Title Page

Protocol Title: A Phase 2b open-label clinical study to evaluate the tolerability and safety of an initiation dose of 5 mg of Vericiguat in participants with chronic heart failure with reduced ejection fraction

Protocol Number:	21683
Protocol Version:	1.0
Amendment Number:	Not applicable
Compound Number:	BAY 1021189, Vericiguat, Verquvo
Short Title:	Vericiguat 5 mg initiation study
Study Phase:	2
Acronym:	VELOCITY HF
Sponsor Name:	Bayer AG

Legal Registered Address:

Non-US: Bayer AG, 51368 Leverkusen, Germany

US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA

Regulatory Agency Identifier Numbers:

Registry	**ID**
EU CT:	2023-507682-25-00
IND:	116,743

Protocol Date: 29 NOV 2023

Name: PPD Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Medical Monitor name and contact information can be found in the Trial Master File.

Table of Contents

Table of Tables

Table of Figures

List of Abbreviations

ACCF	American College of Cardiology Foundation
ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
AESI	adverse event of special interest
AHA	American Heart Association
ALBI	albumin to bilirubin ratio
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
ARB	angiotensin II receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitor
AST	aspartate aminotransferase
BP	blood pressure
CABG	coronary artery bypass grafting
cGMP	cyclic guanosine monophosphate
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRT	Cardiac resynchronization therapy
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CTIS	Clinical Trials Information System
CV	cardiovascular
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EoS	end of study
ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDMT	guideline-directed medical therapy for heart failure
hCG	human chorionic gonadotropin
HF	heart failure
HFH	heart failure hospitalization
HFrEF	heart failure with reduced ejection fraction
HRT	hormone replacement therapy
ICD	implantable cardioverter-defibrillator
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
LPLV	last patient last visit
LVEF	Left ventricle ejection fraction
MRA	mineralocorticoid receptor antagonist
NO	nitric oxide

NSTEMI	non-ST elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PDE5	phosphodiesterase type 5
PD	pharmacodynamic
PID	participant identification number
PK	pharmacokinetic
QD	once daily
QTL	quality tolerance limit
RAS	Renin-angiotensin-system
SAE	serious adverse event
SAF	safety analysis set
SBP	systolic blood pressure
SC	subcutaneous
sGC	soluble guanylate cyclase
SGLT2i	sodium-glucose cotransporter 2 inhibitor
SmPC	summary of product characteristics
SoA	schedule of activities
SOC	System Organ Class
STEMI	ST elevation myocardial infarction
SUSAR	suspected unexpected serious adverse reaction
TIA	transient ischemic attack
UHF	urgent heart failure
ULN	upper limit of normal
UNS	unscheduled
VICTOR	**V**er**IC**igua**T** Gl**O**bal Study in Participants With Chronic Heart Failure With **R**educed Ejection Fraction
VICTORIA	**V**er**IC**igua**T** Gl**O**bal Study in Subjects With Heart Failure With **R**educed Eject**I**on Fr**A**ction
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 2b open-label clinical study to evaluate the tolerability and safety of a starting dose of 5 mg of Vericiguat in participants with chronic heart failure with reduced ejection fraction

Short Title: Vericiguat 5 mg initiation study

Regulatory Agency Identifier Number(s):

Registry ID

EU CT: 2023-507682-25-00

IND: 116, 743

Envisaged indication:

Chronic heart failure with reduced ejection fraction

Rationale:

The objective of this study is to evaluate the tolerability of a 5 mg starting dose of vericiguat. The aim of this study is to generate evidence to support streamlining the titration regimen steps from 2 to 1 and enable HFrEF patients to achieve the target dose of 10 mg vericiguat daily within 1 titration step.

Objectives, Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the tolerability of 5 mg as a starting dose of vericiguat	• Treatment tolerability, defined as the completion of the two-week 5 mg dose without discontinuation of study intervention and without moderate to severe symptomatic hypotension between Visit 1 and Visit 2.
Secondary	
• To describe safety events of initiation of 5 mg dose • To further evaluate the tolerability of 5 mg as a starting dose of vericiguat	• Any AE reported between Visit 1 and Visit 2. • Absence of AE related to study intervention between Visit 1 and Visit 2. • Continuous intake of study intervention between Visit 1 and Visit 2 or restart of study intervention after any temporary interruption.

Overall Design Synopsis:

This is multi-center, a single arm, open label study of vericiguat initiation at 5 mg in HFrEF patients with EF <45%. Participants will undergo a screening visit to assess eligibility. Eligible participants must wait a mandatory 2 weeks before returning for Visit 1 in order to be clinically and hemodynamically stable.

At Visit 1, participants will receive vericiguat with directions to take a 5 mg tablet once daily for 2 weeks. Participants will return for Visit 2 after 2 weeks of treatment.

Unscheduled visits may be utilized between Visits 1 and 2 at the discretion of the investigator.

Number of Participants:

Approximately 120 participants will be screened to achieve at least 100 participants who are assigned to study intervention and complete the treatment period of up to 2 weeks.

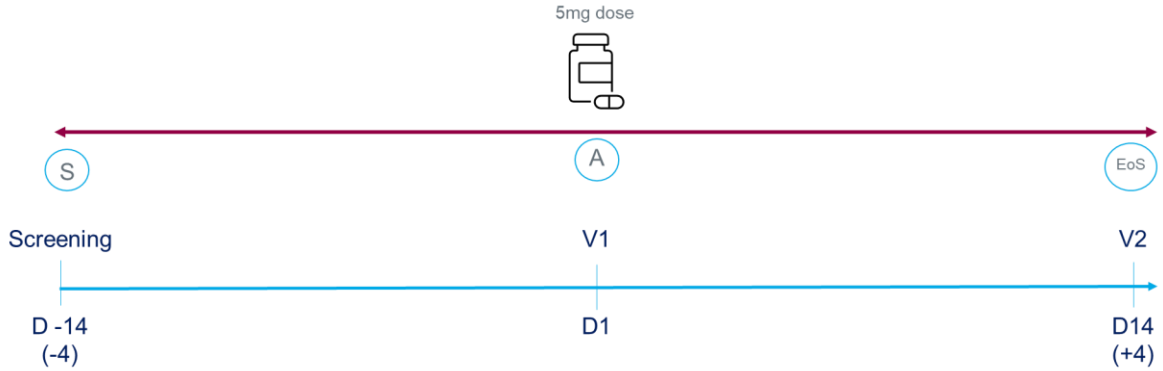
Study Arms and Duration:

This is a single arm, open label study. The total study duration is approximately 4 weeks, including a 2-week screening period and a 2-week treatment period.

