood pressure <95 mmHg; nitrates or nitric oxide donors (such as amyl nitrite) in any form including recreational drugs)
12. Participation in any clinical drug trial within 4 weeks prior or 5 half-lives, whichever longer, to screening of this study and/or patient, who is scheduled to receive an investigational medicinal product (IMP) during the course of this study
13. Background therapy with highly anti-fibrotic drugs (pirfenidone) or nintedanib, prednisolone >10 mg/day

6.5 Criteria for Removal or Withdrawal

6.5.1 Withdrawal of Subjects

A subject will be withdrawn from the trial treatment for the following reasons:

1. at their own request or at request of their legal representative
2. if, in the investigator's opinion, continuation of the trial would be detrimental to the subject's well-being
3. occurrence of a severe serious adverse event (SAE) caused by the IMP
4. The participant has a medical condition or personal circumstance which, in the opinion of the investigator placed the participant at unnecessary risk from continued administration of study treatment. This includes progression or aggravation of the pulmonary hypertension, so that appropriate PAH targeted therapy may be introduced without delay.
5. The participant has a confirmed positive serum pregnancy test.

The Coordinating Investigator decides about withdrawal of subjects from trial treatment in case of occurrence of criteria mentioned above.

Patients with a serious adverse event occurring during the study treatment will be followed by the study team until the serious adverse event will have resolved to the pre-study level and/or will have been addressed according to best clinical practice. The patient, either willingly withdrawn from the study or due to premature termination, will be asked thoroughly to complete all examinations scheduled for the final trial day, and these will be performed as far as possible and documented.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject’s medical records.

In case of withdrawal of a subject at his/ her own request, the reason should be asked for as extensively as possible and documented.

All efforts will be made to follow up the subject.

A subject may/ will be withdrawn from all trial related procedures (including follow-up visits) for the following reasons:

- at his/her own request or at request of his/her legal representative
- non-adherence to the trial-related requirements, which may (have) influence(d) the validity of the trial data

6.5.2 Replacement of Subjects

Per treatment arm, 35 subjects will be enrolled and included into the modified intention to treat (ITT) and safety analysis (SA) (total n=70). Subjects who terminate the study prematurely will not be replaced as a 15% drop-out rate is included in this sample size calculation.

6.5.3 Premature Closure of the Clinical Trial

The trial can be prematurely closed or suspended by the Coordinating Investigator in case if new serious risks for subjects become known. The Ethics Committee (EC) and the competent regulatory authorities must then be informed. Furthermore, the Ethics Committee(s) and competent regulatory authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (completed, partially completed, and blank CRF, randomization envelopes, IMP, etc.) must be returned to and/or kept within the files of the Coordinating Investigator.

All involved investigators have to be informed immediately about a cessation/ suspension of the trial. The decision is binding to all trial centers and investigators.

6.6 Prior and Concomitant Illnesses

Relevant additional illnesses present at the time of informed consent are regarded as concomitant illnesses and will be documented on the appropriate pages of the CRF as medical history. Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Abnormalities which appear for the first time or worsen (intensity, frequency) during the trial are adverse events (AEs) and must be documented on the appropriate pages of the CRF.

6.7 Prior and Concomitant Treatments

Any prior or concomitant therapy must be assessed in terms of potential interactions with the study drug as listed in the most current version of the riociguat summary of product characteristics. Relevant additional treatments administered to the subjects on entry to the trial or at any time during the trial are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.

In case of clinical worsening and if clinically indicated additional PAH-targeted rescue medication will be initiated at the discretion of the investigators. If patients present with manifest PAH after 24 weeks at the end of the double-blind phase, patients will be offered targeted treatment according to current PH guidelines. Participants will not be included if scheduled to receive another investigational drug during the course of this study.

Patients receiving highly anti-fibrotic drugs (pirfenidon), nintedanib, prednisolone >10 mg/day or any other PAH specific treatment may not participate in this study. Sildenafil and tadalafil must be discontinued at least 24 hours and at least 48 hours respectively prior to first administration of riociguat. Moreover, administration of concomitant drugs that may decrease riociguat plasma concentration as listed in the current summary of product characteristics should be avoided (e.g. strong CYP3A4 inducers).

7 Investigational Medicinal Product

7.1 General Information about the Investigational Medicinal Product

7.1.1 Riociguat

International Nonproprietary Name (INN): riociguat

Investigational medicinal product code of MSD: MK-4836

ATC code: C02KX05

Chemical formula: $C_{20}H_{19}FN_8O_2$

Pharmaceutical form: film-coated tablet

Route of administration: oral

Time and frequency of administration: tid

Dosage: individual titration starting at 1.0 mg with maximum dosage of 2.5 mg three times/day

Storage conditions: 15-30°C

Clinical drugs supplied by MSD SHARP&DOHME GmbH, Germany

Devices: none

7.1.2 Placebo

Placebo medication consists of tablets indistinguishable from the riociguat (MK-4836) tablets supplied by MSD SHARP&DOHME GmbH, Germany

7.2 Therapeutic Effects

Pulmonary arterial hypertension is defined by an increased mean pulmonary arterial pressure and pulmonary vascular resistance. Patients with systemic sclerosis or other forms of connective tissue disease have an increased risk to develop pulmonary arterial hypertension which significantly impairs their prognosis.

Riociguat is the first drug that has been approved for the treatment of both PAH and CTEPH (Ghofrani et al. 2013). The 12-week PATENT-1 study showed a significant improvement of the

primary endpoint 6MWD and of secondary endpoints such as PVR, NT-proBNP levels, WHO-FC, time to clinical worsening and Borg dyspnea score (Ghofrani et al. 2013). An exploratory analysis of the first 12 weeks of the long-term extension study (PATENT-2) showed further significant improvement of 6MWD in the 215 PAH-patients receiving up to 2.5 mg of riociguat tid (Rubin et al. 2015).

In CTEPH-patients the 12-week CHEST-1 study revealed a statistically significant improvement of 6MWD (primary endpoint) and in PVR, NT-proBNP serum values, and in WHO-FC (secondary end points) (Ghofrani, et al. 2013). Further studies investigating the effect of riociguat in an uncontrolled design were the early access study (EAS) in patients with CTEPH (McLaughlin et al. 2017) and PATENT plus in PAH (Galiè et al. 2015).

In a retrospective analysis of patients with CTD-APAH receiving riociguat in PATENT-1 and PATENT-2, mean improvement of PVR after 12 weeks was 132±140 dynes*sec*cm^{-5} in patients with SSc (equals 1.65±1.75 WU).

Up to now, it is not known, whether targeted treatment for PAH provides a benefit in patients with early pulmonary vascular disease.

7.3 Benefit/ Risk Assessment

An early detection and treatment of CTD-PAH is especially important, as patients tend to have a poor prognosis with a median survival rate of one year after diagnosis if left untreated.

Patients with SSc and mildly elevated mPAP of 21-24 mmHg have been shown to be more likely to develop PH than patients with mPAP <21 mmHg ($p < 0.001$ by log rank test, hazard ratio 3.7). A TPG >11 mmHg at baseline also predicted PH ($p < 0.001$ by log rank test, hazard ratio 7.9), yielding a sensitivity of 87% and a specificity of 70% (Valerio et al. 2013). Development of PH was associated with a mortality of 18% within 3 years in this cohort. Early treatment with riociguat might have a beneficial impact on pulmonary vascular disease, hemodynamics and thus improve prognosis.

Early diagnosis of SSc-APAH is of utmost importance, since it leads to significant improvement of survival rates through the implementation of PAH-targeted therapies. (Humbert et al. 2011)

Therefore, a new hemodynamic definition of PAH was proposed at the 6th World Symposium of PH (Simonneau et al. 2019), which lowered the cut-off for mPAP from ≥25 mmHg (as stated in the actual PH guidelines, Galiè et al. 2016) to >20 mmHg in combination with PAWP ≤15mmHg and PVR ≥3WU. The change in the hemodynamic definition of pre-capillary PH represents a step

towards the upper limit of physiological hemodynamic thresholds as shown in a systemic review of Kovacs et al. (Kovacs et al. 2009) including 1187 healthy subjects presenting with an upper limit of normal for mPAP of 20.6mmHg (mean + 2 standard deviations).

The effects of an early treatment have already been indicated by a study of Kovacs et al. (2012). In a small cohort of ten patients with SSc, which were observed for a period of 12 months without treatment and then treated with bosentan for six months, bosentan treatment led to a reduction of mPAP and PVR. During the observation period patient's hemodynamic values worsened. Thus, a beneficial effect is expected to be demonstrable after a period of 6 months.

Risks of treatment with riociguat (MK-4836) include the known side effects listed below.

7.4 Known Side Effects

Treatment with riociguat (MK-4836) may cause side effects. Side effects are summarized in the most recent summary of product characteristics.

