Document Type:	Study Protocol
Official Title:	A randomized parallel-group, placebo-controlled, double-blind, multi-center trial to evaluate the efficacy and safety of the oral sGC stimulator vericiguat to improve physical functioning in activities of daily living in patients with heart failure and preserved ejection fraction (VITALITY-HFpEF)
NCT Number:	NCT03547583
Document Date:	22-Feb-2018

1. Title page

A randomized parallel-group, placebo-controlled, double-blind, multi-center trial to eValuate the effIcacy and safeTy of the orAL sGC stImulator vericiguaT to improve phYsical functioning in activities of daily living in patients with heart failure and preserved ejection fraction (VITALITY-HFpEF)

Short title: Patient-reported outcomes in vericiguat-treated patients with HFpEF

Acronym:	VITALITY-HFpEF		
Test drug:	Vericiguat / BAY 1021189		
Study purpose:	To assess the safety and efficacy of vericiguat in reducing physical limitations in patients with heart failure and preserved ejection fraction		
Clinical study phase:	Phase IIb	Date:	22 FEB 2018
Registration:	2018-000298-65	Version no.:	1.0
Sponsor's study no.:	19334		
Sponsor:	Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, PO box 915, Whippany, NJ 07981-0915 United States		
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD Role: PPD

Date: Feb 22, 2018 Signature:

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis

Title	A randomized parallel-group, placebo-controlled, double-blind, multi-center trial to evaluate the efficacy and safety of the oral sGC stimulator vericiguat to improve physical functioning in activities of daily living in patients with heart failure and preserved ejection fraction (HFpEF)
Short title	Patient-reported outcomes in vericiguat-treated patients with HFpEF
Acronym	VITALITY-HFpEF
Clinical study phase	Phase IIb
Study objectives	Primary objectives: • To evaluate the efficacy of vericiguat 10 mg in comparison to placebo on improving physical functioning from baseline to week 24. • To evaluate the efficacy of vericiguat 15 mg in comparison to placebo on improving physical functioning from baseline to week 24. • To evaluate the safety and tolerability of vericiguat. Secondary objectives: • To evaluate the efficacy of vericiguat 10 mg in comparison to placebo on improving distance traveled on a 6-minute walk test (6MWT) from baseline to week 24 • To evaluate the efficacy of vericiguat 15 mg in comparison to placebo on improving distance traveled on a 6 MWT test from baseline to week 24. • To evaluate the efficacy of vericiguat 10 mg in comparison to placebo in increasing the proportion of patients with Kansas City Cardiomyopathy Questionnaire (KCCQ) physical limitation score (PLS) improvement from baseline by >5 points at 24 weeks and other thresholds (e.g. >3, >7, >10, >15, >20), and the proportions with these improvements in the other KCCQ domains; overall symptom score (OSS), clinical summary score (CSS), total symptom score (TSS) and symptom frequency score (SFS). • To evaluate the efficacy of vericiguat 15 mg in comparison to placebo in increasing the proportion of patients with KCCQ PLS improvement from baseline by >5 points at 24 weeks and other thresholds (e.g. >3, >7, >10, >15, >20), and the proportions with these improvements in the other KCCQ domains OSS, CSS, TSS and SFS. • To evaluate the efficacy of vericiguat 10 mg in comparison to placebo in decreasing the proportion of patients with KCCQ PLS decline from baseline by >5 points at 24 weeks and the proportions with decline in the other KCCQ domains OSS, CSS, TSS and SFS. • To evaluate the efficacy of vericiguat 15 mg in comparison to placebo in decreasing the proportion of patients with KCCQ PLS decline from baseline by >5 points at 24 weeks and the proportions with decline in the other KCCQ domains OSS, CSS, TSS and SFS.

	Other objectives: • To evaluate the efficacy of vericiguat 15 mg and the efficacy of vericiguat 10 mg in comparison to placebo on improving o Symptom frequency as measured by the KCCQ SFS o Other patient-reported outcomes such as the generic health-related quality of life measure EuroQoL five dimensions five levels questionnaire (EQ-5D-5L) and the Fried-based frailty score o New York Heart association (NYHA) class o Laboratory variables such as N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline to 24 weeks • To collect and summarize death including cardiovascular death, and CV hospitalizations including heart failure hospitalizations, myocardial infarction and stroke, and outpatient HF events. • To analyze the cumulative distribution function of KCCQ PLS, OSS, CSS, TSS and SFS change from baseline at 24 weeks • To evaluate pharmacokinetics of vericiguat in patients with HFpEF. • To evaluate the concentration-QTc relationship of vericiguat at the 15 mg dose level. • Optional pharmacogenetic research: To explore the relationship between genetic variation and clinical characteristics of patients, independent and dependent of the treatment administered. Variations across the human genome may be analyzed for association with clinical data collected in this study. • To evaluate further biomarkers to investigate the drug (i.e. mode-of-action-related effect and/or safety) and/or the mechanisms of the disease • Optional accelerometry substudy: To collect exploratory data by activity tracking
Test drug	Vericiguat, BAY 1021189
Name of active ingredient	Vericiguat, BAY 1021189
Doses	2.5 mg, 5 mg, 10 mg, 15 mg
Route of administration	Oral
Duration of treatment	24 weeks
Reference drug	Placebo
Name of active ingredient	N/A
Doses	N/A
Route of administration	Oral
Duration of treatment	24 weeks

Background treatment	Standard diuretic and comorbidity treatment
Indication	Treatment of chronic heart failure with preserved ejection fraction
Diagnosis and main criteria for inclusion /exclusion	Male and female patients aged 45 years or older, with chronic HF (NYHA class II or III), preserved left ventricular ejection fraction (LVEF ≥45%), elevated natriuretic peptides, and previous HF decompensation will be enrolled in this trial. Main inclusion criteria: • Previous diagnosis of chronic HF • HF decompensation within 6 months prior to randomization, defined as hospitalization for HF or intravenous (IV) diuretic treatment for HF without hospitalization. • N-terminal pro brain natriuretic peptide (NT-proBNP) ≥300 or brain natriuretic peptide (BNP) ≥100 pg/mL in sinus rhythm, or NT-proBNP ≥600 or BNP ≥200 pg/mL in atrial fibrillation within 30 days prior to randomization • Diagnostic criteria of HFpEF by echocardiography assessed within 12 months prior to randomization (most recent measurement must be used to determine eligibility with no interim event signaling potential deterioration in ejection fraction) o Left ventricular ejection fraction (LVEF) ≥45% **and** o Structural changes indicated by at least one of the following parameters: ▪ Left ventricle (LV) hypertrophy (any of the following: intraventricular septal or posterior wall thickness ≥1.1 cm, and/or LV mass index ≥115 g/m^2 in male and ≥95 g/m^2 in female), **or** ▪ Left atrium (LA) enlargement (any of the following: left atrial volume (LAV) index ≥29 ml/m^2, or LAV >58 mL in male and >52 mL in female patients, or LA area >20 cm^2, or LA diameter >40 mm in male and >38 mm in female patients) • NYHA class II or III at randomization Main exclusion criteria: • Clinical instability at randomization, defined by o Any IV treatment within 24h prior to randomization, and/or o SBP ≥160 mmHg o SBP <110 mmHg and/or DBP <40 mmHg and/or symptomatic hypotension o Resting heart rate (HR) <50 or ≥100 beats per minute (bpm) • Use of IV inotropes at any time between qualifying HF event and

	randomization • Previous diagnosis of reduced ejection fraction (EF) (EF <40%) • Hypertrophic obstructive cardiomyopathy, acute myocarditis, amyloidosis, sarcoidosis, or pericardial disease • Primary valvular heart disease requiring surgery or intervention, or within 3 months after valvular surgery or intervention, or active endocarditis • Acute coronary syndrome, including unstable angina, Non ST-elevation myocardial infarction or ST-elevation myocardial infarction, or Coronary artery bypass grafting (CABG) within 60 days prior to randomization, or indication for Percutaneous coronary intervention or CABG at the time of randomization • Symptomatic carotid stenosis, or transient ischemic attack or stroke within 60 days prior to randomization • Complex congenital heart disease • Non-cardiac comorbidity (any of the following) o Estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m2 calculated by Modification of Diet in Renal Disease formula o Hepatic insufficiency classified as Child-Pugh B or C o Morbid obesity with a body mass index >45 kg/m2 o Malignancy or other non-cardiac condition limiting life expectancy to <1 year, per physician judgment o Requires continuous home oxygen for severe pulmonary disease or has interstitial lung disease o Patients with allergies, intolerance or hypersensitivity to investigational drug or any of the excipients • Concurrent or anticipated use of nitrates or NO donors, phosphodiesterase type V (PDE5) inhibitors, or a Soluble guanylate cyclase (sGC) stimulator
Study design	Randomized parallel-group, placebo-controlled, double-blind, multi-center trial
Methodology	Patients will be randomized 1:1:1 within 4 weeks after the Screening Visit to either: • Placebo arm: placebo and sham up-titration at weeks 2, 4, and 6. • 10 mg arm: vericiguat, which will be started at 2.5 mg at randomization and up-titrated to 5 mg at week 2 and to 10 mg at week 4, with sham titration at week 6. • 15 mg arm: vericiguat, which will be started at 2.5 mg at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, and to 15 mg at week 6.

	The first dose of trial treatment will be administered at the trial site at the randomization visit. Subsequent dosing will be performed once daily by the patient at approximately the same time each day. Patients will be instructed to take vericiguat with food. The titration will be based on systolic blood pressure (SBP) measurement prior to intake and safety considerations, at the discretion of the investigator as follows: • Increase dose: if SBP ≥100 mmHg and ≤20 mmHg decreases from previous visit, and not yet on highest dose (sham titration will occur if dose increase is chosen from 10 mg in the 10 mg arm) • Maintain dose: if SBP between ≥90 and <100 mmHg or SBP ≥100 mmHg and >20 mmHg decreases from previous visit, or if already on highest dose step (after 3 uptitrations) • Decrease the dose: if SBP <90 mmHg without symptoms of hypotension if on vericiguat at a blinded dose step >2.5 mg, or temporarily interrupt if on 2.5 mg (starting dose or after down titration from a higher dose) • Interrupt the dose: if SBP <90 mmHg with symptoms of hypotension. Down-titration is possible at any time during the study. In case of temporary discontinuation or dose reduction after the titration period, up-titration is also possible at scheduled visits. If the period between the scheduled visits is more than 17 and less than 11 days, the patient should attend an unscheduled visit.
Type of control	Placebo
Data Monitoring Committee	Yes
Number of patients	Approximately 735 patients are planned to be randomized, 245 patients per arm.
Primary variable	Change in KCCQ PLS from baseline to week 24
Time point/frame of measurement for primary variable	KCCQ PLS will be assessed at baseline, at weeks 2, 6, 12, and 24
Plan for statistical analysis	The primary endpoint will be change from baseline to week 24 in physical limitations as measured by the KCCQ PLS. The primary analysis of the primary endpoint will be performed using a repeated-measures mixed model (MMRM), including all assessments post baseline, with baseline values, region, heart rhythm, treatment group, study visit, and the interaction between study visit and treatment group as covariates. The analysis will be performed in the Full Analysis Set. The study is powered at 80% for rejecting either of the primary hypotheses (vericiguat 15 mg arm vs. placebo arm and vericiguat 10 mg arm vs. placebo arm), with the assumption of a mean difference from placebo in KCCQ PLS of 5 points for both dose groups and a common SD of 21 points, under two sided alpha level of 0.05. A planned futility analysis will be performed by data monitoring committee (DMC) when 50% of patients complete Visit 7 (week 12) and their KCCQ data become available. An observed treatment effect of 0.6 point will serve as

	the boundary for futility for both dose groups, which is approximately equivalent to a joint conditional power (CP) of 23%. An observed difference <0.6 in both comparisons would therefore signal to the DMC that the trial should be terminated early. At this futility boundary the trial has a joint probability of 9% to observe a >5 point improvement in either of the dose groups. In addition, a blinded anchor-based interim analysis will be conducted upon the completion of the 3-month assessments by all trial participants. A non-parametric discriminant analysis will be used to determine the discrimination point between “no change” and “a little better” categories, which is considered to be Minimal clinically important difference (MCID). Based on the blinded anchor-based interim analysis, the percentages of responders with MCID, moderate, and large differences at each visit will be summarized, and nominal p-values will be also provided. The study uses the graphical method of Maurer and Bretz (2013) to provide strong multiplicity control across the primary KCCQ PLS hypotheses and the secondary 6 MWT hypotheses. The overall two sided alpha level will be controlled at 0.05. The two primary hypotheses will be tested using Bonferroni procedure, each at a splitted alpha of 0.025. The two secondary hypotheses will be tested based on parallel gatekeeping principle. If both primary hypotheses can be rejected, the secondary family will be tested at a full alpha level 0.05 (two sided). If only one primary hypothesis has shown to be statistically significant, then only the secondary hypothesis based on the same dose group can be tested at an alpha level carried forward from the primary family testing, i.e., 0.025 (two sided). In this case, if the secondary hypothesis is rejected, the alpha spending associated with this dose group (0.025) will be re-utilized to test the other failed primary hypothesis again. Overall, the primary analysis will be claimed to have a positive outcome if the null hypothesis for at least one of the two primary hypotheses can be rejected.

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6MWT	6 minute walk test
ACE	angiotensin converting enzyme
AE	Adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Partial Thromboplastin time, activated
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AV	Atrioventricular
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CCSA	Canadian Cardiovascular Society angina (classification)
CEC	Central clinical events committee
cGMP	Cyclic guanosine monophosphate
CP	Conditional power
CR	Category Ratio
CRO	Clinical research organization
CSR	Clinical study report
CSS	Clinical Summary Score
CV	Cardiovascular
DBP	Diastolic blood pressure
dL	Deciliter
DMC	Data monitoring committee
e.g.	Exempli gratia, for example
ECG	Electrocardiogram
(e)CRF	(Electronic) case report form
EDC	Electronic data collection
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EoT	End of treatment
EQ-5D-5L	EuroQoL five dimensions five levels questionnaire
ESC	European Society of Cardiology
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FU	Follow up
GCL	Global clinical lead
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
GMP	Good manufacturing practice
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
Hct	Hematocrit
HDL	High density lipoprotein
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction

HFrEF	Heart failure with reduced ejection fraction
HR	Heart rate
i.e.	*Id est*, in other words
IB	Investigator's brochure
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
IEC	Independent ethics committee
INR	International normalized ratio
IR	Immediate release
IRB	Institutional review board
IV	Intravenous
IxRS	Interactive voice / web response system
K	Potassium
KCCQ	Kansas City Cardiopathy Questionnaire
L	Liter
LA	Left atrium, left atrial
LAE	Left atrial enlargement
LAV	Left atrial volume
lb(s)	Pound(s)
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLOQ	lower limit of quantification
LS	Least squares
LSH	Life Sciences Data Hub
LV	Left ventricle, left ventricular
LVAI	Left volume atrial index
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCID	Minimal clinically important difference
MCV	Mean corpuscular volume
MD	Medical doctor
MDRD	Modification of Diet in Renal Disease
mEq	Milliequivalents
mg	Milligram
MDDT	Medical Device Development Tool
mIU	Milli-International Units
MID	Minimally important difference
mL	Milliliters
min	Minute
mmHg	Millimeters of mercury
MMRM	Mixed model repeated-measures
Na	Sodium
NA	Not applicable
NO	Nitric oxide
NSTEMI	Non ST-elevation myocardial infarction
NTG	Nitroglycerin
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
o.d.	Once daily
OSS	Overall summary score
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PDE5	Phosphodiesterase type V
pg	Picograms
PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity

PH	Pulmonary Hypertension
PID	Patient identification number
PK	Pharmacokinetic(s)
PKS	Pharmacokinetics analysis set
Plc	Placebo
PLS	Physical limitation score
PPS	Per protocol analysis set
PR	PR interval
(e)PRO	(Electronic) patient reported outcome
PTT	Partial thromboplastin time
QC	Quality control
QoL	Quality of Life
QRSD	QRS duration
QT	QT interval
QTc	QT interval corrected for HR
QTcB	Formula of Bazett
QTcF	Formula of Fridericia
RAVE	Electronic data capture system used by the sponsor
RBC	Red blood cells
RDW	Red cell distribution width
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SFS	Symptom frequency score
sGC	Soluble guanylate cyclase
STEMI	ST-elevation myocardial infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Systemic vascular resistance
TIA	Transient ischemic attack
TSS	Total symptom score
US	United States of America
VAS	Visual analogue scale
VO_2	Oxygen uptake
WBC	White blood cells

3. Introduction

3.1 Background

Heart failure is a leading cause of CV morbidity and mortality, and constitutes a major public health problem worldwide. Patients suffering from HFpEF are a large and growing population; the relative proportion of HFpEF has increased to more than 50% of all HF hospitalizations (1). Predisposing conditions for HFpEF are advanced age, female gender, diabetes, obesity, arterial hypertension, and LV hypertrophy. While mortality in outpatient cohorts appears to be lower for HFpEF than HFrEF, hospitalizations for HFpEF have increased over time. HFpEF patients also have substantially reduced functional capacity and quality of life (2), and they need a therapy that addresses these limitations. However, no specific therapy has been approved to reduce cardiovascular risk or to improve functional status in patients with HFpEF, and recommendations have thus far been limited to symptomatic treatment of congestive symptoms by diuretics, and to treating causes and comorbidities including hypertension, coronary artery disease, and atrial fibrillation (3). US guidelines were recently updated with a new class IIb recommendation stating that aldosterone receptor antagonists might be considered to decrease hospitalizations in appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L) (4). ESC guidelines on HF also provide no evidence level A recommendations for the treatment of patients with HFpEF and reiterate that no treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF (5). Trials that established the clinical benefits of ACE inhibitors, angiotensin receptor antagonists and ß-blockers beyond their use in arterial hypertension, CAD or for rate control have all selected patients on the basis of their reduced EF. Subsequent trials in patients with HFpEF did not confirm equal effectiveness in this patient group (6). Since patients with HFpEF are highly symptomatic with a poor quality of life, it is important to find new therapies that can alleviate symptoms and improve patient well-being (5). Therefore, there is need for new drug targets such as cGMP. The nitric oxide-soluble guanylate cyclase-cGMP signaling pathway is a relevant mechanism in HF that remains unaffected by neurohumoral antagonists. cGMP deficiency causes two important pathophysiologies in HF:

1. Myocardial dysfunction including impaired relaxation, diastolic stiffening and myocardial energy wastage. cGMP is a powerful antihypertrophic mediator in the heart (7). It is specifically reduced in myocardial biopsies of patients with HFpEF, and bypassing the cGMP deficiency by in vitro protein kinase G administration corrects inappropriately high resting tension forces of human cardiomyocytes (8). In a genetic sGC knockout model sGCα1$^{-/-}$ mice (deficiency in the α1 subunit results in decreased enzymatic sGC activity, whereas the total sGC knockout is not viable) increased cardiac contractility, arterial elastance and impaired ventricular relaxation were observed (9).
2. Endothelial dysfunction, i.e. disturbed endothelium-dependent vasotone regulation due to a reduced NO bioavailability, including the myocardial microcirculation. Endothelial dysfunction contributes to the pathophysiology of HFpEF (10).

Previous attempts to increase cGMP remain limited. The long-term effects of nitrates and exogenous NO donors are limited by tolerance (11), and they also cause endothelial dysfunction, oxidative stress, and release of endothelin-1 (12). The venoselectivity of these

drugs may restrict their hemodynamic tolerability (13), as the dependency of nitrates and exogenous NO donors on biotransformation to the active, NO-containing compound causes different regional responses in the venous vs. arterial system (14, 15). A novel class of sGC compounds directly stimulate the NO receptor sGC with a dual mode of action; they sensitize sGC to endogenous NO by stabilizing the NO-sGC binding, and also directly stimulate sGC via a different binding site, independently of NO. Their regional vasoactivity and potential direct myocardial effects are independent of biotransformation and, therefore, might differ from nitrates. Due to this unique mode of action direct oral sGC stimulators could provide a novel, tolerable option to restore cGMP signaling in HFpEF (16).

The sGC stimulator riociguat has previously been studied in patients with HFpEF and secondary pulmonary hypertension. Although the study missed its primary endpoint of pulmonary artery pressure reduction, single doses of riociguat increased stroke volume and decreased SVR at the highest dose step of 2 mg without changing pulmonary capillary wedge pressure, indicating that increases in stroke volume upon afterload reduction could be achieved without increasing LV filling pressures (17). These results point at different hemodynamic effects of the direct sGC stimulator riociguat compared to the PDE5 inhibitor inhibitor sildenafil. Patients with HFpEF in the RELAX-DHF study treated with sildenafil remained without any effects on SVR at 6 months (17), and in another study 12 weeks of sildenafil treatment did not improve invasive haemodynamic or clinical parameters in patients with HFpEF and PH (18). The hemodynamic effects of single doses of riociguat in the DILATE-1 study in patients with PH and diastolic heart failure also differed from sodium nitroprusside, which frequently decreased stroke volume upon acute administration in patients with HFpEF, potentially owing to excessive preload reduction in line with venodilation (19). In contrast, a decrease in heart rate upon treatment with the sGC stimulator vericiguat was associated with unchanged cardiac output in non-invasive echocardiographic hemodynamic measurements in the 10 mg arm of the SOCRATES-PRESERVED study (Study 15829) at 12 weeks (20).

The NEAT study showed that patients with HFpEF receiving isosorbide mononitrate were less active and did not show improvement in QoL or submaximal exercise capacity (21). Based on these data, the 2017 ACC/AHA/HFSA guideline update stated that the routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HFpEF is ineffective (a class III, or “no benefit” recommendation). Limitations specific to the mode of action of NO substitution with nitrates and to the dependency on PDE5 overexpression for PDE5 inhibitor treatment are hypothesized to be the reason for failed clinical efficacy. These limitations may be overcome by the different mode of action of direct sGC stimulators, and exploratory clinical data suggest potential benefit of oral sGC stimulator treatment in heart failure. Therefore, vericiguat, a novel oral sGC stimulator half-life long enough for once daily dosing, is currently being developed for the treatment of heart failure.

Further details can be found in the latest available version of the investigator's brochure, which contains comprehensive information on the study drug.

3.2 Previous experience in humans

Vericiguat has been evaluated in approximately 65 preclinical studies and has been administered to over 500 healthy patients in 19 completed Phase I studies with single- and multiple-dose administration, and in approximately 740 heart failure patients in two Phase IIb studies that studied vericiguat in worsening chronic heart failure patients with HFrEF and

with HFpEF. In the ongoing phase III event-driven outcome trial VICTORIA (NCT02861534), as of Dec 1 2017, 2279 patients with HFrEF out of a planned total sample size of 4872 have been randomized to vericiguat 10 mg target dose or placebo with a median study drug treatment duration at that time of 5 months. The study treatment duration is planned to continue until 2020 for a median follow-up duration of 18 months.

A detailed description of the properties of vericiguat and the results of the nonclinical and clinical pharmacology studies conducted so far are given in the IB.

3.2.1 Dose selection

The starting dose, as well as the dose range in this study, are based on data from the Phase IIb study SOCRATES, as well as on the Phase I program in healthy volunteers.

In SOCRATES-PRESERVED 4 different dose regimens of vericiguat were studied in patients with chronic HFpEF enrolled within 1 month after a qualifying heart failure decompensation event (20). Data from SOCRATES-PRESERVED established 2.5 mg vericiguat as the safe and well tolerated starting dose. Uptitration by two dose doublings with 14 day intervals each to a target dose of 10 mg was tolerated in patients with HFpEF without an increase in adverse events compared to placebo, with low discontinuation rates in all groups, and no changes in blood pressure at 10 mg compared to placebo. Although analyses of the primary efficacy variables in SOCRATES-PRESERVED did not demonstrate changes in NT-proBNP and LAV at 12 weeks in the vericiguat dose groups compared to placebo, patients receiving vericiguat in the 10 mg target dose arm experienced a more pronounced improvement in health related QoL, physical limitations, NYHA class, signs and symptoms of congestion and trends towards improved diastolic function at 12 weeks (20, 22). These data generate the hypothesis that vericiguat improves physical functioning and clinically relevant patient-reported outcomes in patients with HFpEF. In the parallel SOCRATES-REDUCED study (Study 15371) vericiguat treatment of patients with HFrEF in the 10 mg target dose arm was safe and well tolerated, and resulted in a large biological effect on the primary endpoint NT-proBNP when added to standard of care. Based on these data, the currently ongoing VICTORIA trial evaluates the efficacy of vericiguat in comparison to placebo on a background of standard of care in increasing the time to first occurrence of the composite of CV death or HF hospitalization in patients with HFrEF.

Ad hoc application without prior titration of the 15 mg dose step as an oral polyethylene glycol solution was not well tolerated, and led to orthostatic reactions and syncope in the single dose escalation phase I study 15355 in 3 out of 4 healthy volunteers. Therefore 10 mg was chosen as the highest dose in SOCRATES-PRESERVED. In parallel with SOCRATES studies another phase I study, 15838, was conducted. In this study administration of single doses of 15 mg to 14 healthy volunteers in fasted state as three 5 mg IR tablets in the formulation used for the clinical development program was generally well tolerated even without prior uptitration. Therefore, since no dose limiting intolerabilities were observed within the dose range of up to 10 mg studied in SOCRATES-PRESERVED, in this study (19334) a higher dose arm with a third uptitration step to 15 mg will be studied in addition to the 10 mg arm. The objective of this additional dose arm is to test whether titration to the higher target dose of 15 mg is tolerable and safe over 24 weeks, and associated with an even greater improvement in physical functioning. As with uptitration to 10 mg, the titration will start from 2.5 mg, not in a forced manner but adapted to individual tolerability as objectively defined by lack of any decrease in blood pressure below limits established for titration in SOCRATES, and in addition to the subjective well-being of patients.

There is limited ability to add blood pressure lowering doses of vericiguat to the guideline-recommended regimen for HFrEF patients, given the baseline blood pressures in these patients and the fact that these latter agents lower blood pressure (23). In contrast, the higher baseline blood pressure in HFpEF and the flexibility of adjusting concomitant risk factor controlling therapy that has not been established as life-saving, allow studying doses with potential blood pressure reducing potential in this study 19334.

Based on the exploratory improvement of physical functioning measured by the KCCQ PLS at the 10 mg target dose in SOCRATES-PRESERVED, this dose regimen will also be studied in a parallel arm next to the higher 15 mg target dose. This design will allow testing of the primary hypothesis that vericiguat will improve KCCQ PLS over the treatment duration of 24 weeks compared to placebo individually in the 10 mg and in the 15 mg dose titration arms and to establish the benefit/risk ratio of the 10 mg and of the 15 mg dose titration of vericiguat in separate arms.

3.3 Rationale of the study

Vericiguat, an sGC stimulator, was studied in a Phase IIb dose-finding study (SOCRATES-PRESERVED) in patients with HFpEF. Even though a 10 mg dose of vericiguat over a 12 week treatment period did not change NT-proBNP or LAV as pre-specified primary endpoints in this trial, exploratory post-hoc analyses showed an improvement in the patient-relevant domains of KCCQ and related patient reported (EQ-5D-5L) and physician assessed (NYHA class, clinical congestions score) endpoints (20, 22) in the highest target dose group.

KCCQ is widely used in HF trials. In SOCRATES-PRESERVED, an improvement in the KCCQ OSS as well as the CSS was observed. Consistent changes in other domains of the KCCQ were also noted. However, the improvement appeared to be driven primarily by improvements in the PLS. KCCQ PLS has previously been validated against the distance covered in a 6MWT, NYHA class, and physical limitation domains within other QoL instruments including the 36-Item Short Form Survey in patients with HF (24). Improvements in physical functioning and reduction in symptom frequency are considered to be direct measures of treatment benefit in patients with HFpEF (2). This observation led to the hypothesis that vericiguat improves physical functioning in patients with HFpEF.

Benefit-risk assessment

Although in the phase IIb SOCRATES-PRESERVED study vericiguat did not reveal changes in the two primary efficacy variables (NT-proBNP and LAV at 12 weeks), the exploratory finding of clinically meaningful increases (i.e. improvements compared to placebo of equal to or larger than 5 points) in KCCQ PLS, CSS and OSS suggest that vericiguat can improve physical limitations in patients with HFpEF.

Daily activities of patients with HFpEF are limited due to common HF symptoms. Patients are especially affected by breathlessness and fatigue, which have a major impact on daily activities and are central to the patient experience (25). These, in turn, have an impact on wider concepts of patient health-related quality of life which are not addressed due to a lack of approved medications for the treatment of HFpEF patients. The changes in KCCQ PLS and consistent improvements in EQ-5D-5L observed in SOCRATES-PRESERVED together with trends in NYHA class and physician-assessed congestion indicate vericiguat's potential to improve functioning in patients with HFpEF.

The main risk of vericiguat is hypotension. There was only a small increase in the rate of hypotension AEs at the starting dose of 2.5 mg (4.4% of patients in the first 2 weeks compared to 3.3% with placebo) in SOCRATES-REDUCED, and these occurred only transiently upon initiation of vericiguat treatment in the majority of cases (26). In SOCRATES-PRESERVED, treatment-emergent hypotension adverse events were similar in all arms including placebo. Therefore, by using the titration rules from SOCRATES-PRESERVED, a safe uptitration to the target dose of 10 mg is expected in patients with HFpEF. In the absence of existing data with 15 mg vericiguat in patients with heart failure, the risks of hypotension and syncope with 15 mg vericiguat require further characterization. Based on previous experience from SOCRATES-PRESERVED with doses up to 10 mg vericiguat, the risk of hypotension, syncope or any other intolerability is expected to be manageable and minimized through a non-forced titration also for the 15 mg dose.

Given the absence of life-saving drugs and the particular relevance of physical limitations in daily activities for patients with HFpEF, the potential for vericiguat to improve physical functioning based on exploratory data from SOCRATES-PRESERVED appears to outweigh the manageable risks of hypotension and syncope observed with the 10 mg target dose. Therefore, before data for the 15 mg dose in patients with HFpEF will become available, there is equipoise with respect to the benefit-risk assessment for vericiguat 15 mg for the treatment of symptomatic HF in patients with chronic HFpEF, and we expect potential benefit in this indication.

4. Study objectives

The primary hypothesis in this trial is that the treatment with vericiguat 10 mg or 15 mg in patients with HFpEF improves the KCCQ PLS compared to placebo after 24 weeks of treatment.

Primary objectives:

- To evaluate the efficacy of vericiguat 10 mg in comparison to placebo on improving physical functioning from baseline to week 24.
- To evaluate the efficacy of vericiguat 15 mg in comparison to placebo on improving physical functioning from baseline to week 24.
- To evaluate the safety and tolerability of vericiguat.

Secondary objectives:

- To evaluate the efficacy of vericiguat 10 mg in comparison to placebo on improving distance traveled on a 6MWT from baseline to week 24.
  - To evaluate the efficacy of vericiguat 15 mg in comparison to placebo on improving distance traveled on a 6MWT from baseline to week 24.
  - To evaluate the efficacy of vericiguat 10 mg in comparison to placebo in increasing the proportion of patients with KCCQ PLS improvement from baseline by >5 points at 24 weeks and other thresholds (e.g. >3, >7, >10, >15, >20), and the proportions with these improvements in the other KCCQ domains OSS, CSS, TSS and SFS.
  - To evaluate the efficacy of vericiguat 15 mg in comparison to placebo in increasing the proportion of patients with KCCQ PLS improvement from baseline by >5 points at

24 weeks and other thresholds (e.g. >3, >7, >10, >15, >20), and the proportions with these improvements in the other KCCQ domains OSS, CSS, TSS and SFS.