Data Monitoring/Other Committee: Yes

1.2 Schema

Figure 1-1: Schema



A = assignment to study intervention, D = day, EoS = end of study, S= screening, V = visit

1.3 Schedule of Activities (SoA)

Visit Number	Screening	V1	V2[b]	UNS [c]	Notes
Study Day, Window	**D -14**	**D1**	**D14**		
Window (Days)	**-4 [a]**		**+4**		
Informed consent	X				
Inclusion and exclusion criteria	X	X			Recheck clinical status before assignment and/or 1st dose of study intervention.
Demography	X				
Full physical examination including height and weight	X				
Optional: local lab- clinical chemistry, hematology	X				eGFR, albumin, hemoglobin, total bilirubin, ALT and AST values must be available at screening. Values obtained as part of routine management should be used if measured within 30 days prior to Visit 1. If data is unavailable, values should be determined using a local lab.
Serum OR urine pregnancy test (WOCBP only)		X			If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.
Medical history	X				Includes substance usage and family history of premature CV disease
Current status of heart failure medical conditions		X	X		Collect any changes to heart failure medical condition (hospitalization, worsening of condition).
Prior and current medications	X	X	X	X	Assess at any visit including daily dose, time of intake and dosing regimen
Local 12-lead ECG	X				
Vital signs	X	X	X	X	Vital signs should be measured before study intervention intake. See Section 8.3.2.
Study Intervention Assignment		X			
Intake of Study Intervention		X			Study intervention should be taken orally with food at the same time each day, preferably in the morning. Date and time of study intervention intake will be recorded at Visit 1. Participants must remain at the site for 2 h after intake of first dose of study intervention. Study intervention is self-administered between Visit 1 and Visit 2. See Section 6 for additional details. .
Study Intervention Accountability			X	X	
AE review		X	X	X	See Section 8.4.Includes AESI. At Visit 1, the AE review should be conducted before and 2h after dosing. If AE review is suggestive of symptomatic hypotension, date, time, and severity will be recorded and vital signs should be re-assessed post dose.

AE = adverse event, AESI = adverse event of special interest, ALT = alanine transaminase, AST = aspartate aminotransferase, CV = cardiovascular, D = day, ECG = electrocardiogram, UNS = unscheduled, V = visit, WOCBP = women of child-bearing potential

a Screening must be completed 14-18 days before Visit 1.

b Visit 2 is the end of intervention visit.

c For Unscheduled Visits for AE review and reporting, assessments indicated in the SoA are mandatory. All other procedures selected and performed at unscheduled visits are at the discretion of the investigator and as clinically indicated.

2. Introduction

Chronic HFrEF is a major source of morbidity and mortality. Clinical outcomes for patients with chronic HFrEF remain poor, despite contemporary evidence-based therapies. Therefore, drugs are needed that effectively target disease mechanisms not addressed by current standard therapy.

Vericiguat, a novel soluble sGC stimulator, is approved for the treatment of HFrEF. Decreased NO availability, sGC desensitization to NO, sGC deficiency, and cGMP signaling are potential contributing factors for HF disease progression. Vericiguat works via stimulation of sGC in the critical NO-sGC-cGMP pathway. Vericiguat has a novel mode of action that targets endothelial dysfunction to improve regulation of vascular tone and myocardial function. Pharmacokinetic, pharmacodynamic, safety and efficacy profiles of vericiguat have been well characterized in a series of Phase 1 (29 studies), Phase 2 (3 studies) and Phase 3 (1 study) studies. In the global Phase 3 study, VICTORIA, treatment of 5050 patients with chronic HF with reduced ejection fraction with vericiguat on top of the standard of care resulted in a 10% reduction in the primary outcome of a composite of death from cardiovascular causes or first hospitalization for HF after a median treatment period of 10.8 months (Armstrong et al. 2020).

In VICTORIA, vericiguat was generally safe and well tolerated with low incidence of symptomatic hypotension and syncope, using a titration regimen (a starting dose of 2.5 mg followed by a 2-step up-titration to the target 10 mg dose) guided by symptoms and SBP to mitigate the risk of hypotension. Correlation between vericiguat plasma concentrations and hemodynamic parameters such as heart rate and SBP has been observed following first dose administration but dissipated with repeated dosing. In addition, no meaningful exposure-response relationship was observed for the incidence of symptomatic hypotension or syncope – after first dose and further during the study. This led to the implementation of a symptom- and SBP-guided 2-step titration scheme for vericiguat posology. A detailed description of the chemistry, pharmacology, efficacy, and safety of vericiguat is provided in the investigator's brochure.

2.1 Study Rationale

The objective of this study is to evaluate the tolerability of a 5 mg starting dose of vericiguat in HFrEF patients; the aim of the study is to generate evidence to support streamlining the titration regimen from 2 steps to 1 step and enable HFrEF patients to achieve the target maintenance dose of 10 mg vericiguat daily.

2.2 Background

In clinical practice, titration of HF medications, including vericiguat, is often compromised by limited follow-up opportunities and complexity of care at each follow-up visit. This results in under treatment of HFrEF patients due to failure to achieve the maximum efficacious dose for treatments with established benefit. Achieving the target dose of HF treatments in a safe and fast manner remains a large unmet medical need in HFrEF patients. Keeping drug initiation/titration regimens as simple and as safe as possible is critical to HFrEF patients in order to achieve optimal doses of GDMT.

Currently, initiation of vericiguat starts with 2.5 mg, increasing to 5 mg at 2 weeks, then 10 mg at 4 weeks. Removing the 2.5 mg step has the benefit of patients starting on a more efficacious dose and achieving maximal (target) dose with a single titration. In VICTORIA,

>80% of HFrEF participants were successfully titrated to the 10 mg dose , with minimal decrease in blood pressure after placebo adjustment, such that only 10% of patients remained on the starting dose of 2.5 mg of vericiguat, similar to 9% remaining on “2.5 mg” after sham titration in the placebo arm. Indeed, in VICTORIA, following initiation of the 2.5 mg starting dose, 96.1% of participants on vericiguat and 96.4% of those on placebo remained on treatment through the day 14 visit without interruption.

During the first 14 days of treatment with vericiguat, adverse events of clinical interest of symptomatic hypotension or syncope occurred in 2.0% of those on vericiguat and 1.2% of those on placebo. It was also observed that a slightly higher incidence of hypotensive events was seen in vericiguat arm during first 1-2 weeks since initiation but not later in titration.

