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

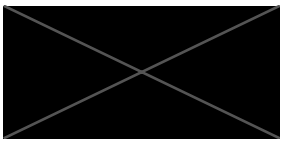
Statistical Analysis Plan

Version V1.1 of 07.08.2025

Investigational medicinal product:	Riociguat (MK-4836)
Comparator	Placebo
Indication:	Early pulmonary arterial hypertension
Sponsor:	Thoraxklinik Heidelberg gGmbH
Supplier:	MSD/Merck
Protocol registry identification:	Local Project ID: 2020-01RCT Supplier's Protocol No. (MSD): MK-4836-004 EU CT No.: 2023-509695-42-00 EudraCT No.: 2021-001633-40 NCT number: NCT05339087
Development phase:	IIa

Approved by

Principal Investigator



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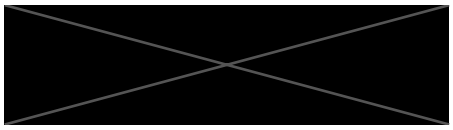

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Statistician

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1 Background

1.1 Trial objective

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.

Primary objective

1) To investigate the effect of riociguat (MK-4836) treatment on pulmonary vascular resistance in patients with early pulmonary vascular disease, defined as stated above 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 in patients with early pulmonary vascular disease, defined as stated above as change from baseline to 24 weeks of treatment.
3) To assess safety and tolerability of riociguat (MK-4836) treatment in patients with early pulmonary vascular disease, defined as stated above as change from baseline to 24 weeks of treatment.

1.2 Trial design

Randomized (1:1), double-blind, placebo-controlled, multicenter, multinational study. Investigator-Initiated-Trial (IIT)

After the pre-treatment phase, eligible subjects were 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).

1.3 Randomisation, stratification, blinding and replacement of patients

Randomisation was performed by permuted block randomization, stratified by centre. Treatment was allocated by consecutive patient numbers for each centre with respective blinded medication included in the investigational medicinal product packages for each visit. Patients and investigators were blinded to treatment assignment. The statistician will be blinded to treatment assignment during the statistical analysis. In case of dropout, loss to

follow-up, early withdrawal or other cases of incomplete data, patients were not replaced. However, patients were encouraged to perform their final assessment in case of early termination or withdrawal. The results will be included in the analysis.

1.4 Data collection and monitoring

Data was entered into a paper-based CRF which was monitored for data quality, consistency and completeness. The monitored data was forwarded to data management for database entry, data checks and queries to the study site. For database closure, all queries have to be addressed and closed.

2 Definitions of patient populations to be analyzed - Analysis sets

2.1 Definitions

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 have seemed unethical in patients, who are in clear indication of targeted treatment, patients with manifest PAH according to the current definition could 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) were eligible to be enrolled into this study. Both a) and b) represent one phenotype with early pulmonary vascular disease/pathology.
All patients randomized and treated will be valid for the intention-to-treat population, hence the numbers of patients in the safety and intention-to-treat populations will be identical. In the intention-to-treat analysis set, patients will be analysed according to the group allocation they were randomized into. The primary endpoint will be analysed in a complete case analysis.
As sensitivity analysis, multiple imputation for the primary endpoint will be performed and analyzed.
A randomized patient is valid for safety / 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 / intention-to-treat analysis 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”.

2.2 Application

The primary efficacy analysis will be performed in patients valid for intention-to-treat analysis. The per-protocol analysis will be supportive. The safety analysis set will be equal to the intention-to-treat analysis set.

