	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

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

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

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.

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.

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

"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).

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

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

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

5. Study design

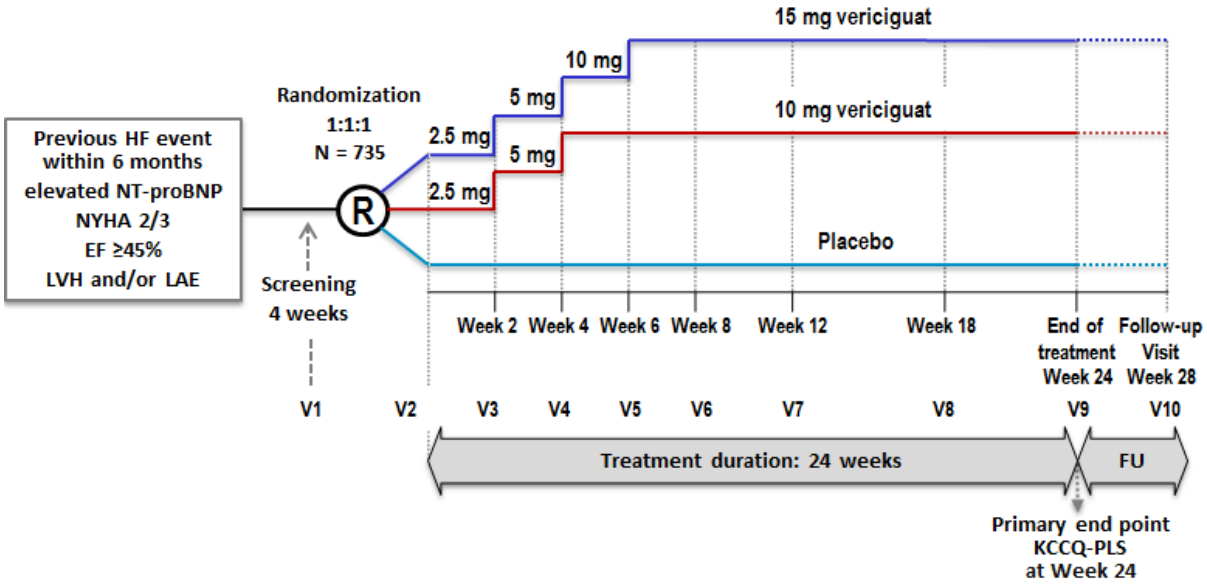
Design overview

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.

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%)

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

- 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.

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.

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