Another large clinical trial, VICTOR, currently underway is assessing the efficacy and tolerability of vericiguat compared with placebo in stable HFrEF patients treated with current GDMT (Heidenreich et al. 2022, McDonagh et al. 2021). Overall, there is a pertinent need to investigate the effects of vericiguat in optimally treated, lower-risk HFrEF patients (i.e. those without recently worsening heart failure).

In a real-world setting, two sets of data on the use of vericiguat are available: one in the US and one in Germany.

In the United States (Victores et al. 2023), among 3,578 patients treated with vericiguat (mean age 67.4 years, 68.1% male), only 34% reaching the target dose of 10 mg. This was more likely to occur in patients treated by SGLT2i or on both ARNi and SGLT2i.

In Germany (Kerwagen et al. 2023), during the 16-month study period since the launch of vericiguat in September 2021, initiation of vericiguat was observed in n=2,916 (median age 75 years, 72% male) patients. During a median follow-up of 150 days, 33% of the patients reached the 5 mg, and 36% reached the 10 mg dose.

This real-world data provides background to explore initiating treatment at dose 5 mg to achieve the 10 mg target dose of vericiguat in a safe and faster manner.

2.3 Benefit/Risk Assessment

The results of the VICTORIA study showed a favorable benefit-risk profile for the use of vericiguat in patients with chronic HFrEF following a recent worsening event. In VICTORIA, patients were allowed to titrate to the target dose of 10 mg. Vericiguat has a clinically meaningful benefit on the endpoints of HF hospitalizations and CV death. The AE profile in VICTORIA was predominantly associated with vericiguat’s mechanism of action as a sGC stimulator (i.e., relaxation of smooth muscle leading to vasodilation, hemodynamic changes and gastrointestinal side effects).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of vericiguat may be found in the VERQUVO Investigator’s Brochure and approved labeling.

2.3.1 Risk Assessment

The general risks of vericiguat are known. During the VICTORIA study, AEs more frequently reported in the vericiguat group compared to placebo included hypotension, dyspepsia, nausea, dizziness, and headache. Anemia was also more frequently reported in the vericiguat group compared to placebo. Similar results were reported with riociguat, another sGC

stimulator. Overall, these events are generally nonserious and manageable (Ghofrani et al. 2013a, Ghofrani et al. 2013b).

Pharmacokinetic-pharmacodynamic (PK-PD) analysis of SOCRATES-REDUCED and VICTORIA revealed a small but statistically significant linear relationship between the change in SBP from baseline to 2 hours post dose and the measured vericiguat C_{max} (PH-38550 2020, R-13340 2020) following initiation of vericiguat treatment. However, no statistically significant relationship was observed between C_{max} and changes in SBP from baseline at later visits, suggesting that subsequent titrations to higher doses had minimal hemodynamic effects.

Based on PK-PD modeling of data from SOCRATES-REDUCED, the mean SBP is predicted to decrease from baseline by an additional 2.0 to 2.5 mmHg (i.e., a 4.0 -5.0 mmHg total decrease) when the starting dose is increased from 2.5 mg to 5 mg (i.e. when exposure is doubled) (PH-38545 2015, PH-38550 2020).

The pharmacodynamic effects of vericiguat were evaluated after single and multiple-dose administrations in healthy participants. All tested doses (up to 15 mg) were administered with ad-hoc dosing (without titration). In a pooled analyses across Phase 1 healthy participant studies, the most frequent AEs were headache, dyspepsia and dizziness, consistent with the predicted effects of an sGC stimulator on smooth muscle relaxation and vasodilation (PH-40726 2020). Generally, the incidence of AEs decreased after multiple dosing and when taken with food as directed (for details, see Section 4.3).

Overall, the anticipated risks associated with a starting dose of 5 mg of vericiguat are deemed in line with the established safety profile of the product.

In addition, the risk assessment will involve addressing risks related to the use of SGLT2i and ARNI in the study population as we foresee an adoption of these classes larger than in VICTORIA based on current GDMT. Both VICTORIA and VICTOR included recommendations to treat participants to GDMT; however, given the time lapse between the two studies, the recommendations were to different standards. VICTORIA included approximately 15% of patients on ARNI at randomization and only 3% of patients on SGLT2i after randomization, while VICTOR protocol encourages use of ARNI and SGLT2i at baseline with goals of at least 30% and 15%, respectively.

2.3.2 Benefit Assessment

The results from the Phase 3 VICTORIA study provide evidence of an important clinical benefit of vericiguat in adult patients with symptomatic chronic HF and ejection fraction less than 45% following a worsening HF event. Although participants of the present study are unlikely to benefit from the study intervention directly due to the short duration of treatment with vericiguat not achieving the target dose, reducing the current titration regimen from 2 steps to 1 step will enable HFrEF patients to achieve the target dose of 10 mg vericiguat daily in a shorter period of time while starting on a dose with higher pharmacological activity.

2.3.3 Overall Benefit: Risk Conclusion

Vericiguat is a new therapeutic option to fulfill the unmet medical need in patients with chronic HFrEF. Based on current clinical evidence, vericiguat provides an important clinical benefit to adult patients with symptomatic chronic HFrEF, and is well tolerated at doses up to 10 mg daily. The currently known risks associated with the mechanism of action are deemed well characterized. With the higher starting dose of 5 mg only a small decrease in blood pressure of about 4.0-5.0 mmHg is expected after administration of the first dose. In order to

manage potential side effects, participants will be asked to stay at the site for 2 hours after the first dose.

Considering the measures taken to minimize risks to participants in this study and the expected clinical benefit in patients with worsening HF, the benefit/risk assessment is considered positive and the conduct of the planned study in heart failure patients who will not directly benefit from the study intervention is justified.

3. Objectives, Endpoints

Objectives	Endpoints
Primary	
• To evaluate the tolerability of 5 mg as a starting dose of vericiguat	• Treatment tolerability, defined as the completion of the two-week 5 mg dose without discontinuation of study intervention and without moderate to severe symptomatic hypotension between Visit 1 and Visit 2.
Secondary	
• To describe safety events of initiation of 5 mg dose • To further evaluate the tolerability of 5 mg as a starting dose of vericiguat	• Any AE reported between Visit 1 and Visit 2. • Absence of AE related to study intervention between Visit 1 and Visit 2. • Continuous intake of study intervention between Visit 1 and Visit 2 or restart of study intervention after any temporary interruption.

4. Study Design

4.1 Overall Design

This is a single arm, open label study of vericiguat initiation at 5 mg in HFrEF patients with EF <45%. The total study duration is approximately 4 weeks, including a 2-week screening period and a 2-week treatment period.

