Title Page

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

Protocol Number: 21683

Compound Number: BAY 1021189, Vericiguat, Verquvo

Short Title: Vericiguat 5 mg initiation study

Acronym: VELOCITY HF

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This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.
The approval of the Statistical Analysis Plan is documented in a separate signature document.

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Version History

This Statistical Analysis Plan (SAP) for Study 21683 is based on the protocol Version 1.0 dated 29 NOV 2023.

SAP Version	Date	Change	Rationale
1.0		Not applicable	Original version

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ARNI	angiotensin receptor-neprilysin inhibitor
ATC	Anatomical Therapeutic Chemical
cGMP	cyclic guanosine monophosphate
CSP	Clinical Study Protocol
CV	cardiovascular
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic Case Report Form
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GDMT	guideline-directed medical therapy for heart failure
hCG	human chorionic gonadotropin
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
IRT	interactive response technology
LLOQ	lower limit of quantification

NO	nitric oxide
PT	preferred term
SAF	safety analysis set
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
sGC	soluble guanylate cyclase
SGLT2i	sodium-glucose cotransporter 2 inhibitor
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULOQ	upper limit of quantification
VICTORIA	**V**er**IC**igua**T** Gl**O**bal Study in Subjects With Heart Failure With **R**educed Eject**I**on Fr**A**ction

1. 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 heart failure 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.

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.

This SAP is based on the clinical study protocol version 1.0 (dated 29 NOV 2023). The SAP describes the final analysis of the study. No statistical interim analysis will be performed. Table, figure and listing specifications are contained in a separate document. There are no changes to the analyses described in the protocol.

1.1 Objectives and 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.

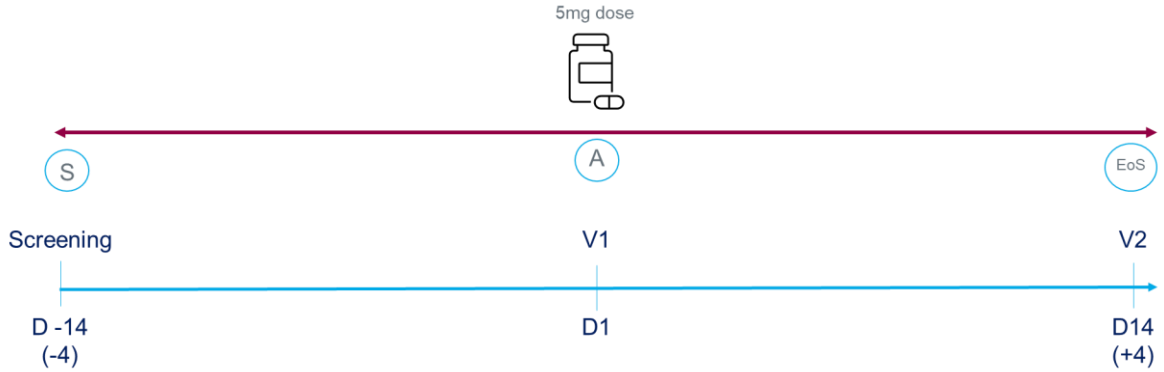
1.2 Study Design.

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.

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

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

Figure 1-1: Schema



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

This is an open label study. 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. Any analysis of study data, including the analysis of the primary endpoint, will be performed after database release.

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.

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.

2. Statistical Hypotheses

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

2.1 Multiplicity Adjustment

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

3. 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.

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to the analysis sets.

4. Statistical Analyses

4.1 General Considerations

The statistical evaluation will be performed by using the software SAS (release 9.4 or higher; SAS Institute Inc., Cary, NC, USA).

All analyses will be performed on the SAF.

In general, continuous data will be summarized using the number of participants, mean, standard deviation, minimum, median, and maximum. For categorical data frequency tables will be provided. Summary statistics and frequency tables will be presented for Vericiguat, i.e. overall, and by visit (if applicable).

All data will be presented in the participant data listing as they are recorded on the eCRF, i.e., partially missing data will appear as such. Imputation of missing data is not planned.

