EMADOC-1700519818-1988760
Committee for Medicinal Products for Human Use (CHMP)

Type II group of variations assessment report

Procedure No. EMA/VR/0000257213

Invented name: Verquvo

International non-proprietary name: Vericiguat

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Background information on the procedure 3

2. Overall conclusion and impact on the benefit/risk balance 3

3. Recommendations 4

4. EPAR changes 5

Annex: Rapporteur's assessment comments on the type II variation 6

5. Introduction 7

6. Clinical Efficacy / Real-world data 8

Discussion 11

7. Clinical Safety aspects 12

7.1. Methods – analysis of data submitted 12

7.2. Results 13

7.3. Discussion 21

8. Changes to the Product Information 22

9. Request for supplementary information 23

9.1. Major objections 23

9.2. Other concerns 23

10. Assessment of the responses to the request for supplementary information 24

10.1. Major objections 24

10.2. Other concerns 28

11. Further request for supplementary information 37

11.1. Major objections 37

11.2. Other concerns 37

12. Assessment of the responses to the further request for supplementary information 37

12.1. Major objections 37

12.2. Other concerns 37

13. Attachments 38

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Bayer AG submitted to the European Medicines Agency on 04 March 2025 an application for group of variations.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.z	C.I.z Other variation	Variation type IB
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

A grouped application consisting of: Type II (C.I.4): Update of section 4.2 of the SmPC to update posology recommendations based on results from study VELOCITY as well as additional post-hoc analyses from VICTORIA. VELOCITY is 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. The Package Leaflet is updated accordingly. Type IB (C.I.z): to propose minor corrections in Module 2.7.4 and Module 5.3.5.4 CSR of the VITALITY study.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

The Applicant provided 4 Real-World-Data sources pointing toward underdosing or a lack of titrating of vericiguat in clinical practice around the globe. Across the sources, the proportion of patients reaching the target dose was in the low range of 26% to 36%, but unfortunately the reasons are not well described. The HOVER US study found that patients starting on a 5 mg dose of vericiguat had a higher likelihood of reaching the 10 mg target dose than those starting on 2.5 mg of vericiguat, indicating that a single-step titration could be more successful than a 2-step titration in achieving the 10 mg target dose. The HOVER study also found that compared to the 2.5 mg starting dose, a vericiguat starting dose of 5 mg/day or 10 mg/day was not associated with an increased risk of hypotension or syncope. Overall, this real-world data shows that similar to other guideline directed medical therapy, vericiguat is also underdosed and that there is an adequate rationale for developing a simpler titration regimen starting with 5 mg vericiguat in those patients not at risk of hypotension. To support this regimen, the Applicant performed the study VELOCITY. VELOCITY was 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. Both patients with recent worsening of a HF event (Group 1) and without recent worsening of a HF event (Group 2) were included, to align with the populations studied in the earlier VICTORIA trial (with recent worsening) and the ongoing VICTOR trial (without worsening). The study was intended to evaluate tolerability and safety of the increased starting dose of vericiguat 5 mg, thus efficacy was not studied, which is acceptable. The primary endpoint of the study was 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 (which also led to treatment discontinuation).

Of the 106 patients included, 93.4% of patients met the primary endpoint; 90.6% of patients with

recent HF worsening event, and 96.2% of patients without recent HF worsening event. To compare this result with tolerability of the current dosing titration, the Applicant performed a post-hoc analysis of the VICTORIA data by implementing the same definition of treatment tolerability used in VELOCITY. In VICTORIA, 97.2% of patients met the primary endpoint. Overall, these data provide support from a safety perspective for the proposed change in the posology.

There were some disbalances in SBP and medical histories, which high likely did not result in a relevant difference in the risk for hypotension between the subgroup of patients with WHF< 6 months in the VELOCITY study and the patients in the VICTORIA study. HF status has not been collected in the VELOCITY study, which hampers proper patient comparisons between both studies. However, due to changes in HF treatment in the recent years, patients in VELOCITY are more representative for present-day HF patients, making comparisons between VICTORIA and VELOCITY patients less relevant. In this respect, it is reassuring that there appears no increased risk for hypotension using the proposed 1-step up-titration for vericiguat **on top of current SoC** as demonstrated by the VELOCITY trial.

Based on above, the proposed change to a 1-step instead of a 2-step up-titration recommendation of vericiguat in section 4.2 of the SmPC is considered acceptable.

The benefit-risk balance of Verquvo remains positive and the proposed changes are acceptable.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.z	C.I.z Other variation	Variation type IB
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

A grouped application consisting of: Type II (C.I.4): Update of section 4.2 of the SmPC to update posology recommendations based on results from study VELOCITY as well as additional post-hoc analyses from VICTORIA. VELOCITY is 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. The Package Leaflet is updated accordingly. Type IB (C.I.z): to propose minor corrections in Module 2.7.4 and Module 5.3.5.4 CSR of the VITALITY study.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion Procedure No. EMA/VR/0000257213

Following the review of VELOCITY study and additional post-hoc analyses from VICTORIA study, the recommended starting dose of vericiguat is 5 mg vericiguat once daily. The dose should be doubled after approximately 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.

For patients with symptomatic hypotension within the past 4 weeks, the recommended starting dose is 2.5 mg vericiguat once daily. The dose should be doubled approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Vericiguat has received marketing authorization in multiple countries worldwide for the treatment of HFrEF. Vericiguat is a soluble guanylate cyclase (sGC) stimulator. Impairments in the NO-sGC-cGMP pathway (sGC deficiency, sGC desensitization, decreased NO availability) contribute to the disease progression in HFrEF patients. Vericiguat stimulates sGC and restores activity in the NO-sGC-cGMP pathway, which is highly expressed in cardiomyocytes, vascular smooth muscle cells, and fibroblasts. Vericiguat has a mode of action that targets endothelial dysfunction to improve regulation of vascular tone and myocardial function.

Vericiguat is available in 3 dose strengths containing 2.5 mg, 5 mg, and 10 mg of the drug substance. The Applicant proposes a change to the posology text to include a recommended starting dose of 5 mg instead of the currently approved 2.5 mg. The recommendation to up-titrate every 2 weeks to 10 mg vericiguat target dose, as tolerated by the patient, remains unchanged. For patients with symptomatic hypotension within the past 4 weeks, the Applicants proposes to maintain a start dose of 2.5mg.

Evaluations of the clinical implementation of HFrEF therapies have consistently demonstrated underdosing of guideline directed medical therapy (GDMT) in clinical practice compared to what was observed in the pivotal trials for these treatments. For instance, the US registry ("Change the Management of Patients With Heart Failure, CHAMP-HF)", prior to the introduction of SGLT2i showed that <25% of outpatient population with chronic HFrEF eligible for all 3 therapies (ACEI/ARB/ARNI, beta-blocker, and MRA) were prescribed triple therapy, and only 1% of eligible patients were prescribed triple therapy at target doses (Greene et al 2018).

This gap between recommended and achieved doses leads to the majority of HFrEF patients living at a significantly greater risk of HF events than is necessary and results in a greater burden of disease for individuals and society than is need (Greene et al 2018, Wachter et al 2019). In an acknowledgement of the need to bridge this gap both the ESC 2021 and the AHA 2022 HF Guidelines emphasize the need to start foundational HF treatments in a short time frame and to focus on up-titration of HF medications to the target doses.

Based on the VICTORIA trial results, it is expected that in routine clinical practice vericiguat titration to 10 mg would be well-tolerated with respect to hemodynamic changes. However, there is a marked discrepancy between the proportion of patients reaching the target dose of vericiguat in the VICTORIA trial setting and the proportion of those being fully titrated in clinical practice. Data from real-world settings across various geographies show that vericiguat is underdosed, with only approximately 30% of participants reaching the target dose and approximately two-thirds remaining on 2.5 or 5 mg. The reasons for this are likely common to those noted for other HFrEF GDMT medications (i.e., limited follow-up opportunities, along with complexity of care and polypharmacy), leading to an inertia for physicians to frequently adjust multiple medication doses (Greene et al 2018, Wachter et al 2019). Failure to achieve the maximum efficacious dose in turn leads to undertreatment of HFrEF patients.

Simplifying the initiation of vericiguat may help overcome the current underdosing of vericiguat observed in clinical practice, in two ways. First, patients would immediately start on what is expected to be a more efficacious dose and second, with a single titration they would reach the target dose of 10 mg.

VELOCITY, a 2-week single-arm study, was designed to provide evidence that starting treatment with vericiguat 5 mg is safe and well tolerated to use in clinical practice.