Screening: Approximately 120 participants will be screened to achieve at least 100 participants who are assigned to study intervention and complete the treatment period of up to 2 weeks. Participants will undergo a screening visit to assess eligibility. Eligible participants must wait a mandatory 2 weeks before returning for Visit 1 in order to be clinically and hemodynamically stable.

Treatment: At Visit 1, participants will receive vericiguat 5 mg (on top of standard of care) with directions to take once daily for 2 weeks. Participants will return for Visit 2 after 2 weeks of treatment.

Unscheduled visits may be utilized between Visits 1 and 2 at the discretion of the investigator for AE review and reporting.

4.2 Scientific Rationale for Study Design

The objective of this study is to evaluate the tolerability of a 5 mg starting dose of vericiguat. The current dosing regimen for vericiguat requires a 2-step titration to the target dose of 10 mg; the initial dose of the 2-step titration is 2.5 mg. The aim of this study is to generate evidence to support streamlining the titration steps from 2 to 1 and ease reaching the target dose of 10 mg vericiguat daily.

The proposed study aims at providing evidence of tolerability of initiating treatment with a starting dose of 5 mg vericiguat. Tolerability of the subsequent up-titration step from 5 mg to 10 mg has been extensively investigated in VICTORIA and is currently being investigated in VICTOR. Thus, in this respect, a 2-week study is considered to provide the additional evidence for the evaluation of 5 mg as a starting dose with the aim to support a 1-step titration regimen.

The target population for this study is adults with chronic HFrEF with EF < 45% with and without a recent (<6 months) worsening HF event. This study population therefore is representative of the patient populations of both VICTORIA and VICTOR. Vericiguat was shown to improve outcomes in patients with HFrEF in the VICTORIA trial, which included patients with recent worsening HF. VICTOR is evaluating the efficacy and safety of vericiguat in lower-risk HFrEF patients. Indeed, all key HFrEF medications have been evaluated in both higher- and lower-risk populations, and the treatment effect was not always consistent across the risk spectrum. Furthermore, post-hoc analyses of the VICTORIA trial have suggested that sGC stimulators may have cardioprotective effects that may be more apparent when the medication is initiated earlier in the disease process. Finally, the effect of vericiguat on cardiovascular mortality was uncertain in VICTORIA and a trial of vericiguat with a longer follow-up in a lower-risk HFrEF population such as VICTOR may shed light on its effect on cardiovascular mortality.

The present study will support initiation of vericiguat at 5 mg dose, streamlining the titration regimen from 2 steps to 1 step and enabling all HFrEF patients to achieve the target dose of 10 mg vericiguat daily within 1 titration step. In order to support the posology section change in the current (worsening HF) and the expanded (stable HFrEF) label, conditional to a positive outcome of VICTOR, there is a pertinent need to investigate the effects of vericiguat in both optimally treated, high-risk (with a recent worsening heart failure event) and low-risk (without a recent worsening heart failure event) HFrEF patients. These two subpopulations in this study are intended to be comparable to those addressed in VICTORIA and VICTOR, in terms of demographics, severity of disease and comorbidities, with the potential difference stemming from a better background treatment compared with VICTORIA, based on the latest standards of GDMT.

Vericiguat's mechanism of action results in increased intracellular cGMP levels in cardiac myocytes and smooth muscle cells. These changes are associated with smooth muscle relaxation and a reduction in vascular tone. Throughout the clinical development of vericiguat, dose up-titration was dependent upon maintaining adequate SBP and the presence or absence of hypotensive symptoms. Tolerability and safety monitoring during this study will focus on continuation of study intervention and absence of symptomatic hypotension of moderate to severe intensity.

4.3 Justification for Dose

The study will assess the tolerability of a starting dose of 5 mg vericiguat, once daily.
In the initial clinical pharmacology studies in healthy volunteers, 5 mg (and 10 mg) of vericiguat were administered as an initial dose and were well tolerated (Boettcher et al. 2021).

The approved target dose and titration regimen for vericiguat are based on data from the Phase 1 program in healthy volunteers, the Phase 2b study SOCRATES-REDUCED in HFrEF, and the Phase 3 VICTORIA study in HFrEF. The goal of the present study is to provide tolerability and safety evidence to enable starting treatment on dose 5 mg.

Several stepwise titration schemes were assessed in the Phase 2 SOCRATES-REDUCED trial, with titration guided by clinic-based BP measurements in each scheme. Comparison of NT-proBNP reduction from baseline at 12 weeks across titration schemes demonstrated a clear trend of larger reductions in NT-proBNP in those titrated to higher target vericiguat doses. The greatest reduction occurred in those titrated to a target dose of 10 mg with this target also having an acceptable safety profile. This led to the 2.5 mg to 5.0 mg to 10 mg titration scheme being adopted for the VICTORIA trial. In VICTORIA, up- and down-titration at the study visits was guided by SBP and the presence or absence of symptomatic hypotension. Overall, this titration regimen was well tolerated and a total of 74% of participants reached the 10 mg target by the end of the titration period (73% of those randomized to vericiguat; 75% of those randomized to placebo;); for participants followed for up to one year, 90% reached 10 mg (89% of those randomized to vericiguat; 91% of those randomized to placebo).

Over the course of VICTORIA, the effect of vericiguat on BP was small, with mean SBP generally < 2 mmHg lower in those treated with vericiguat compared to placebo. The main blood pressure effect was observed early after the first 2.5 mg dose of vericiguat (SBP reduction of about 3 mmHg) in participants who received vericiguat compared with placebo. This small vericiguat-induced decrease in BP did not translate into a meaningful exposure-response relationship for the incidence of symptomatic hypotension or syncope – after first dose and during the further study.

PK-PD analysis of SOCRATES-REDUCED and VICTORIA revealed a small hemodynamic effect (2.0-2.5 mmHg SBP reduction) following initiation of vericiguat treatment, but subsequent titrations to higher doses had minimal hemodynamic effects. Based on PK/PD modeling of data from SOCRATES-REDUCED, an additional 2.0-2.5 mmHg (i.e., 4.0-5.0 mmHg total) decrease in SBP is predicted when the starting dose is increased from 2.5 mg to 5 mg.

Finally, symptomatic hypotension and syncope events were collected as events of clinical interest in VICTORIA. Randomization to vericiguat resulted in a 1.8 percentage point increase of reported events of clinical interest of symptomatic hypotension or syncope compared to placebo over the duration of the study. These ECIs were more frequent during the earlier phases of the titration, though no clustering of symptomatic hypotension events was observed following the very first dose, or immediately following each titration step.