Listings will be provided sorted by participant identifier.

Data from unscheduled measurements will be listed, but not included in summary statistics or frequency tables.

4.1.1 Baseline

Regarding vital signs the baseline assessment will be the assessment at Day 1 (Visit 1). If the assessment on Day 1 (Visit 1) is missing, then baseline will be the last available assessment before first study drug intake (i.e. usually the screening assessment).

Other parameters, such as ECG and laboratory data, will only be assessed once, therefore no baseline is defined.

4.1.2 Repeated Measurements

If more than one measurement is available at screening, the last observation of those will be used for descriptive statistics tables as well as for frequency tables. In case of multiple measurements at planned time points after intake of study intervention, the earliest measured value will be used for descriptive statistics tables as well as for frequency tables.

4.1.3 Laboratory Values outside the calibration range

For the calculation of descriptive statistics, a data point present in the database as '<x' or '>x' will be substituted by x itself. In tables showing mean values, where such values are included in the calculation of mean values, these means will be marked. Corresponding tables will get a footnote indicating this. Tables displaying minimum and maximum values will present "<x" and ">x" as minimum and maximum, respectively.

4.2 Primary Endpoint Analysis

4.2.1 Definition of Endpoints

The primary endpoint of tolerability is 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 between Visit 1 and Visit 2. Participants with discontinuation of study intervention or symptomatic hypotension of moderate to severe intensity would not meet criteria for the primary endpoint of treatment tolerability. Discontinuation is defined as the inability to complete treatment between Visit 1 and Visit 2 where one missing/forgotten dose is permitted.

4.2.2 Main Analytical Approach

To assess the primary objective the proportion of participants reaching tolerability as defined in Section 4.2.1 will be calculated.

The proportion will be derived by dividing the number of participants reaching tolerability by all participants 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 (where one missing/ forgotten dose is permitted) and without symptomatic hypotension of moderate to severe intensity. See also Table 4-1. The absolute number of participants reaching tolerability will be provided in addition.

4.2.3 Sensitivity Analyses

Table 4-1 describes the different proportions of participants included in the primary, secondary and sensitivity tolerability analysis. While the denominator will, for all cases, contain all participants included in the SAF, the numerator will contain the following listed subgroups of participants.

Table 4-1 Proportions for primary and primary sensitivity tolerability analyses

Analysis	Participants included in numerator	Explanation
Primary	Participants who completed the two-week treatment with maximum one day interruption and without symptomatic hypotension of moderate to severe intensity between Visit 1 and Visit 2.	Tolerability assessment as defined in the CSP.
Sensitivity	Participants who completed the two-week treatment with maximum two days interruption and without symptomatic hypotension of moderate to severe intensity between Visit 1 and Visit 2.	More generous compared to primary considering that a second day with interruption, independent from reason of interruption, might still indicate tolerability of intervention.

4.2.4 Supplementary Analysis/Analyses

There will be no supplementary analyses.

4.3 Secondary Endpoints Analysis

4.3.1 Definition of Endpoints

The secondary endpoints are defined as follows:

- Any AE reported between Visit 1 and Visit 2.
- Absence of AEs 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.

4.3.2 Main Analytical Approach

4.3.2.1 Analyses of adverse events

For a detailed description of the AE analysis please refer to Section 4.5.2.

4.3.2.2 Secondary tolerability analyses

To assess the secondary objective regarding tolerability, the proportion of participants as described in Table 4-2 will be calculated.

Table 4-2 Proportions for secondary tolerability analyses

Analysis	Participants included in numerator	Explanation
Secondary 1 (tolerability)	Participants who did not have an AE related to study intervention between Visit 1 and Visit 2.	As defined in the CSP. Tolerability in the sense of looking at AEs; independent from compliance, as lack of compliance could have different reasons.
Secondary 2 (tolerability)	Participants who completed the two-week treatment with continuous intervention intake or were able to restart intervention after temporary interruption.	As defined in the CSP. Restart of intervention even after interruptions due to AEs is allowed.