The currently known most serious side effects are

- coughing up blood (hemoptysis) (common side effect, may affect up to 1 in 10 people),
- acute bleeding from the lungs (pulmonary hemorrhage) may result in coughing up blood, cases with fatal outcomes were observed (uncommon side effect, may affect up to 1 in 100 people).

Overall list of possible side effects:

Very common: may affect more than 1 in 10 people

- headache, dizziness, indigestion (dyspepsia), swelling of limbs (edema peripheral), diarrhea, feeling or being sick (nausea and vomiting)

Common: may affect up to 1 in 10 people

- inflammation of the stomach (gastritis), inflammation in the digestive system (gastroenteritis), reduction of red blood cells (anemia) seen as pale skin, weakness or breathlessness, awareness of an irregular, hard, or rapid heartbeat (palpitation), low blood pressure (hypotension), nose bleed (epistaxis), difficulty breathing through your nose (nasal congestion), pain in the stomach, intestine or abdomen (gastrointestinal and abdominal pain), heartburn (gastro-esophageal reflux disease), difficulty in swallowing (dysphagia), constipation, bloating (abdominal distension)

According to the current summary of product characteristics, smoking may lead to a reduced response to riociguat. Therefore, participating current smokers will be advised to stop smoking.

7.5 Dosage Schedule, Titration and Administration

Dose titration

The recommended starting dose is 1.0 mg three times daily for 2 weeks. Tablets should be taken three times daily approximately 6 to 8 hours apart.

Dose should be increased by 0.5 mg three times daily every two weeks to a maximum of 2.5 mg three times daily, if systolic blood pressure is ≥95 mmHg and the patient has no signs or symptoms of hypotension. If systolic blood pressure falls below 95 mmHg, the dose should be maintained provided the patient does not show any signs or symptoms of hypotension. If at any time during the up-titration phase systolic blood pressure decreases below 95 mmHg and the patient shows signs or symptoms of hypotension the current dose should be decreased by 0.5 mg three times daily. The maintenance dose should be at least 1.5 mg tid after the titration phase.

If a participant does not tolerate the study medication, the investigator may down-titrate the dose by 0.5 mg. If down-titration occurs during the titration period, re-uptitration may be attempted until the end of week 12. Re-uptitration may be performed via titration phone-call. Re-uptitration can be done using originally assigned medication doses from the most recent study treatment dispensing visit (baseline). No dose adjustment is allowed during the maintenance period after week 12, except for safety reasons.

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons.

If study treatment is interrupted by the participant for any reason, they must immediately inform the investigator. Interruptions of study treatment must be kept as short as possible. Treatment should be restarted according to the instructions in the most recent summary of product characteristics of riociguat, i.e. in case treatment has to be interrupted for 3 days or more, it should be restarted with 1 mg three times daily for 2 weeks and continued with the dose titration regimen as described.

If treatment is stopped for more than 14 consecutive days, re-introduction is not permitted, and treatment must be permanently discontinued. Study treatment dose adjustments / interruptions must be recorded in the eCRF.

If a patient does not tolerate a dose of 1.5 mg three times daily after reasonable attempt, he/she has to stop study treatment.

Maintenance dose

The established individual dose should be maintained unless signs and symptoms of hypotension occur. The maximum total daily dose is 7.5 mg i.e., 2.5 mg 3 times daily. If a dose is missed, treatment should be continued with the next dose as planned. If not tolerated, dose reduction should be considered at any time.

Administration

Tablets are for oral use and can generally be taken with or without food. For patients prone to hypotension, as a precautionary measure, switches between fed and fasted riociguat (MK-4836) intake are not recommended because of increased peak plasma levels of riociguat (MK-4836) in the fasting compared to the fed state.

7.6 Treatment Assignment

Patients who have signed the consent form will be given a unique screening number including center number (e.g. 01, 02…) and patient ID (001, 002, …). Screening number will ascend, starting with 001, 002, etc. If the patient is eligible for the prospective drug trial, a 1:1 randomization will be performed into riociguat (MK-4836) and placebo group and a consecutive randomization number will be allocated to the patient.

The trial medication will be administered to subjects only after confirming their eligibility after the initial screening. Study drug will be supplied at baseline and consecutive visits.

Subjects withdrawn from the trial retain their identification codes (e.g. randomization number, if already given). New subjects must always be allotted a new identification code.

7.7 Randomization and blinding

After the pre-treatment phase, eligible subjects will be randomized at Visit 1 in a1:1 ratio to the following 2 treatment groups:

- Riociguat (MK-4836) 1.0-2.5 mg group (titration between 1.0 mg and 2.5 mg tid based on an individual dose titration scheme) (35 subjects planned)
- Placebo group (placebo tid) (35 subjects planned)

Investigator, sponsor, study personnel, monitor, biometrician, and the patient will be blinded to treatment. The sponsor will engage an independent qualified external service (e.g. pharmacy) to

centrally generate the randomization envelopes and emergency envelopes for each participating center.

Earlier screening failures may be rescreened once for possible study entry. Patients who dropped out of the study are not allowed to re-enter or to be enrolled again.

Randomization to one of the groups will be performed by permuted block randomization. Blocks will be stratified according to centre. Randomization lists will be created by the above-mentioned unblinded independent, central external service designated by the sponsor. The randomization list will be kept centrally in safe and confidential custody at the external service in compliance with applicable local laws/regulations.

Emergency Envelopes: In addition to the trial medication the investigator will receive a set of sealed envelopes, one for each randomization number. These envelopes will be created by the unblinded independent, central external service (e.g. pharmacy) in charge of randomization and provided according to the random number with the study medication. An identical set of sealed envelopes will be held at Pharmacovigilance Safety Officer. These envelopes contain information on the subject's trial medication and are to be opened only under circumstances in which it is medically imperative to know what the subject is receiving. Date and reason for opening a sealed envelope must be documented. If possible, the investigator will confer with the Coordinating Investigator before unblinding. The randomization envelopes are not to be opened by the investigator at the end of the trial. All envelopes will be collected by the monitor at the end of the trial.

7.8 Labelling and Supply

Study medication will be labelled according to the requirements of local law and legislation by MSD SHARP&DOHME GmbH Germany and provided to the only single site in a country or a central pharmacy in case there are several sites in a country as determined by the principle investigator/sponsor. Each center will receive the study medication in a blinded fashion.

Medication of the maintenance phase will be packed in bottles containing medication for 12 weeks ± 14 days. At the week 12 visit, the bottle number will be allocated to the respective patient according to the dosage selected during the visit.

7.9 Supplies and Accountability

The investigator will keep an account of the trial medication and acknowledge the receipt of all shipments of the trial medication. All investigational drugs used during the trial will be stored at

the investigational sites in a place inaccessible to unauthorized personnel. The study drug must be stored between 15°C and 30°C. The investigator will also keep accurate records of the quantities of trial medication dispensed, used, and returned by each subject. The documentation has to include date of dispensing, subject identification, batch number and medication number of trial medication. The site monitor will periodically check the supplies of trial medication held by the investigator to ensure the correct accountability of all trial medication used. At the end of the trial, any unused drug supply will be documented by the study site and destroyed in compliance with the institution's procedures and applicable local laws/regulations. Unused trial medication returned by patients will be sealed during monitoring visits and destroyed at the end of the study. The procedure will be documented and archived. It will be assured that a final report of the drug accountability is prepared and maintained by the investigator.

7.10 Compliance

Trial medication will be dispensed to the subjects by the investigator. Subjects will be instructed to bring all trial medication to the trial site at every visit. Compliance will be assessed by tablet count. Details will be recorded in the CRF. Treatment effects will be assessed and the dosage will be discussed at each visit.

The patient will adapt the dose from 1.0 mg to 2.5 mg three times/day during the 8-week titration phase according to tolerability and after consultation (by phone or personally) with one of the investigators as to common practice of the clinic.

Furthermore, the patients will receive a patient diary recording medication intake and time points. The patient diary will be checked for compliance at each study visit.