4.4 End-of-Study Definition

The end of the study and primary completion date are defined as the date of the last visit of the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed Visit 2 (end of intervention visit).

5. Study Population

The study will enroll participants with chronic heart failure with ejection fraction <45%, with and without recent worsening HF. Enrollment caps will be applied to ensure enrollment of the desired proportion of participants with (group 1) and without (group 2) recent HF event (approximately 50% in each group). These two groups will also reflect contemporary standards of care in HF, with a goal of enrolling at least 30% of participants receiving an ARNI and 30% a SGLT2 inhibitor. The desired proportion of participants on GDMT may be

achieved by capping the number of participants not on ARNI or SGLT2i therapy. These enrollment caps will be managed in the IRT.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants (male and female) must be ≥18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Has an LVEF of <45% assessed within 12 months before Visit 1 by local any imaging method, and no subsequent LVEF measurement > 45%. The most recent measurement must be used to determine eligibility.

   NOTE: Participants who have undergone a coronary revascularization (PCI or CABG), valve repair/replacement, or implantation of CRT device or any other surgical, device, or pharmacological intervention (i.e., initiation of a GDMT) that might improve LVEF, must have a measurement of LVEF <45% at least 3 months after the intervention to be eligible.

3. SBP ≥ 100 mmHg at screening and Visit 1 (pre-treatment).
4. No changes in GDMT dosing (including beta blockers, ACEI/ARBs, ARNI, MRAs, hydralazine-nitrate combinations, SGLT2 inhibitors, ivabradine, or oral diuretics)
   - Within 4 weeks of screening for participants without a HF event ≤6 months prior to screening
   - within 2 weeks of screening for participants with a HF event ≤6 months prior to screening
   - planned during study participation
5. No expected medical procedures to occur 2 weeks before screening or during study participation.
6. Participants with (group 1) *OR* without (group 2) recent worsening HF event

   Group 1: History of chronic HF (NYHA class II symptomatic-IV) on GDMT with recent HF event within 6 months of screening or outpatient IV / SC diuretic use within 3 months before screening.

   OR

   Group 2: History of chronic HF (NYHA class II symptomatic-IV) on GDMT without recent HF event within 6 months of screening or outpatient IV / SC diuretic use within 3 months before screening.

Sex and Contraceptive/Barrier Requirements

7. Male or female

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants: No measures.

Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
    - Is a woman of nonchildbearing potential (WONCBP) as defined in Section 10.4.

      OR
    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Section 10.4 during the study intervention period and for at least 1 month after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24h before the first dose of study intervention, see Section 8.3.5.
    - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Cardiac conditions

1. History of symptomatic hypotension 4 weeks before screening.
2. Primary valvular heart disease requiring surgical procedure or intervention or has undergone a valvular surgical procedure or intervention within 3 months before Visit 1.
3. Hypertrophic cardiomyopathy.
4. Acute myocarditis or Takotsubo cardiomyopathy.

5. Awaiting heart transplantation (United Network for Organ Sharing Class 1A /1B or equivalent) or has or anticipates receiving an implanted ventricular assist device, or has received a heart transplant.

6. Tachycardia-induced cardiomyopathy and/or uncontrolled tachyarrhythmia.

7. Acute coronary syndrome (unstable angina, NSTEMI, or STEMI), undergone CABG or PCI within 3 months before Visit 1, or indication for coronary revascularization at the time of treatment assignment.

8. Symptomatic carotid stenosis, TIA, or stroke within 3 months before Visit 1.

9. History of repaired or unrepaired simple congenital heart disease (e.g., atrial or ventricular septal defects, or patent ductus arteriosus) with ongoing hemodynamically significant residual lesions, or any history of complex congenital heart disease (e.g. tetralogy of Fallot, transposition of the great arteries, single ventricle disease) regardless of repair status.

10. Active endocarditis or constrictive pericarditis.

11. Hemodynamic instability or hypovolemia within 4 weeks of screening and during the screening period.

Medical Conditions

12. Currently hospitalized.

13. eGFR based on the CKD-EPI Creatinine Equation of <15 mL/min/1.73 m^2 within 30 days before Visit 1 or on chronic dialysis. For participants with multiple eGFR results during screening, the most recent value will be used to determine eligibility.

14. Severe hepatic insufficiency defined as ALBI Grade 3 or hepatic encephalopathy, or has hepatic laboratory abnormalities (ALT or AST ≥3 × ULN or total bilirubin ≥2 × ULN). Exceptions for Gilbert's syndrome will be considered. Albumin, ALT, AST, and total bilirubin results within 30 days before Visit 1 may be used for assessment of laboratory abnormalities or the calculation of the ALBI score. For participants with multiple albumin and/or total bilirubin results during screening, the most recent value for each test will be used to calculate ALBI score.

15. Malignancy or other noncardiac condition limiting life expectancy to <3 years.

16. Requires continuous home oxygen for severe pulmonary disease.

17. Interstitial lung disease.

18. Known allergy or hypersensitivity to vericiguat, any of its constituents, or any other sGC stimulator.

19. Amyloidosis or sarcoidosis.

Prior/Concomitant Therapy

20. Concurrent or anticipated concomitant use of PDE5 inhibitors such as vardenafil, tadalafil, and sildenafil during the study.

21. Concurrent use of an sGC stimulator such as riociguat or vericiguat.

22. Prior (within 2 weeks prior to screening) or anticipated concomitant administration of IV / SC diuretics or inotropes.

Prior/Concurrent Clinical Study Experience

23. Participated in another interventional clinical study or has been treated with another investigational product ≤30 days before Visit 1 or plans to participate in any other study or study intervention during this study.

Other Exclusion Criteria

24. Recent history (within the last year) of drug or alcohol abuse or dependence.

25. Is pregnant or breastfeeding or plans to become pregnant or to breastfeed during the study.

26. Medical disorder, condition, or history thereof that in the opinion of the investigator would impair the participant's ability to participate in or complete the study.

27. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

No restrictions required.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study but is not subsequently assigned to study intervention (vericiguat). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, last visit date and SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. The following conditions are pre-requisites of re-screening:

- A minimum of 1 month between the initial Screening visit and re-screening.
- Before re-screening, new documented informed consent must be obtained.
- Allocation of a new participant identification number.
- All screening assessments for the study must be repeated.

5.5 Criteria for Temporarily Delaying Study Intervention

Not applicable.