6. Clinical Efficacy / Real-world data

The scope of the type II variation concerns primarily the safety of simplifying the titration schedule of vericiguat. However, to support the need for such a simplification, the Applicant has submitted real-world data demonstrating the underdosing of vericiguat in clinical practice. Since underdosing is a potential cause of reduced efficacy for vericiguat, the real-world data is presented here.

In VICTORIA, >80% of HFrEF participants were successfully titrated to the 10 mg dose, with minimal decrease in BP. Since the launch of vericiguat, studies have evaluated its use in clinical practice, with a focus on titration patterns, as well as the occurrence of known safety outcomes. As vericiguat is a globally approved therapy, titration patterns have been evaluated in multiple countries with four sets of data from real-world practice: 2 from the US, and 1 each from Germany and Japan.

All 4 sets of data presented here point at underdosing, with approximately 30% of participants achieving the vericiguat target dose in clinical practice as compared to 81.9% in VICTORIA.

Victores et al, US Study (abstract)

The TriNetX Open Claims Database was used to identify US adults who filled a prescription for vericiguat between 1 Jan 2021 and 24 April 2023. Patient demographics, comorbidity burden, and comedication (including GDMT for HFrEF) were described by achievement of vericiguat target dose (10 mg). Categorical variables were compared across groups using Pearson Chi-Square tests, and continuous variables were compared using non-parametric Kruskal-Wallis tests.

Among 5527 patients treated with vericiguat, median age was 69 years. Most patients in the sample were male (67%), and most covered (47%) by Medicare. Patients were more commonly from the South (49%) as compared with other US regions (P<0.02). The most utilized drug classes of other GDMT included beta-blockers (71%), ARNi (47%), MRA (38%) and SGLT2i (39%). Frequency of combination therapy with multiple GDMT classes was low overall, with 25% of patients co-prescribed both SGLT2i and ARNi with vericiguat, and 16% of patients co-prescribed all GDMT drug classes (ACEi/ARB/ARNi + MRA + Beta blocker + SGLT2i) with vericiguat. Although overall comorbidity burden and specific comorbidities of interest were similar between groups, utilization of the most prescribed GDMT classes was significantly higher among patients with a record of achieving target dose of vericiguat (*P*<0.05). A total of 33.8% of patients reached the target dose of 10 mg, whereas 66.2% did not.

HOVER, US Study (manuscript in preparation)

This was a retrospective database study conducted in the US to determine the titration patterns among participants receiving the first outpatient prescription of vericiguat between JAN 2021 and APR 2023 and to evaluate their disease characteristics and frequencies of hypotension and syncope.

Study design: This was a single-arm cohort study of adults with HF from the US who initiated vericiguat between 01 JAN 2021 (corresponding to the date of US marketing authorization) and 01 APR 2023. The study population (N=1361) was defined by adult patients who initiated vericiguat from closed claims (i.e. index date) during the identification period and who had at least 6 months of prior observability. The study period, including the 6-month baseline period, spanned from 01 JUL 2020 to 01 JUL 2023 (i.e. end of available data), and allowed for 3 months of follow-up (i.e. 90 days after vericiguat initiation) for all patients. Cohort members were followed up until the occurrence of the outcome of interest, treatment discontinuation, disenrollment or death, or end of follow-up, whichever occurred first.

Objectives: The primary objective was to describe titration patterns among patients initiating vericiguat in the US, including starting dose and up-titration patterns. Secondary objectives were to

describe demographics, comorbidities, procedures, co-medications, clinical characteristics and laboratory results in the 6 months before vericiguat initiation (overall and in selected subgroups), to describe the number, percentage, and rate of hypotension or syncope (separately and as a composite endpoint) during the entire 90 days after vericiguat initiation as well as across 30-day intervals (overall and in selected subgroups). The last secondary objective was to evaluate factors associated with having a dose of 10 mg/day (i.e. target dose) at any time during the 90 days after vericiguat initiation in a combination of selected subgroups.

Exposure: Exposure to vericiguat was identified using relevant treatment terminologies (i.e. generic name or World Health Organization [WHO] Anatomical Therapeutic Chemical [ATC] codes). Start of exposure (treatment episode) was defined as the first exposure to vericiguat during the identification period with no previous vericiguat exposure in the 180 days before the index date. Duration of a vericiguat treatment episode was defined as the total number of days supplied (if blank, no refill was assumed) across first vericiguat fill and subsequent refills, with an allowed gap of 30 days (i.e. grace period) between two fills. Vericiguat discontinuation was defined as having a gap exceeding 30 days after the end of the last vericiguat treatment episode observed during follow-up. Depending on the first prescribed dosage of vericiguat, 3 subgroups were built (2.5 mg, 5 mg, 10 mg), in addition from the 5 mg starters and 10 mg starters we identified those patients without a HF hospitalization (HFH) during the 4 weeks before start (subgroups 4 and 5).

Co-variates included sociodemographics, clinical characteristics, previous HF treatments and procedures, laboratory values, comorbidities, and comedications. The HealthVerity HF dataset was used – part of the HealthVerity™ Marketplace, which comprised anonymized merged data from closed medical claims, open and closed pharmacy claims, electronic medical records (EMRs), laboratory data and mortality data sources in the US.

Results: A total of 1361 patients were included in the study cohort. Mean age was 61.8 years and approximately 17% were 75 years or older. Approximately half (44.7%) were insured with Medicaid. There were no major differences in the distribution of age, sex, region or health plan across subgroups.

Vericiguat titration patterns: Over half of the study cohort (56.6%) started on vericiguat at a daily dose of 2.5 mg/day, 24.2% had 5 mg/day as their first prescription, and 19.2% 10 mg/day. The largest patient group (38.4 %) were those starting with 2.5 mg and having no further up-titration. A quarter of patients (25.6%) reached the target dose over 90 days of follow-up.

Factors associated with having a daily vericiguat dose of 10 mg/day: In the multivariable adjusted Cox regression model, there was evidence that having a 5 mg vericiguat daily dose was associated with a 3-fold increased likelihood of reaching the target dose over the follow-up period (adj. Hazard ratio (HR) 3.08, 95% confidence interval (CI): 1.96–4.84, p <0.0001), compared to the 2.5 mg starters (in the sensitivity analysis HR 3.01 , 95% C.I. 1.88-4.82)

Comorbidities and Comedications: The study cohort had a high level of comorbid cardiovascular disease as shown by the substantial percentage of patients with hypertension (90.4%), hyperlipidemia (73.7%), coronary artery disease (68.9%), ischemic heart disease (67.7%) and diabetes mellitus (61.4%). Use of comedications reflected the cohort's comorbidity profile with high use of lipid-lowering drugs, antidiabetics, platelet aggregation inhibitors (including aspirin), and anticoagulants. Regarding GDMT, approximately 35% were on triple-and 20% on quadruple therapy. The frequencies of comorbidities and comedications were similar across the five subgroups. A history of hypotension or syncope was more frequent in the subgroup starting with the 2.5 mg dosage, compared to the higher dosage groups.

Worsening events: Less than half of the cohort (42.2%) had a worsening event (HFH or prescription for i.v. diuretics) in the 6 months before the start of vericiguat (37% had a HFH and 14.0% had a prescription for an i.v. diuretic). Similar frequencies of worsening events were seen between patients starting vericiguat on 2.5mg, 5 mg and 10 mg.

Hypotension and/or syncope occurrence: Hypotension/syncope during follow-up occurred in 12.5% of patients. Hypotension was recorded more frequently than syncope (9.6% and 4.9% of patients, respectively). Among the total cohort, the incidence of hypotension was 418.39 (95% CI: 338.74 – 498.04) per 1000 person-years, of syncope was 223.82 (95% CI: 166.22 – 281.42) per 1000 person-years, and of the first event of the composite outcome hypotension/syncope was 580.62 (95% CI: 485.78 – 675.45) per 1000 person-years.

In the multivariate adjusted Cox regression-model there was strong evidence that hypotension at baseline was associated with an increased likelihood of hypotension/syncope (first event) during follow-up (adj. HR 2.73, 95% CI: 1.83–4.08, p <0.0001). Anaemia was associated with an increased likelihood of hypotension/syncope (first event) during follow-up (adj. HR 1.64 (1.111 – 2.407)). Calcium channel blocker usage was associated with a lower likelihood of hypotension/syncope during follow-up (adj. HR 0.32, 95% CI: (0.153 – 0.668)).

Compared to the 2.5 mg starting dose, a vericiguat starting dose of 5 mg/day or 10 mg/day was not associated with an increased risk of hypotension or syncope (adj. HR 0.67 (95% CI: 0.414-1.088) and 0.77 (95% CI: (0.465-1.28).