The proportions will be derived by dividing the number of participants reaching tolerability by all participants included in the SAF.

4.3.3 Sensitivity Analyses

Not applicable.

4.3.4 Supplementary Analyses

Not applicable.

4.4 Tertiary/Exploratory/Other Endpoints Analysis

Not applicable.

4.5 Other Safety Analyses

4.5.1 Extent of Exposure

Treatment duration will be defined as the number of days from the day of first study intervention intake up to and including the day of last study intervention intake excluding any gaps in study intervention intake (according to exposure data from the eCRF) and will be summarized using descriptive statistics.

The total intervention dose (according to drug accountability data from the eCRF) will be summarized in mg per day using descriptive statistics.

Compliance (as percentage) will be calculated as follows:

number of tablets actually taken / number of tablets planned to be taken * 100.

The number of tablets planned to be taken is one tablet per study day based on the planned two-week intervention period. It is 14 at least but considering the allowed extension by up to four days, the denominator will be calculated as

max(14, date of final visit - date of first intervention intake + 1).

Participants ending the study before day 14 will have a compliance below 100%.

The compliance will be summarized descriptively. In addition, percent of compliance will be categorized into >100%, =100% and < 100% and these categories will be summarized descriptively as well.

4.5.2 Adverse Events

All AEs will be summarized using the Medical Dictionary for Regulatory Activities (the current version at the time of analysis) PTs grouped by SOC.

Any medical occurrences/conditions that begin in the period between signing the informed consent form 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.

Any AEs related to study procedures recorded after signing of informed consent but prior to first treatment with study intervention will be considered as pre-treatment AEs.

AEs are considered to be treatment-emergent if they started or worsened after first administration of study intervention until completion of study for the respective participant. Therewith pre-treatment AEs and non-treatment-emergent AEs are equivalent and there are no post-treatment AEs defined in this study.

Symptomatic hypotension as assessed by the investigator is considered an adverse event of special interest in this study.

Individual listings of all AEs will be provided including AE onset and end date relative to start and end date of intervention and the duration of the AE. Listings of treatment-emergent as well as non-treatment emergent serious AEs, AEs with fatal outcome and deaths not attributed to AEs as well as AEs resulting in discontinuation will be provided in addition.

Overall summaries of the number of participants with any AEs, pre-treatment AEs, TEAEs and treatment-emergent AESIs, treatment-emergent AESIs restricted to moderate and severe intensity and deaths together with AEs with fatal outcome will be generated.

The number of participants with serious AEs, TEAEs, intervention related TEAEs TEAEs leading to discontinuation of study intervention, intervention-related TEAEs leading to discontinuation of study intervention, TEAEs by maximum intensity, intervention-related TEAEs by maximum intensity, non-serious TEAEs, serious TEAEs, intervention-related serious TEAEs, deaths together with AEs with fatal outcome and TEAEs with fatal outcome will be summarized using PTs grouped by SOC. Treatment-emergent AESIs and treatment-emergent AESIs restricted to moderate and severe intensity will be summarized using PTs.

An overview of TEAEs and serious TEAEs by demographic subgroups will be provided.

TEAEs leading to discontinuation will be summarized graphically by showing cumulative incidence estimates using Aalen-Johansen estimator.

In case of events with different intensity within a participant, the maximum reported intensity will be used. If intensity is missing, the event will be considered as severe. If the same event is reported as both unrelated and related to the study intervention within a participant, the event will be considered as related to study intervention. If the study intervention relationship is missing, the event will be considered as being related to the study intervention.

4.5.3 Additional Safety Assessments

4.5.3.1 Laboratory Data

Continuous laboratory parameter values measured at screening will be summarized using arithmetic mean, standard deviation, median, minimum, and maximum and the number of measurements.

Results from the urine hCG (and serum, if applicable) pregnancy test (as needed for women with childbearing potential) will be listed.

4.5.3.2 Vital Signs

Vital sign values including the change from baseline will be summarized by visit using arithmetic mean, standard deviation, median, minimum, and maximum and the number of measurements.