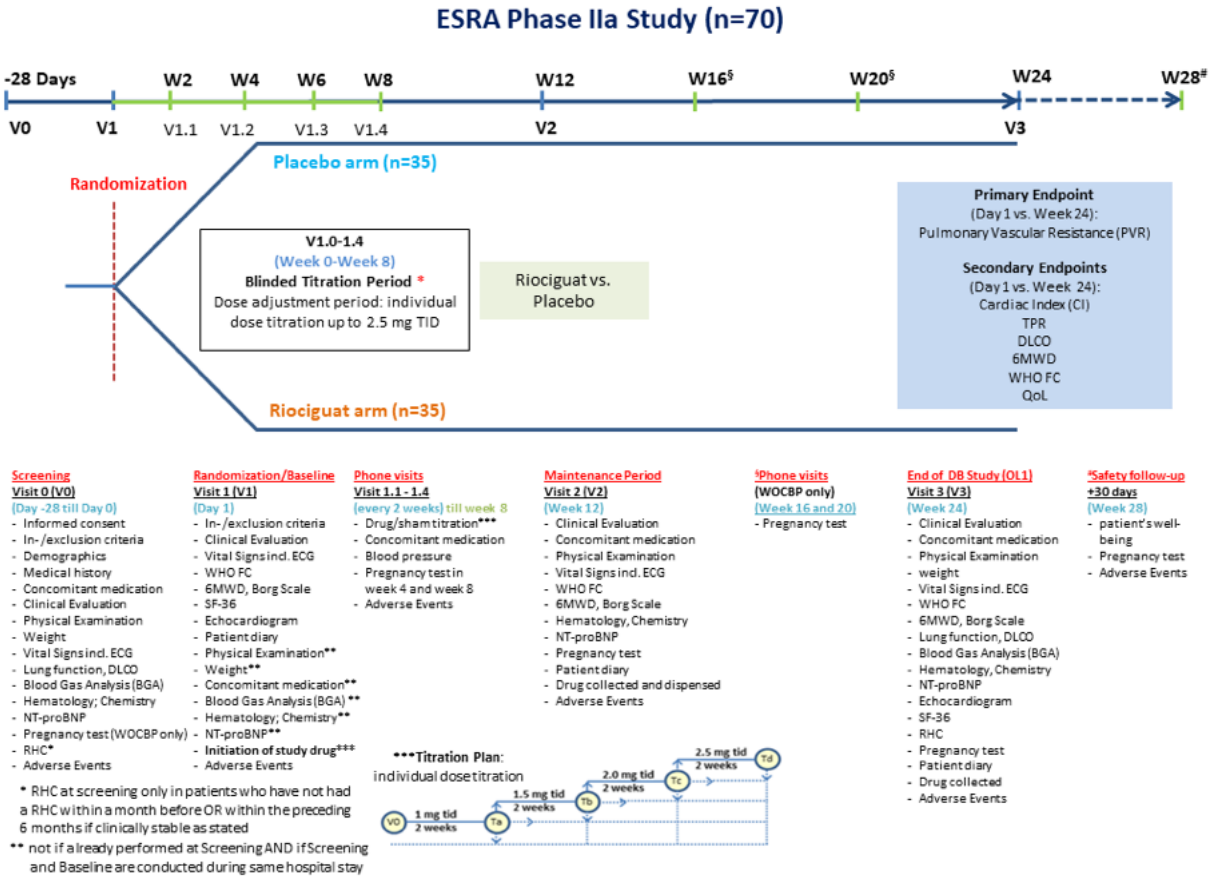
3 Trial centres

Patient numbers included per centre.

Centre	**Planned number of patients**	**Actual number of patients**
Heidelberg, Germany	25	23
Dresden, Germany	5	0
London, England	20	3
Lille, France	4	3
Zurich, Switzerland	4	3
Graz, Austria	4	2
Linz, Austria	4	1
Naples, Italy	4	0
Oslo, Norway	*Site considered but eventually not selected*	
Total	70	35*

*Reduced sample size due to early termination of the study for strategic reasons.

4 Visit schedule



* RHC at screening only in patients who have not had a RHC within a month before OR within the preceding 6 months if clinically stable as stated

** not if already performed at Screening AND if Screening and Baseline are conducted during same hospital stay

Overview of visit 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.

5 Analysis variables

5.1 Efficacy Variables

The primary efficacy variable is the change of PVR from baseline to 24 weeks.