6. Study Intervention and Concomitant Therapy

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions (e.g., surgical and behavioral) intended to be administered to the study participants during the study conduct.

Refer to the approved labeling / most recent investigator's brochure for vericiguat for more details regarding study intervention properties and formulation.

6.1 Study Intervention Administered

Study intervention should be taken orally with food at the same time each day, preferably in the morning. If a dose is missed, it should be taken as soon as the participant remembers on the same day of the missed dose. But there should be consistency with respect to dosing intervals (the recommendation is to have at least a 20-hour interval between doses). Participants should not take 2 doses of study intervention on the same day. The investigator should be informed if the dose of Vericiguat taken has exceeded the scheduled dose.

Table 6-1: Study Intervention Administered

Intervention Label	Vericiguat
Intervention Name	Vericiguat
Intervention Description	Tablet 5 mg/day
Type	Small molecule drug
Dose Formulation	Tablet
Unit Dose Strength(s)	5 mg
Dosage Level(s)	1 x 5 mg daily for 14 (+4) days
Route of Administration	Oral
Use	Experimental
Sourcing	Vericiguat will be provided centrally by the Sponsor.
Packaging and Labeling	Vericiguat tablets are available in high density polyethylene (HDPE) bottles with a white child resistant closure and induction seal. The packaging configuration is 18 tablets Vericiguat 5 mg per bottle. The bottles will be labelled as required per country requirement.
Current/Former Name(s) or Alias(es)	VERQUVO®, BAY 1021189

6.2 Preparation, Handling, Storage, and Accountability

1. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare or administer study intervention.
2. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Study intervention returns, reconciliation and destruction return information will be captured in IRT.
4. Further guidance and information for the final disposition of unused study interventions are provided in the site file.

Handling/Storage/Accountability at the participant's home

Participants will follow the instructions provided by authorized site staff for storage and administration of study intervention at home, as well as for return of unused study intervention to the site.

6.3 Assignment to Study Intervention

Randomization is not applicable for the study. All participants will receive the same study intervention.

All participants will be centrally assigned to the study intervention using an IRT. Enrollment caps defined in Section 5 will be managed by the IRT. Participants will be given a unique PID (9 digit number) at the start of screening. The PID consists of a unique country number (digits 1 to 2), unique center number (digits 3 to 5) and the participant number within the center (digits 6 to 9). Participants who meet the entry criteria will be sequentially assigned to a treatment allocation number (TNR) in ascending order.

6.4 Blinding

Not applicable. This is an open label study. For details on ensuring data integrity, see Section 9.4.

6.5 Study Intervention Compliance

A participant will receive exactly one bottle of vericiguat 5 mg tablets containing 18 tablets for any unforeseen events (e.g. loss or damage of single tablets or to allow for visit window).

Compliance with study intervention (vericiguat) self-administered at home between Visit 1 and Visit 2, will be assessed at Visit 2 (Day 14). Compliance will be assessed by counting returned tablets during the site visit and documented in the source documents and relevant form.

Deviation(s) from the prescribed dosage regimen should be recorded. Any discrepancies between actual and expected amount of returned study intervention must be discussed with the participant at the time of the visit, and any explanation must be documented in the source records. An adequate record of receipt, distribution, and return/destruction of all study intervention must be kept.

A record of the quantity of vericiguat tablets dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. An adequate record of receipt, distribution, and return/destruction of all study intervention must be captured on the dispensing log and/or in the IRT. Intervention start and stop dates, including dates for intervention delays will also be recorded in the CRF/ eCRF.

Participants will be instructed to take study intervention as scheduled, and to return all of the study intervention packaging including unused study intervention and empty packaging.

Study intervention tablets not returned will be considered to have been taken unless otherwise specified. At the end of the study, any remaining study intervention will be collected and destroyed as per local regulations. Any discrepancies between the returned and expected returned study intervention should be explained.

6.6 Dose Modification

The intention of the protocol is to maintain participants on the 5 mg dose of study intervention for the 2-week treatment period. Dose modifications are not planned within the scheme of this study. See Section 7.1.1 for details on temporary discontinuation of study intervention.

6.6.1 Retreatment Criteria

All participants entered into the study will be treated from Day 1 to Day 14 inclusive. See Section 7.1.2 for details on treatment resumption after temporary interruption of study intervention.

6.7 Continued Access to Study Intervention after the End of the Study

No continued access to the study intervention is planned following the end of the study. Participants may continue treatment on commercially available vericiguat at the discretion of their treating physician.

6.8 Treatment of Overdose

In this study, an overdose is any dose higher than 5 mg vericiguat QD.

Limited data are available with regard to overdosage in patients treated with vericiguat. In the event of an overdose, hypotension may result. Symptomatic treatment should be provided. Vericiguat is unlikely to be removed by hemodialysis because of high protein binding.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications following a suspected overdose will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

- Dosage information including dose and frequency

All participants should receive GDMT based on locally relevant guidelines such as ESC and ACC/AHA Guidelines for Management of Heart Failure applied individually to the discretion of the treating investigator and in line with individual tolerability, aiming at reflecting the current standard of care in the largest proportion of patients (Heidenreich et al. 2022, McDonagh et al. 2021). This includes medications such as beta blockers, ACEIs, ARBs, ARNI, MRAs, hydralazine-nitrate combinations, SGLT2 inhibitors, ivabradine, and cardiac device therapies such as ICDs and biventricular pacemakers. At least 30% of participants receiving an ARNI and 30% a SGLT2i should be enrolled in the study in order for the study to meet contemporary GDMT standards. Dose changes in GDMT medications (RAS blockade, Beta-blocker, MRA, or SGLT2i) or oral diuretics should be discouraged, except when mandated by known side-effects for individual drug classes (e.g., hyperkalemia for MRA or angioedema for ACE-inhibitors / ARNI). Use of short and long-acting nitrates is permitted.

Medications specifically prohibited in the exclusion criteria are not allowed for concomitant use with study intervention. In particular, the following are prohibited:

- Use of IV diuretic or inotropes
- PDE5i such as vardenafil, tadalafil, and sildenafil
- sGC stimulators (e.g., riociguat or vericiguat)

If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. This would result in not meeting criteria for the primary endpoint treatment tolerability. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any medical therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the participant and the information of the Sponsor.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Rescue Medicine

No rescue or supportive medications are specified for use in this study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.

7.1 Discontinuation of Study Intervention

Discontinuation is defined as the inability to complete treatment between Visit 1 and Visit 2. One missing/forgotten dose is permitted. All cases exceeding one missing dose will not be counted for the analysis of the primary endpoint.