The number and percentage of participants will be categorized by their maximum post-baseline SBP and DBP. A summary of postbaseline hypotension criteria will be given.

4.5.3.3 Electrocardiogram

Electrocardiogram values measured at screening will be summarized using arithmetic mean, standard deviation, median, minimum, and maximum and the number of measurements.

4.6 Other Analyses

4.6.1 Other Variables and/or Parameters

Not applicable.

Subgroup Analyses

The following subgroups as defined in the CSP will be regarded:

- Participants with recent worsening HF event (group 1)
- Participants without recent worsening HF event (group 2)
- Participants receiving an ARNI, total and in group 1/ 2, respectively.
- Participants receiving an ARNI and no SGLT2 inhibitor, total and in group 1/ 2.
- Participants receiving a SGLT2 inhibitor, total and in group 1/ 2, respectively.
- Participants receiving an SGLT2 inhibitor and no ARNI, total and in group 1/ 2.
- Participants receiving both, an ARNI and a SGLT2 inhibitor, total and in group 1/ 2, respectively (only for vital signs and AESIs and only if >10% of all participants).
- Participants receiving neither an ARNI nor a SGLT2 inhibitor, total and in group 1/ 2, respectively (only for vital signs and AESIs and only if >10% of all participants).

The occurrence of all above defined subgroups will be summarized in the demographics section.

All ratios specified in Table 4-1 will be regarded restricted to the above specified subgroups as well.

Additionally, tables summarizing heart rate and blood pressure measurements will be shown for the above defined subgroups as well to account for changes in vital signs in the particular groups.

Also, tables summarizing AESIs, if occurred, will be shown for the subgroups listed above.

4.7 Interim Analyses

No interim analysis is planned.
Due to the nature of this study, participant-level intervention 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.

4.8 Changes to Protocol-planned Analyses

Not applicable.

5. Sample Size Determination

Based on the evidence of a strong safety profile of vericiguat and the recommendation provided by FDA, the sample size of approximately 100 participants is considered appropriate to assess the tolerability of the 5 mg initiation dose for vericiguat.

6. Supporting Documentation

6.1 Population characteristic

6.1.1 Participant disposition

The number of participants enrolled, assigned to study intervention and valid for the SAF will be summarized for each study site.

The number of all participants as well as the number of sites will further be summarized by country/region.

The number of participants with important protocol deviations and the number of screen failures will be summarized overall and by country/region and study site.

The number of participants per important deviation category and validity finding will be presented.

A disposition summary will be presented summarizing the number of participants starting and completing the respective study phase, the number of participants discontinuing it and the primary reason for discontinuation. The number of participants completing the overall study will be provided in addition. Participants who completed the study are those who were followed for the duration of the study irrespective of discontinuation of study intervention.

6.1.2 Demography and other baseline characteristics

All demographic and baseline characteristics will be summarized using descriptive statistics by intervention, i.e. overall.

Demographic and baseline assessments to be summarized will include the following age groups:
< 18 years, 18-64 years, 65-84 years, >= 85 years and < 65 years, >= 65 years.

6.1.3 Protocol deviations

The number of participants with important protocol deviations and the number of screen failures will be summarized by country. In addition, the important protocol deviations will be listed and summarized in a frequency table (based on all participants randomized).

6.1.4 Medical history

Medical history will be tabulated using medical dictionary for regulatory activities (current version at the time of analysis) terms. The number of participants with medical history findings will be presented by primary system organ class and preferred term.

6.1.5 Prior and concomitant medication

For prior and concomitant medications, the following definitions apply:

- Prior medication: Medication taken before start of the study intervention intake, (regardless of when it ended).
- Concomitant medication: Medication taken after first study intervention intake (regardless of when it started or ended).

Prior and concomitant medication will be coded to ATC classification codes according to the World Health Organization Drug Dictionary (current version at the time of analysis). The number of participants taking prior and concomitant medication will be presented by study arm and overall using ATC classes and subclasses.

7. 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.