5.1.1 Sample size considerations

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 were 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 were to 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 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%.				

With the sample size of 70 patients and a dropout of 15% (valid sample size n = 58), a 90.2% power will be achieved to reject the null hypothesis, if the true treatment effect is at least a 30% reduction of PVR and both groups have an equal standard deviation of 34.5%, according to the two-sample student's t-test, with a type I error of 0.05 (two-sided). A sample of 70 patients (35 patients in each group), allocated in a 1:1 ratio, was therefore aimed to 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.

5.2 Demography and baseline characteristics

Age, height, weight, medical history, PAH classification, WHO functional class, Vital signs, oxygen saturation, hemodynamics (invasively assessed by right heart catheterization and by echocardiography), laboratory, quality of life.

5.3 Secondary analysis

5.3.1 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)

The following parameters will be assessed in every patient according to the visits schedule and analyzed as **exploratory variables**. Changes between groups will be compared by student's t-test or Welch-test if variances are not equal. Nonparametric data will be compared by Wilcoxon-Mann-Whitney test. Frequency data will be compared with chi-square tests. Exploratory endpoints will be analyzed as change from baseline to 12 and 24 weeks as available per assessment schedule. According to the study protocol, patients were encouraged to perform their final assessment visit in case of any premature termination of study treatment or study participation.

QoL assessed by the SF-36 questionnaire
Short form health survey 36, including 2 summation scores and 8 subscores.
QoL will be assessed using the SF 36-questionnaire 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.

WHO functional class
Analysis of changes between baseline and first/second follow-up.

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

5.4 Tolerability, safety and survival

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 adverse events and serious adverse events. Further tables will be produced for serious adverse events.

Mortality will be summarized descriptively. Any deaths in the study period (until survival follow-up) will be listed, with day of death relative to start and stop of study drug and cause of death.

Safety variables include:

Electrocardiogram (ECG)

Vital signs: Blood pressure, heart rate/pulse, oxygen saturation

Hemodynamics: Cardiac Output, SvO2 (during RHC)

Echocardiography

Clinical laboratory investigations

Concomitant medication

Concomitant diseases

Adverse events

Clinical worsening was 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

5.4.1 Health economics

Clinical worsening events including need of initiation of targeted PAH treatment, hospitalization due to worsening of right heart function and all cause death or lung-transplantation may be analysed in consideration of health economics in case of sufficient events.

6 Handling of missing values and outliers

6.1 Missing values

All missing data or inconsistencies are to be reported back to the center and clarified by the responsible investigator. Data will be primarily analyzed in the intention-to-treat analysis set. As sensitivity analysis, multiple imputation will be performed and analyzed for the primary endpoint.

6.2 Outliers

Outliers will be defined as values from 1.5 to 3 x interquartile range. Values above 3 x interquartile range will be defined as extreme outliers. For the primary endpoint and secondary efficacy endpoints a sensitivity with exclusion of extreme outliers will be performed.

7 Statistical analyses / methods

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.

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.
Demographic variables and baseline characteristics will be summarized by treatment group for the valid for safety / modified intention to treat analysis (ITT). Due to the reduced sample size, centre effects may not be considered in the analyses.

7.1 Subject disposition

Type of pulmonary arterial hypertension, hemodynamics, WHO functional class, physical exercise capacity.

7.2 Demography and baseline characteristics

Demographic variables and baseline characteristics will be summarized by treatment group for the valid for safety / modified intention to treat analysis (ITT). Differences will be considered to be at random.

7.3 Prior or concomitant medication and diseases

Frequencies will be listed for each group.

7.4 Exposition to treatment/Compliance

Duration of intake or application, total intake, difference between treatment groups will be analysed and displayed by tabulation of results.

7.5 Primary analysis

Null-Hypothesis (H_0):
The means of the treatment and control group of the primary endpoint is the same at baseline and after 24 weeks.
Alternative hypothesis (H_1):
The mean of the treatment group of the primary endpoint after 24 weeks differs from the mean of 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 $\alpha = 0.05$

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 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).