PAVER Study from Germany

This was a retrospective nationwide longitudinal cohort study conducted in Germany to evaluate real-world characteristics and use patterns of participants treated with vericiguat. In this study, vericiguat was initiated in 2916 adult participants (mean age 73 years, 66.3% male) over a 16-month study period, starting from the launch of vericiguat in SEP 2021 and ending in DEC 2022. The proportion of participants who started on vericiguat 2.5 mg was 84%, and the proportion of participants who started on 5 mg and 10 mg were 12% and 4%, respectively (first ambulatory prescription). During a median follow-up of 150 days, 30.6% remained at 2.5 mg and 33.3% at 5 mg as their maximum dose, and 36.1% reached the full 10 mg target maintenance dose. The median time to up-titration from 2.5 mg to 10 mg was 37 days. Women and older patients reached the maximal dose of 10 mg vericiguat less often and received other substance classes of GDMT less frequently.

PAVER Study from Japan

This was a retrospective nationwide cohort study to evaluate vericiguat use in participants with HF in real-world setting. We identified 1086 patients who were prescribed vericiguat during the study period. After excluding 175 patients with <6 months of observability before the initiation of vericiguat treatment, one patient with missing age or sex records, and 81 patients who lacked follow-up records, 829 (76.3%) patients were included in the study. Of these patients, 520 (62.7%) initiated vericiguat treatment in hospital settings. A total of 738 (89.0%) patients were prescribed 2.5 mg of vericiguat as their first-observed dose ("starting dose"), and 75 (9.0%) patients were prescribed higher first-observed doses than 2.5 mg. The patterns of vericiguat dose titration were assessed in a subset of patients who underwent at least 90 days of follow-up (n = 424). The proportion of patients receiving intermediate and maximal daily doses increased steadily over 90 days, with marked increases observed on days 14 and 28. The proportion of patients who experienced uptitration at 30, 60, and 90 days were 55.0, 63.7, and 65.8%, respectively. 32.3% of patients reached the maximal daily dose on day 90.

Discussion

The real-world data above points toward underdosing or a lack of titrating of vericiguat in clinical practice. Across the sources, the proportion of patients reaching the target dose was in the low range of 26% to 36%, but unfortunately the reasons are not well described. The HOVER US study found that patients starting on a 5 mg dose of vericiguat had a higher likelihood of reaching the 10 mg target dose than those starting on 2.5 mg of vericiguat, indicating that a single-step titration could be more successful than a 2-step titration in achieving the 10 mg target dose. The HOVER study also found that compared to the 2.5 mg starting dose, a vericiguat starting dose of 5 mg/day or 10 mg/day was not associated with an increased risk of hypotension or syncope. Furthermore, it is worth noting that in the VICTORIA trial, 89.2% in the vericiguat group and 91.4% in the placebo group reached the 10 mg dose (Armstrong et al. 2020). This highlights that not reaching the target dose may not just be related to the drug and adverse events of it, but possibly also the titration algorithm.

Overall, the real-world data provided by the Applicant shows that similar to other guideline directed medical therapy, vericiguat is also underdosed and that there is an adequate rationale for developing a simpler titration regimen starting with 5 mg vericiguat in those patients not at risk of hypotension.

7. Clinical Safety aspects

VELOCITY
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

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 a two to one and enable HFrEF patients to achieve the target dose of 10 mg vericiguat daily within one titration step. The study was not designed to evaluate efficacy, as this was already evaluated in the VICTORIA study. In addition to VICTORIA, the ongoing VICTOR study will also evaluate the treatment effect of vericiguat in adults with chronic HFrEF without a recent HF event.

7.1. Methods – analysis of data submitted

Study design
This was a single arm, open-label study of vericiguat initiation at 5 mg in HFrEF participants with ejection fraction <45%. The total study duration was approximately 4 weeks, comprising a 2-week screening period followed by a 2-week treatment period. During the treatment period participants received once daily (Visit 1) 5 mg vericiguat for 2 weeks and returned for an end of study evaluation (Visit 2).

Study participants
The study enrolled male and female patients with chronic heart failure with ejection fraction <45%, with and without recent worsening HF. Enrolment caps were applied to ensure enrolment of the desired proportion of participants with (group 1) and without (group 2) recent HF event (approximately 50% in each group). These two groups are aimed to 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.

Inclusion/ exclusion criteria

This study enrolled male and female participants ≥18 years of age with chronic heart failure with reduced ejection fraction that met the following criteria:

- LVEF of <45% assessed within 12 months before Visit 1 by any local imaging method, and no subsequent LVEF measurement > 45%.
- SBP ≥ 100 mmHg at screening and Visit 1 (pre-treatment).
- No changes in GDMT dosing (including beta blockers, ACEI/ARBs, ARNI, MRAs, hydralazine-nitrate combinations, SGLT2 inhibitors, ivabradine, or oral diuretics)
    - o Within 4 weeks of screening for participants without a HF event ≤6 months prior to screening
    - o Within 2 weeks of screening for participants with a HF event ≤6 months prior to screening
    - o Planned during study participation
- 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.

Participants with a history of symptomatic hypotension 4 weeks before screening were excluded from this study. Participants with an eGFR based on the CKD-EPI Creatinine Equation of <15 mL/min/1.73 m2 within 30 days before Visit 1 or on chronic dialysis were also excluded.

Objectives and endpoints

Objective	Endpoint
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.

Sample size

Approximately 120 participants were planned be screened to achieve at least 100 participants who were assigned to study intervention and completed the treatment period of up to 2 weeks.

Statistical methods

No hypothesis testing was planned or performed. Descriptive statistics were provided for data collected. All analyses were performed on the safety analysis set (SAF).

7.2. Results

Participants

A total of 125 participants were enrolled into the screening period, and 106 were assigned to and received treatment (19 screen failures). While 102 participants completed study intervention, 4 participants discontinued study intervention due to AEs. All participants who were assigned to treatment and were exposed to study intervention at least once (N=106) were considered valid for safety analysis.

Exposure

Mean duration of treatment was 14.6 (±1.8) days and median duration was 15 days with a majority of participants (86.8%) receiving 5 mg vericiguat dose between 14 and 16 days, with 8 patients less than 14 days exposure and 6 patients more than 16 days exposure. Median treatment compliance was 100%, and a majority (96.2%) of study participants completed treatment without any interruption.

Baseline characteristics

Baseline characteristics are summarized in Table 1. More males (71.7%) than females (28.3%) participated in the study, and most participants (60.4%) were ≥65 years of age. Majority of the study population (96.2%) was white, and 63.2% were not Hispanic or Latino. There was an equal number (50%) of participants with and without recent worsening HF events. The reported medical history in all study participants was consistent with the overall HFrEF patient population according to the Applicant. Medical history showed that participants had hypertension (76.4%), dyslipidemia (36.8%), type 2 diabetes mellitus (36.8%), atrial fibrillation (34%), acute coronary syndrome (28.3%), chronic kidney disease (25.5%), coronary artery disease (22.6%), and hyperlipidemia (22.6%).

As required per protocol, all participants were on GDMT prior to and during enrollment in the study. Approximately half of the study population received a combination of SGLT2i and ARNI and one-third received SGLT2i and no ARNI at baseline (Table 2).

Table 1: Demographics and other baseline characteristics

	Vericiguat 5 mg N=106 (100%)
Sex	
Female	30 (28.3%)
Male	76 (71.7%)
Race	
BLACK OR AFRICAN AMERICAN	3 (2.8%)
NOT REPORTED	1 (0.9%)
WHITE	102 (96.2%)
Ethnicity	
HISPANIC OR LATINO	39 (36.8%)
NOT HISPANIC OR LATINO	67 (63.2%)
Age (YEARS)	
n	106
Mean (SD)	66.9 (11.3)
Median	67.5
Min, Max	32, 91
Age Classification Type 1	
Adults (between 18 and 64 years)	42 (39.6%)
From 65 to 84 years	61 (57.5%)
85 years and over	3 (2.8%)
Age Classification Type 2	
< 65 years	42 (39.6%)
≥ 65 years	64 (60.4%)
Screening Weight (kg)	
n	106
Mean (SD)	84.758 (19.280)
Median	82.000
Min, Max	50.00, 130.90
Screening Height (cm)	
n	106
Mean (SD)	169.190 (9.398)
Median	170.000
Min, Max	147.00, 189.00
History of HF event	
Participants with recent worsening HF event (Group 1)	53 (50.0%)
Participants without recent worsening HF event (Group 2)	53 (50.0%)
GDMT use	
ARNI USE, TOTAL	57 (53.8%)
ARNI USE WITHOUT SGLT2 INHIBITOR USE	7 (6.6%)
SGLT2 INHIBITOR USE, TOTAL	86 (81.1%)
SGLT2 INHIBITOR USE WITHOUT ARNI USE	36 (34.0%)
SGLT2 INHIBITOR AND ARNI USE (COMBINED)	50 (47.2%)
NO SGLT2 INHIBITOR AND NO ARNI USE	13 (12.3%)
Other HF drugs at baseline (post-hoc)	
HIGH-CEILING DIURETICS	40 (37.7%)
CARDIOVASCULAR SYSTEM; ALDOSTERONE ANTAGONISTS	60 (56.6%)
BETA BLOCKING AGENTS	100 (94.3%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	99 (93.4%)