Participants may discontinue study intervention or be discontinued from the study at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. If study intervention is permanently discontinued, the participant should

remain in the study to be evaluated at Visit 2 (Day 14). Discontinuation of study intervention does not represent withdrawal from the study.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant experiences symptomatic hypotension of moderate to severe intensity (Section 10.3.3) during the treatment period.
- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance, which in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.

7.1.1 Temporary Interruption

Temporary interruption of study intervention is permitted at any time during the study at the investigator's discretion.

7.1.2 Rechallenge

Upon temporary interruption of the study intervention, resumption of treatment at 5 mg is allowed if the interruption was not related to symptomatic hypotension of moderate to severe intensity. Intake should be resumed as soon as medically acceptable at the discretion of the investigator. In all cases, the reason for study intervention interruption must be recorded in the eCRF and the participant's medical records.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request, for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an unscheduled visit should be conducted, as shown in the SoA. See SoA for the data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if the participant fails to return for Visit 2 and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered lost to follow up.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., local laboratory) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

8.1 Administrative and Baseline Procedures

Administrative and baseline procedures are summarized in the SoA (Section 1.3).

8.2 Efficacy Assessments

There are no efficacy assessments in this study.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3). Participants will be assessed to determine tolerability as described in Section 9.3.2.

8.3.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Skin temperature, and respiratory rate will be recorded at screening.

BP and pulse rate will be assessed at the timepoints defined in Section 1.3. Measurements will be done in triplicate, and the average value will be recorded in the CRF.

Accurate measurement of BP is essential to assess tolerability and to detect potential safety signals during the study. Several factors related to the participant can cause significant deviations in measured BP. These include room temperature, exercise, alcohol or nicotine consumption, positioning of the arm, muscle tension, bladder distension, talking, and background noise.

- No other procedures may be performed during the BP and pulse rate measurements.
- The participant should be asked to remove all clothing that covers the location of cuff placement.
- BP and pulse rate measurements should be preceded by at least 10 minutes of rest with the participant comfortably seated in a chair with the legs uncrossed and the back and arm supported in a quiet setting without distractions. Measurements should not be made while the participant is on an examining table. The participant should be instructed to relax as much as possible and to not talk during the measurement procedure.
- BP and pulse rate measurements will be assessed with the participant in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available. Whenever possible, BP measurements should be obtained using the same arm, same BP monitoring device, and same examiner at each visit.
- The examiner should ensure that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum).
- 3 consecutive BP measurements will be recorded at intervals of approximately 2 minutes apart. Record the time, positioning, and arm used for each measurement.
- Assessment of pulse rate can be manual (rather than using an automated device). When performed manually, pulse rate must be measured in the brachial/radial artery for at least 30 seconds.

8.3.3 Electrocardiograms

Single 12-lead ECG will be obtained at screening visit as outlined in the SoA and reviewed by an investigator or medically qualified designee (consistent with local requirements) using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and QTc intervals, estimated by formulas Bazett - QTcB - and Fridericia – QTcF calculated by data management in the eCRF.

Participants will refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the procedure.

12-lead ECGs should be performed after the participant has rested quietly for approximately 10 minutes.

8.3.4 Clinical Safety Laboratory Tests

There are no clinical laboratory tests planned during this study, with the exception of the following:

1. select clinical labs in the event that historical values are not available at screening
2. serum pregnancy tests in the event of an ambiguous urine result at Visit 1

See Section 10.2 for details.

8.3.5 Pregnancy Testing

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at Visit 1.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

NOTE: If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

(S)AEs will be collected from the start of study intervention until the end-of-study visit (Visit 2) at the timepoints specified in the SoA (Section 1.3). (S)AEs which are related to protocol-required study procedures (e.g., (S)AE related to invasive study procedures or adjustment of therapy to comply with inclusion or exclusion criteria of the study) will be recorded as (S)AEs from the signing of the ICF.

Any medical occurrences/conditions that begin in the period between signing ICF and the start of study intervention, and which are not related to a protocol-required study procedure, will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator

considers the event to be reasonably related to vericiguat, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.4.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- For all studies except those using medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention. The time period for reporting pregnancies should align with the time period for post-intervention contraception determined in Section 5.1.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.6 Adverse Events of Special Interest

Symptomatic hypotension is an AESI as assessed by the investigator.

8.5 Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity Assessments

There are no immunogenicity assessments planned in this study.

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

A statistical analysis plan will be prepared and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. The analysis and reporting will be done on all data from all participants at the time the study ends.

9.1 Statistical Hypotheses

The analyses presented here will be descriptive in nature and thus no statistical hypothesis tests will be performed.

9.1.1 Multiplicity Adjustment

There will be no multiplicity adjustment performed as it is not applicable to this study.

9.2 Analysis Sets

For the purposes of analysis, the following analysis set is defined:

Participant Analysis Set	Description
Safety analysis set (SAF)	• All participants assigned to investigational intervention who were exposed to study intervention at least once.

9.3 Statistical Analyses

9.3.1 General Considerations

No hypothesis testing will be performed. Instead, given the nature of the trial, descriptive statistics will be provided for data collected. All analyses will be performed on the safety analysis set (SAF).

9.3.2 Primary Endpoint Analysis

9.3.2.1 Definition of Endpoint(s).

The primary endpoint of tolerability will be defined as the completion of the two-week 5 mg dose without discontinuation of study intervention and without symptomatic hypotension of moderate to severe intensity (Section 10.3.3) between Visit 1 and Visit 2. Participants with discontinuation of study intervention (described in Section 7.1) or symptomatic hypotension of moderate to severe intensity would not meet criteria for the primary endpoint of treatment tolerability.

9.3.2.2 Main Analytical Approach

Participants who meet the criteria for tolerability as defined in Section 9.3.2.1 will be considered for the numerator in the proportion of participants reaching tolerability. The denominator will contain all participants who were included in the SAF. Thus in the case of 100 participants included in the SAF, all 100 will be included as part of the denominator and the numerator will only include the number of participants who completed the two week 5 mg dose without any study intervention discontinuation and without symptomatic hypotension of moderate to severe intensity. There will be no imputation of missing data. A similar approach will be taken for the derivation of the proportion for the secondary endpoint analyses.

9.3.2.3 Sensitivity Analyses

Additional proportions will be derived as sensitivity analyses. These analyses will be described in detail in the statistical analysis plan.

9.3.2.4 Supplementary Analyses

There will be no supplementary analyses.