8 Trial Methods

8.1 Overview of visits and assessments

	Double-blind						
Assessments	**Screening** -28 days	**Visit 1 Baseline** Day 1	**V 1.1-1.4 Phone Visits Titration** Week 2, 4, 6 and 8 ±2 days	**Visit 2 Interim visit** Week 12 ±7 days	**V 2.1-2.2 Phone Visits** Only WOCBP Week 16 and 20 ±2 days	**Visit 3 Termination visit** Week 24 ±14 days	**Visit 4 Safety FU** 30 days after last IMP intake ±14 days
Informed Consent	1	-	-	-	-	-	-
Inclusion / exclusion criteria	1	1	-	-	-	-	-
Patient diary(handing out / compliance check)	-	1	-	1	-	1	-
Prior and concomitant medication	1	1°	4	1	2	1	1
Demography, height and medical history	1	-	-	-	-	-	-
PAH classification, etiology, diagnosis date	1	-	-	-	-	-	-
WHO-FC	-	1	-	1	-	1	-
Vital signs, incl. heart rate, SpO_2 (%)	1	1	-	1	-	1	-
6MWD, Borg Dyspnea Score	-	1	-	1	-	1	-
Weight	1	1°	-	1	-	1	-
ECG	1	1°	-	1	-	1	-
Blood gas analysis	1	1°	-	-	-	1	-
Lung function testing (Plethysmography)	1	1°	-	-	-	1	-
Diffusing capacity of the lung	1	1°	-	-	-	1	-
Right heart catheter	1*	-	-	-	-	1	-
Physical examination	1	1°	-	1	-	1	-
Laboratory Hematology, Chemistry, Hemostaseology, NT-proBNP	1	1°	-	1	-	1	-
Pregnancy test (only WOCBP)	1	1°¶	2^+ (week 4 and 8)	1	2^+ (week 16 and 20)	1	1^+
Echocardiography	-[#]	1[#]	-	-	-	1	-
Quality of life (SF-36)	-	1	-	-	-	1	-
Adverse Events	1	1	4	1	2	1	1
Systolic blood pressure and dose adjustment	-	-	4	-	-	-	-
Drug dispensed	-	1	-	1	-		-
Drug collected	-	-	-	1	-	1	-
Drug compliance	-	-	-	1	-	1	-
Phone visits	-	-	4	-	2	-	1

* RHC at screening will only be performed in patients who have not had a RHC within the preceding 1 month at screening. A preceding RHC from the last 6 months can be used if the patient had no signs of clinical changes defined as change of 6MWD >10%, WHO-FC change or >30% change in NT-proBNP. RHC must have been measured in the participating center under standardized conditions.

[+] Pregnancy test at home.

¶ Handing out pregnancy tests for home use

° Will not be performed if already performed at Screening AND if Screening and Baseline are conducted during same hospital stay.

[†] Optional during the SARS-CoV2-pandemic.

[#] If, due to organisational reasons, echocardiography cannot be performed at Baseline, it can be performed during Screening period and it can be used as baseline value. Echocardiography cannot be performed after baseline.

8.2 Assessments

8.2.1 Physical examination and demographic data

The physical examination comprises measurement of body weight and height (height will be measured only once) and a routine internal medical examination. Physical examinations will be performed to ensure suitability according to the inclusion and exclusion criteria and to document the health status before and following treatment with the IMP.

Connective tissue disease will be diagnosed by rheumatologists based on the current classification criteria for connective tissue diseases (van den Hoogen et al. 2013, Anger et al. 2019, Shiboski et al. 2017).

Underlying causes of pulmonary vascular disease will be ruled out according to the guidelines (Galiè et al. 2015).

8.2.2 Hemodynamic parameters

Hemodynamic parameters will be determined by right heart catheterization according to current guidelines (Opitz et al. 2011). The right heart catheterization (RHC) will be performed at screening only in patients who have not performed a RHC within the preceding 1 month or in the last 6 months if the patient had no signs of clinical changes defined as change of 6MWD >10%, WHO-FC change or >30% change in NT-proBNP. RHC must have been measured in the participating center under standardized conditions. RHC may involve exposure to ionising radiation only if clinically indicated.

Directly, invasively measured parameters are: CI, sPAP, mPAP, dPAP, PAWP, RAP, PVR, CO, SvO_2. During the right heart catheterization, a continuous ECG will be performed. The values will be based on three measurements at one time point. The three values of CO should not differ by more than 10% from each other. Optionally, arterial blood gas saturation can be measured in wedge position.

Directly non-invasive measured parameters: heart rate, blood pressure

Methodology: Swan-Ganz catheterization and thermodilution methodology

The primary endpoint PVR (in WU) will be calculated by the formula PVR = (mPAP-PAWP)/CO*80. CI (in l/min/m^2) will be calculated by CO/Body mass area.

The data will be directly measured in the participating centers and will be transferred to the CRF. In addition, RHC recordings will be centrally read by two experienced physicians who are blinded

to study treatment. Original RHC data will be submitted for central reading with pseudonymized pressure curves and data of thermodilution.

8.2.3 Echocardiography

Echocardiography will be performed according to current guidelines (Rudski et al. 2010).

Following parameters will be assessed: sPAP, RV-area and RA-area, TAPSE, LV-EI, RV-pump function and LV-EF.

8.2.4 Determination of WHO functional class

Functional assessment of pulmonary hypertension will be performed according to the WHO-Functional Class, i.e. the Evian Symposium, 1998, modified New York Heart Association (NYHA) Classification:

Class I: Patients with PH 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 PH 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 PH 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.

8.2.5 Lung function tests and blood gas analysis

Lung function test: Body plethysmography including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), total lung capacity (TLC), residual volume (RV), and diffusion capacity diffusion-limited carbon monoxide (DLCO), DLCO/VA (Krogh index).

Blood gas analysis: capillary or arterial blood gas analysis; partial pressure of oxygen and carbon dioxide, SpO_2, pH values, bicarbonates, base excess.

If the patient receives oxygen the amount will be recorded in the CRF in liters/minute.

8.2.6 6-minute walking distance and Borg dyspnea Score (CR 10)

6-minute walking test will be performed according to ATS guidelines (ATS 2002). The patient is asked to walk along a prescribed path as far as possible during a 6-minute interval of time. The patient may walk at whatever pace he/she feels comfortable with the goal of walking the most

distance he/she feels possible. If the patient feels the need to rest, he/she may do this. Blood pressure, heart rate and oxygen saturation will be measured before and after the test.

The Borg Scale (Breathlessness Scale) is commonly used to measure shortness of breath of patients or in sports medicine. In this study, the Borg Scale will be applied to record dyspnea immediately following the 6-minute walk test.

The Borg Scale comprises the following parameters according to the ATS guidelines (ATS 2002):

0	Nothing at All
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat Moderate
5	Severe
6	
7	Very Severe
8	
9	Very, very severe (almost maximal)
10	Maximal

8.2.7 Quality of Life (QoL)

QoL will be assessed using the SF 36-questionnaire (see Appendix) that will be handed out to the patients. Scoring will be carried out according to the test manual.

The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale, i.e. a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. The eight sections are: vitality; physical functioning; bodily pain; general health perceptions; physical role functioning; emotional role functioning; social role functioning; mental health. Two summation scores, physical summation score and mental summation score, will be calculated.

8.2.8 Vital signs

Blood pressure, heart rate and oxygen saturation will be measured after the patient has been at rest for at least 5 minutes.

Blood pressure (systolic and diastolic) will be measured by means of a standard manual or an automatic blood pressure measuring device (cuff method) in sitting or supine position. Nevertheless, the same method and body posture should be used during the entire study period (the type of device has to be recorded into the CRF). The same upper arm will be used for each

measurement of blood pressure, preferably the left arm. Heart rate and SpO_2 will be measured by pulse oximetry.

8.2.9 Electrocardiography

A 12-lead electrocardiogram (ECG) will be performed. For deriving the 12-lead ECGs the patients should always be in supine position. The 12-lead ECGs should be derived after a resting period of at least 10 minutes. The investigator will review the ECGs for potential AEs.

A continuous 12-lead ECG monitoring will be applied during right heart catheterization.

8.2.10 Clinical laboratory investigations

Clinical laboratory investigations will comprise:

Hematology	Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets
Substrates	Bilirubin, cholesterol, triglycerides, creatinine, uric acid, urea, total protein, glucose
Electrolytes	Sodium, potassium, calcium, chloride
Enzymes	SGOT/ASAT, SGPT/ALAT, Gamma-GT, AP, LDH, CK
Others	INR, PTT, β-HCG test or urine dipstick for WOCBP
Biomarkers	CRP, NT-proBNP

All laboratory assessments will be determined locally on-site. Any leftover biomaterials will be destroyed in line with local regulations.

8.3 Study Phases and Visits

8.3.1 Screening Phase

Patients who sign the informed consent form to participate in the medical trial will undergo the screening examinations: medical history, demographics, checking of in- and exclusion criteria, physical and weight examination, vital signs (blood pressure, heart rate, SpO_2), lung function test (body plethysmography and diffusion capacity), blood gas analysis (BGA), echocardiography at rest, right heart catheterization with continuous 12-lead ECG at rest, clinical laboratory, including pregnancy test (only WOCBP), survey of concomitant medication and diseases and recording of adverse events. Measurements/assessments taken during screening visit will be recorded as baseline values for study assessment of endpoints unless described otherwise.

The right heart catheterization should not be older than 1 month at screening or not older than 6 months if the patient had no signs of clinical changes defined as change of 6MWD >10%, WHO-FC change or >30% change in NT-proBNP. RHC must have been measured in the participating

center under standardized conditions. Patients without recent RHC fulfilling the above-mentioned criteria, will receive a RHC at screening, be before the beginning of the intervention. Baseline will be within 28 days after screening.