Table 2: Baseline characteristics: GDMT use by history of recent worsening heart failure event (SAF)

	Vericiguat 5 mg N=106 (100%)	
	With Recent Worsening HF Event (Group 1)	Without Recent Worsening HF Event (Group 2)
ARNI USE, TOTAL	24 (22.6%)	33 (31.1%)
ARNI USE WITHOUT SGLT2 INHIBITOR USE	3 (2.8%)	4 (3.8%)
SGLT2 INHIBITOR USE, TOTAL	43 (40.6%)	43 (40.6%)
SGLT2 INHIBITOR USE WITHOUT ARNI USE	22 (20.8%)	14 (13.2%)
SGLT2 INHIBITOR AND ARNI USE (COMBINED)	21 (19.8%)	29 (27.4%)
NO SGLT2 INHIBITOR AND NO ARNI USE	7 (6.6%)	6 (5.7%)

ARNI = Angiotensin Receptor-neprilysin Inhibitor, GDMT = Guideline-directed Medical Therapy for Heart Failure, HF = heart failure, N = number of participants, SAF = safety analysis set, SGLT2 = Sodium-glucose Cotransporter 2

Treatment tolerability

A majority of the study population completed the 2-week treatment period without moderate to severe symptomatic hypotension and without temporary treatment interruptions (Table 3). Of the 7 participants who did not meet the primary endpoint, 3 participants had interruptions exceeding 1 day (2 days of treatment interruption), and 4 participants discontinued treatment.

Two of the 4 discontinuations were due to symptomatic hypotension. One symptomatic hypotension event was of moderate intensity, which was a protocol-defined criterion for discontinuation of study intervention. The second symptomatic hypotension event was of mild intensity, and was reported in a participant with a concurrent SAE of *Upper gastrointestinal haemorrhage*. The remaining 2 discontinuations were due to AEs not related to hypotension according to the Investigator. The reported PTs for these events were *Angioedema* and *Gastroesophageal reflux disease*.

Table 3: Primary, secondary and sensitivity analyses: Treatment tolerability of Vericiguat 5mg (SAF)

Analysis type	Overall N=106 Num/Den(%)	With Recent Worsening HF Event (Group 1) N=53 Num/Den(%)	Without Recent Worsening HF Event (Group 2) N=53 Num/Den(%)
Primary	99 / 106 (93.4%)	48 / 53 (90.6%)	51 / 53 (96.2%)
Sensitivity	102 / 106 (96.2%)	50 / 53 (94.3%)	52 / 53 (98.1%)
Secondary 1	96 / 106 (90.6%)	49 / 53 (92.5%)	47 / 53 (88.7%)
Secondary 2	102 / 106 (96.2%)	50 / 53 (94.3%)	52 / 53 (98.1%)

Den = denominator, HF = heart failure, Num = numerator, SAF = safety analysis set
Number of participants in denominator is number of participants in SAF in the respective subgroup
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.
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
Secondary 1: Participants who did not have an AE related to study intervention between Visit 1 and Visit 2.
Secondary 2: Participants who completed the two-week treatment with continuous intervention intake or were able to restart intervention after temporary interruption.

Adverse events

The most frequently reported PTs for TEAEs were *Hypotensio*n and *Dyspepsia*; all other PTs were reported in <1% of the study population (Table 4). Six of the 7 participants that were reported with

Hypotension events were considered symptomatic by the investigator. There were 4 participants who were reported with TEAEs leading to discontinuation of study, as described earlier.

There were no deaths during the study. One participant was reported with a serious TEAE (*Upper gastrointestinal haemorrhage*); this event was assessed by the investigator as not related to study intervention.

Table 4: Treatment-emergent adverse events: number of participants by primary system organ class, preferred term (SAF)

Primary system organ class **Preferred term** **MedDRA version 27.0**	**Vericiguat 5 mg** **N=106 (100%)**
Number (%) of participants with at least one such adverse event	14 (13.2%)
Cardiac disorders	2 (1.9%)
Cardiac failure	1 (0.9%)
Cardiac failure congestive	1 (0.9%)
Gastrointestinal disorders	5 (4.7%)
Dyspepsia	3 (2.8%)
Gastrooesophageal reflux disease	1 (0.9%)
Upper gastrointestinal haemorrhage	1 (0.9%)
Infections and infestations	1 (0.9%)
Gastroenteritis	1 (0.9%)
Nervous system disorders	2 (1.9%)
Dizziness	1 (0.9%)
Dysgeusia	1 (0.9%)
Skin and subcutaneous tissue disorders	1 (0.9%)
Angioedema	1 (0.9%)
Vascular disorders	7 (6.6%)
Hypotension	7 (6.6%)

AESI - Hypotension

Six of the 7 patients with hypotension were symptomatic. Four participants reported with symptomatic hypotension were participants with recent a worsening HF event (Group 1) and 3 of these participants were receiving combined treatment with an SGLT2 inhibitor and ARNI. Two participants reported with symptomatic hypotension were participants without a recent worsening HF event (Group 2) and both of these participants were receiving combined treatment with an SGLT2 inhibitor and ARNI.

Five symptomatic hypotension events were mild in intensity and one event of moderate intensity. Per protocol, the event of moderate intensity led to discontinuation of study intervention. One mild event also resulted in discontinuation of study intervention, as the participant was also reported with a concurrent serious TEAE with a PT of *Upper gastrointestinal haemorrhage*, which was assessed by the investigator as not related to study intervention. This patient received combination therapy with an SGLT2 inhibitor and ARNI.

Table 5: Treatment-emergent adverse events of special interest: overall summary of number of participants - Symptomatic hypotension (SAF)

	Vericiguat 5 mg N=106 (100%)
Number (%) of participants with treatment-emergent adverse events	
Any TEAE of special interest	6 (5.7%)
Maximum intensity for any TEAE of special interest	
MILD	5 (4.7%)
MODERATE	1 (0.9%)
Any intervention-related TEAE of special interest	6 (5.7%)
Any TEAE of special interest leading to discontinuation of intervention	2 (1.9%)
Any TESAE of special interest	0
Any intervention-related TESAE of special interest	0
TESAE of special interest with fatal outcome	0

Vital signs

There was a small decrease in mean blood pressure from baseline (−3.2 mmHg for systolic and −2.4 mmHg for diastolic).