A multiple imputation strategy will be implied and analyzed for the primary endpoint (25 imputations) in case of missing data for the primary endpoint.

7.6 Secondary analyses

7.6.1 Efficacy

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, or in case of non-normally distributed data with medians and variances. Changes will be displayed with means and standard deviations with respective 95% confidence intervals.

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. p-values <0.05 will be considered as statistically significant.

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)

.

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. Normally distributed data will be compared by two-sided student's t-tests or Welch-test in case of unequal variances. Non-normally distributed data will be analysed by nonparametric analysis methods such as the Wilcoxon-Mann-Whitney test. Frequency data will be compared by Chi square test, if preconditions are met. 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.

7.6.2 Safety/Tolerability

The safety analysis will be performed in the population valid for safety. All tabulations will be descriptive only.
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

7.6.2.1 Adverse events

Tables will be produced for adverse events with a frequency ≥ 5%, drug-related adverse events and serious adverse events. Serious adverse events, adverse events with a frequency ≥ 5% and drug-related adverse events will be displayed separately. In case of paired frequency data, analyses will be performed with McNemar Bowker test, or Wilcoxon signed rank test if preconditions are not met. Differences between therapy groups will be displayed by tabulation of results.
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.

7.6.2.2 Laboratory parameters

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 for women with childbearing potential at initial screening visit and visits 1, 3 and 5
Biomarkers	CRP, NT-proBNP

Efficacy laboratory will include analysis of N-terminal pro brain natriuretic peptide.
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.

7.6.2.3 Vital signs

Blood pressure, heart rate, SpO_2 will be analysed descriptively. Frequency of systolic blood pressure <95 mmHg will be displayed by group.

7.6.2.4 Pharmacokinetics

Not available

7.6.3 Exploratory analysis

Changes between baseline and 12 weeks, and between baseline and 24 weeks will be compared between groups by two-sided student's t-tests or Chi-square tests. For parameters see section 5.2.

7.7 Planned subgroup analyses

Subgroup analyses may not be performed due to insufficient sample size. In the original protocol, sensitivity analyses were planned including: investigation of the effect on patients with higher vs. lower PVR and higher vs. lower mPAP in case of sufficient sample size. Subgroup analyses by centre will be performed in case of sufficient sample size.

7.8 Interim analyses

Not available

8 Deviations from the original protocol

The study was ended prematurely, leading to a sample size reduction to 35 patients (planned 70 patients).

The study was terminated early due to a strategic decision of MSD/Merck:

"After reviewing the timelines, remaining payments, and considering the changing landscape and altered feasibility of this study, a strategic prioritization was made to select this study for early termination."

As a result of this decision, the final sample size reached 50% of the originally planned enrolment (n= 35). All statistical analyses will be conducted based on the available data at the time of study cessation. The reduction in sample size may limit the statistical power, particularly given the double blinded two-armed design of the study. According to the study protocol, patients were encouraged to perform their final assessment visit in case of any premature termination of study treatment or study participation. This data will be included into the final analysis according to the intention-to-treat principle.

Subgroup analyses may not be performed due to insufficient sample size.

9 Interpretation of results

Interpretation of data is limited by the early termination of the whole trial. This led to a reduction of sample size to 35 patients in total instead of per group, and to a premature study termination in a subset of patients. As the treatment effect is anticipated to be less distinct in a shorter period of time in the verum group and worsening of clinical parameters is expected to be less pronounced in the control group, early study termination will reduce the effect size and does therefore not bear the risk of overestimation of the clinical effects of the study treatment. A shorter study duration is expected to reduce the statistical power (reduction of sample size and effect size).

Safety data will comprise of less investigational medicinal production exposition than planned. As the study medication is already an approved treatment and extensive data on safety and tolerability is already available, a substantial impact on safety and tolerability results of the study is not anticipated.