9.3.3 Secondary Endpoints Analysis

Analysis of secondary endpoints will include tabulation of the following using descriptive statistics:

- Any AE reported between Visit 1 and Visit 2
- Proportion of participants who did not have an AE related to study intervention between Visit 1 and Visit 2

- Proportion of participants who took study intervention continuously between Visit 1 and Visit 2 or were able to restart of study intervention after any temporary interruption

9.4 Interim Analysis

No interim analysis is planned.

Due to the nature of this study, participant-level treatment assignment information is available during study conduct.

However, manual interim calculations of tolerability rates will not be done in order to protect the integrity of the study.

9.5 Sample Size Determination

Based on the evidence of a strong safety profile of vericiguat and the CCI [redacted], the sample size of approximately 100 participants is considered appropriate to assess the tolerability of the 5 mg initiation dose for vericiguat.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted, reviewed and approved in accordance with national legislation and undergo scientific and ethical assessment before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants or their legally authorized representative and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA), where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participants or their legally authorized representative.
- Participants who are rescreened are required to sign a new ICF

10.1.4 Recruitment Strategy

Detailed description of the recruitment strategy will be provided in country-specific documentation as required.

10.1.5 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6 Committees Structure

Steering Committee

The Steering Committee, which consists of external experts in the area of heart failure, will ensure the overarching integrity of the study, including:

- Consultation on study-related activities, including guidance and support on study enrollment
- Provision of recommendations regarding amendments to the protocol
- Contribution to and oversight of publications and communication of study results
- Participant safety: this will be continuously monitored by the Steering Committee and the sponsor, and include safety signal detection at any time during the study
- All safety data collected will be summarized and reviewed by the Steering Committee and the sponsor for agreement of next steps.

10.1.7 Dissemination of Clinical Study Data

Bayer fulfills its commitment to publicly disclose study results through posting the result of its studies on public registries in accordance with applicable law and regulations.

Result Summaries of Bayer's sponsored clinical studies in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trials Explorer application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded websites, ClinicalTrials.gov, and EU Clinical Trials Information System (CTIS) in line with the applicable regulations.

In accordance with the current EU regulations, result summaries will be submitted within one year from the end of the study in all participating countries for studies in adult populations, or within 6 months from the Last Patient Last Visit (LPLV) date for studies in pediatric populations. No preliminary data analysis based on regional requirements (e.g., on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study. Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States and European Union (EU) on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in scientific literature, irrespective of whether the results of the clinical trials are positive or negative.

10.1.8 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF Completion Guidelines
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the integrated data review plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Data Location List
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source

documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Study and Site Start and Closure

Study Start

The study start date is the date on which the clinical study will be open for recruitment of participants.

The start of a clinical study in the EU is defined as the date on which the first site is declared by the sponsor to be ready to enroll in a country and clinical study will be open for recruitment of participants.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual

site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 may be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1: Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Pregnancy testing	• Highly sensitive urine hCG pregnancy test (as needed for women of childbearing potential)
Clinical Chemistry	• eGFR, albumin, total bilirubin, , ALT and AST (as needed for screening if not available based on routine measurements [see Section 1.3])
Hematology	• Hemoglobin

ALT = alanine aminotransferase, AST = aspartate aminotransferase, eGFR = estimated glomerular filtration rate, HCG = human chorionic gonadotropin

NOTES:

Local urine pregnancy testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC

eGFR, albumin, hemoglobin, total bilirubin, ALT and AST values must be available at screening. Values obtained as part of routine management should be used if measured within 30 days prior to Visit 1. If data is unavailable, values should be determined using a local lab.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the

medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Sign, symptoms, or the clinical sequelae of suspected medication errors, misuse and abuse of either study intervention or a concomitant medication. Medication errors, misuse and abuse per se will not be reported as an AE/SAE, unless it is resulting in AE/SAE. Such medication errors, misuse and abuse should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets the one or more of the criteria listed:

a. **Results in death**

b. **Is life threatening**

- The term *life threatening* in the definition of *serious* refers to an event in which the participant 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**

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

f. **Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:
  - Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causality assessment, the investigator will also consult the investigator's brochure and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology, if available.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in Investigator Site File.

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the Investigator Site File.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are considered WOCBP (fertile)

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below):
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement > 40 mIU/mL (for United States only: FSH levels > 40 mIU/mL and estradiol < 20 pg/mL) is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:

a) Documented hysterectomy

b) Documented bilateral salpingectomy

c) Documented bilateral oophorectomy

d) For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >40 mIU/mL (for United States only: FSH levels >40 mIU/mL and estradiol <20pg/mL) is required.
    - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

11. References

Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020 May;382(20):1883-93.

Boettcher M, Thomas D, Mueck W, Loewen S, Arens E, Yoshikawa K, et al. Safety, pharmacodynamic, and pharmacokinetic characterization of vericiguat: results from six phase I studies in healthy subjects. Eur J Clin Pharmacol. 2021 Apr;77(4):527-37.

Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013a Jul 25;369(4):319-29.

Ghofrani HA, Galiè N, Grimminger F, Grünig E, Humbert M, Jing ZC, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med. 2013b Jul;369(4):330-40.

Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 Apr 1:101161CIR0000000000001063.

Kerwagen F, Ohlmeier C, Evers T, Herrmann S, Bayh I, Michel A, et al. Indicators of adherence and persistence to vericiguat in Germany: a prescription claims data analysis. DGK Herztage, Bonn. Clin Res Cardiol. 2023;112:1713.

McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-726.

PH-38545. Population pharmacokinetic modeling of BAY 1021189 in healthy volunteers and virtual heart failure patients. 2015.

PH-38550. Exploratory population pharmacokinetic / pharmacodynamics analysis to characterize the variability in the exposure-response relationship of vericiguat (BAY 1021189) in worsening heart failure patients in the study 15371. (Study 17401 PH-38550, version 2.0). Bayer Healthcare AG. 2020.

PH-40726. Pooled safety and PD evaluation of Phase 1 single and multiple dose studies with vericiguat in healthy volunteers. 2020.

R-13340. Exposure-Response (Safety/Efficacy) Analysis of Vericiguat (MK-1242) in Subjects With HFrEF in the Phase 3 Study VICTORIA. (Study 20965 R-13340, version 1.0). Merck and Co., Inc. 2020.

Victores A, Bash L, Ru X, McMullan CJ, Melaragno, Stevenson AL, et al. . Who? Characterizing vericiguat use in a real-world HFrEF patient

population. Abstract: 23-A-12830-ACC (American College of Cardiology Conference, March 4 – 6, 2023, New Orleans, US). 2023.