If, due to organisational reasons, echocardiography cannot be performed at Baseline, it can be performed during Screening period and it can be used as baseline value. Echocardiography cannot be performed after baseline.

8.3.2 Visit 1 Baseline / Randomization - Day 1

Baseline visit may be performed according to the hospital's routine practice as in-hospital stay.

The baseline visit includes the following assessments/measurements: physical examination, SSc characteristics including the WHO-FC, vital signs (blood pressure, heart rate, SpO_2), weight, 12-lead ECG, clinical laboratory (including pregnancy test only for WOCBP), echocardiography, 6MWD including Borg Dyspnea Score, QoL questionnaire (SF-36), concomitant medications, diseases/clinical symptoms and adverse events. If it is not possible to perform all requested assessments for visit 1 at one day, it is allowed to split the visit and to conduct the required measurements at two consecutive days. If screening and baseline are conducted during the same hospital stay following assessments will only be performed once, otherwise at screening and baseline: 12-lead ECG, physical examination, concomitant medication, lung function testing, DLCO, blood gas analysis pregnancy test (WOCBP only), hematology, chemistry and NT-proBNP.

If, due to organisational reasons, echocardiography cannot be performed at Baseline, it can be performed during Screening period and it can be used as baseline value. Echocardiography cannot be performed after baseline.

Patient's eligibility to participate in the trial will be confirmed. Subsequently, patients will be randomized. After the explanation of intake and titration, study medication (riociguat (MK-4836) or placebo) and the patient diary will be handed out to patients.

8.3.3 Visit 1.1- Visit 1.4 - Titration phase (week 2, 4, 6, 8 ± 2 days)

Double-blind riociguat (MK-4836) vs. placebo treatment will be initiated and individually adjusted according to systolic blood pressure and tolerability. During the titration phase, each patient will be asked to measure their peripheral systolic blood pressure and the heart rate at home three times

per day and document the values in the patient diary. The results will be examined by the investigator during each visit/phone call-visit. The patient will be handed out a diary to document the blood-pressure at study start (see Appendices). Provided that the systolic blood pressure is ≥ 95 mmHg measured at trough before intake of each dose and the patient has no signs or symptoms of hypotension, the dose of study medication will be titrated by +0.5 mg tid every 2 weeks until the maximal tolerated dosage with a maximal permitted dosage of 2.5 mg tid under consideration of the titration algorithm (= individual dose titration scheme). After the titration period, blood pressure should be measured upon signs or symptoms of hypotension. WOCBP have to perform pregnancy tests at home in week 4 (visit 1.2) and 8 (visit 1.4). Adverse events and concomitant medication will be recorded.

To ensure blinding, subjects allocated to the placebo group undergo a sham titration from Visit 1 onwards that follows the rules of the individual dose titration scheme. Independently of the investigator's decision to increase, maintain or decrease the dose of the study medication blinded placebo medication will be allocated.

8.3.4 Visit 2 - 12 weeks assessment (± 7 days)

During the main study phase (weeks 9-24), all subjects are to remain on their optimal dose of riociguat (MK-4836) or placebo. Dose reductions for safety reasons are allowed, but a subsequent re-increase during the main study phase is not possible. In case of dose delays, patients may be further titrated according to tolerability up to week 12. Clinical evaluations and phone visits are to be scheduled according to the physician's estimation and patient safety.

Visit 2 procedures/assessments include the following: WHO-FC, vital signs, physical examination, laboratory, 6MWD and Borg dyspnea score will be assessed and concomitant medications, weight, ECG, drug compliance, adverse events and diseases/clinical symptoms will be recorded. The patient dairy will be examined. Unused study drug will be collected and medication for the remaining 12 weeks at maintenance dose will be dispensed.

8.3.5 Phone visit 2.1 and phone visit 2.2 – WOCBP only (week 16 and 20 ± 2 days)

WOCBP have to perform pregnancy tests at home in week 16 (visit 2.1) and 20 (visit 2.2) and the results will be assessed by phone.

8.3.6 Visit 3 – 24 weeks assessment ± 14 days (termination of double-blind study)

After 24 weeks ± 14 days, patients will be assessed by clinical evaluation.

Visit 3 procedures/assessments include the following: physical examination, WHO-FC, vital signs, laboratory (including pregnancy test only for WOCBP), weight, ECG, lung function test (plethysmography and diffusion capacity test), BGA, QoL (SF-36 questionnaire), 6MWD and Borg dyspnea score, echocardiogram, right heart catheterization, drug compliance, concomitant medications, adverse events and diseases/clinical symptoms will be recorded. Unused study drug will be collected and the patient diary examined.

8.3.7 Visit 4 - Safety follow-up 30 days after last IMP intake

Patients will be contacted via phone 30 days after their last intake of study drug (±14 days). The assessment will serve to monitor adverse events, concomitant medication, safety and tolerability, and in case of WOCBP pregnancy test results. Clinical follow-up of all SAEs will be performed until they have been resolved, if possible.

8.3.8 Unscheduled visit

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator, and the AEs will be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule as originally planned.

8.4 Methods of Data Collection

Data will be entered by the center's study nurses. The data entered in the CRFs will be checked by the clinical monitor for data quality and integrity. All data will be entered into one database and signed by the principal investigator or study physician. Data management will perform data cleaning (e.g. range checks), pose queries and prepare the data for data analysis.

8.4.1 Efficacy Parameters

The primary efficacy variable is the change in pulmonary vascular resistance from baseline to week 24.

Secondary efficacy endpoints will be tested hierarchically:

- change of cardiac index at rest (baseline to 24 weeks)
- change of total pulmonary resistance (baseline to 24 weeks)
- change of diffusion capacity of the lung (baseline to 24 weeks)
- change of 6-minute walking distance (baseline to 24 weeks)
- change of WHO functional class (baseline to 24 weeks)
- change in QoL (SF-36, physical summation score; baseline to 24 weeks)

Exploratory endpoints

The following parameters will be assessed in every patient according to the visits schedule and analyzed as **exploratory variables**. Exploratory endpoints will be analyzed as change from baseline to 12 and to 24 weeks as available according to assessment schedule.

QoL assessed by the SF-36 questionnaire

- mental summation score as well as the 8 sub scores

WHO functional class

Echocardiography

- systolic pulmonary arterial pressure (sPAP, mmHg), right ventricular area (RV-area, cm^2), and right atrial area (RA-area, cm^2), tricuspid annular plane systolic excursion (TAPSE), left ventricular eccentricity index (LV-EI), RV-pump function and LV-pump function (LV-EF, %).

Lung function

- FEV1 (forced expiratory volume in 1 second), TLC (total lung capacity), DLCO (diffusing capacity of the lung)

Analyses of blood samples
Venous blood will be analyzed to determine:

- NT-pro BNP

Blood for blood gas analyses

- oxygen partial pressure, carbon dioxide partial pressure, oxygen saturation of the blood (SpO_2), pH values, bicarbonates, base excess

Pulmonary hemodynamics by right heart catheterization

- sPAP, mPAP, diastolic pulmonary artery pressure (dPAP), pulmonary artery wedge pressure (PAWP), right atrial pressure (RAP), cardiac output and ejection fraction (CO), central venous saturation, via blood gas analysis from pulmonary artery (SvO_2)

8.4.2 Safety Parameters

Safety variables include and will be determined:

1. Electrocardiogram (ECG)
2. Vital signs: Blood pressure, heart rate/pulse, oxygen saturation
3. Hemodynamics: Cardiac Output, SvO_2 (during RHC)
4. Echocardiography
5. Clinical laboratory investigations
6. Concomitant medication
7. Concomitant diseases
8. Adverse events

Clinical worsening will be defined as time to first event out of:

- worsening of WHO functional class
- deterioration of 6MWD >15% compared to baseline
- need of initiation of targeted PAH treatment
- hospitalization due to worsening of right heart function
- all cause death or lung-transplantation
- atrial septostomy

Safety variables

Laboratory, electrocardiogram, vital signs, assessment of adverse events and serious adverse events will serve as safety parameters.

Patients with a serious adverse event occurring during the study treatment will be followed by the study team until the serious adverse event will have resolved to the pre-study level and/or will have been addressed according to best clinical practice. Patients withdrawing from the study prematurely will have a final examination.

If a patient withdraws from study treatment and agrees to stay in the study, study related examinations will be performed and data will be obtained according to protocol.

8.5 End of Trial

The trial will end once the last patient has had their safety follow-up visit by phone 30 ± 14 days after last intake of study drug.