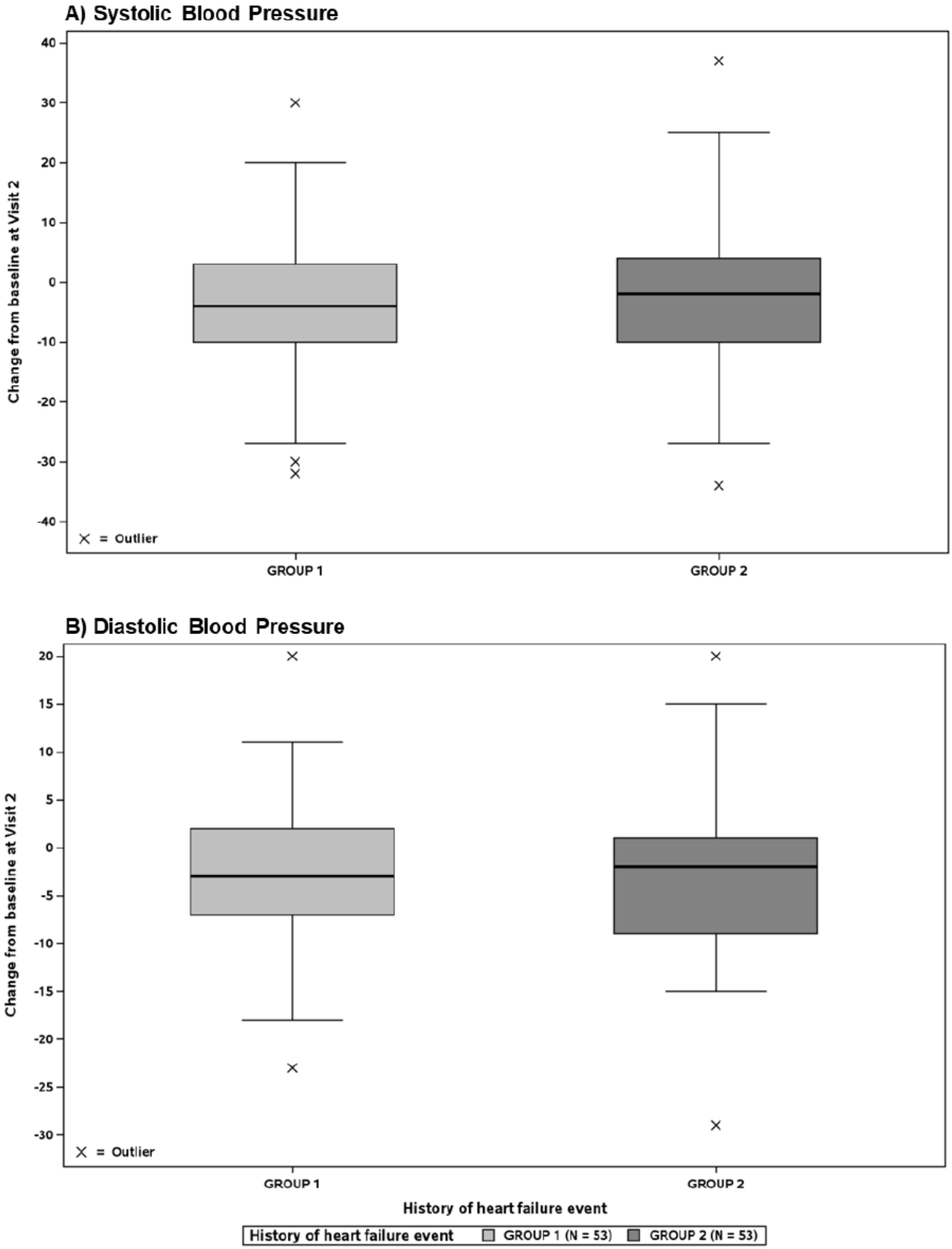
Table 6: Vital signs - Systolic and Diastolic Blood Pressure (mmHg): summary statistics and changes from baseline by visit (SAF)

		Value at Visit				Change from Baseline			
	Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
SBP	Screening	106	124.9 (16.0)	125.0	101, 192				
	Visit 1	106	125.5 (16.8)	125.0	101, 190				
	Visit 2	106	122.3 (17.6)	120.0	85, 207	106	-3.2 (12.8)	-3.5	-34, 37
DBP	Screening	106	76.4 (12.5)	74.5	35, 115				
	Visit 1	106	75.9 (10.9)	75.5	39, 115				
	Visit 2	106	73.5 (10.8)	73.0	41, 101	106	-2.4 (7.9)	-2.0	-29, 20

Table 7: Vital signs - Systolic and Diastolic Blood Pressure (mmHg) by history of heart failure: summary statistics and changes from baseline by visit (SAF)

			Value at Visit				Change from Baseline			
		Visit	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
SBP	Group 1	Screening	53	122.9 (13.6)	123.0	102, 154				
		Visit 1	53	125.8 (16.3)	125.0	101, 175				
		Visit 2	53	122.1 (15.4)	122.0	85, 172	53	-3.7 (12.3)	-4.0	-32, 30
	Group 2	Screening	53	126.8 (18.0)	125.0	101, 192				
		Visit 1	53	125.2 (17.4)	122.0	101, 190				
		Visit 2	53	122.5 (19.7)	119.0	85, 207	53	-2.7 (13.3)	-2.0	-34, 37
DBP	Group 1	Screening	53	73.7 (12.8)	72.0	35, 112				
		Visit 1	53	74.7 (11.1)	76.0	39, 115				
		Visit 2	53	72.5 (10.2)	73.0	41, 97	53	-2.2 (7.6)	-3.0	-23, 20
	Group 2	Screening	53	79.1 (11.7)	77.0	56, 115				
		Visit 1	53	77.1 (10.7)	75.0	62, 103				
		Visit 2	53	74.5 (11.4)	73.0	55, 101	53	-2.6 (8.2)	-2.0	-29, 20

Figure 1: Vital signs – Box plot for Systolic and Diastolic Blood Pressure (mmHg) by history of heart failure: change from baseline at Visit 2 (SAF)



Comparison of VELOCITY study results with VICTORIA

To compare results of the VICTORIA trial with VELOCITY, the Applicant performed a post-hoc analysis on the results of VICTORIA in order to use the same definition of the primary endpoint treatment definition.

To allow for a valid comparison between the studies, baseline characteristics of VICTORIA and VELOCITY (stratified to recent worsening HF event or not), were depicted in Table 8.

Table 8: Baseline patient characteristics in VICTORIA and VELOCITY – safety analysis set

	VICTORIA	**VELOCITY**		
	Vericiguat n=2519 (100%)	**Overall n=106 (100%)**	**With WHF, <6 months n=53 (100%)**	**Without WHF <6 months n=53 (100%)**
Age (years), mean (SD)	67.47 (12.2)	66.9 (11.3)	67.2 (11.4)	66.6 (11.3)
Female	604 (24.0)	30 (28.3)	16 (30.2)	14 (26.4)
Race				
White	1614 (64.1)	102 (96.2)	51 (96.2)	51 (96.2)
Asian	571 (22.7)	-	-	-
Multi-Racial	183 (7.3)	-	-	-
Black or African/American	123 (4.9)	3 (2.8)	2 (3.8)	1 (1.9)
American Indian or Alaska Native	24 (1.0)	-	-	-
Native Hawaiian or other Pacific Islander	3 (0.1)	-	-	-
Not Reported	1 (<0.1)	1 (0.9)	0 (0)	1 (1.9)
Baseline Vital Signs, Laboratories				
Systolic blood pressure, mean (mmHg ± SD)	121.2 (15.7)	125.5 (16.8)	125.8 (16.3)	125.2 (17.4)
Diastolic blood pressure, mean (mmHg ± SD)	72.5 (11.1)	75.9 (10.9)	74.7 (11.1)	77.1 (10.7)
Heart rate, mean (bpm ± SD)	72.9 (12.9)	69.6 (10.5)	70.0 (11.1)	69.2 (9.9)
Body mass index, mean (kg/m^2 ± SD)	27.7 (5.8)	29.5 (6.0)	28.7 (6.2)	30.3 (5.8)
eGFR, mean (mL/min/1.73m^2 ± SD)	61.3 (27.0)	65.1 (22.8)	57.7 (21.8)	72.5 (21.6)
Past Medical History				
Hypertension	1998 (79.3)	81 (76.4)	43 (81.1)	38 (71.7)
Coronary artery disease	1508 (59.9)	24 (22.6)	13 (24.5)	11 (20.8)
Chronic kidney disease	632 (25.1)	27 (25.5)	19 (35.8)	8 (15.1)
Diabetes mellitus / Type 2 diabetes [a]	1222 (48.5)	39 (36.8)	21 (39.6)	18 (34.0)
Atrial fibrillation	1095 (43.5)	36 (34.0)	22 (41.5)	14 (26.4)
Cerebrovascular accident	281 (11.2)	8 (7.5)	3 (5.7)	5 (9.4)
Chronic obstructive pulmonary disease	430 (17.1)	15 (14.2)	7 (13.2)	8 (15.1)
Background Medications [b]				
High-ceiling diuretics / Loop diuretic	2285 (90.7)	72 (67.9)	45 (84.9)	27 (50.9)
ACEI / ARB / ARNI	2192 (87.0)	99 (93.4)	47 (88.7)	52 (98.1)
ARNI use, total	359 (14.3)	52 (49.1)	21 (39.6)	31 (58.5)
Beta-blocker	2348 (93.2)	100 (94.3)	50 (94.3)	50 (94.3)
MRA (aldosterone antagonists)	1746 (69.3)	87 (82.1)	46 (86.8)	41 (77.4)
SGLT2i use total	58 (2.3)	82 (77.4)	40 (75.5)	42 (79.2)
Both ARNI and SGLT2i	13 (0.5)	45 (42.5)	19 (35.8)	26 (49.1)
No ARNI and no SGLT2i	2115 (84.0)	17 (16.0)	11 (20.8)	6 (11.3)

[a] In VICTORIA, this was collected under "diabetes mellitus'; In VELOCITY under 'Type 2 diabetes'

[b] ARNI use, SGLT2i use, SGLT2i + ARNI use and no SGLT2i and no ARNI use at baseline, derived by using ATC codes
Source: VICTORIA 16943_ema, Table 1/1; VELOCITY 21683_ema, Table 1/1 – 1/5 and 1/8 - Table 1/11

Results of the first 14 days of VICTORIA are compared with VELOCITY in Table 9: VICTORIA comparison to VELOCITY: Vericiguat treatment tolerability. Treatment was well tolerated in both studies according to the Applicant, with 97.2% participants in VICTORIA and 93.4% participants in the overall VELOCITY study population. In the VELOCITY subgroup of participants matching the VICTORIA population, i.e. those with a recent worsening HF event, 90.6% of participants completed the two-week treatment.