- To evaluate the efficacy of vericiguat 10 mg in comparison to placebo in decreasing the proportion of patients with KCCQ PLS decline from baseline by >5 points at 24 weeks and the proportions with decline in the other KCCQ domains OSS, CSS, TSS and SFS.
- To evaluate the efficacy of vericiguat 15 mg in comparison to placebo in decreasing the proportion of patients with KCCQ PLS decline from baseline by >5 points at 24 weeks and the proportions with decline in the other KCCQ domains OSS, CSS, TSS and SFS.

Other objectives:

- To evaluate the efficacy of vericiguat 10 mg and the efficacy of vericiguat 15 mg in comparison to placebo on improving:
  - Symptom frequency as measured by the KCCQ SFS
  - Perceived exertion experienced by patients during 6MWT as measured by Borg CR 10.
  - Other patient-reported outcomes such as the generic health-related quality of life measure EQ-5D-5L and the Fried-based frailty score
  - NYHA class
  - Laboratory variables such as NT-proBNP from baseline to 24 weeks
- To collect and summarize death including cardiovascular death and CV hospitalizations including heart failure hospitalizations, MI and stroke, and outpatient HF events.
- To analyze the cumulative distribution function of KCCQ PLS, OSS, CSS, TSS and SFS change from baseline at 24 weeks.
- To evaluate PK of vericiguat in patients with HFpEF, and
- To evaluate the concentration-QTc relationship of vericiguat at the 15 mg dose level.
- Optional pharmacogenetic research: To explore the relationship between genetic variation and clinical characteristics of patients, independent and dependent of the treatment administered. Variations across the human genome may be analyzed for association with clinical data collected in this study.
- To evaluate further biomarkers to investigate the drug (i.e. mode-of-action-related effect and / or safety) and / or the mechanisms of the disease
- Optional accelerometry substudy: to collect exploratory data by activity tracking

5. Study design

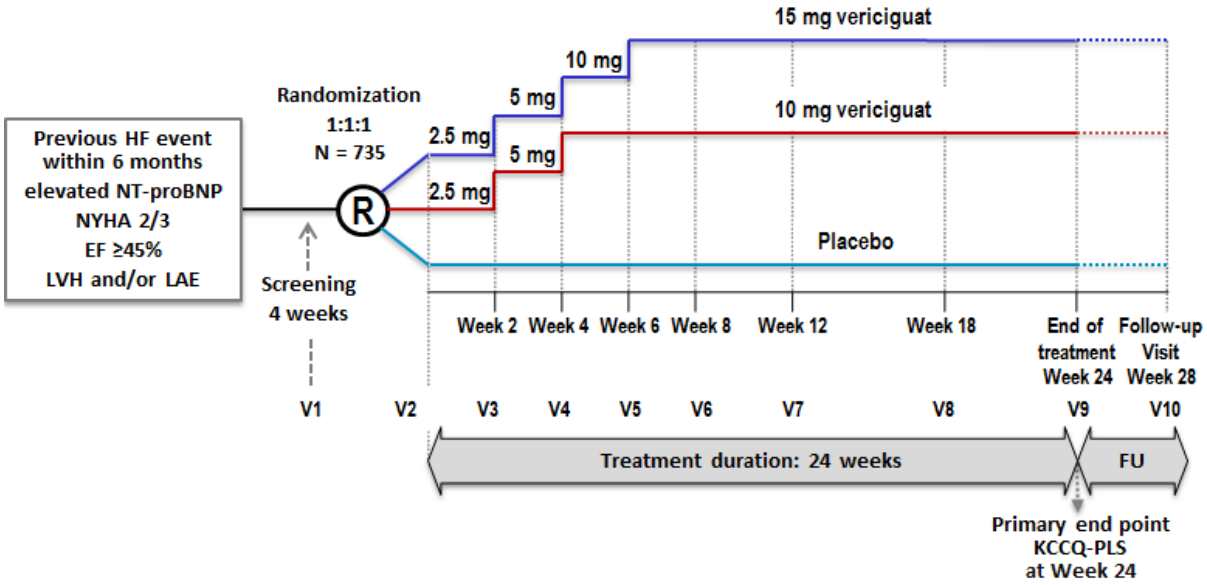
Design overview

This is a randomized parallel-group, placebo-controlled, double-blind, multi-center trial of vericiguat in patients with HFpEF to be conducted in conformance with GCP. Approximately 735 patients will be randomized as described in Figure 5–1 to evaluate the efficacy of vericiguat 10 mg and 15 mg in comparison to placebo on improving physical functioning from baseline to week 24. To reduce heterogeneity in the studied population patients younger than 45 years of age are not eligible. Patients are expected to be on a background treatment for co-morbidities like hypertension (see Section 8.1), and diuretics in the presence of symptoms due to volume overload.

Screening may be initiated any time after admission of a patient to the hospital for HF, before or after discharge, and up to 6 months after hospitalization for HF. Use of IV diuretic treatment for HF, even without hospitalization, is indicative of HF decompensation and accepted as a qualifying HF event equivalent to hospitalization. The most recent decompensation should be considered for qualifying the patient for the study. In either scenario, HF must be the primary reason for hospitalization or IV diuretic treatment. Patients will be randomized within up to 4 weeks after the screening visit (see Section 7.3) and within up to 6 months after the onset of the qualifying event of hospitalization for HF or treatment with IV diuretic for HF (see Figure 5–1), and treated as given in Sections 7.1 and 7.3.

Primary endpoint assessment is at week 24. All patients will be followed until study completion to assess for vital status and all study endpoints.

Figure 5–1 Study design



EF, ejection fraction; FU, follow-up; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PLS, physical limitation score; V, Visit.
KCCQ as the entire questionnaire is administered, not just the PLS domain.

Primary variable

Change in KCCQ PLS from baseline to week 24.

Justification of the design

The study is designed to evaluate the safety and efficacy of the 10 mg and of the 15 mg dose regimens of vericiguat at 24 weeks in separate parallel arms. Placebo control is used in a parallel comparator arm to control for observer and patient bias, and randomization to control for assignment bias.

Rationale of study endpoints

To demonstrate durability of efficacy in improving physical functioning and to study safety beyond the previously studied time period of 12 weeks in SOCRATES-PRESERVED, longer treatment duration of 24 weeks has been chosen for this study. This endpoint gives a valid and appropriate measure of the limitations in activities of daily living that are impacted by HF symptoms of breathlessness and fatigue, and represent the key burden of patients suffering from HFpEF. In SOCRATES-PRESERVED in the 10 mg arm a constant rise in KCCQ PLS that did not yet reach a maximum by week 12 was observed. This was opposed to a smaller improvement in placebo that reached its peak at 8 weeks and subsequently decreased. Based on the exploratory finding of a clinically meaningful improvement in KCCQ PLS (i.e. an improvement compared to placebo larger than 5 points upon 12 weeks treatment with a 10 mg target dose regimen) consistent with parallel improvements in EQ-5D-5L in SOCRATES-PRESERVED, the change in KCCQ PLS from baseline to week 24 is defined as the primary endpoint in the present study. This endpoint will serve for confirmatory testing of the hypothesis that vericiguat improves KCCQ PLS compared to placebo on top of background standard of care in a durable manner upon 24 weeks of treatment. Notably, the parallel ongoing event-driven HFrEF outcome trial VICTORIA plans median treatment duration of 18 months to add long-term safety and tolerability data of the 10 mg target dose in HFrEF.

End of study

The end of the study as a whole will be reached as soon as the last visit of the last patient has been reached in all centers in all participating countries (EU and non-EU).

Primary completion

The primary completion event for this study is last patient last treatment.

The primary completion date for this study according to the FDA Amendment Act is specified in a separate document (not part of this study protocol).

6. Study population

6.1 Inclusion criteria

1. Provided written informed consent
2. Aged 45 years and older
3. Previous history of chronic HF
4. HF decompensation within 6 months prior to randomization, defined as hospitalization for HF or IV diuretic treatment for HF without hospitalization.

5. NT-proBNP ≥300 or BNP ≥100 pg/mL in sinus rhythm, or NT-proBNP ≥600 or BNP ≥200 pg/mL in atrial fibrillation within 30 days prior to randomization.

   The most appropriate natriuretic peptide level cut-off should be guided by the investigator's judgment of the impact of the heart rhythm at the time of blood draw on natriuretic peptide levels.
6. Diagnostic criteria of HFpEF by echocardiography assessed within 12 months prior to randomization (most recent measurement must be used to determine eligibility with no interim event signaling potential deterioration in ejection fraction)
   - LVEF ≥45% **and**
   - Structural changes indicated by at least one of the following parameters:
     - LV hypertrophy (any of the following: intraventricular septal or posterior wall thickness ≥1.1 cm, and/or LV mass index ≥115 g/m^2 in male and ≥95 g/m^2 in female), **or**
     - LA enlargement (any of the following: LAV index ≥29 ml/m^2, or LAV >58 mL in male and >52 mL in female patients, or LA area >20 cm^2, or LA diameter >40 mm in male and >38 mm in female patients)
7. NYHA class II or III at randomization
8. Men or women
   - Women of childbearing potential can only be included in the study if a pregnancy test is negative and if they agree to use acceptable effective contraception when sexually active. This applies for the time period between signing of the informed consent form and time point after the last administration of study drug. The definition of acceptable effective contraception will be based on the judgment of the investigator and on local requirements.
   - Women are considered post-menopausal and/or not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL [for US only: and estradiol <20 pg/mL] or have had surgical treatment such as bilateral tubal ligation, bilateral ovariectomy, or hysterectomy

6.2 Exclusion criteria

1. Clinical instability at randomization, defined by any of the following:
   - Any IV treatment including IV diuretics or IV fluids within 24h prior to randomization
   - SBP ≥160 mmHg
   - SBP <110 mmHg and/or DBP <40 mmHg and/or symptomatic hypotension
   - Resting HR <50 or ≥100 bpm
2. Use of IV inotropes at any time between qualifying HF event and randomization
3. Previous diagnosis of reduced EF (EF <40%)

4. Hypertrophic obstructive cardiomyopathy, acute myocarditis, amyloidosis, cardiac sarcoidosis, or constrictive pericarditis
5. Primary valvular heart disease requiring surgery or intervention, or within 3 months after valvular surgery or intervention, or active endocarditis
6. Acute coronary syndrome (unstable angina, NSTEMI or STEMI) or PCI or CABG within 60 days prior to randomization, or indication for PCI or CABG at the time of randomization
7. Symptomatic carotid stenosis, or TIA or stroke within 60 days prior to randomization
8. Complex congenital heart disease
9. Non-cardiac comorbidity (any of the following)
    - eGFR <30 ml/min/1.73 m^2 calculated by MDRD formula
    - Hepatic insufficiency classified as Child-Pugh B or C
    - Morbid obesity with a BMI >45 kg/m^2
    - Malignancy or other non-cardiac condition limiting life expectancy to <1 year, per physician judgment
    - Requires continuous home oxygen for severe pulmonary disease or has interstitial lung disease
    - Patients with allergies, intolerance or hypersensitivity to the investigational drug or any of the excipients
    - Medical, psychiatric, or other condition or history thereof that in the opinion of the investigator would impair the ability to complete the planned study procedures
10. Concurrent or anticipated use of PDE5 inhibitors
11. Concurrent or anticipated use of an sGC stimulator
12. Concurrent or anticipated use of long-acting and short -acting nitrates or NO donors for any route, including isosorbide dinitrate, isosorbide 5-mononitrate, pentaerythritol tetranitrate, nicorandil, NTG and molsidomine
13. Previous (within 30 days of randomization) or concomitant participation in another clinical study with investigational medicinal product(s)
14. Close affiliation with the investigational site; e.g., a close relative of the investigator, dependent person (e.g., employee or student of the investigational site)
15. Previous assignment to treatment during this study to prevent randomizing patients twice
16. Illiteracy and /or inability to read the questionnaire for any reason, as the primary endpoint is based on data collected from a self-administered patient-reported questionnaire
17. Patients who are non-ambulatory or in the view of the investigator are not able to perform a 6MWT. For ATS Statement: Guidelines for the 6MWT see Section 16.1).
18. Pregnancy or lactation
19. Previous use of vericiguat
20. Known current alcohol and/or illicit drug abuse that may interfere with the patient's safety and / or compliance at the discretion of the investigator

6.3 Withdrawal of patients from study

6.3.1 Withdrawal

Withdrawal from study

Unnecessary withdrawal of patients from the study follow-up should be avoided and all efforts should be taken to motivate patients to adhere to all study procedures and to be followed until the end of the trial.

The investigator should explore all possible options to reach a patient who fails to return to a visit or to respond to the site contact attempts. The site must document all attempts to try to contact the patient in the medical records / source documents. In order to avoid loss-to-follow-up, the investigator should ask the patient at the study start for the contact details of a relative or friend who can be contacted in case the patient cannot be reached. Patients should not be withdrawn from follow-up unless the patient explicitly withdraws consent to be contacted. All efforts should therefore be made to discuss solutions with the patient that would enable the patient to continue with follow-up in order to minimize the number of patients who withdraw such consent. The vital status will be collected for all randomized patients who have not specifically withdrawn consent for further study follow-up by any method (telephone call, email etc.), irrespective of completion of study procedures.

Withdrawal from study drug treatment

Withdrawal from study drug treatment does not represent withdrawal from the study. As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study.

Before permanently discontinuing study drug treatment (either initiated by the patient or the investigator) a temporary interruption should be considered. Patients who have temporarily discontinued from study drug treatment should resume in line with the temporary interruption rules as soon as medically justified in the opinion of the investigator (see Section 7.4). In addition, patients should not be discontinued from the study drug or withdrawn from the study solely for reaching a potential cardiovascular event.

If permanent discontinuation of study drug treatment becomes necessary due to intolerance even at the lowest dose step or any other reason, this does not mean that the patient has withdrawn from the study follow-up. Participants may be allowed to begin study treatment again if deemed medically appropriate, unless the participant's treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician.

For participants who are discontinued from study treatment but continue to be monitored in the study, all visits and procedures, as outlined in the schedule of assessments, should be completed. If the patient is unable to attend scheduled study visits, follow-up of clinical events specified as exploratory endpoints may continue by phone, unless the patient explicitly withdraws his/her consent to any type of follow-up.

Withdrawal criteria

Patients *must* be withdrawn from the **study drug**, while all efforts should be made to continue all protocol procedures also upon study drug discontinuation, if any of the following occurs:

- In case of pregnancy or breastfeeding.
- If the investigator believes that for safety reasons (i.e., adverse event) it is in the best interest of the subject to stop study drug even at the lowest dose.

Patients *may* be withdrawn from the **study drug** if any of the following occurs:

- If a significant violation of the protocol occurs, as defined by the sponsor and the coordinating investigator.
- If the randomization code is broken via IxRS.

Patients *must* be withdrawn from the **study** if any of the following occurs:

- At their own request; at any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.

Patients *may* be withdrawn from the **study** if any of the following occurs:

- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well-being.
- At the specific request of the sponsor and in liaison with the investigator (e.g., obvious non-compliance, safety concerns).

Depending on the time point of withdrawal, a withdrawn patient is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

A patient who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure".

Re-starting the defined set of screening procedures to enable the "screening failure" patient's participation at a later time point is not allowed – with the following exceptions:

- The patient had successfully passed the screening procedures, but could not be randomized to start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the patient's initial attempt to participate have been changed (via protocol amendment).