8.6 Plan for Treatment of Care after the Trial

Riociguat (MK-4836) is not approved for the indications studied and therefore cannot be further prescribed after the end of the study. In case of development of manifest PAH, measured by RHC

during Visit 3, a targeted PAH therapy will be initiated according to the guidelines. Otherwise the study medication will be discontinued. Patients will be offered a follow-up for 6 more months in terms of early detection any clinical deterioration.

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An AE is any unfavorable and unintentional change in the body temporally associated with the use of a drug whether or not considered related to the use of the product. A clinically significant worsening of a pre-existing condition is also assumed to be an adverse event. AEs may also occur subsequent to overdose, improper use, or due to premature withdrawal of a product.

An AE may be:

- New symptoms/ medical conditions
- New diagnosis
- Significant changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening (change in nature, severity or frequency) of medical conditions/ diseases existing before clinical trial start
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.
- Events related or possibly related to concomitant medications

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

AEs are classified as "non-serious" or "serious".

All AEs need to be documented in data entry forms and sent to the sponsor.

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose:

- Results in death

- Is life-threatening (the term life-threatening refers to an event in which the subject was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe)
- Requires subject hospitalization or prolongation of existing hospitalization (unless the admission results in a stay of less than 12 hours or the admission is pre-planned or the admission is not associated with an adverse event)
- Results in persistent or significant disability/ incapacity or is a congenital anomaly/ birth defect.
- Is another important medical event which may not fulfil the aforementioned criteria but may jeopardize the patient based upon appropriate medical judgment. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations. These should also usually be considered serious (e.g. treatment at home for allergic bronchospasm).

The following events don't need to be reported as an SAE:

- Planned hospitalization due to scheduled elective catheterization (e.g. scheduled re-evaluation of pulmonary disease), scheduled hospitalization for further diagnostics or therapeutic measures.

9.1.3 Expectedness

An 'unexpected' adverse event is one the nature or severity of which is not consistent with the applicable "Summary of Product Characteristics" (SmPC) or scientific literature. Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute 'unexpected' events.

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to IMP and 'unexpected', i.e. the nature and/ or severity of which is not consistent with the applicable product information are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs). The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

In case, either the investigator who primarily reported the SAE or the second assessor classify the SAE as 'suspected' (i.e. either related or *probably* or *possibly related* to the IMP *or not assessable*) and the SAE is unexpected it will be categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible IRB / EC and to all participating investigators.

9.1.5 Grading of AEs

The **grading** of an AE should be assessed by the investigator according to the 5-grade scale as follows:

Grade 1: mild AE, temporary event which is tolerated well by the subject

Grade 2: moderate AE; event which results in discomfort for the subject and impairs his/ her normal activity

Grade 3: severe AE; event which results in substantial impairment of normal activities of subject

Grade 4: life-threatening AE or AE causing disablement

Grade 5: death related to AE

9.1.6 Relationship and outcome of AEs, action taken

Causality assessment of an AE/SAE regarding an investigational product (causality) is determined and documented by the investigator based on the following criteria:

definite: There is a definite relationship.

probable: An AE that has a reasonable possibility that the event is likely to have been caused by IMP. The AE has a **timely relationship** and **follows a known pattern of response**, but a potential alternative cause may be present.

possible: An AE that has a reasonable possibility that the event may have been caused by IMP. The AE has a **timely relationship** to the IMP; **however, the pattern of response is untypical**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.

unlikely: Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.

Definitely not: No relationship. An AE that does not follow a reasonable temporal sequence related to IMP and is likely to have been produced by the subject's clinical state, other modes of therapy or other known etiology.

not assessable: There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

An AE/SAE will be classified as drug-related if the relationship determined by the investigator is possible, probable, or definite (causal relationship).

The **outcome** of an AE at the time of the last observation will be classified as:

Recovered/ resolved	all signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation
Recovering/ resolving	the intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution
Not recovered/ not resolved	signs and symptoms of an AE are mostly unchanged at the time of the last interrogation
Recovered/ resolved with sequel	actual signs and symptoms of an AE disappeared but there are sequels related to the AE
Fatal	resulting in death. If there is more than one adverse event only the adverse event leading to death (possibly related) will be characterized as ‘fatal‘
Unknown	the outcome is unknown or implausible and the information cannot be supplemented or verified

The **action taken** with the IMP will be assigned to one of the following categories:

‘Dose not changed’: no change in the dose of IMP.

‘Dose reduced’: reduction in the dose of IMP.

‘Dose increased’: increase in the dose of IMP.

‘Drug withdrawn’: discontinuation of IMP.

‘Unknown’: the information is unknown or implausible and it cannot be supplemented or verified.

‘Not applicable’: the question is implausible (e.g. the subject is dead).

The term ‘Countermeasures’ refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequels. The following categories will be used to categorize the countermeasures to adverse events:

None: no action taken

Drug treatment: newly-prescribed medication or change in dose of a medication

Others: other countermeasures, e.g. an operative procedure

9.2 Period of Observation and Documentation

All AEs reported by the subject or detected by the investigator, will be collected during the trial and must be documented on the appropriate pages of the CRF. AEs must also be documented in the subject's medical records.

In this trial, all AEs that occur after first administration of the IMP up to the last visit (i.e. follow-up visit) will be documented on the pages provided in the CRF. AEs will be assessed by the investigator using no-leading questions or observed during any visit during the whole study. The patient should be motivated to report any AEs by phone to the investigator occurring in between study visits. All subjects who have AEs, whether considered associated with the use of the trial medication or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition.

Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

9.3 Reporting of Serious Adverse Events by the Investigator

All SAEs must be reported by the investigator to the responsible Pharmacovigilance Safety Officer immediately without exceeding 24 hours after the SAE becomes known to the study team using the "Serious Adverse Event" form. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, information regarding onset, end date, severity, outcome and action taken with the IMP, an assessment of the causal relationship between the event and the trial medication.

All facts which require a benefit-risk reassessment of the study drug have to be reported promptly (that is within 15 days at latest) to IRB / EC. This includes particularly: expected SAE with unexpected outcome, increase in frequency of clinically relevant SAEs, unexpected SAE with assumed causal relationship after finalization of the investigator sponsored study and events which probably may harm the safety of the study patients. In the event of premature termination of the trial for safety reasons, the sponsor will inform the competent authority and IRB / EC without delay within a maximum period of 15 days.

If measures to protect study patients from immediate danger are taken IRB / EC have to be notified immediately.

At the time of the initial report, the investigator will fill in a SAE form comprising the following information:

- Patient/subject demographics
- Start and end date of treatment with the IMP
- Nature of the SAE including date of onset, severity and treatment (including hospitalization)
- Action taken with respect to the IMP
- Relationship to the IMP in the opinion of the investigator
- Relevant concomitant drug therapy, relevant medical history, relevant test and diagnostic procedures
- Outcome (clinical state at time of current observation)
- Recovery date (if available)
- In the case of death, the cause and post-mortem findings (if available).

9.4 Expedited Reporting

Unexpected SAE with assumed causal relationship (SUSARS) have to be promptly (that is within 15 days at latest; in case of SAEs, that lead to death or are life threatening: within 7 days and a follow up report within further 8 days) reported to all involved investigators and competent IRB / EC.

Investigators participating in this trial will report all SAEs to the responsible **Pharmacovigilance Safety Officer** by fax or e-mail using the **SAE form** as soon as possible but **not later than 24 hours** after their notification.

Additionally, all serious events as well as all other relevant safety information (e.g. pregnancy) have to be reported within one (1) working day following notice to

MSD SHARP & DOHME GmbH, department of Pharmacovigilance

Fax No. +49 89 / 4561-1352 or e-mail to Arzneimittelsicherheit@msd.de

Any requested supporting documentation (e.g. ECG, laboratory results, autopsy report) should be sent to the same address stated above. This documentation may only be sent in pseudonymized form. The original SAE-reports and all other reports will be kept by the investigator.
Additionally, a list of all SAEs as well as a report about the safety of the study patients' needs to be submitted annually (or on demand) to the competent IRB / EC during the investigator sponsored study.

All initial reports and follow-up information (as many as required) will be pseudonymized and sent by fax or via e-mail.
At the time of the initial report, the investigator will fill in a SAE form comprising the following information:

- Patient/subject demographics
- Protocol number
- Start and end date of treatment with the IMP
- Nature of the SAE including date of onset, severity, chronicity and treatment (including hospitalization)
- Action taken with respect to test drug
- Relationship to test drug in the opinion of the investigator
- Concomitant drug therapy at the time of the adverse event
- Outcome (if available)
- Recovery date (if available)
- In the case of death, the cause and post-mortem findings (if available).

The assessor will fill out a 'Narrative Second Assessment Form' for each SAE containing at least the following information:

i) Assessment of relationship between SAE and IMP;
ii) Assessment of expectedness of SAE (derived from SmPC);
iii) Assessment of relationship between SAE and underlying disease
iv) Statement if the benefit/ risk assessment for the trial did change as a result of the SAE.