Table 9: VICTORIA comparison to VELOCITY: Vericiguat treatment tolerability

Study	Analysis	Participants treated	Number of participants (%) [c]
VICTORIA	Primary[a]	2519	2448 (97.2)
VELOCITY	Primary[a]	106	99 (93.4)
	Sensitivity[b]	106	102 (96.2)
VICTORIA comparison with VELOCITY subgroup, HFrEF participants with a recent worsening HF event			
VICTORIA	Primary[a]	2519	2448 (97.2)
VELOCITY	Primary[a]	53	48 (90.6)
	Sensitivity[b]	53	50 (94.3)

[a] *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.
[b] *Sensitivity*: Participants who completed the two-week treatment with maximum two-day interruption and without symptomatic hypotension of moderate to severe intensity between Visit 1 and Visit 2.
[c] Participants who met the respective endpoint definition.

7.3. Discussion

The Applicant proposes to update the posology section of the VERQUVO product information that will allow initiation of vericiguat with a 5 mg starting dose and a single up-titration to reach the 10 mg target maintenance dose, instead of the currently approved 2-step up-titration scheme from the starting dose of 2.5 mg and subsequently up-titration to 5 mg and 10 mg vericiguat. Simplifying the initiation of vericiguat may help overcome the current underdosing of vericiguat observed in clinical practice. First, patients would immediately start on what is expected to be a more efficacious dose and second, with a single titration they would reach the target dose of 10 mg.

To support that starting treatment with vericiguat 5 mg is safe and well-tolerated in clinical practice, VELOCITY, a 2-week single-arm study, was designed and conducted. Patients with chronic heart failure with ejection fraction <45%, with and without recent worsening HF event (1:1) were included. The primary endpoint of the study was 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 (which also led to treatment discontinuation).

Of the 106 patients included, 93.4% of patients met the primary endpoint; 90.6% of patients with recent HF worsening event, and 96.2% of patients without recent HF worsening event. To compare this result with tolerability of the current 2-step up-titration regimen, the Applicant performed a post-hoc analysis of the VICTORIA study (in which patients had a recent worsening of HF event) by implementing the same definition of treatment tolerability used in VELOCITY. Although the tolerability observed in the subgroup of patients with recent HF worsening events observed in the VELOCITY trial

appears relatively high, it is lower compared with the 97.2% tolerability observed in the VICTORIA trial.

The Applicant provided an overview of patients' reasons for discontinuation in VICTORIA and VELOCITY. The proportion of patients who did not meet the primary endpoint defined in VELOCITY was higher in the VELOCITY patients with WHF <6 months (9.4%) compared with the VICTORIA patients (3.7%). The primary reason for discontinuation in these patients was symptomatic hypotension (2 patients, 3.8%) compared with 2 patients (<0.1%) in VICTORIA. In VELOCITY, the discontinuations were due to an event of symptomatic hypotension of moderate intensity (requiring discontinuation as per protocol-defined criterion) in one participant and to an event of mild symptomatic hypotension in another participant who had a concurrent SAE of upper gastrointestinal bleeding. Overall, although a higher percentage of patients discontinued due to hypotension in the VELOCITY study compared with the VICTORIA study, the numbers were small and the events were mild or moderate in severity, which is reassuring and do not raise concerns on the newly proposed dosing titration strategy.

There were some disbalances in SBP and medical histories, which high likely did not result in a relevant difference in the risk for hypotension between the subgroup of patients with WHF< 6 months in the VELOCITY study and the patients in the VICTORIA study. HF status has not been collected in the VELOCITY study, which hampers proper patient comparisons between both studies. However, due to changes in HF treatment in the recent years, patients in VELOCITY are more representative for present-day HF patients, making comparisons between VICTORIA and VELOCITY patients less relevant.

Based on above, the proposed change to a 1-step instead of a 2-step up-titration recommendation of vericiguat in section 4.2 of the SmPC is considered acceptable.

8. Changes to the Product Information

Reference is made to the separate document on the SmPC changes.

9. Request for supplementary information

9.1. Major objections

Clinical aspects

1. Although the VELOCITY data suggest a potential basis for a higher initial starting dose,

   it is currently unclear if the patients with recent HF worsening (group 1) included in the VELOCITY study are similar to the patients enrolled in the VICTORIA study, since baseline characteristics of the VELOCITY patients are not stratified according to groups with or without recent HF worsening. This is of particular importance for characteristics that might be associated with an increased risk of treatment discontinuation and/or development of hypotension, such as baseline SBP and DBP. The Applicant is requested to provide a table comparing the baseline characteristics from VICTORIA and VELOCITY. For VELOCITY, data should be shown for the overall population as well as stratified on recent HF event (to facilitate comparison to VICTORIA). The comparison should also include LVEF, NYHA, baseline blood pressure and medication usage. Any discrepancies between VICTORIA and VELOCITY should be discussed in relation to the change in posology.

9.2. Other concerns

Clinical aspects

2. The current analyses focus on moderate and severe symptomatic hypotension. To obtain a more comprehensive understanding of the incidence of hypotensive events, the Applicant is requested to provide additional analyses of VELOCITY (group 1 and 2 separate) and VICTORIA that include mild hypotension, asymptomatic hypotension, and the combination of both symptomatic and asymptomatic events. Furthermore, the definitions of mild, moderate and severe hypotension was not provided. The Applicant is requested to provide their definition of mild, moderate and severe hypotension.
3. Of the patients who did not meet the primary endpoint treatment tolerability, the reason for treatment discontinuation was not clear for all patients (VELOCITY) or for any of the patients (VICTORIA). The Applicant is requested to compare and discuss the reason for discontinuation for the patients who did not meet the primary endpoint between the studies.
4. The HOVER study could be used as useful information in this application as a large cohort of patients did not show an increased risk of syncope or hypotension in the higher dosage regimens with a starting dose of 5 mg and 10 mg compared to 2.5 mg which could point to the tolerability of higher dosages. No other factors were associated with the outcome. There was strong evidence that hypotension at baseline was associated with an increased likelihood of hypotension/syncope (first event) during follow-up in addition to anaemia and usage of calcium channel blockers. However, the trial does not seem to be entirely balanced between subgroups as it is stated that a history of hypotension or syncope was more frequent in the subgroup starting with the 2.5 mg dosage, compared to the higher dosage groups. The study results

have not been published, and as this is a study sponsored by the Applicant, it would be of high relevance if the Applicant could state if confounding could be an issue seen for the results of the 2,5 mg and 5 mg starting dose comparison in incidence of syncope or if the measure could be reliable

5. The Applicant should expand in more detail on the reasons why it has been observed that vericiguat is underdosed in the real-world setting as this is only shortly summarised in the clinical overview and the Applicant should specifically outline if there has been a signal of underdosing due to patients not tolerating higher doses of vericiguat.

10. Assessment of the responses to the request for supplementary information

10.1. Major objections

Clinical aspects

Question 1
Although the VELOCITY data suggest a potential basis for a higher initial starting dose, several important issues preclude implementation of the proposed changes at this time:

It is currently unclear if the patients with recent HF worsening (group 1) included in the VELOCITY study are similar to the patients enrolled in the VICTORIA study, since baseline characteristics of the VELOCITY patients are not stratified according to groups with or without recent HF worsening. This is of particular importance for characteristics that might be associated with an increased risk of treatment discontinuation and/or development of hypotension, such as baseline SBP and DBP. The Applicant is requested to provide a table comparing the baseline characteristics from VICTORIA and VELOCITY. For VELOCITY, data should be shown for the overall population as well as stratified on recent HF event (to facilitate comparison to VICTORIA). The comparison should also include LVEF, NYHA, baseline blood pressure and medication usage. Any discrepancies between VICTORIA and VELOCITY should be discussed in relation to the change in posology.