In any case, the investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. Also, for re-screening, the patient has to re-sign the informed consent form, even if it was not changed after the patient's previous screening.

Dropout

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has already been randomized.

General procedures

In all cases, the reason for discontinuation from the study drug and / or withdrawal from the study must be recorded in the CRF and in the patient's medical records.

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Any patient removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

Patients may be allowed to begin treatment again if deemed medically appropriate, unless he/she has been unblinded.

6.3.2 Replacement

Randomized patients who withdraw prematurely will not be replaced.

6.4 Patient identification

The patient number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center

7. Treatments

7.1 Treatments to be administered

Patients will be randomized 1:1:1 within 4 weeks after the Screening Visit to either:

1. Placebo arm: placebo and sham up-titration at weeks 2, 4, and 6
2. 10 mg arm: vericiguat, which will be started at 2.5 mg at randomization and up-titrated to 5 mg at week 2, and to 10 mg at week 4, with sham titration at week 6.
3. 15 mg arm: vericiguat, which will be started at 2.5 mg at randomization and up-titrated to 5 mg at week 2, to 10 mg at week 4, and to 15 mg at week 6.

Study drug treatment will be initiated after clinical stabilization, within 6 months after the onset of the qualifying HF decompensation, defined as HF hospitalization or IV diuretic treatment for HF without hospitalization. End of treatment is reached at visit 9 after 24 weeks of treatment.

Dose modification will depend on mean sitting SBP and the absence of symptoms indicative of hypotension before intake of the dose as described in Section 7.4. The intention of the protocol is to reach and maintain the target study drug dose upon uptitration. If the patient does not reach the 15 mg dose step by the time of the week 6 visit (42±3 days after randomization), or the dose is temporarily interrupted and when the investigator feels it is medically appropriate to resume it afterwards, uptitration should be considered at any subsequent visit at the discretion of the investigator according to the SBP criteria in Section 7.4.

If in the opinion of the investigator the patient does not tolerate the target dose of the study drug and presents symptoms of orthostatic hypotension, in addition to considering the reduction of the study drug the investigator should also consider the volume status, and whether there is a necessity to change the dose of diuretics. If such adjustment or discontinuation of concomitant diuretic or other medications (such as anti-hypertensive therapy, in the case of excessive blood pressure lowering) is not possible or does not resolve signs and symptoms of intolerability, the investigator may at any time during the course of the trial reduce the dose or interrupt study treatment in patients who no longer tolerate the current study drug dose.

Down-titration is possible at any time during the study if the investigator feels this is justified for safety reasons. Reasons for dose modifications (maintenance, increase, decrease, or interruption) will be collected at all planned or unscheduled visits. In case of temporary discontinuation or dose reduction after the titration period, up-titration is also possible at scheduled visits.

7.2 Identity of study treatment

Table 7–1: Identity of test drug

INN	vericiguat
Substance code number	BAY 1021189
Formulation	IR tablets
Strength	2.5 mg, 5 mg or 10 mg BAY 1021189

Table 7–2: Identity of matching placebos

INN	N/A
Substance code number	N/A
Formulation	Tablets
Strength	N/A

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

7.3 Treatment assignment

Following a screening visit, eligible patients stabilized after a HF decompensation will be randomly allocated 1:1:1 via block randomization to one of the 3 equally sized groups (2 vericiguat groups, 1 placebo group) using IxRS and will receive treatment with study drug or placebo for 24 weeks. The IxRS will determine the kit number for the study site investigator or designee to select for the subject. Patients are to take 2 tablets once daily, preferably in the morning with food, throughout study drug treatment. In case patient is randomized in the afternoon first tablets can be taken then and should be continued the next day in the morning.

Patients will be randomized within 4 weeks of the screening visit and within up to 6 months after the date of hospitalization for HF or treatment with IV diuretic for HF, and randomization will be stratified according to region and heart rhythm at baseline ECG.

Region

- Americas
- Europe (incl. Israel and South Africa)
- Asia/Pacific (including Australia)

Heart rhythm

- Atrial fibrillation (defined as atrial fibrillation or atrial flutter in baseline ECG)
- Sinus rhythm (defined as no atrial fibrillation and no atrial flutter in baseline ECG)

To avoid over-representation of patients with atrial fibrillation (AF) in the trial, randomization of patients with AF on their baseline ECG may be stopped at the discretion of the Steering Committee when this randomized cohort comprises approximately 40% of the total planned randomized population. The exact proportion of patients randomized with AF will be determined by the Steering Committee following a review of the blinded baseline clinical characteristics of this group compared to those without AF.

7.4 Dosage and administration

Patients will take two tablets once daily preferably in the morning with food. The starting dose will be 2.5 mg of vericiguat or matching placebo.

Titration steps at 2, 4 and 6 weeks include sham titration in placebo arm. Titration step at 6 weeks includes sham titration in10 mg arm. The maximal dose of vericiguat is 10 mg o.d. in the 10 mg treatment arm, and 15 mg (5 mg + 10 mg tablet) o.d. in the 15 mg arm (Table 7–3). For justification of dose selection see Section 3.2.1.

Table 7–3: Dosing plan

Dose step	Arm		
	Placebo	10 mg target dose	15 mg target dose
1	placebo	2.5 mg	2.5 mg
2	placebo	5 mg	5 mg
3	placebo	10 mg	10 mg
4	placebo	10 mg	15 mg

Titration will be based on systolic blood pressure (SBP) measurement, before intake of the study drug as follows:

- **Increase dose**: if SBP ≥100 mmHg and SBP decrease is ≤20 mmHg from previous visit, and not yet on highest dose
- **Maintain dose**: if SBP is between 90 mmHg and <100 mmHg, or SBP ≥100 mmHg and SBP decrease is >20 mmHg from previous visit, or if already on highest dose step (after 3 uptitrations)
- **Decrease the dose**: if SBP <90 mmHg without symptoms of hypotension if on dose steps 2-4 (see Table 7–3) >2.5 mg, or temporarily interrupt if on 2.5 mg (starting dose or after down titration from a higher dose)
- **Interrupt the dose**: if SBP <90 mmHg with symptoms of hypotension

Dose decrease is possible at any time if the physician feels this is necessary for safety reasons.

The first dose of trial treatment will be administered at the trial site at the randomization visit. Subsequent dosing will be performed once daily preferably in the morning by the patient at approximately the same time each day. Patients will be instructed to take vericiguat with food.

Resumption of study drug after temporary interruption

Upon temporary interruption of the study drug due to intolerability, intake should be resumed as soon as medically justified at the discretion of the investigator. There is no defined maximum time limit for temporary treatment interruption. In all cases, the reason for study drug interruption or permanent study drug discontinuation must be recorded in the eCRF and in the patient's medical records. Titration rules following restart of study drug after temporary interruption of study drug are as follows:

- If restart before visit 5 (week 6): Restart at a scheduled visit and titrate according to the intervals in Table 7–4.
- If restart after visit 5 (week 6) restart as soon as possible (with an unscheduled visit if required) and up-titrate according to Table 7–4. Patient will then resume the planned visit schedule. Unscheduled clinic and/or phone contacts can be conducted at the discretion of the investigator. The titration steps must be at least 11 days apart, and if the period between resumption and the next scheduled visit is more than 17 (14+3) days, the patient can attend an unscheduled visit.

Table 7–4: Resumption of study drug intake

Dose step at time of interruption	(mg) at time of interruption	Length of interruption	Restart dose	1st titration (14±3 days after resumption)	2nd titration (28±3 days after resumption)	3rd titration (42±3 days after resumption)
1	Plc or 2.5	Any	Plc or 2.5	Plc or 5	Plc or 10	Plc or 10 or 15
2	Plc or 5	Any	Plc or 2.5	Plc or 5	Plc or 10	Plc or 10 or 15
3	Plc or 10	>5 days	Plc or 2.5	Plc or 5	Plc or 10	Plc or 10 or 15
		≤5 days	Plc or 5	Plc or 10	Plc or 10 or 15	NA[a]
4	Plc or 10 or 15	>5 days	Plc or 2.5	Plc or 5	Plc or 10	Plc or 10 or 15
		≤5 days	Plc or 5	Plc or 10	Plc or 10 or 15	NA[a]

a highest dose achieved in the second titration

NA, not applicable; Plc, placebo

For follow-up of patients after discontinuation see Section 9.1

7.5 Blinding

Tablets containing 2.5 mg and 5 mg vericiguat and the respective matching placebo tablets will be identical in appearance. 10 mg vericiguat and matching placebo to 10 mg tablets will be identical in appearance. The packaging and labeling are designed to maintain the blinding of the investigator's team and to the patients. The study data will remain blinded for each treatment group, until database lock and authorization of data release.

Unblinding

In compliance with applicable regulations, in the event of a SUSAR (see Section 9.6.1.5) related to the blinded treatment, the patient's treatment code will usually be unblinded before reporting to the health authorities. Notifications of ethic committees and investigators will be done according to all applicable regulations (see Section 9.6.1.4).

In this study, the following events are outcome events and will be considered as disease related in the defined study population. For the purposes of this trial, these events will not be subject to systematic unblinding and expedited reporting process, if reported as serious adverse drug reactions.

- Acute heart failure
- Chronic heart failure
- Worsening chronic heart failure
- Cardiac arrest
- Myocardial Infarction
- Stroke
- CV death

These events will be captured in the eCRF, and will undergo regular central adjudication by central CEC, and unblinded DMC review. If an event submitted for adjudication is determined by the CEC not to meet the endpoint criteria in the CEC charter and meets seriousness criteria, it will then be subject to expedited reporting (as appropriate, based upon both investigator and Bayer company causality assessment of drug relationship, as required by local legislation).

Emergency unblinding by the investigator

In case of emergency or any finding that requires unblinding, the investigator will be able to break the blind for an individual patient via IxRS according to the unblinding procedure implemented. This will allow breaking the blind for an individual patient without impairing the study as a whole unless safety findings required unblinding.

The code can be broken by the investigator, or other responsible person, when knowledge of the patient's treatment is required for the clinical management of the patient. Whenever possible, the sponsor is to be contacted to discuss the case before the code is broken. If it becomes necessary to know the individual treatment during the study and thus to break the code for that patient, the date, time, and reason are to be recorded in the patient's medical notes and relevant eCRF page. The investigator is required to promptly document and explain to the sponsor any premature unblinding (e.g. unblinding due to a serious adverse event) of the study treatment.

Unblinding for ongoing safety monitoring

To allow ongoing safety monitoring during the conduct of the study by an external DMC, members of the Committee will receive unblinded safety data. The involvement of an external Statistical Analysis Center in this process will ensure that unblinded information is not available for third parties. Details of the process are described in the DMC charter.

7.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/contract research organization), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study drug via IxRS. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

If performing drug accountability implies a potential risk of contamination, a safety process/ guidance for handling returned study drug will be provided.

7.7 Treatment compliance

To monitor compliance, completing a drug dispensing log for each patient will be required. Overall compliance with study drug intake should be between 80% and 120% of the scheduled study drug intake at the end of study drug treatment. The date of dispensing the study drug to the patient will be documented.

Study drug will be dispensed at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7 and Visit 8. Patients should return all remaining unused study drug at each visit.

Accountability will be determined by tablet count at each visit. To facilitate this, patients must be instructed to return all of the study drug packaging including unused study drug and empty packaging.

Any discrepancies between actual and expected amount of returned study medication must be discussed with the patient at the time of the visit, and any explanation must be documented in the source records as well as in the eCRF.

8. Non-study therapy

8.1 Prior and concomitant therapy

Permitted background treatment

- Diuretics are recommended in congested patients in order to alleviate symptoms and signs (5).
- Treatment of comorbidities like hypertension, coronary and vascular diseases, hyperlipidemia, diabetes, atrial fibrillation and other arrhythmias should follow the local/regional Guidelines. Any dose adaptations, addition, changed or added route of administration, omission or cessation of concomitant therapy including diuretics, anti-hypertensives such as ACE inhibitors, ARB, or rate control such as ß blockers and digoxin are possible whenever deemed necessary by the investigator irrespective of blinded titration of the study drug.

Prohibited prior and concomitant medications:

- Nitrates or NO donors including isosorbide dinitrate, isosorbide 5-mononitrate, pentaerythritol tetranitrate, nicorandil, NTG and molsidomine: all routes are not allowed during study drug treatment; IV therapy with nitrates or NO donors is only allowed until 24 h prior to randomization.

  It is recommended that nitrates should not be administered to any patient previously on study drug earlier than 3 days after the last dose of study drug. Should there be an urgent need for nitrate administration, they should be administered in a monitored inpatient setting.
- PDE5 inhibitors: Sildenafil and Vardenafil are allowed only until 24 h prior to randomization, Tadalafil until 48 h prior to randomization.
- sGC stimulators other than the study drug are not allowed during study drug treatment

8.2 Post-study therapy

The investigator must provide follow-up medical care for all patients who complete the study or who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care as required.

9. Procedures and variables

9.1 Tabular schedule of evaluations

Table 9–1: Tabular schedule of assessments

Trial Periods		Screening[a]	Base-line	Titration / Sham titration			Treatment			End of treatment	Safety Follow-Up[b]	Premature Treatment Discontinuation	
Visit Number		1	2	3	4	5	6	7	8	9	10	11	12
Week				2	4	6	8	12	18	24	28		
Visit Window (Days)		-28-1	1	14±3	28±3	42±3	56±3	84±3	126±3	168±3	196±7	At time of permanent treatment discon	28±7 days after last dose
• Informed consent main study • Demographic data • Medical and surgical history		●											
Optional - Informed consent for pharmacogenetic research		●[c]											
Optional - Informed consent for accelerometry		●											
Concomitant medication		●	●	●	●	●	●	●	●	●	●	●	●
Inclusion / exclusion criteria		●	●										
Urine pregnancy test (local)[q]		●	●					●					
Randomization (IxRS)			●										
ePRO: KCCQ, PGIC[d], PGIS, EQ-5D-5L			●	●		●		●	●	●	●[e]	●	●[e]
Fried Frailty score			●							●		●	
NYHA class		●	●	●	●	●	●	●	●	●	●	●	●
Blood pressure, pulse rate [f]		●	●	●	●	●	●	●	●	●	●	●	●
ECG			●[g]							●[h]		●[r]	
Only in patients eligible for PK/QT assessment [j]	ECG		●[i]			●[i]				●[i]			
	PK sample predose					●				●			
	PK sample 1-2 h, and 3-6h post		●[k]			●				●			
6 MWT		●	●					●		●	●	●	●
Local lab blood sample [l]		●											
Central lab blood sample [m]			●				●			●[s]		●	
Optional pharmacogenetic research blood sample			●[c]										
Physical exam, weight, height [n]		●	●	●	●	●	●	●		●	●	●	●
Adverse events		●	●	●	●	●	●	●	●	●	●	●	●
Drug accountability [o]				●	●	●	●	●	●	●		●	
Dispense study drug			●	●	●	●	●	●	●				
Optional uptitration [p]							●	●	●				
Optional accelerometry		●[t]	●[u]				●[t]	●[u]	●[t]	●[u]			

Footnotes:

a. Can start as early as at time of hospitalization or IV diuretic treatment for HF or up to 6 months after. Should start no more than 4 weeks before randomization. Screening visit and baseline visit can take place on the same day.

b. In case of premature discontinuation of study treatment, vital status will be collected at week 28 by any method (e.g. via telephone call or e-mail), unless the patient has specifically withdrawn consent for further study follow-up.

c. Optional pharmacogenetic informed consent and blood collection may also be performed at a later visit. Blood sample for genetic analysis will only be taken if the patient signed the separate consent for the pharmacogenetic research study.

d. Not performed at baseline visit.

e. Only KCCQ and EQ-5D-5L performed at visit 10 and 12.

f. 3 measurements, 2 min apart; measurements are taken prior to study drug intake. Additional measurement at 2h ± 15 min post study drug intake will be performed only at visit 2, and at visits 5-8 if dose is uptitrated from dose step 3 to step 4.

g. Assessment of eligibility for PK/QT assessment.

h. Only for patients not eligible for QT assessment
i. Central 12-lead ECGs should be recorded only in patients eligible for PK/QT assessment, just before the collection of the blood sample for PK, to enable PK/QT assessments. Exact date and time of the ECG recording and date and time of last study drug intake (either at home on the day before the sample or at site) must be documented.
j. In case the PK sample at the specified visits cannot be obtained at a specified time point, 12-lead ECG and the PK sample can be taken at the subsequent (scheduled or unscheduled) visits. Exact collection date and time of the PK samples and date and time of last study drug intake before PK sampling (either at home on the day before the sample or at site) must be documented.
k. Only PK sample 1-2h post study drug will be collected at this visit.
l. Only if not available within 30 days prior to randomization for eligibility, creatinine and NT-proBNP or BNP (or both if available)
m. NT-proBNP, clinical chemistry, hematology, coagulation, biomarker testing, and other laboratory tests (for full list see Section 9.7.1.2)
n. Full physical examination to be performed at Visit 1 and 2. Focused cardiovascular examination to be performed in all other visits. Height will be only measured once at the screening visit. Automatic calculation of body mass index (BMI) in the electronic case report form (eCRF) will use this result.
o. Collect unused study drug.
p. In case of temporary discontinuation or dose modification after the titration period. An unscheduled visit is possible if the period between resumption and the next scheduled visit is more than 17 days. Time between uptitration steps must be no less than 11 days.
q. A local lab urine or serum pregnancy test will be conducted for women of childbearing potential according to local procedures. If required by national / institutional regulations, a serum or urine pregnancy test in patients of childbearing potential should be performed more often (e.g. at every visit).
r. In case of premature discontinuation, ECG is performed as a safety measure.
s. PK sample predose will be collected together with the central lab sample for all patients.
t. Only for patients participating in the optional accelerometry substudy, activity tracking devices are planned to be handed out as specified in the accelerometry procedure manual.
u. Activity tracking devices are planned to be collected from patients participating in the optional accelerometry substudy as specified in the accelerometry procedure manual.