The expedited reporting (to IRB / EC and investigators) will be carried out by the responsible Safety Officer.
The expedited reporting will be carried out after unblinding. Only SUSARs/SAEs occurring after administration of the IMP will undergo expedited reporting. In case of a SUSAR after

administration of placebo a decision regarding the need of expedited reporting will be taken after deliberation between the assessor and the Principal Investigator.

9.5 Emergency Unblinding

If it is medically imperative to know which trial medication the subject has received, the investigator or authorized person should open the emergency envelope. The investigator or the person who breaks the blind must record the date and the reasons for doing so in the CRF, in the subject's medical record, and on the emergency envelope. Whenever possible, the Coordinating Investigator should be contacted before the blind is broken.

9.6 Emergency Treatment

During and following a subject's participation in the trial, the investigator should ensure that adequate medical care is provided to a subject for any AE including clinically significant laboratory values. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

In case of clinical worsening and if clinically indicated additional PAH-targeted rescue medication will be initiated.

10 Statistical Procedures

10.1 Sample Size Calculation

In this randomized study patients with early pulmonary vascular disease, indicated by either a) mPAP ≥25 mmHg with PVR ≥2 to <3 WU and PAWP ≤15 mmHg or b) mPAP 21-<25 mmHg with PVR ≥2 WU and PAWP ≤15 mmHg will be randomized into two groups: one group receiving riociguat (MK-4836) and one placebo group.

In the EDITA study (Pan et al. 2019) SSc patients with mildly elevated mPAP 21-24 mmHg showed a significant reduction of PVR after 6 months of treatment (control-group 0.02±0.76 vs. intervention group -0.59±0.79 WU; effect size 0.77). The changes in PVR were equal to a 23.87±35.68% reduction in the intervention group and increase by 5.44±36.61% in the control group (effect size 0.81).

A meta-analysis showed an effect size of 0.88 in both PAH and CTEPH (Zhao et al. 2019).

In the retrospective analysis of patients with CTD-APAH receiving riociguat in PATENT-1 and PATENT-2, mean improvement of PVR after 12 weeks was 132±140 dynes*sec*cm^{-5} in patients with SSc (equals 1.65±1.75WU; effect size 0.94; Humbert et al. 2017). Patients with SSc-PAH had an effect size of 0.97 (Humbert et al. 2017).

In this study, patients with PVR ≥2WU will be included. The use of the effect size of the EDITA study for sample size calculation leads most likely to an underestimation of the effect, as in this study with ambrisentan most patients showed a PVR <2 WU at baseline. Furthermore, all studies reported in the table below had a study duration of 12 weeks. A study duration of 24 weeks will lead to a higher effect and reduction of PVR. Therefore, we assume an effect size of 0.87 of riociguat (MK-4836) treatment in this study. A comparable effect size for both included subgroups is anticipated for this study.

Reference	Change / difference in PVR	Effect size	Power	Sample size without dropout
Pan 2019; EDITA	SSc: 0.61±0.79 WU (Ambrisentan)	0.77	80%	56
Pan 2019; EDITA	**SSc: -23.87±35.68% (n=17) in the intervention group and increase by 5.44±36.61% (n=15) in the control (Ambrisentan)**	**0.81**	**90%**	**66**
Zhao 2019 Meta-analysis Riociguat	PH (PAH and CTEPH): n=695 (Riociguat)	0.88	85%	50
Humbert 2017 CTD-APAH from PATENT-1 and 2	SSc: 1.65±1.75 WU Other CTD: 3.45±3.54 WU (Riociguat)	0.94 0.97	90% 90%	50 48
A sample size of 58 will lead to n=70 with dropout of 15%.				

If the true treatment effect is at least a 30% reduction of PVR (effect size is 0.87), a sample size of 29 patients/group (total 58 patients) achieves a statistical power of 90.2% to reject the null hypothesis, according to the two-sample student's t-test, with a type I error of 0.05 (two-sided).

With the sample size of 70 patients and a dropout of 15% (valid sample size n=58), we achieve a 90.2% power, if the means of PVR differ by at least 30% and both groups have an equal standard deviation of 34.5%. A sample of 70 patients (35 patients in each group), allocated in a 1:1 ratio, will therefore be included.

The primary endpoint will be analyzed by an analysis of covariance (ANCOVA) with baseline values as covariates, which has a power advantage over the student's t-test, achieving a statistical power of 90.2% or more. If the preconditions for ANCOVA are not met, a student's t-test assuming unequal variances (Welch-test) will be performed.

10.2 Definition of Trial Population to be analyzed

All patients randomized and treated will be valid for the modified intention-to-treat population, hence the numbers of patients in the safety and modified intention-to-treat populations will be identical. In the modified intention-to-treat analysis set, patients will be analyzed according to the group allocation they were randomized into. The primary endpoint will be analyzed in a complete case analysis.

As patients with only mild changes of hemodynamics will be included in this study, it is not assumed that the severity of pulmonary vascular disease will affect the participation in the follow-up examination. A complete case analysis is considered as valid, as participation of the follow-up examination is assumed to be completely at random.

As sensitivity analysis, multiple imputation for the primary endpoint will be performed and analyzed.

A randomized patient is valid for safety / modified intention-to-treat analysis, if at least one dose of study medication was administered.

A patient is valid for the per protocol analysis, if the patient is valid for the safety / modified intention-to-treat analysis, has an adequate PVR investigation at baseline and at week 24 or if withdrawn due to lack of efficacy has an adequate PVR investigation at any time post-baseline up to week 24, and shows no major protocol deviations.

Major protocol deviations are:

1. Patients who do not meet the inclusion criteria
2. Administration of IMP not according to protocol (e.g. compliance less than 80% or greater than 120% (corresponding to an overdose))

The above specifications of the analysis populations are in accordance with the recommendations given in the ICH-E9 Guideline “Note for guidance on statistical principles for clinical trials”.

10.3 Statistical Methods

10.3.1 General

Descriptive statistics

All variables will be analyzed descriptively with appropriate statistical methods: data (demographic and other baseline characteristics, continuous data at each visit and their change to baseline) will be listed and trial summary tables will be provided.

Descriptive statistics will be displayed by treatment, including the usual location and scale statistics (mean, median, standard deviation, standard error, first and third quartiles, minimum and maximum) and 95% confidence limits of mean and median.

Frequency tables for qualitative data will be provided.

Demographic variables and baseline characteristics will be summarized by treatment group for both analysis populations (i.e. valid for safety / modified intent to treat analysis (ITT), valid for per protocol analysis). Wherever possible (i.e. sufficient sample size), centres will be considered for the analyses.

Hypotheses and statistical interference

Null-Hypothesis (H_0):

The means of the changes of the primary endpoint from baseline to follow-up after 24 weeks in the treatment and control group are the same.

Alternative hypothesis (H_1):

The mean change of the primary endpoint from baseline to follow-up after 24 weeks in the treatment group differs from the mean change in the control group.

Type I error

If not mentioned otherwise, all statistical tests will be performed with a type I two-sided error rate of $\alpha = 0.05$

Efficacy analysis

The primary efficacy analysis will be performed in patients valid for modified intention-to-treat analysis. The per-protocol analysis will be supportive.

Primary endpoint

The evaluation of the primary efficacy endpoint will be the change from baseline to 24 weeks in pulmonary vascular resistance. The primary analysis set will be a complete case analysis of the modified intention to treat set.

The main comparison will be the difference in treatment effect between riociguat (MK-4836) and placebo. 95% confidence intervals of treatment difference will also be calculated. The primary comparison will be an ANCOVA model including baseline scores as covariate.

If the preconditions for an ANCOVA analysis are not met, the primary endpoint will be analyzed by robust, two-sided t-test (Welch-test).

Secondary efficacy variables

All secondary analyses will be exploratory and will be considered descriptively. Secondary parameters at baseline and during follow-up will be compared between groups comparing the difference between baseline and follow-up visits. Data will be displayed by means and standard deviations, medians and variances with respective 95% confidence intervals. p-values <0.05 will be considered as statistically significant.

Secondary endpoints will be statistically analyzed by a hierarchical testing strategy using the two-sided student's t-test with comparison of the differences between riociguat (MK-4836) and placebo.

The sequential testing procedure will be performed for these six secondary efficacy variables, strictly in the order listed

- change of cardiac index at rest (baseline to 24 weeks)
- change of total pulmonary resistance (baseline to 24 weeks)
- change of diffusion capacity of the lung (baseline to 24 weeks)
- change of 6-minute walking distance (baseline to 24 weeks)
- change of WHO functional class (baseline to 24 weeks)
- change in QoL (SF-36, physical summation score; baseline to 24 weeks)

It is assumed that WHO functional class will either remain the same, improve by one or two categories, or deteriorate by one category in most cases. A change score (baseline minus end of study) will be calculated, which could go from -3 (class IV at baseline and class I at end of study) to +4 (class I at baseline, death at end of study), but in practice for those patients still alive at the end of the study it will most likely range from -2 to +1.