Summary of the MAH's response
In VELOCITY, the study population was representative of HFrEF participants included in the two phase 3 studies conducted with vericiguat, VICTORIA (completed) and VICTOR (at that time ongoing). Study participants were balanced with regards to the time elapsed between the last WHF and enrolment: 50% had a WHF < 6 months prior to enrolment (VICTORIA-like) and 50% had a WHF > 6 months prior to enrolment or no prior WHF (VICTOR-like).

We acknowledge that comparing the tolerability of vericiguat observed in VELOCITY to the one observed in VICTORIA is limited because the two populations were recruited at different timepoints and changes in the adoption of background therapies occurred in the meantime. As such, differences in relevant baseline characteristics are inevitable. The magnitude of these differences can be appreciated in **Table 10**, in which participants' relevant baseline characteristics are displayed for vericiguat-treated participants included in VICTORIA, for the overall VELOCITY population and for the two VELOCITY subgroups (with or without recent WHF event).

Table 10: Baseline patient characteristics in VICTORIA and VELOCITY – safety analysis set

	VICTORIA	VELOCITY		
	Vericiguat n=2519 (100%)	**Overall n=106 (100%)**	**With WHF, <6 months n=53 (100%)**	**Without WHF <6 months n=53 (100%)**
Age (years), mean (SD)	67.47 (12.2)	66.9 (11.3)	67.2 (11.4)	66.6 (11.3)
Female	604 (24.0)	30 (28.3)	16 (30.2)	14 (26.4)
Race				
White	1614 (64.1)	102 (96.2)	51 (96.2)	51 (96.2)
Asian	571 (22.7)	-	-	-
Multi-Racial	183 (7.3)	-	-	-
Black or African/American	123 (4.9)	3 (2.8)	2 (3.8)	1 (1.9)
American Indian or Alaska Native	24 (1.0)	-	-	-
Native Hawaiian or other Pacific Islander	3 (0.1)	-	-	-
Not Reported	1 (<0.1)	1 (0.9)	0 (0)	1 (1.9)
Baseline Vital Signs, Laboratories				
Systolic blood pressure, mean (mmHg ± SD)	121.2 (15.7)	125.5 (16.8)	125.8 (16.3)	125.2 (17.4)
Diastolic blood pressure, mean (mmHg ± SD)	72.5 (11.1)	75.9 (10.9)	74.7 (11.1)	77.1 (10.7)
Heart rate, mean (bpm ± SD)	72.9 (12.9)	69.6 (10.5)	70.0 (11.1)	69.2 (9.9)
Body mass index, mean (kg/m^2 ± SD)	27.7 (5.8)	29.5 (6.0)	28.7 (6.2)	30.3 (5.8)
eGFR, mean (mL/min/1.73m^2 ± SD)	61.3 (27.0)	65.1 (22.8)	57.7 (21.8)	72.5 (21.6)
Past Medical History				
Hypertension	1998 (79.3)	81 (76.4)	43 (81.1)	38 (71.7)
Coronary artery disease	1508 (59.9)	24 (22.6)	13 (24.5)	11 (20.8)
Chronic kidney disease	632 (25.1)	27 (25.5)	19 (35.8)	8 (15.1)
Diabetes mellitus / Type 2 diabetes [a]	1222 (48.5)	39 (36.8)	21 (39.6)	18 (34.0)
Atrial fibrillation	1095 (43.5)	36 (34.0)	22 (41.5)	14 (26.4)
Cerebrovascular accident	281 (11.2)	8 (7.5)	3 (5.7)	5 (9.4)
Chronic obstructive pulmonary disease	430 (17.1)	15 (14.2)	7 (13.2)	8 (15.1)
Background Medications [b]				
High-ceiling diuretics / Loop diuretic	2285 (90.7)	72 (67.9)	45 (84.9)	27 (50.9)
ACEI / ARB / ARNI	2192 (87.0)	99 (93.4)	47 (88.7)	52 (98.1)
ARNI use, total	359 (14.3)	52 (49.1)	21 (39.6)	31 (58.5)
Beta-blocker	2348 (93.2)	100 (94.3)	50 (94.3)	50 (94.3)
MRA (aldosterone antagonists)	1746 (69.3)	87 (82.1)	46 (86.8)	41 (77.4)
SGLT2i use total	58 (2.3)	82 (77.4)	40 (75.5)	42 (79.2)
Both ARNI and SGLT2i	13 (0.5)	45 (42.5)	19 (35.8)	26 (49.1)
No ARNI and no SGLT2i	2115 (84.0)	17 (16.0)	11 (20.8)	6 (11.3)

[a] In VICTORIA, this was collected under "diabetes mellitus'; In VELOCITY under 'Type 2 diabetes'

[b] ARNI use, SGLT2i use, SGLT2i + ARNI use and no SGLT2i and no ARNI use at baseline, derived by using ATC codes

Source: VICTORIA 16943_ema, Table 1/1; VELOCITY 21683_ema, Table 1/1 – 1/5 and 1/8 - Table 1/11

While a higher proportion of participants had a history of coronary artery disease at baseline in VICTORIA, this imbalance is unlikely to have played a role in the tolerability of vericiguat. In VICTORIA, a subgroup analysis of AEs of symptomatic hypotension showed no influence of the baseline Canadian

Cardiovascular Society angina classification on the incidence of symptomatic hypotension in the two treatment arms (Table 14.3-25, VICTORIA CSR).

As expected in consideration of its geographic footprint, the VELOCITY trial enrolled predominantly White participants. Based on the integrated population pharmacokinetic/pharmacodynamic analysis of VICTORIA and SOCRATES, race and ethnicity are no relevant factors for vericiguat exposure nor tolerability (Module 2.7.2, Section 2.5 and 3.3, VICTORIA submission).

The difference in mean SBP and DBP observed at baseline between VICTORIA and VELOCITY is more relevant for the tolerability of a vasoactive drug like vericiguat. In VICTORIA, the mean SBP and DBP were 121 mmHg and 72.5 mmHg respectively, while the VELOCITY subgroup with WHF in the prior 6 months had a mean SBP of 126 mmHg and a mean DBP of 75 mmHg. While this imbalance, probably due to chance as both trials had very similar entry criteria with respect to baseline BP, can't be ignored, it remains nevertheless modest.

When comparing VELOCITY participants with WHF <6 months to vericiguat-treated VICTORIA participants, we can also observe a discrepancy in the proportion of participants with CKD at baseline (35.8% vs. 25.1%) and for the mean eGFR at baseline (57.7 vs. 61.3 mL/min/1.73m²). However, VICTORIA data show no evidence that these participants experience more symptomatic hypotension with vericiguat. Adverse event rates, including SAEs, drug-related SAEs, and AEs leading to discontinuation, were similar between vericiguat and placebo groups across eGFR categories (VICTORIA, Module 2.5). Additionally, eGFR had no significant impact on vericiguat exposure.

LVEF and NYHA class at baseline were not collected in the small and streamlined VELOCITY study, preventing direct comparisons with the VICTORIA population for these characteristics. However, VELOCITY enrolled 50% VICTORIA-like and 50% VICTOR-like participants. Given that the mean LVEF at baseline was 30.4% in VICTOR (1), the difference compared to the mean LVEF of 29.0% in VICTORIA is expected to be minimal. Additionally, considering that the proportion of participants in NYHA class II was 79% in the overall VICTOR population and 59% in VICTORIA, this proportion may be higher in VELOCITY compared to VICTORIA. This potential imbalance is unlikely to be clinically relevant, as the incidence of symptomatic hypotension in VICTORIA showed no significant differences between treatment arms when considering NYHA class at baseline (Table 14.3-25, VICTORIA CSR).

Other differences between the groups presented in the table are those related to background therapies. In the years following the conduct of VICTORIA, the adoption of ARNI (sacubitril/valsartan) and SGLT2 inhibitors has increased substantially in this indication. While an ARNI or an SGLT2 inhibitor were taken by 14.3% and 2.3% of vericiguat-treated VICTORIA participants, more than 39% and 75% of participants were taking these medications in the VELOCITY subgroup with HF decompensation in the prior 6 months. The hypotensive effect of an ARNI treatment already described in the literature (2) was also observed in the VICTORIA dataset, in which placebo-treated participants experienced a higher incidence of symptomatic hypotension if treated with ARNI at baseline (11.6% vs. 7.2%, VICTORIA CSR PH-41322, Table 14.3-25). Although less pronounced than ARNI, a hypotensive effect has been observed also for other HFrEF background medications (3). Hence, considering the higher use of ARNIs and other background medications observed in VELOCITY, the good tolerability shown by a 5 mg vericiguat starting dose when taken on top of these medications appears reassuring.