Abbreviations: 6MWT, 6-minute walk test; BMI, body mass index; BNP, brain natriuretic peptide; ECG, electrocardiogram; eCRF, electronic case report form; ePRO, electronic patient reported outcome; EQ-5D-5L, EuroQoL Group 5-dimension, 5-level questionnaire; HF, heart failure; IxRS, interactive voice/web response system; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PGIC, Patient Global Impression of Change questionnaire; PGIS, Patient Global Impression of Severity questionnaire; PK, pharmacokinetics

9.2 Visit description

Before any screening examination takes place, potentially eligible patients will be given a full explanation as to what the study would involve. This will be done both verbally and in writing in the form of a written patient information leaflet. Patients will be given sufficient time to consider their participation in the study and to ask any questions. Patients who are willing to take part in the study will then be asked to sign a patient information / informed consent form. This signature must be collected prior to the screening visit.

Screening examinations will only be performed after having received the patient's written informed consent. If not stated otherwise, the measures listed in the following sections will be performed by or under the supervision of a study site investigator.

Procedures for the screening visit can be performed on several days. Alternatively, screening visit and Visit 1 including randomization of patients can take place on the same day.

All visits from Visit 1 to Visit 9 must be started in the morning. Patients will be instructed to take their daily dose at the study site (not taken at home) as indicated in the study procedures.

9.2.1 Visit 1 Screening Visit – Day -28-1

Screening can start as early as at time of hospitalization for HF, before or after discharge, or upon intravenous diuretic treatment for heart failure without hospitalization, and up to 6 months after hospitalization for HF or intravenous diuretic treatment for HF.

The following procedures will be performed within 4 weeks before randomization of the patient.

- Confirm signed informed consent is available
- Confirm signed informed consent for optional pharmacogenetic research is available, for those who wish to participate in pharmacogenetic research (Informed consent for pharmacogenetic research may also be performed at later visit)
- Confirm signed informed consent for optional accelerometry substudy is available, for those who wish to participate in the optional accelerometry substudy at sites participating in the optional accelerometry substudy (see Section 9.7.8)
- Allocation of unique PID number (see Section 6.4)
- Demographic data and other population characteristics (see Section 9.3.1)
- Medical and surgical history (see Section 9.3.2)
- Prior and concomitant medications (see Section 8.1)
- Urine pregnancy test, if applicable.
- Physical examination including height and weight (BMI will be calculated automatically in the eCRF) (see Section 9.7.2)
- Vital signs (BP and pulse rate) in sitting position after resting for at least 10 min, 3 measurements, 2 min apart; means will be calculated in the eCRF (See Section 9.7.5).
- Continuous assessment of AEs will start immediately after signing the informed consent until the follow-up visit (if applicable)
- Assess inclusion and exclusion criteria (see Sections 6.1 and 6.2), including previously recorded local laboratory and echocardiography results for entry in the eCRF:
    - NT-proBNP or BNP or both within 30 days prior to randomization
    - Serum creatinine to calculate eGFR
    - LVEF
    - Intraventricular or posterior wall thickness
    - LVAI or LAV or LA area or LA diameter
- 6MWT (familiarization test if screening is done on a separate day from randomization, perform only once if screening and randomization are on the same day)
- Only for patients participating in the optional accelerometry substudy: activity tracking devices are planned to be handed out with instructions to use as specified in the accelerometry procedure manual.
- Schedule Visit 2 (Baseline) within 4 weeks after screening

9.2.2 Visit 2 Baseline and Randomization – Day 1

Randomization occurs latest within 4 weeks after informed consent.

- Before randomization:
  - Assess patient eligibility (see Sections 6.1 and 6.2; for echo criteria see below)
  - KCCQ, EQ-5D-5L, PGIS (see Section 9.4)
  - Frailty assessment based on the Fried score
  - Assessment of NYHA class
  - Concomitant medications, record new or ongoing medication or changes in dosage (see Section 8.1)
  - Urine pregnancy test, if applicable.
  - Adverse events (see Section 9.6.1)
  - Only for patients participating in the optional accelerometry substudy: Activity tracking devices are planned to be collected (see accelerometry manual).
  - Physical examination including height and weight (BMI will be calculated automatically in the eCRF) (see Section 9.7.2)
  - Vital signs (BP and pulse rate), See Section 9.7.5.
  - 12-lead ECG to evaluate the eligibility of the patient for PK/QT assessment (see Section 9.7.4)
  - 6MWT
- Randomization to vericiguat once daily or placebo (see Section 7.3)
- Central lab blood samples for NT-proBNP, hematology, clinical chemistry, coagulation and biomarkers (see Section 9.7.1)
- Only to be collected for patients who signed the optional pharmacogenetics research informed consent: Central lab blood sample for pharmacogenetics (obtaining the informed consent for optional pharmacogenetics research and blood collection may also be performed at a later visit).
- Dispense study drug for the first 2 week interval until Visit 3 and instruct the patient on how to take the study drug
- Patient to take first dose of study drug (exact time of intake must be documented)
- Only in patients eligible for PK/QT assessment (all patients assessed as eligible based on the baseline ECG, see Section 9.7.4) – ECG and PK sample should be collected time-matched, first ECG, subsequently PK sample:
  - 12-lead ECG (to be performed just before the PK sample is taken) 1-2h after study drug intake (exact collection times must be documented)
  - Blood sample for PK 1-2h after study drug intake (exact collection time must be documented)

- 2 h ± 15 min after study drug intake: Vital signs (BP and pulse rate) in sitting position after resting for at least 10 min, 3 measurements, 2 min apart. See Section 9.7.5.
- Schedule Visit 3 for Day 14±3

Visit 1 (Screening visit) and Visit 2 (Day1) including randomization of patients can take place on the same day. In this case, procedures listed for both visits need to be performed only once.

9.2.3 Visit 3 – Day 14±3 (week 2)

Patients need to come for this visit without taking the morning dose of the study drug (this applies only for the study drug. All others medications shall be taken as scheduled).

- Before titration / sham titration
  - KCCQ, EQ-5D-5L, PGIC/S
  - Assessment of NYHA class
  - Concomitant medications (see Section 8.1)
  - Adverse events (see Section 9.6.1)
  - Physical examination
  - Vital signs (BP and pulse rate). See Section 9.7.5.
  - Drug accountability, and collect unused study drug
- Titration/sham titration in accordance with dosing regimen in Section 7.3 and dispense study drug accordingly for the 2 week interval until Visit 4 and instruct the patient on how to take the study drug
- Patient to take first dose of titrated / sham titrated study drug (exact time of intake must be documented)
- Schedule Visit 4 for Day 28±3

9.2.4 Visit 4 – Day 28±3 (week 4)

Patients need to come for this visit without taking the morning dose of the study drug (this applies only for the study drug. All others medications shall be taken as scheduled)

- Before titration / sham titration
  - Assessment of NYHA class
  - Concomitant medications (see Section 8.1)
  - Adverse events (see Section 9.6.1)
  - Physical examination
  - Vital signs (BP and pulse rate). See Section 9.7.5.
  - Drug accountability, and collect unused study drug

- Titration/sham titration in accordance with dosing regimen in Section 7.4 and dispense study drug accordingly for the 2 week interval until Visit 5 and instruct the patient on how to take the study drug
- Patient to take first dose of titrated / sham titrated study drug (exact time of intake must be documented)
- Schedule Visit 5 for Day 42±3
- For PK sampling at visit 5: Remind the patient to report the date and time of the last study drug intake the day before visit 5.

9.2.5 Visit 5 – Day 42±3 (week 6)

Patients need to come for this visit without taking the morning dose of the study drug (this applies only for the study drug. All others medications shall be taken as scheduled)

- Before titration / sham titration
  - KCCQ, EQ-5D-5L, PGIC/S (see Section 9.4)
  - Assessment of NYHA class
  - Concomitant medications (see Section 8.1)
  - Adverse events (see Section 9.6.1)
  - Physical examination
  - Vital signs (BP and pulse rate). See Section 9.7.5.
- Only in patients eligible for PK/QT assessment (all patients assessed as eligible based on the baseline ECG, see Section 9.7.4) – ECG and PK sample should be collected time-matched, first ECG, subsequently PK sample::
  - 12-lead ECG (to be performed just before the PK sample is taken) prior to study drug intake (exact collection times must be documented)
  - Blood sample for PK prior to study drug intake (exact collection time to be documented)
  - Drug accountability, incl. exact time of last dose intake the day before, and collect unused study drug
- Titration/sham titration in accordance with dosing regimen in Section 7.4 and dispense study drug accordingly for the 2 week interval until Visit 6 and instruct the patient on how to take the study drug
- Patient to take first dose of titrated / sham titrated study drug (exact time of intake must be documented)
- Only in case of uptitration from dose step 3 to dose step 4, at 2 h ± 15 min after study drug intake: Vital signs (BP and pulse rate). See Section 9.7.5.

- Only in patients eligible for PK/QT assessment (all patients assessed as eligible based on the baseline ECG, see Section 9.7.4) – ECG and PK sample should be collected time-matched, first ECG, subsequently PK sample:
    - 12-lead ECG (to be performed just before the PK sample is taken) to be taken 1-2 h after study drug intake, exact collection times must be documented)
    - Blood sample for PK 1-2 h after study drug intake (exact collection time must be documented)
    - 12-lead ECG (to be performed just before the PK sample is taken) to be taken within the time interval of 3-6 h study drug intake (exact collection times must be documented)
    - Blood sample for PK within the time interval of 3-6 h after study drug intake (exact collection time must be documented)
- Schedule Visit 6 for Day 56±3

9.2.6 Visit 6 – Day 56±3 (week 8)

Patients need to come for this visit without taking the morning dose of the study drug (this applies only for the study drug. All others medications shall be taken as scheduled)

- Assessment of NYHA class
- Concomitant medications (see Section 8.1)
- Adverse events (see Section 9.6.1)
- Physical examination
- Vital signs (BP and pulse rate). See Section 9.7.5.
- Central lab blood samples for NT-proBNP, hematology, clinical chemistry, coagulation and biomarkers prior to study drug intake (exact collection time to be documented; see Section 9.7.1)
- Drug accountability, incl. exact time of last dose intake the day before, and collect unused study drug
- Optional uptitration/sham titration if not yet on target dose, dispense study drug in accordance with dosing regimen for the 6 week interval until Visit 7 and instruct the patient on how to take the study drug.
- Patient to take the study drug (exact time of intake must be documented)
- Only in case of uptitration from dose step 3 to dose step 4, 2 h ± 15 min after study drug intake: Vital signs BP and pulse rate). See Section 9.7.5.
- Schedule Visit 7 for Day 84±3
- Only for patients participating in the optional accelerometry substudy: activity tracking devices are planned to be handed out with instructions to use as specified in the accelerometry procedure manual.

9.2.7 Visit 7 – Day 84±3 (week 12)

Patients need to come for this visit without taking the morning dose of the study drug (this applies only for the study drug. All others medications shall be taken as scheduled)

- KCCQ, EQ-5D-5L, PGIC/S (see Section 9.4)
- Assessment of NYHA class
- Concomitant medications (see Section 8.1)
- Adverse events (see Section 9.6.1)
- Only for patients participating in the optional accelerometry substudy: Activity tracking devices are planned to be collected (see accelerometry manual).
- Physical examination
- Vital signs in sitting position (BP and pulse rate). See Section 9.7.5.
- 6 MWT
- Drug accountability, incl. exact time of last dose intake the day before, and collect unused study drug
- Optional uptitration/sham titration if not yet on target dose, dispense study drug in accordance with dosing regimen for the 6 week interval until Visit 8 and instruct the patient on how to take the study drug.
- Patient to take the study drug (exact time of intake must be documented)
- Only in case of uptitration from dose step 3 to dose step 4, 2 h ± 15 min after study drug intake: Vital signs (BP and pulse rate). See Section 9.7.5.
- Schedule Visit 8 for Day 126±3

9.2.8 Visit 8 – Day 126±3 (Week 18)

Patients need to come for this visit without taking the morning dose of the study drug (this applies only for the study drug. All others medications shall be taken as scheduled)

- KCCQ, EQ-5D-5L, PGIC/S (see Section 9.4)
- Assessment of NYHA class
- Concomitant medications (see Section 8.1)
- Adverse events (see Section 9.6.1
- Physical examination
- Vital signs in sitting position (BP and pulse rate). See Section 9.7.5
- Drug accountability, and collect unused study drug.
- Optional uptitration/sham titration if not yet on target dose, dispense study drug in accordance with dosing regimen for the 6 week interval until Visit 9 and instruct the patient on how to take the study drug.

- Patient to take the study drug (exact time of intake must be documented)
- Only in case of uptitration from dose step 3 to dose step 4, 2 h ± 15 min after study drug intake: Vital signs (BP and pulse rate). See Section 9.7.5.
- Schedule Visit 9 for Day 168±7
- For PK sampling at visit 9: Remind the patient to report the date and time of the last study drug intake the day before visit 9.
- Only for patients participating in the optional accelerometry substudy: activity tracking devices are planned to be handed out with instructions to use as specified in the accelerometry procedure manual.

9.2.9 Visit 9 End of treatment – Day 168±7 (week 24)

Patients need to come to site without taking the morning dose of the study drug (this applies only for the study drug. All other medications shall be taken as scheduled).

The end of treatment visit should be scheduled at Day 168±7 also in case of premature discontinuation of study drug. All other visits and procedures should continue also if the study drug has been permanently discontinued.