Exploratory endpoints

Further outcome parameters will be tested exploratory and reported with 95% confidence intervals of the difference between changes in the intervention and placebo group, mean and standard deviation of the mean. Parameters will be analyzed as change from baseline to 24 weeks riociguat (MK-4836) vs. placebo; if available as per visit and assessment schedule, changes between baseline and 12 weeks will also be analyzed.

Patients who withdraw from the study will be asked to complete a final examination which will be included in the data analysis.

Parameters for explorative data analysis include

WHO functional class (baseline to 12 weeks)

Echocardiography

- sPAP, RV-area and RA-area, TAPSE, LV-EI, RV-pump function and LV-EF.

QoL assessed by the short form of the medical outcome questionnaire (SF-36 questionnaire)

- (mental summation score as well as the 8 sub-scores)

Lung function and lung diffusing capacity

- FEV1 (forced expiratory volume in 1 second), TLC (total lung capacity), DLCO (diffusing capacity of the lung)

Blood for blood gas analyses:

- oxygen partial pressure, carbon dioxide partial pressure, SpO_2, pH values, bicarbonates, base excess

Analyses of blood samples:

- NT-pro BNP

Pulmonary hemodynamics by right heart catheterization:

- CI, sPAP, mPAP, dPAP, PAWP, RAP, PVR, CO, SvO_2

Sensitivity analyses

Sensitivity analyses will be performed to investigate the effect on patients with higher vs. lower PVR and higher vs. lower mPAP. A multiple imputation strategy will be implied and analyzed for the primary endpoint.

Safety analysis

The safety analysis will be performed in the population valid for safety. All tabulations will be descriptive only. Tables will be produced for drug-related treatment-emergent adverse events and serious adverse events. Further tables will be produced for serious and/or drug-related treatment-emergent adverse events.

Mortality in the 24-week period of the study will be summarized descriptively. Any deaths in the study period will be listed, with day of death relative to start and stop of study drug and cause of death.

The safety evaluation of laboratory data will include:

listings of laboratory data out of normal range, evaluation of the significance if they are out of normal range, descriptive analysis of continuous laboratory parameters and their changes from baseline by visit and treatment group. Vital signs will be summarized by visit and treatment group.

Clinical worsening (as exploratory safety endpoint) will comprise of the following parameters:

- worsening of WHO functional class
- deterioration of 6MWD >15% compared to baseline
- need of initiation of targeted PAH treatment
- hospitalization due to worsening of right heart function
- all cause death or lung-transplantation
- atrial septostomy

Biometric analysis will be defined in the statistical analysis plan which has to be authorized before data base lock by the biometrician and the Coordinating Investigator.

11 Data Management

11.1 Data Collection

All entries made in the CRF must be verifiable against source documents. The source data parameters are to be verified and the identification of the source data must be documented.

All findings including clinical and laboratory data will be documented in the subject's medical record and in the CRF. The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data. Any errors should have a single line drawn through them so that the original entry remains legible. The correct data should be entered at the site with the investigator's signature, date and reason for change to confirm the correctness of entries. Self-explanatory corrections need not to be justified.

The correctness of entries in CRF will be confirmed by dated signature of the responsible investigator.

11.2 Data Handling

After completion of data entry, checks for plausibility, consistency, and completeness of the data will be performed. Based on these checks, queries will be produced combined with the queries generated by visual control.

All missing data or inconsistencies will be reported back to the center and clarified by the responsible investigator. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

11.3 Storage and Archiving of Data

All important trial documents (e.g. CRF) will be archived for at least 25 years after the trial termination.

The investigator(s) will archive all trial data (source data and Investigator Site File (ISF) including subject identification list and relevant correspondence) according to the section 4.9 of the ICH Consolidated Guideline on GCP E6 (R2) and to local law or regulations.

12 Ethical and Legal Aspects

12.1 Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the

ICH-GCP E6 (R2) and the Declaration of Helsinki. The trial will be carried out in keeping with applicable European, national, local or other relevant legal and regulatory requirements.

12.2 Subject Information and Informed Consent

Before being admitted to the clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The subject must give consent in writing. The signed Informed Consent Form will be filed by the investigator.

A copy of the signed informed consent document must be given to the subject. The documents must be in a language understandable to the subject and must specify who informed the subject.

The subjects will be informed as soon as possible if new information may influence his/her decision to participate in the trial. The communication of this information should be documented.

12.3 Confidentiality

The data obtained in the course of the trial will be treated pursuant to the General Data Protection Regulation (GDPR) (EU) 2016/679 and relevant national law.

During the clinical trial, subjects will be identified solely by means of their initials, year of birth, and an individual identification code (subject number, randomization number). Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of EU and national data legislation will be fulfilled in its entirety.

The subject consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors).

According to relevant European and national provisions authorized persons (clinical monitors, auditors, inspectors) may inspect the subject-related data collected during the trial.

The investigator will maintain a subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. Subjects who did not consent to circulate their pseudonymized data will not be included into the trial.

12.4 Responsibilities of the Investigator

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions.

The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.5 Approval of Trial Protocol and Amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the competent IRB / EC for all participating centers.

A written favorable vote of the respective EC and an (implicit) approval by the competent IRB are a prerequisite for initiation of this clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

Before the first subject is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes will be submitted to IRB / EC in writing as protocol amendments, if required by applicable law.

The investigator will keep a record of all communication with IRB / EC.

12.6 Continuous Information to Independent Ethics Committee

If required by national law, IRB / EC will be informed of all suspected unexpected serious adverse reactions (SUSARs). Both institutions will be informed in case the risk/ benefit assessment did change or any others new and significant hazards for subjects' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) will be submitted once a year – Development Safety Update Report (DSUR).

IRB / EC must be informed of the end of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase, i.e. after last subject out (LSO).

12.7 Notification of Regulatory Authorities

The local regulatory authorities responsible for each particular investigator will be informed before the beginning, during and at the end of the trial according to the applicable regulations.

12.8 Registration of the Trial

Prior to the beginning of the clinical phase (FPI) the coordinating/ principal investigator will register the trial at the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/) . Thus, the trial will be given a unique EudraCT number, which is a prerequisite for a publication in a peer-review paper.

12.9 Insurance

Sponsor must subscribe to an insurance policy covering its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company named in the patient's informed consent form. The subject is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the subject must not undergo other clinical treatment except for cases of emergency. The subject is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the subject.

The insurance company has to be informed about all amendments that could affect subjects' safety.

13 Quality Assurance

13.1 Monitoring

Monitoring will be done by personal visits from a clinical monitor in order to comply with GCP guidelines. The center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP and legal aspects.

The monitor will review the entries into the CRFs on the basis of source documents. This will include on-site checking of the CRF for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. The investigator must allow the monitor to verify all essential documents including source documents and must provide support at all times to the monitor.

By frequent communications (letters, telephone, fax), the site monitor will ensure that the trial is conducted according to the protocol and regulatory requirements.

13.2 Quality checks

Quality checks will be done by review of the entries into the CRFs. This will include checking of the CRF/data for completeness and clarity, cross-checking for plausibility.

13.3 Inspections/ Audits

Regulatory authorities may request access to all source documents, CRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities.

14 Agreements

14.1 Financing of the Trial

The trial will be co-financed using funds of MSD SHARP&DOHME GmbH Germany.

This funding source had no role in the design of this study and will not have any role during analyses, interpretation of the data, or decision to submit results.

14.2 Financial Disclosure

Before the start of the trial, the investigator will disclose any proprietary or financial interests he or she might hold in the sponsors/ a funding company, in the investigational product(s) or any commercial organization being involved in the clinical trial. The investigator has also to confirm that he/she has not entered into any financial arrangement, whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

14.3 Reports

The Biometrician will prepare the biometrical report. The final trial report will be prepared by the biometrician and the independent Steering Committee members.

14.4 Publication

All information concerning the trial is confidential before publication, which will be coordinated by the independent steering committee members of the trial.

15 Sponsor Signatures

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- the current risk-benefit assessment of the investigational medicinal product
- The moral, ethical, and scientific principles governing clinical research as set out in the applicable version of Declaration of Helsinki and the principles of GCP.

The investigator will be supplied with details of any significant or new finding including AEs relating to treatment with the investigational medicinal product.

Date: [redacted] Signature: [redacted]

Name (block letters): Sebastian Frank

Function: Sponsor; manager Thoraxklinik Heidelberg gGmbH

Date: [redacted] Signature: [redacted]

Name (block letters): Prof. Dr. med. Ekkehard Grünig

Function: Coordinating Investigator/ Investigator

Date: [redacted] Signature: [redacted]

Name (block letters): [redacted]

Function: Biometrician

16 Declaration of Investigator

I have read the above trial protocol and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enroll the first subject only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for trial participation from all subjects.