Due to the reduced sample size, subgroup analyses such as centre effects may not be further analysed as sample sizes for each center and for hemodynamics subgroups are not high enough.

10 Data problems

Analysis of PVR distribution identified an outlier at visit 3, which could be corrected by calculation of PVR from the formula PVR = (mPAP – PAWP)/ CO * 80

PVR was therefore recalculated for all values at visit 3.

11 Software

Data analysis with SPSS V29, IBM Somers, New York.

12 References

NA

13 Appendices – List of Tables

All tables with mean ± standard deviation or n and % for frequency data.

Tables with comparisons between groups will additionally include p-values and 95% confidence intervals.

Table 1. Demographics and Baseline Characteristics for the whole dataset and by group.

(table may be split for better readability)

Female sex no. [%]	
Age [years]	
Height [cm]	
Weight [kg]	
PH duration [months]	
Vital signs	
	Systolic blood presure
	Diastolic blood pressure
	SpO_2 [%]
	Heart rate
WHO FC no. [%]	
	I
	II
	III
	IV
PAH Etiology	
	Idiopathic
	Heritable
	CTD-associated-PAH
	Other
Concominant diseases	
Blood gas analysis	
	SaO_2 [%]
	PaO_2 [mmHg]
	$PaCO_2$ [mmHg]
	pH
	Bicarbonates
Hemodynamics at rest	
	RAP [mmHg]
	sPAP [mmHg]
	dPAP [mmHg]
	mPAP [mmHg]
	PAWP [mmHg]

	CO [l/min]
	CI [l/min/m^2]
	PVR [WU]
	SvO_2 [%]
6MWD	
	6MWD [m]
	SpO_2 [%] test end
	Borg dyspnea score
Short Form-36 Health Survey	
	Physical functioning
	Physical role function
	Pain
	General health perception
	Vitality
	Social functioning
	Emotional role function
	Mental well-being
	Physical summation score
	Mental summation score
Echocardiography at rest	
	Estimated sPAP [mmHg]
	RA area [cm^2]
	RV area [cm^2]
	TAPSE [cm]
	LV-EI
	Left ventricular ejection fraction [%]
Lung function	
	FVC [L]
	FEV1 [%predicted]
	TLC [%predicted]
	Residual Volume [%predicted]
	DLCO % predicted
	DLCO VA % predicted
Laboratory	
	Hemoglobin [g/dl]
	Creatinine [mg/dl]
	Urea [mg/dl]
	Uric acid [mg/dl]
	SGPT [U/l]
	CRP [mg/l]
	NTproBNP [pg/ml]

Table 2

Comparison of changes between groups

WHO FC Change (Visit 1-2)
Improvement (- 1)
Worsening (+1)
Unchanged
Blood gas analysis
SaO2 [%]
PaO2 [mmHg]
PaCO2 [mmHg]
pH
Bicarbonates
Hemodynamics at rest
RAP [mmHg]
sPAP [mmHg]
dPAP [mmHg]
mPAP [mmHg]
PAWP [mmHg]
CO [l/min]
CI [l/min/m2]
TPR mmHg [min l− 1]
PVR [WU]
SvO2 [%]
6MWD
6MWD [m]
Short Form-36 Health Survey
Physical functioning
Physical role function
Pain
General health perception
Vitality
Social functioning
Emotional role function
Mental well-being
Physical summation score
Mental summation score
Echocardiography at rest
Estimated sPAP [mmHg]
RA area [cm^2]
RV area [cm^2]
TAPSE [cm]
LV-EI
Left ventricular ejection fraction [%]

LV-function improvement (+1)
LV-function unchanged
LV-function deterioration (-1)
Lung function
FEV1 [%predicted]
TLC [%predicted]
DLCO [% predicted]
Laboratory (V1-3)
NTproBNP [pg/ml]

Table 3

Safety analysis

All frequency data will be provided with n and %

- Tabulation of Adverse events (> 5 % of patients)
- Adverse events with suspected relation to the investigational medicinal product
- Serious adverse events