- KCCQ, EQ-5D-5L, PGIC/S (see Section 9.4)
- Frailty assessment based on the Fried score
- Assessment of NYHA class
- Concomitant medications (see Section 8.1)
- Adverse events (see Section 9.6.1
- Only for patients participating in the optional accelerometry substudy: Activity tracking devices are planned to be collected (see accelerometry manual).
- Physical examination
- Vital signs in sitting position (BP and pulse rate). See Section 9.7.5.
- 6MWT
- 12-lead ECG in patients not eligible for PK/QT assessment, see Section 9.7.4
- Only in patients eligible for PK/QT assessment (all patients assessed as eligible based on the baseline ECG, see Section 9.7.4) – ECG and PK sample should be collected time-matched, first ECG, subsequently PK sample:
    - 12-lead ECG (to be performed just before the PK sample is taken) to be taken prior to study drug intake (exact collection time must be documented)
    - Blood sample for PK prior to study drug intake (exact collection time to be documented)
- Central lab blood samples for NT-proBNP, hematology, clinical chemistry, coagulation and biomarkers 9.7.1 and blood sample for PK prior to study drug intake (exact collection time to be documented) in all patients, see Section 9.7.4

- Drug accountability, incl. exact time of last dose intake the day before, and collect unused study drug
- Patient to take study drug (exact time of intake must be documented)
- Only in patients eligible for PK/QT assessment (all patients assessed as eligible based on the baseline ECG, see Section 9.7.4) – ECG and PK sample should be collected time-matched, first ECG, subsequently PK sample:
    - 12-lead ECG (to be performed just before the PK sample is taken) to be taken 1-2 h after study drug intake, exact collection times must be documented)
    - Blood sample for PK 1-2 h after study drug intake, exact collection time must be documented)
    - 12-lead ECG in supine position, after resting for at least 10 min (to be performed just before the PK sample is taken) to be taken within the time interval of 3-6 h study drug intake (exact collection times must be documented)
    - Blood sample for PK within the time interval of 3-6 h after study drug intake (exact collection time must be documented)
- Schedule Follow-Up visit for Day 196±7

9.2.10 Visit 10 Safety follow-up – Day 196±7

- KCCQ and EQ-5D-5L (see Section 9.4)
- Assessment of NYHA class
- Adverse events (see Section 9.6.1)
- Physical examination incl. weight
- Vital signs (BP and HR). See Section 9.7.5.
- 6MWT
- Vital status will be collected for all randomized patients, including those who did not attend the visit or were permanently discontinued, by any method (e.g. via telephone call or e-mail), unless the patient has specifically withdrawn consent for further study follow-up.

9.2.11 Premature discontinuation visit – at time of permanent discontinuation

This visit is applicable only for patients who prematurely discontinue the study drug intake (Either by decision of the investigator or by the patient.)

- KCCQ, EQ-5D-5L, PGIC/S (see Section 9.4)
- Frailty assessment based on the Fried score
- Assessment of NYHA class
- Concomitant medications (see Section 8.1)

- Adverse events (see Section 9.6.1)
- Physical examination incl. weight
- Vital signs (BP and pulse rate). See Section 9.7.5.
- 12-lead ECG (see Section 9.7.4)
- 6MWT
- Central lab blood sample for NT-proBNP, hematology, clinical chemistry, coagulation and biomarkers.
- Drug accountability, incl. exact time of last dose intake the day before, and collect unused study drug
- Schedule Visit 12 for 30±7 days after last dose

9.2.12 Safety follow-up visit after premature discontinuation– 28 ±7 days after last dose

This visit is applicable only for patients who prematurely discontinue the study drug intake (Either by decision of the investigator or by the patient.)

- KCCQ and EQ-5D-5L (see Section 9.4)
- Assessment of NYHA class
- Adverse events (see Section 9.6.1)
- Physical examination incl. weight
- Vital signs (BP and pulse rate). See Section 9.7.5.
- 6MWT

9.3 Population characteristics

9.3.1 Demographic

The following demographic characteristics will be collected:

- Year of birth
- Age at Informed Consent
- Gender
- Race (as allowed by local regulation) and
- Ethnicity (as allowed by local regulation)

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the patient's study eligibility.
- Previous diagnosis of HFpEF
- Number of previous hospitalizations for HF prior to the qualifying event (these are not mandatory for inclusion but recorded as clinical characteristics)
- Angina pectoris (CCSA class in patients with a medical history of angina)
- Medical history related to concomitant medication
- Comorbidities (medical history of atrial fibrillation is collected in addition to collection of atrial fibrillation in local baseline ECG before randomization for stratification: arterial hypertension, hyperlipidemia, CAD, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, sleep apnea, anemia, erectile dysfunction
- Smoking history
- Alcohol consumption

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.4 Efficacy

- The primary efficacy variable is the change in KCCQ PLS from baseline to week 24, for the 10 and 15 mg vericiguat arms compared to placebo.
- The secondary efficacy variable is the change in the 6MWT from baseline to week 24, for the 10 and 15 mg vericiguat arms when compared to placebo
- Exploratory efficacy variables:
    - KCCQ domains of PLS, Symptom Frequency, Symptom Burden, Social limitation, QoL and the summary scores TSS, CSS and OSS measured values and change from baseline, by visit.
    - Cumulative distribution function of – and proportions of patients with – change from baseline at 24 weeks for the KCCQ domains of PLS, Symptom Frequency, Symptom Burden, and summary scores TSS, CSS and OSS.
    - EQ-5D-5L domain and Visual Analogue Scale responses and change from baseline, by visit.
    - PGIS response level and change from baseline, by visit
    - PGIC response level, proportion with response of important improvement from baseline, proportion with response of important deterioration, by visit.
    - Change in Fried-based frailty assessment at 24 weeks
    - Change in NYHA class from baseline at 24 weeks

- NT-proBNP
- Incidences of cardiovascular death and total heart failure hospitalizations, as well as all-cause mortality, CV hospitalizations including MI and stroke, and outpatient HF events.
- Time to first occurrence of the composite of CV death or heart failure hospitalization.
- Time to first occurrence of the composite of CV death, HF hospitalization, worsening from baseline in NYHA class, or worsening from baseline in PGIC
- Time to first occurrence of the composite of CV death, heart failure hospitalization, worsening from baseline in NYHA class, or worsening from baseline in KCCQ CSS

- Other efficacy variables:
  - Planned Genetic analysis

9.4.1 KCCQ

KCCQ, is a widely used 23-item, disease-specific health status measure intended for the assessment of heart failure patients' perspectives of how their disease impacts their lives (24). It is a self-administered PRO instrument and requires, on average, 4–6 minutes to complete. Patients are asked to recall how their heart failure impacted their life over a 2-week recall period. Response options are on a 5- to 7-point Likert-type scale with varying response options depending on the question.

The KCCQ measures the impact of patients' heart failure, or its treatment, on 6 domains; Physical Limitation, Symptom (with subscores for frequency and burden), Quality of Life, Social Limitations, Symptom Stability and Self-Efficacy. Scores are calculated by summing domain responses and then transforming scores to a 0-100 unit scale with higher scores indicating better health status. In addition, the KCCQ includes 2 summary scores, CSS an equally weighted composite of Physical limitation and Total Symptom domain scores, and OSS which additionally combines the social limitation and quality of life domain scores to the CSS (Table 9–2).

Table 9–2: KCCQ Domains and Summary Scores

KCCQ Domain	Description[a]
	Efficacy Domains
Physical Limitation[b]	The limitations patients' experience, due to their heart failure symptoms, in performing routine activities. Activities are common, gender-neutral, and generalizable across cultures, while also capturing a range of exertional requirements.
Symptom[c]	The frequency and burden of clinical symptoms in heart failure, including fatigue, shortness of breath, paroxysmal nocturnal dyspnea and patients' edema/swelling. An overall symptom score is generally used in analyses; subscale scores for both frequency and severity are also available.
Quality of Life	Designed to reflect patients' assessment of their quality of life, given the current status of their heart failure.
Social Limitation	The extent to which heart failure symptoms impair patients' ability to interact in a number of gender-neutral social activities.
	Non-Efficacy Domains
Symptom Stability	Measures recent changes in patients' symptoms; their shortness of breath, fatigue or swelling. It is compares patients frequency of heart failure symptoms at the time of completing the KCCQ with their frequency 2 weeks ago. This domain is not included in the summary scores.
Self-efficacy	Patient perceptions of how to prevent heart failure exacerbations and manage complications when they arise. This scale is not included in the summary scores.
	Summary Scores
Clinical Summary	Includes total symptom and physical function scores to correspond with NYHA Classification.
Overall Summary	Includes the total symptom, physical function, social limitations and quality of life scores

a Descriptions of KCCQ Domain and summary scores are taken from the FDA document Medical Device Development Tool (MDDT) Qualification Decision Summary for Kansas City Cardiomyopathy Questionnaire (KCCQ) (27) with minor editing for brevity.
b 'Physical Function' also used as domain name.
c Often reported as 'Total Symptom Score'.

KCCQ Physical Limitation Score (PLS) has been selected as the primary endpoint in the trial as it is a direct measure of the hypothesized treatment effect; improvement in functional capacity in activities of daily life limited by the symptoms of heart failure. PLS measures the limitations patients' experience, due to their heart failure symptoms (shortness of breath or fatigue), in performing routine activities of daily life (Table 9–3). The PLS is calculated through an algorithm applying equal weighting to each of the items and a transformation to a 0-100 scale. Other KCCQ domains including Symptom (frequency, burden and overall), Quality of life and Social limitation together with the Clinical and Overall summary scores will be reported as exploratory endpoints. The KCCQ domains of Symptom Stability and Self-efficacy will be reported but will not be considered measures of treatment efficacy.

Table 9–3: KCCQ - Physical Limitation domain item wording

Item activity description[a]	Response scale (for all items)
(a) Dressing his/herself	1. Extremely limited
(b) Showering / bathing	2. Quite a bit limited
(c) Walking 1 block on level ground	3. Moderately limited
(d) Doing yard work, housework or carrying groceries	4. Slightly limited
(e) climbing a flight of stairs without stopping	5. Not at all limited
(f) Hurrying or jogging (as if to catch a bus)	6. Limited for other reasons or did not do the activity

a The patient is asked to indicate how much he/she is limited by heart failure (shortness of breath or fatigue) in his/her ability to do the described activities over the past 2 weeks.

9.4.2 EQ-5D-5L

The EQ-5D-5L is a self-administered generic measure of health-related quality of life which includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients provide a rating for each question on a five-level Likert scale: having no problems, having slight problems, having moderate problems, having severe problems and being unable to do/having extreme problems. In addition, patients are asked to self-rate their own health today on a vertical 0-100 unit visual analogue scale (VAS), with 0 corresponding to "the worst health you can imagine", and 100 corresponding to "the best health you can imagine".

9.4.3 Patient Global Impression of Change (PGIC), and Severity (PGIS)

PGIC contains one question (1a) asking the patient to assess the degree of change in physical limitation due to heart failure compared to the start of the treatment using the following response options: “much better”, “better”, “a little better”, “the same”, “a little worse”, “worse”, or “much worse”. A subsequent question (1b) then asks the patient to indicate whether he/she feels the degree of change reported is important or not (yes/no).

PGIS contains one question asking the patient to assess the current severity of their physical limitations due to heart failure using the following response options: “No limitations”, “Mild”, “Moderate”, “Severe”, or “Very severe”

It is anticipated to take approximately 2-3 minutes to complete both the PGIC and PGIS questions. Data from these questions will be used to provide anchors for estimating minimally important differences in physical limitations in heart failure.

9.4.4 Fried frailty score

The Fried frailty phenotype defines 5 key domains for frailty (28) weakness, low energy, slowed walking speed, decreased physical activity, and weight loss. It quickly garnered attention in the CV community (29). Fried’s frailty score is on the basis of an integrated biological perspective, without focus on a single aspect of decline but the overall context of homeostasis. The Fried score differentiates frailty from multimorbidity and disability,

articulating that frailty predisposed to the other conditions, but frailty was a distinct biologic syndrome (30).

The questions patterned from the Fried Frailty score domains are assessed at baseline and at 24 weeks (31). The questions address five domains of the frailty phenotype: (a) shrinking (weight loss of ⩾10 pounds in the prior year); (b) weakness (decreased or weakened grip strength); (c) exhaustion (fatigue or declining endurance); (d) slowness (slower walking pace); and (e) low activity (decline in physical activity). The 5 questions are as follows:

Questions at baseline:

Within the last 12 months has the patient experienced any of the following?

- Unintentional weight loss (5 kg/10 lbs).
- Developed decreased grip strength.
- Developed increasing fatigue/lethargy or declining endurance.
- Walks a distance of 5 m/15 feet at a slower pace.
- Decline in typical activity level.

Questions at 24 weeks:

Within the last 6 months has the patient experienced any of the following?

- Unintentional weight loss (5 kg/10 lbs).
- Developed decreased grip strength.
- Developed increasing fatigue/lethargy or declining endurance.
- Walks a distance of 5 m/15 feet at a slower pace.
- Decline in typical activity level.

9.4.5 Assessment of NYHA class

NYHA class will be assessed according to the classification below:

- Class I: No limitation of physical activity
- Class II: Slight limitation of physical activity in which ordinary physical activity leads to fatigue, palpitation, dyspnea, or anginal pain; the person is comfortable at rest
- Class III: Marked limitation of physical activity in which less-than-ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain; the person is comfortable at rest
- Class IV: Inability to carry on any physical activity without discomfort but also symptoms of heart failure or the anginal syndrome even at rest, with increased discomfort if any physical activity is undertaken

9.4.6 NT-proBNP

NT-proBNP measurements will be assessed by the central lab. NT-proBNP or BNP measurements for screening will be assessed locally.

9.4.7 Clinical outcome events

Potential pre-specified clinical outcome events will be submitted for adjudication to an independent CEC. The following events will be collected and analyzed to explore the efficacy of study drug treatments on clinical outcomes:

- All deaths (CV and non-CV, including outpatient death)
- CV hospitalizations including HF and non-HF hospitalizations and non-HF CV hospitalizations (i.e. myocardial infarction and stroke)
- Outpatient HF events, such as IV diuretic use for HF or urgent HF visits

The CEC will adjudicate all deaths as either CV or non-CV, and other events listed above in accordance with the pre-specified endpoint criteria in the adjudication charter. Investigators are mandated to report all suspected potential outcomes for adjudication by the CEC.

Events for adjudication should be reported as soon as critical data as defined in the eCRF page to the event adjudication is available. A query will be posted for events that require additional supporting documentation from the sites in order to render an adjudicated result and will be followed up by the sponsor. Every effort will be made to provide the CEC with clean eCRF data and required clinical data prior to event adjudication.

9.4.8 Six-minute walk test

The 6MWT is designed to evaluate a patient's exercise capacity while performing an everyday activity (32). During this study, a 6MWT including Borg CR 10 Scale will be conducted at different time points as specified in Section 9.2, for further details on assessment refer to Section 16.1. A familiarization 6MWT will be performed during the run-in phase. To avoid any interactions, it is not permitted to perform the familiarization test on the same day as the baseline 6MWT.

9.5 Pharmacokinetics / pharmacodynamics

For the investigation of systemic exposure to vericiguat and its relationship with efficacy, the plasma concentrations of vericiguat will be determined at different time points using a sparse sampling approach mainly in patients eligible for PK/QT assessment. EoT PK predose sample should be collected for all patients.

Blood samples will be collected at the time points indicated in Study Flow Chart in Section 9.1 and described in the visit description in Section 9.2. PK samples obtained at additional time points based on the investigator's discretion and/or from patients not eligible for PK/QT assessment will not qualify as a protocol deviation and will be analyzed. Deviations from the specified time points will be documented and taken into account. Date and time of the PK sample collection and date and time of last study drug intake (either at home on the day before the sample or at site) must be documented.

Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. sample handling sheets or lab manual).