I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described. I will provide a Curriculum Vitae (CV) before trial start. I agree that the CV may be submitted to the responsible regulatory authorities

Date:_____ Signature:_____

Name (block letters): _____

Function: Investigator

Trial Center (address): _____

_____

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18 Appendices

SF-36 (English version „Health status questionnaire“),

Patient diary (English version)

Patient trial ID-card (English version)

HEALTH STATUS QUESTIONNAIRE

This questionnaire is about your assessment of your health status over the past 4 weeks. The sheet allows you to track over time how you are feeling and how you are doing in your daily life.

Please answer each of the following questions by ticking the number that best applies to you in the answer options.

2) In general, how would you describe your health over the past 4 weeks?

(Please tick only one number).

Excellent 1

Very good 2

Good 3

Not too good 4

Bad 5

2. Compared to a year ago, how would you describe your health a year ago.
(Please tick only one number)

Currently much better than a year ago. 1

Currently somewhat better than a year ago. 2

About the same as a year ago. 3

Currently a little worse than a year ago. 4

Currently much worse than a year ago. 5

3. The following are some activities you might do on a normal day. Are you limited by your current health condition in these activities? If so, to what extent?
(Please tick only one number in each line.)

ACTIVITIES	Yes, very limited	Yes, somewhat limited	No, not limited at all
a. exhausting activities, e.g. running fast, lifting heavy objects, strenuous sports	1	2	3
b. moderately difficult activities, e.g. moving a table, vacuuming, bowling, playing golf, etc.	1	2	3
c. Lifting or carrying shopping bags	1	2	3
d. climbing several staircases	1	2	3
e. climbing a staircase	1	2	3
f. bending, kneeling, crouching	1	2	3
g. walking more than 1 kilometer	1	2	3
h. walking across several intersections	1	2	3
i. walking across an intersection	1	2	3
j. bathing or getting dressed	1	2	3

4. In the past 4 weeks, have you had any difficulties at work or other daily activities at work or at home because of your physical health?
(Please tick only one number in each line)

DIFFICULTIES	YES	NO
a. I could not work as long as usual	1	2
b. I have managed less than I wanted	1	2
c. I could do only certain things	1	2
d. I had difficulties performing (e.g. I had to make an extra effort)	1	2

5. In the past 4 weeks, did you have any difficulties at work or other daily activities at work or at home due to mental health problems (e.g., because you felt down or anxious)?
(Please mark only one number in each line)

DIFFICULTIES	YES	NO
a. I could not work as long as usual	1	2
b. I have managed less than I wanted	1	2
c. I could not work as carefully as usual	1	2

6. During the past 4 weeks, how much have your physical health or mental health problems affected your normal contacts with family members, friends, neighbors, or acquaintances
(Please tick only one number)

Not at all 1

A little 2

Moderately 3

Pretty much 4

Very much 5

7. How severe has your pain been in the past 4 weeks?
(Please tick only one number)

I have not had any pain. 1

Very slight. 2

Slight 3

Moderate 4

Severe 5

Very severe 6

8. In the past 4 weeks, to what extent has the pain interfered with you performing your daily activities at home and at work?
(Please tick only one number)

Not at all 1

A little 2

Moderately 3

Pretty much 4

Very much. 5

9. These questions are about how you are feeling and how you have been feeling over the past 4 weeks. (Please tick the number in each line that most accurately reflects how you are feeling). In the past 4 weeks, how often have you been....
(Please tick only one number in each line).

PERSONAL FEELING	always	mostly	quite often	sometimes	rarely	never
a. ... full of vim and vigor?	1	2	3	4	5	6
b. ...very nervous?	1	2	3	4	5	6
c. ... so depressed, that nothing could have cheered you up?	1	2	3	4	5	6
d. ... calm and relaxed?	1	2	3	4	5	6
e. ...full of energy?	1	2	3	4	5	6
f. ... discouraged and sad?	1	2	3	4	5	6
g. ...exhausted?	1	2	3	4	5	6
h. ...happy?	1	2	3	4	5	6
i. ...tired?	1	2	3	4	5	6

10. In the past 4 weeks, how often have your physical health or mental health problems affected your contacts with other people (visits to friends, relatives, etc.)?
(Please tick only one number)

Always 1

Mostly 2

Sometimes 3

Rarely 4

Never 5

11. To what extent does each of the following statements apply to you?
(Please tick only one number in each line)

STATEMENT	absolutely true	Largely true	I do not know	Largely not true	Not true at all
a. I seem to get sick a little easier than others	1	2	3	4	5
b. I am as healthy as everyone else I know	1	2	3	4	5
c. I expect my health to decline	1	2	3	4	5
d. I am in excellent health	1	2	3	4	5

Title page

Patient Diary

Study name: ESRA

Center no.: …….

Patient no.: …….

Randomization-no.: …….

Next study visit: …….

Please bring this diary with you to every study visit.

User instructions for taking the study medication: ESRA.

The study medication must be kept only in the original bottle (inaccessible to children).

The study medication must be taken three times a day, always at the same time of day,

independently of meals:

• Please record the date and time of taking the tablets in the patient diary until visit 3. One diary page is provided for each month (Table 1 of diary).

• Tablets should be taken in the morning, at noon and in the evening at intervals of at least 6 hours apart.

• Please bring any tablets you do not need back to the clinic using the original bottle.

- Blood pressure measurements at home: Since the drug may lower blood pressure, we would like to ask you to measure your blood pressure with your device three times a day (morning, noon and evening) during the study for the first 8 weeks (titration phase) until you reach the dosage you tolerate best (target dose). After measuring your blood pressure, please record the upper and lower readings (syst. / diast.) as well as the pulse with date and time of the measurement in the patient diary (Table 1 of the diary). Please bring the diary with the measured values to all visits at the clinic. In addition, we will ask for the values during the telephone visits every two weeks (weeks 2, 4, 6 and 8) and enter them into our database. If the blood pressure values are lowered too far by the medication, it is not possible to increase the medication dose any further. Therefore, the measurements are important for therapy adjustment. After reaching the target dose, it is sufficient to measure the blood pressure only when necessary, e.g. when one feels unwell or other complaints occur. In preparation for the telephone visits, please complete Table 2 of the patient diary.
- Home pregnancy test: women will perform a home pregnancy test in the morning before the telephone visits at weeks 4, 8, 16, 20 and for telephone follow-up 30 days after the end of the study. Please record the result (negative or positive) as well as date and time of the test in the patient diary (Table 2 of the diary). A single table is provided for all telephone visits. Pregnancy tests will be provided to you in advance by your study team.

Please note:

If possible, always take the study medication at the same time of day. If you forget to take it at one point in time, do not take a double dose at the next point in time. The bottles of tablets you will receive will last until your next visit to the hospital.

Please take the medicine three times a day.

Center No.: Patient No.:

Month/Year:

Diary - Table 1: Tablet intake and vital parameters

Day	**Dose and time of tablet intake** **Vital parameters (VP)=blood pressure and pulse (VP) from week 0-8 only.**						
	morning hh:mm blood pressure/pulse		noon hh:mm blood pressure/pulse		evening hh:mm blood pressure/pulse		comments
1	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
2	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
3	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
4	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
5	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
6	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
7	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
8	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
9	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
10	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
11	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
12	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
13	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
14	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
15	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
16	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
17	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
18	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	

19	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
20	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
21	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
22	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
23	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
24	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
25	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
26	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
27	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
28	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
29	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
30	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	
31	_____mg	___:___	_____mg	___:___	_____mg	___:___	
VP	___/___mmHg	___/min	___/___mmHg	___/min	___/___mmHg	___/min	

Diary - Table 2: Telephone visits

Week	**Tolerability**		**Women: Pregnancy test result and time**		
	systolic blood pressure / (upper value) ≥95 mmHg	side effects	neg. / pos.	morning hh:mm	comments
2	☐ yes ☐ no	☐ yes ☐ no			
4	☐ yes ☐ no	☐ yes ☐ no		___:___	
6	☐ yes ☐ no	☐ yes ☐ no			
8	☐ yes ☐ no	☐ yes ☐ no		___:___	
16				___:___	
20				___:___	
Follow-up				___:___	

Patient trial ID-card

ESRA trial

Study Center (Stamp):

Name

_____

Surname

_____

This patient participates in the study

"Efficacy and safety of riociguat (MK-4836) in incipient pulmonary vascular disease as an indicator for early pulmonary arterial hypertension

Double-blind, randomized, multicenter, multinational, placebo-controlled phase IIa study (ESRA)"

Investigational drug: riociguat (MK-4836) vs. placebo

Eudra-CT: 2021-001633-40

For questions please contact

Name_____ Phone _____