Plasma concentrations of vericiguat will be measured using validated methods. QC and calibration samples will be analyzed concurrently with study samples. Concentrations are calculated from the chromatographic raw data in accordance with current Bayer guidelines. The results of calibration samples and QC samples will be reported in the Bioanalytical

Reports which will be included in the Clinical Study Report for this study. The bioanalyst will be unblinded for analysis of study samples.

The PK calculations will be based on the actual sampling and dosing times. Therefore, it is of importance to have this data thoroughly documented in the eCRF. Deviations from the specified time points will be documented and taken into account when calculating the PK parameters. Those deviations do not qualify as protocol violations.

Pharmacokinetics and, if applicable, pharmacokinetics/pharmacodynamics (PK/PD) modeling using population approaches to describe vericiguat PK including potential influence of relevant patient co-variables (e.g., age, gender, body weight, etc.) or potentially to relate parameters of clinical safety and efficacy response (e.g. primary, secondary and/or exploratory variables) with vericiguat plasma concentrations will be investigated under a separate detailed PK/PD evaluation and analysis plan.

9.6 Safety

Safety and tolerability will be assessed by clinical review of all relevant parameters including:

Primary safety variable:

- The incidence of treatment-emergent AEs

Exploratory safety variables:

- Vital signs
- Laboratory data
- 12- lead ECG data

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term “condition” may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory, ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours
   - The admission is pre-planned
     (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
   - The admission is not associated with an AE
     (e.g. social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

   Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild
- Moderate
- Severe

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

Causality should be assessed separately for each study treatment as detailed in the eCRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g. owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”

An assessment of “no” would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient’s response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical

- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual patient's pharmacodynamics should be considered.
- The assessment is not possible

Causal relationship to protocol-required procedures

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of adverse events

The investigator has to record on the respective eCRF pages all adverse events occurring in the period between the signing of the informed consent and the end of the follow-up phase; after the end of the follow-up phase there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

9.6.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF as well as the complementary SAE pages provided in the CRF must be completed for each SAE.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

In addition, adverse events related to study endpoints or underlined diseases may not be considered as SUSAR in this study (see Section 7.5).

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the IB.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.1.6 Adverse events of special safety interest

For this trial, the following safety related event of special interest has been defined:

- Symptomatic hypotension (all hypotension AEs will be captured, only symptomatic hypotension is considered an AESI)
- Syncope

The DMC will monitor with special attention to these AESIs as defined in the DMC charter.

Any of these events have to be reported as an "important medial event" (see Section 9.6.1.6) and therefore as a SAE to the sponsor within 24 hours of becoming aware of the events.

In any case, adverse events of special interest fulfilling any seriousness criterion should be reported as SAE (see also Section 9.6.1.1).

9.6.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a female study patient during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

The child's health should be followed up until up to 4 weeks after discharge.

For a pregnancy in the partner of a male study patient, all efforts will be made to obtain similar information on course and outcome, patient to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

9.6.3 Further safety

Safety assessments will include adverse events (AEs), physical examination findings, and vital signs including pulse rate and blood pressure assessment. Laboratory safety studies will include blood chemistry, hematology, and urine pregnancy testing (performed in women of childbearing potential) (see Section 9.7).

Adverse events may occur during clinical trials from overdose (whether accidental or intentional), from abuse and from withdrawal. In this trial, any dose higher than the maximal target dose prescribed in the study protocol will be considered an overdose. If an adverse event(s) is resulted from the overdose, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met.

In the event of an overdose, the investigator/treating physician should contact the Medical Monitor immediately and closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 4 days. Sponsor does not recommend specific treatment for an overdose.

Medical devices:

The following is Japan specific guidance for reporting medical device failures:

The investigator must report immediately all non-approved medical device failures which could cause health damage, as well as any health damage that may be causally associated with a non-approved medical device failure. For this reporting, the forms provided are to be used and sent to the designated recipient.

9.7 Other procedures and variables

9.7.1 Laboratory assessments

9.7.1.1 Local laboratory

At the screening visit, local laboratory results from routine clinical examinations will be assessed to check the eligibility of the patient.

At least the following parameters must be measured at the screening visit and entered in the eCRF to check the patient's eligibility for the study:

- NT-proBNP or BNP for screening (see Section 9.7.7 for further details)
- Serum creatinine for screening (eGFR will be calculated automatically in the eCRF using the MDRD formula)
- urine pregnancy test, and Serum β-human chorionic gonadotropin (unless requested by local authorities, serum β-human chorionic gonadotropin will only be conducted if urine pregnancy test is positive)

Urine or serum pregnancy test will also be conducted on visits 2 and 7 for women of childbearing potential, according to the local regulations. If required by national / institutional regulations, a serum or urine pregnancy test in patients of childbearing potential should be performed more often (e.g. at every visit).

9.7.1.2 Central Laboratory

Only centrally analyzed blood samples will be considered for analysis.
The name and address for the central lab service provider can be found in the documentation supplied by the vendor. The following laboratory tests will be performed centrally:

Hematology: Hct, Hb, MCV, MCH, MCHC, Platelet count, RBC, RDW, Reticulocytes, and WBC.

Chemistry: ALT, AST, LDH, Bilirubin (Total), Blood glucose, cholesterol (HDL, LDL, total), triglycerides, BUN, creatinine, GGT, K, Na, and Uric acid, high-sensitivity troponin t, HbA1c.

Biomarker: NT-proBNP.

Coagulation: aPTT, INR

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

9.7.2 Physical examination

Full physical examination should be performed by the investigator at Screening and randomization. Physical exams focused on CV assessment will be performed at the other visits. Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

9.7.3 Echocardiography parameters

Echocardiography data from routine clinical exam will be assessed at screening to determine eligibility, according to the following criteria:

- LVEF ≥45% and
- Structural changes indicated by at least one of the following parameters:
    - LV hypertrophy (any of the following: intraventricular septal or posterior wall thickness ≥1.1 cm) and/or LV mass index ≥115 g/m^2 in male and ≥95 g/m^2 in female)
    - LA enlargement (any of the following: LAV index ≥29 ml/m^2, or LAV >58 mL in male and >52 mL in female patients, or LA area >20 cm^2, or LA diameter >40 mm in male and >38 mm in female patients)

9.7.4 12-lead ECG

ECGs will be transferred and analyzed centrally. The reading will be done in a standard way. Standard electrocardiogram (12-lead ECG) in supine position will be recorded after resting for at least 10 min as follows:

1. ECG at baseline in all patients to evaluate the eligibility of the patient for PK/QT assessment. The eligibility for PK/QT will be defined by the investigator in the baseline ECG.

   The ECG is **invalid** for QT assessment if at least one of the following is fulfilled:

   - QRS-Prolongation >120 ms, e.g. in the presence of complete bundle branch block
   - Pacemaker stimulation
   - Arrhythmia and conduction abnormalities such as atrial fibrillation or flutter, 2nd - 3rd degree AV block with ventricular escape rhythm etc.
   - Marked sinus arrhythmia

2. ECG matched with PK

   The ECG will only be performed for patients who are eligible for PK/QT assessment. It will be recorded at visits 2, 5 and 9 just before collection of the blood sample for PK analysis. Non-concordance with subsequent assignment as evaluable or non-evaluable upon central processing by the ECG core lab using different methods for QT assessment will be descriptively summarized and not be considered as deviation.

3. ECG at the end of treatment and in case of premature discontinuation as a safety measure in all patients (for patients who are eligible for PK/QT, assessment as part of PK/QT collection).

Only the results of the central evaluation will be used for statistical evaluation of ECG data. The following ECG parameters will be analyzed: HR, PR, QRS duration (QRSD), QT, and QTc (QTcB and QTcF).

The ECGs must be recorded with a paper velocity of 25 mm per second. The ECG print-outs will be identified with the PID as well as date and time of recording and will be attached to the patient's file.

All ECGs will be examined by the investigator, and any new clinically relevant abnormality will be documented as an AE.

9.7.5 Vital signs

BP and pulse rate measurements will be performed at specific visits. For details see Section 9.2.

Accurate measurement of blood pressure is essential to guide dose titration management and to detect potential safety signals during the trial. A number of factors related to the patient can cause significant deviations in measured blood pressure. These include room temperature, exercise, alcohol or nicotine consumption, positioning of the arm, muscle tension, bladder distension, talking, and background noise.

Blood pressure and pulse rate should be measured under the following conditions:

- Measurement of pulse rate and blood pressure must be conducted after 10 minute resting period with patient comfortably seated in a chair with the legs uncrossed and the back and arm supported. Measurements should not be made while the patient is on an examining table. The patient should be instructed to relax as much as possible and to not talk during the measurement procedure
- The examiner should ensure that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum).
- The patient should be asked to remove all clothing that covers the location of cuff placement.
- The same examiner should assess the patient at all subsequent visits and use the same device under same external conditions.
- The protocol requires 3 measurements – approximately 2 min apart (means will be calculated in the eCRF). Please record the time, positioning and arm used for each measurement

9.7.6 Biomarkers

NT-proBNP will be determined at the time points indicated in Section 9.1. Details on the collection, processing, storage and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or lab manual)

Other biomarkers deemed relevant to gain further knowledge about the mechanisms of the disease or about the drug (i.e. mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and / or literature data but only in countries where it is not excluded by local guidelines.

The additional biomarker results may be reported separately.

9.7.7 Optional pharmacogenetic research

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within the studied clinical trial population correlates with baseline clinical characteristics and the course of disease for the studied outcomes and/or ii) response to the study drug treatment. If genetic variation is found to correlate with clinical characteristics and outcomes, the data might point to novel pathways involved in the disease and thereby inform development of novel medicines. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of the disease in general, as well as efficacy and safety associated with the treatments in this study.

A whole blood sample will be obtained from those patients, who have signed a separate informed consent form for pharmacogenetic research, but only in countries where it is not excluded by local guidelines. The participation in this part of the study is voluntary and has no influence on the participation in this study.

Results will be reported under separate cover, if the evaluations are performed.

9.7.8 Accelerometry

At sites participating in the accelerometry substudy, it is planned that up to approximately 150 patients may consent to undergo activity tracking before randomization, before visit 7, and before visit 9 (end of treatment at 24 weeks).

Subjects are not required to participate in the accelerometry substudy in order to participate in the main trial. In addition, subjects must provide separate informed consent in order to participate in this substudy.

Additional details will be specified in separate site accelerometry procedure manuals and accelerometry substudy analysis plans.

9.8 Appropriateness of procedures / measurements

All parameters, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate, and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analysis will be performed using Statistical Analysis Software; the version used will be specified in the statistical analysis plan.

10.2 Analysis sets

FAS: All subjects randomized and treated (at least one dose of the study treatment), and have at least one observed outcome measure, will be valid for the FAS. The patients will be analyzed based on the planned treatment. The primary analysis for all efficacy endpoints will be based on FAS.

SAF: All patients that received at least one dose of study treatment (vericiguat or placebo). Analyses will be based on actual treatment received, and patients who did not reach maximum titration or received both vericiguat and placebo by mistake will be assigned to the planned treatment. All safety analyses will be based on the SAF.

PPS: All patients who meet the major inclusion and exclusion criteria at randomization that may affect efficacy, who are not taking excluded concomitant medications during the study that could have an effect on efficacy, have the KCCQ assessed at baseline and at least once during the main treatment phase and who are at least 80% compliant with study medication and show no major protocol deviations. The detailed criteria will be described in the SAP. The PPS will only be used in the supportive analysis.

PKS: All subjects with at least one valid pharmacokinetic concentration will be included in the statistical evaluation of pharmacokinetics.

10.3 Variables and planned statistical analyses

10.3.1 Efficacy variables

Primary efficacy variable: The primary endpoint will be change in KCCQ PLS from baseline to week 24.

The estimand of interest is the de facto or treatment policy estimand.

Population: Defined through appropriate inclusion/exclusion criteria (see Section 6.1 and 6.2) to reflect the targeted patient population.

Variable: Change from baseline in KCCQ PLS from baseline to Week 24.

Measurement of intervention effect: Regardless of stopping study treatment or adherence to study treatment.

Summary measure: Difference of LS means at Week 24.

The analysis will include all assessments post-baseline. Graphical method of Maurer and Bretz (33) will be applied for multiplicity control. The two primary hypotheses will be tested with an equally splitted two sided alpha level of 0.025.

The primary analysis of the primary endpoint will be performed using a MMRM, including treatment group (vericiguat versus placebo), study visit as fixed effects, patient as a random effect, interaction between study visit and treatment group, and adjustment for the baseline PLS values as covariates. The model will assume an unstructured covariance matrix for within-patient variability.

The analysis will be performed in the Full Analysis Set. For patients who drop out of the study, a pattern-mixture model with control-based pattern imputation will be implemented. After the patient drops out from the study, it is assumed that patients from the vericiguat arm

will show the same future trend as those on the placebo arm. Patients that discontinue from the placebo arm are assumed to evolve in the same way as placebo patients that remain in the study. For those patients who had died during the study, they will be imputed with the worst case outcome, i.e., a zero score for missing KCCQ PLS.

The model statement is:

$$Y_{ijklm} = \mu + \beta x_i + t_k + r_l + h_m + v_j + (tv)_{jk} + s_i + \varepsilon_{ij}$$

where Y_{ijklm} is the change from baseline in PLS to visit j for patient i; μ is the intercept, β is the baseline covariate effect, x_i is the baseline PLS for patient i, t_k is the fixed effect of treatment k, r_l is the fixed effect of region l, h_m is the fixed effect of heart rhythm m (atrial fibrillation and sinus rhythm), v_j is the fixed effect of visit j, $(tv)_{jk}$ is the interaction effect of treatment k by visit j, s_i is the random effect of patient i and $\varepsilon_{ij} \sim$ Normal(0, σ^2) represents the residual variance component with corr($\varepsilon_{ij}, \varepsilon_{ij'}$) = $\rho_{jj'}$, $j \neq j'$

Further, based on the anchor-based interim analysis (see Section 10.5), the percentages of responders with MCID, moderate, and large differences at each visit will be summarized and nominal p-values will also be provided. In addition, cumulative distribution function of change from baseline at 24 weeks for the KCCQ PLS domain will be plotted to compare the proportion of patients who are meeting certain threshold from vericiguat and placebo arms (see Section 10.5).

As a supportive analysis, the MMRM using the above model will be applied to all assessments post-baseline prior to study drug termination.

Additional sensitivity analyses will be performed. Analysis using data imputation approaches based on different missing data mechanisms will be investigated, including tipping point analysis. Details of such methods will be described in the SAP.

Secondary efficacy variable:

The secondary endpoint is change from baseline in the 6 MWT at 24 weeks.
The estimand of interest is the de facto or treatment policy estimand.

Population: Defined through appropriate inclusion/exclusion criteria (see Section 6.1 and Section 6.2) to reflect the targeted patient population and restricted to those who are able to perform the 6 MWT at baseline.

Variable: Change from baseline in 6 MWT from baseline to Week 24.

Measurement of intervention effect: Regardless of stopping study treatment or adherence to study treatment.

Summary measure: Difference of LS means at Week 24.

The secondary endpoint will be analyzed in the same manner as the primary endpoint. For those patients who are too sick to perform the test at any post baseline visit, a score of 0 will be assumed. further sensitivity analyses will be specified in SAP.

Other efficacy variables:

Other continuous variables including change from baseline to week 24 in other KCCQ domains, EQ-5D-5L, fried frailty score and NT-proBNP, will be analyzed using the MMRM

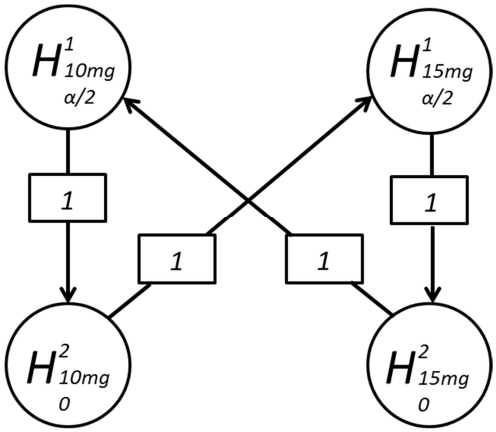
model. For categorical variables such as NYHA class, PGIC, PGIS, the relative response level change will be summarized by each visit. Incidences of cardiovascular death and total heart failure hospitalizations, as well as all-cause mortality and CV hospitalizations, MI and stroke will be summarized. Kaplan Meier curves of the composite endpoints (see Section 9.4) will be presented.

Details on any descriptive subgroup analyses will be specified in the SAP. These will include region, gender, atrial fibrillation status, patient randomization time (before or after discharge from HF hospitalization, or post IV diuretic treatment without hospitalization), and the time from HF hospitalization or IV diuretic treatment to randomization (<3 month vs. ≥3 month).

Multiplicity adjustment:

The study uses the graphical method of Maurer and Bretz (33) to provide strong multiplicity control across the primary KCCQ PLS hypotheses and the secondary 6 MWT hypotheses. The overall two sided alpha level will be controlled at 0.05. The two primary hypotheses will be tested using Bonferroni procedure, each at a splitted level of alpha 0.025. The two secondary hypotheses will be tested based on parallel gatekeeping principle. If both primary hypotheses can be rejected, the secondary family will be tested at a full alpha level 0.05 (two sided). If only one primary hypothesis is shown to be statistically significant, then only the secondary hypothesis based on the same dose group can be tested at an alpha level carried forward from the primary family testing, i.e., 0.025 (two sided). In this case, if the secondary hypothesis is rejected, the alpha spending associated with this dose group (0.025) will be re-utilized to test the other failed primary hypothesis again. Figure 10–1 shows the α-allocation for each hypothesis in the ellipse representing the hypothesis.

Figure 10–1 α-allocation for each hypothesis in the ellipse representing the hypothesis



Overall, the primary analysis will be claimed to have a positive outcome if the null hypothesis for at least one of the two primary hypotheses can be rejected.

10.4 Determination of sample size

The sample size estimation for this study will be based on the analysis of the primary endpoint of KCCQ PLS at 24 weeks comparing vericiguat 15 mg versus placebo and 10 mg versus placebo, to achieve 80% power with two-sided alpha level of 0.05 to detect a treatment difference from placebo in one or both of the dose groups. A mean difference from placebo in KCCQ PLS of 5 points for both dose groups and a common SD of 21 points are assumed. Under the same assumption of treatment effect and standard deviation, the power to detect

difference for any single comparison will be 65%. The 80% power was based on an "either or" success criterion, i.e., if at least one of the primary null hypotheses is rejected. The marginal power to reject any single comparison is 65%.

The given sample size provides 97% power to detect +30 m placebo-corrected increase in the secondary endpoint 6MWT (assumed SD 80 m) for any one dose group, and 80% power to detect an increase by +22.3 m, which is below the 35 m increase associated with a 6.2 point improvement in KCCQ PLS at 24 weeks in FAIR-HF and greater than the 15 m increase at 3-months that was associated with a 2.3 point improvement in KCCQ PLS in ACTION-HF (34).

A 5 point improvement in KCCQ OSS in patients with HFrEF is considered to represent a clinically significant change in heart failure status (35). Similarly, a change of +6.4 and -5.1 points in KCCQ PLS were associated with either small improvements or small deteriorations in clinical status, as determined by a cardiologist, in the Cardiovascular Outcomes Research Consortium study cohort in patients with HFrEF (35, 36). In addition, baseline KCCQ PLS score has also been associated with peak VO_2 and distance traveled on the 6 minute walk test (6 MWT), with 6.4 and 7.5 point differences in PLS being associated with 1SD changes for peak VO_2 and 6 MWT respectively (37). Furthermore, both anchor-based and distribution-based analyses of the SOCRATES-PRESERVED data support an improvement of 5 points in KCCQ PLS as MCID. This effect size has been proposed to the US FDA during a Type C meeting and was considered preliminarily acceptable pending additional data analyses (see Section 10.5) per Agency correspondence following the meeting. As such, this study will be powered to detect a placebo-corrected change of at least 5 point improvement in KCCQ PLS from baseline to 24 weeks. An SD of 21 points was assumed based on studies in which KCCQ PLS has been reported in the literature (38-43). The patients will also be followed until the end of the study regardless of stopping study treatment or not, hence the drop-out rate is considered negligible. Based on these considerations, the total sample size will be N=735 with N=245 each in the placebo, 10 mg vericiguat arm and 15 mg vericiguat arm in a 1:1:1 randomization.

10.5 Planned interim analyses

Futility interim analysis

A single interim assessment by the DMC to evaluate futility is planned for when 50% of the patients complete Visit 7 (week 12) and their KCCQ data become available. Although the effects of 24 weeks of treatment with vericiguat have not been evaluated in patients with HFpEF, prior data in this population suggest that the 12 week timepoint will be sufficiently predictive of the 24 week data to allow for an adequate interim assessment of efficacy. Furthermore, in view of the expected timeline for trial conduct, a sufficiently large proportion of data at the 24 week timepoint will only become available shortly before completion of the trial. Based on a careful analysis of the operating characteristics of a range of futility criteria, an observed treatment effect of 0.6 point difference in KCCQ PLS (vericiguat vs placebo) was chosen to serve as the boundary for futility for both dose groups; this is approximately equivalent to a joint conditional power (CP) of 23% (under the assumption of a true difference of 5 points). An observed treatment effect <0.6 in both comparisons would therefore signal to the DMC to consider their potential recommendation that the trial should be terminated early. The type II error rate spent with this futility rule will be <0.01. Assuming the true treatment

effect is a 5 point difference as expected, the probability of stopping at the interim is approximately 1.3%. Under the null hypothesis, i.e., assuming 0 treatment effect for both vericiguat vs. placebo comparisons, the probability of stopping at the interim for futility for both doses is approximately 43%. Stopping for futility will only be done if both arms are futile. If only one arm is futile then it will not be dropped as enrollment is expected to be completed at the time of the futility analysis. At this futility boundary the trial has a probability of 9% to observe a >5 point improvement in either of the comparison in KCCQ PLS. Details of the futility analysis will be specified in the SAP and in the DMC charter. No formal interim report will be written.

Anchor-based interim analysis

The PGIC will be used to support an anchor-based approach to estimate KCCQ PLS MCID values. These analyses will be performed upon completion of the 3-month assessment by all trial participants and therefore at the time point at which approximately 70% of patients have completed the week 24 visit assessment. The analysis will take place before unblinding and without knowledge of the treatment received by the participants,

Participants will be categorized according to their responses to the PGIC as follows:

- Participant who report “A little better” to PGIC Question #1 as well as “Yes” to Question #1b (Was this improvement in your physical limitations an important change for you?).
- Participants who report “A little worse” to PGIC Question #1 as well as “Yes” to Question #1b (Was this worsening in your physical limitations an important change for you (by important we mean did it bother you?);

Mean KCCQ PLS change scores from baseline will be calculated for each group above to define an anchor-based MID.

In addition, further analysis including non-parametric discriminant analysis will be conducted to explore the MCID using all patient response data available (44). Patients who respond “much better” and “better” will be aggregated to the new category “Much improved”. Patients who respond “the same”, “a little worse”, “worse”, or “much worse” will be combined into the new category “Not improved”. Given sufficient sample size for category responses (at least 20 patients in each of the categories), the KCCQ PLS score densities for each category will be estimated and the intersection point of these density curves will be considered as the discrimination points. The discrimination point between the two categories “a little better” and “Not improved” is considered to be MCID. Similarly, the discrimination point for PGIS categories will be used to inform anchor-based approaches for MID estimates for the KCCQ PLS mean change from baseline.

The blinded information obtained from the above described anchor-based approaches, will have no impact on the trial conduct. These analyses serve to support responder definitions that will be further detailed in the statistical analysis plan prior to unblinding the trial. Therefore, no correction of the family wise error rate of the trial is necessary. No formal interim report will be written.

10.6 PK and PK/QT analyses

PK analysis will be performed in the PKS (see Section 10.2). Vericiguat peak and trough plasma concentrations will be summarized per visit and separated according to assigned dose. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation, geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and geometric coefficient of variation, minimum, median, and maximum value and the number of measurements.

Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the LLOQ. For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

PK/QT analyses

The time-matched placebo-corrected change from baseline of the QT interval corrected according to QTcF after 10 mg vericiguat and after 15 mg vericiguat at steady state will be analyzed.

The individual change from baseline of QTcF after 24 weeks will be analyzed by ANCOVA, including treatment as fixed effects, the subject as random effect and the baseline value as covariate. Based on these analyses, point estimates (LS-Means) and confirmatory two-sided 90% confidence intervals of the true mean difference will be calculated for each time point on week 24.

Further analyses to explore the relationship between PK concentration and QTc will be specified in the SAP.

For further details of other standard PK/PD analyses, see Section 9.5.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (LSH).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access

must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all patients enrolled in this study.

Source documentation

The site must implement processes to ensure availability of all required source documentation (e.g. patient file, local laboratory report, etc.). A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this. It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site. Race, ethnic group, age and gender may be entered directly into the CRF, without availability of corresponding source documentation. Thus, these CRF data will be the source and no additional source documentation needs to be available. For all other data, source documentation must be available at the site.

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (patient number; year of birth / age; sex; if applicable race / ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE such as:
  - The SAE itself
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol,

study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (e.g. IxRS, laboratory, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

After its initial release for biometrical analysis, the clinical database is planned to be re-opened for the inclusion of the following additional data: pharmacokinetic data.

11.4 Missing data

We expect a low number of missing data since investigators and patients are encouraged to complete the visit schedule with all assessments irrespective of whether study drug treatment is completed per protocol or after premature permanent study drug discontinuation.

All missing or partial data will be presented in the data listing as they are recorded on the CRF.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing patients, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section 6.3.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

Sponsor's medical expert

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Title: PPD
Address:
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Rua Cancioneiro de Évora, 255 - Prédio E1 - 1º andar
04708-010 São Paulo - SP Brazil
SP Brazil
Phone no. PPD

Coordinating investigator for the study

Name: PPD
Title: PPD
Address: PPD
Phone: PPD
Fax: PPD

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

External data evaluation bodies

Independent data monitoring committee

Ongoing safety monitoring during the conduct of the study will be performed by an external DMC.

Analysis periods and procedures will be defined in an operational charter (DMC charter) filed in the study file. Following data review, the DMC will provide written recommendations that will be transferred to Bayer. All other definitions will be provided in the DMC charter.

Steering committee

The conduct of this study will be overseen by the steering committee which is made up of a panel of experts in the field.

Central independent blinded clinical events committee (CEC)

Blinded adjudication of all cardiovascular hospitalizations and all deaths will be performed by a central CEC as described in the CEC manual. The committee will be provided with all relevant documentation related to the event. The committee will also adjudicate all events listed in Section 7.5. The procedures followed by the committee will be described in the CEC manual. Adjudication results will be the basis for the final analysis. Further details will be documented in the CEC manual.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Patient information and consent

All relevant information on the study will be summarized in an integrated patient information sheet and informed consent form provided by the sponsor or the study center. A sample patient information and informed consent form is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient / legal representative (if the patient is under legal protection), prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each patient / legal representative will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's consent covers end-of-study examinations as specified in the visit description described in Section 9.2.11 to be conducted after withdrawal of consent.
- The patient's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The patient has the right to object to the generation and processing of this post-withdrawal data. The patient's oral objection may be documented in the patient's source data.

Each patient / legal representative will have ample time and opportunity to ask questions.

Only if the patient / legal representative voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The patient / legal representative will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient´s clinical record must clearly show that informed consent was obtained prior to these procedures.

If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The informed consent form and any other written information provided to patients / legal representatives will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and / or the written informed consent form. The investigator will inform the patient / legal representative of changes in a timely manner and will ask the patient to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of patients / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the CRF, and if the patient name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of

the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

14. Reference list

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15. Protocol amendments

Not applicable

16. Appendices

16.1 Appendix 1: 6 Minute walk test

The 6MWT test must be performed in accordance with the American Thoracic Society Guideline (81). In case of absolute contraindication (i.e. unstable angina and myocardial infarction during the previous month), the 6MWT test must not be performed.

According to the guideline, the 6MWT test should be carried out indoors, along a long, flat, straight, enclosed corridor with hard surface that is seldom traveled. The walking course should be preferably 30 m in length, but not less than 25 m (longer walking courses should be shortened to 30 m). The length of the corridor and turnaround points should be marked.

Patients will be instructed to walk alone, not run, from one end to the other end of the walking course, at their own pace, while attempting to cover as much ground as possible in 6 minutes.

During the walk, patients are allowed to stop, lean against the wall and rest, but should resume walking as soon as they feel able to do so. The resting time will be included in the 6 minutes.

A “warm-up” period before the test should not be performed. The patients should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. Investigators should not walk with the patients. Moreover, only standardized phrases for encouragement must be used during the test. To allow reproducibility, standardized phrases should be used every minute according to the following pattern:

- After the first minute, tell the patient the following (in even tones): “You are doing well. You have 5 minutes to go.”
- When the timer shows 4 minutes remaining, tell the patient the following: “Keep up the good work. You have 4 minutes to go.”
- When the timer shows 3 minutes remaining, tell the patient the following: “You are doing well. You are halfway done.”

- When the timer shows 2 minutes remaining, tell the patient the following: “Keep up the good work. You have only 2 minutes left.”
- When the timer shows only 1 minute remaining, tell the patient: “You are doing well. You have only 1 minute to go.”

To reduce the variability of the 6MWT tests, it is of utmost importance that familiarization-6MWT test, baseline-test and all following tests are performed under the same conditions.

- Wheelchair or scooter dependent / supplemental oxygen patients or those on continuous oxygen for severe pulmonary disease are excluded from the study.
- The use of a cane is allowed in cane dependent patients, but then these patients need to use the same cane at every 6MWT test throughout the study. If the need for walking aids should arise at the baseline visit, the same walking aids should also be used at every subsequent test.
- If a supplemental oxygen therapy should be implemented already at baseline, all subsequent 6MWT tests have to be performed under the same “baseline” conditions (same flow of oxygen, same application route, and same way of carrying the oxygen bottle).
- Even if a supplemental oxygen therapy is implemented or modified during the trial (e.g. increase of oxygen flow), it is not permitted to perform the subsequent 6MWT tests under conditions other than the baseline conditions.

However, a change of test conditions should be avoided, if reasonably possible at least after baseline, to have the same conditions in all 6MWT tests. For quality reasons, the inhalation of supplemental oxygen and the use of walking aids during the 6MWT tests must be documented in the eCRF.

16.2 Appendix 2: Borg CR 10 scale and test instructions

Use this rating scale to report how strong your perception of exertion is. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or “Extremely strong – Maximal” is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is “Very weak”, you should say “1”, if it is “Moderate”, say “3”. Note that “Moderate” is “3” and thus weaker than “Medium”, “Mean” or “Middle”. If the experience is “Strong” or “Heavy” (it feels “Difficult”) say “5”. Note that “Strong” is about half of “Maximal”. Is your feeling “Very strong”, choose a number from 6 to 8. If your perception or feeling is stronger than “10”, “Extremely strong – Maximal” you can use a larger number, e.g. 12 (that’s why “Absolute maximum” is marked with a dot “●”). It is very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

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

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

0.3

0.5 “Extremely weak”, “Just noticeable”

0.7

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

1.5

2 “Weak”, “Light”

2.5

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

4

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

6

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

8

9

10 “Extremely strong – Maximal” is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.

11

≠

● Is “Absolute maximum – Highest possible” for example “12” or even more.