In conclusion, while a mean higher SBP at baseline may have contributed to the tolerability of the 5 mg dose in VELOCITY, other baseline characteristics such as use of vasoactive medications may have had an opposing effect. Consequently, we believe that a comparison of the tolerability observed in VELOCITY against the one observed in VICTORIA remains valid despite its inherent limitations. Based on the cumulative evidence obtained in previous studies (including real-world evidence and post-marketing data), a history of recent symptomatic hypotension and the presence of an SBP<100 mmHg at treatment

initiation are relevant factors in determining the clinical risk of hypotension. Other baseline characteristics do not appear to play a major role in determining treatment discontinuations or interruptions due to hypotension or other reasons and therefore do not need to be considered in the proposed label update.

Assessment of the MAH's response

The Applicant has compared baseline characteristics of the subgroup of patients with WHF <6 months in VELOCITY with those of VICTORIA, and several differences in characteristics were found. Overall, patients in VELOCITY had higher mean baseline systolic blood pressure (125.8 mmHg vs 121.2 in VICTORIA), which could reduce the risk of (symptomatic) hypotension. However, the difference was modest, especially considering the large standard deviations and the mean SPB of both studies was well over 100 mmHg, thus their baseline risk of hypotension based on SBP was considered to be small. Further, there were some disbalances in medical history between the subgroup of patients with WHF< 6 months in VELOCITY and patients in VICTORIA. In the subgroup of VELOCITY, a lower percentage of patients had CAD (24.5% vs. 59.9%), T2DM (39.6% vs. 48.5%) and CVA (5.7% vs. 11.2%), but a higher percentage had CKD (35.8% vs. 25.1%) compared with VICTORIA.

In VICTORIA, no differences in risk of hypotension were seen between vericiguat and placebo with increasing CCSA class, indicating that CAD is not expected to directly affect risk of hypotension. However, the disbalances in medical history in CAD, T2DM and CVA could indicate that patients in VELOCITY were less frail and as their baseline SBP was higher than VICTORIA patients, which both could make patients less at risk for hypotension. In contrary, a higher percentage of patients with WHF < 6 months in the VELOCITY study had CKD, which is a risk factor for hypotension. Overall, the disbalances in medical history had opposing effect on the risk for hypotension.

There were also disbalances in background medication. A higher percentage of patients with WHF< 6 months in VELOCITY compared with the patients in VICTORIA received ARNI (39.6% vs. 14.3%), MRA (86.8% vs. 69.3%), and SGL2i (75.5% vs. 2.3%) as background medication for HF. Although these imbalances could be due to the disbalances in medical history, it is more likely that these disbalances are caused by change in SoC over time (e.g. extensions of indication for SGLT2 inhibitors), as also stated by the Applicant, which is a major drawback in comparing VELOCITY with VICTORIA.

Hypotension is a well-known adverse event of ARNI use (ref: SmPC Entresto), but if patients were truly hypotensive, they were excluded from VELOCITY and if their baseline tension was lower, this should be visible in their baseline tension. MRA and SGLT2 inhibitors are not expected to affect patient's blood pressure. Thus, it is expected that the disbalances in medication use itself have minimal effect on study outcomes in VELOCITY. Furthermore, considering that the patients in the VELOCITY study are more representative for HF patients currently treated with the SoC in the clinical practice than the patients in the VICTORIA study, it is reassuring there appears no increased risk for hypotension using the proposed 1-step uptitration approach in the VELOCITY study.

It is not expected that disbalances in race affect study outcomes for VELOCITY.

It is a major drawback that baseline NYHA class, LVEF and NT-proBNP were not collected for the patients in the VELOCITY study, as it hampers a valid comparison between the VELOCITY and VICTORIA patients. However, the inclusion criteria of VELOCITY and VICTORIA were similar (both NYHA class II-IV and LVEF <45%), probably leading to similar populations included. Moreover, as already indicated above, in recent years treatment of HF has changed, which could also affect patients' HF status (e.g. NYHA class) and thus hampers the comparison between VICTORIA and VELOCITY patients.

In conclusion, there were some disbalances in SBP and medical histories, which high likely did not result in a relevant difference in the risk for hypotension between the subgroup of patients with WHF< 6 months

in the VELOCITY study and the patients in the VICTORIA study. HF status has not been collected in the VELOCITY study, which hampers proper patient comparisons between both studies. However, due to changes in HF treatment in the recent years, patients in VELOCITY are more representative for present-day HF patients, making comparisons between VICTORIA and VELOCITY patients less relevant. In this respect, it is reassuring that there appears no increased risk for hypotension using the proposed 1-step up-titration for vericiguat **on top of current SoC** as demonstrated by the VELOCITY trial.

Issue resolved.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

10.2. Other concerns

Clinical aspects

Question 2

The current analyses focus on moderate and severe symptomatic hypotension. To obtain a more comprehensive understanding of the incidence of hypotensive events, the Applicant is requested to provide additional analyses of VELOCITY (group 1 and 2 separate) and VICTORIA that include mild hypotension, asymptomatic hypotension, and the combination of both symptomatic and asymptomatic events. Furthermore, the definitions for mild, moderate and severe hypotension were not provided. The Applicant is requested to provide their definition of mild, moderate and severe hypotension.

Summary of the MAH's response

In VELOCITY, the definitions of mild, moderate and severe hypotension are as follows:

- *Mild*: A type of AE 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 AE 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 AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

These definitions (based on assessments by the investigator), are consistent with the general characterizations of AE intensity used by sites to describe all AEs in VICTORIA and VELOCITY trials and therefore aid comparison of AE intensity across trials.

Table 11 displays the incidence of all TEAEs with the PT "hypotension", both symptomatic and asymptomatic, reported in vericiguat-treated VICTORIA participants, in the overall VELOCITY population and in two subgroups (with or without recent WHF event). To allow a balanced comparison between VICTORIA and VELOCITY datasets, only the AEs reported within 14 days of treatment initiation are

displayed for the VICTORIA population. These TEAEs were more frequently reported in VELOCITY compared to VICTORIA (7.5% in the subgroup with WHF < 6 months before treatment initiation vs. 2.9% in VICTORIA), but the difference is fully attributable to AEs of mild intensity (5.7% vs. 1.7% in the same subgroups). The incidence of the most clinically relevant AEs, i.e. those with moderate and severe intensity, was very low with small imbalances between the two studies (0.9% in VELOCITY vs. 1.2% in VICTORIA). If we more specifically look at AEs of symptomatic hypotension (per protocol reported as ECI/AESI), the observed imbalance between VELOCITY (subgroup with WHF < 6 months prior to treatment initiation) and VICTORIA is due to AEs of mild (5.7% vs. 0.9%) or moderate (1.9% vs. 0.6%) intensity. No AE of symptomatic hypotension with severe intensity was observed in VELOCITY.

The incidence of asymptomatic TEAEs with the PT "hypotension" was slightly higher in VICTORIA (1.3%) compared to the overall VELOCITY population (0.9%) and to the VELOCITY subgroup with WHF<6 months prior to treatment initiation (0%) (as calculated, subtracting ECI/AESI "symptomatic hypotension events" from total TEAEs with PT hypotension).

Table 11: Incidence of hypotensive events in VICTORIA (up to Day 14) and VELOCITY – safety analysis set

	VICTORIA	VELOCITY		
Events	**Vericiguat n=2519 (100%)**	**Overall n=106 (100%)**	**With WHF <6 months n=53 (100%)**	**Without WHF <6 months n=53 (100%)**
TEAE with PT Hypotension	72 (2.9)	7 (6.6)	4 (7.5)	3 (5.7)
Mild	43 (1.7)	6 (5.7)	3 (5.7)	3 (5.7)
Moderate	25 (1.0)	1 (0.9)	1 (0.9)	0
Severe	4 (0.2)	0	0	0
Intervention-related TEAE with PT Hypotension	35 (1.4)	7 (6.6)	4 (7.5)	3 (5.7)
TEAE with PT Hypotension leading to discontinuation	8 (0.3)	2 (1.9)	2 (3.8)	0
ECI / AESI "Symptomatic hypotension"	41 (1.6)	6 (5.7)	4 (7.5)	2 (3.8)
Mild	22 (0.9)	5 (4.7)	3 (5.7)	2 (3.8)
Moderate	15 (0.6)	1 (0.9)	1 (1.9)	0
Severe	4 (0.2)	0	0	0

Source: VICTORIA 16493_ema, Table 2 / 1; VELOCITY 21683_ema, Table 2 / 1

Assessment of the MAH's response

Despite the relative numbers of hypotensive events were higher in VELOCITY with WHF <6 months (7.5%) compared with VICTORIA (2.9%), the difference was fully attributable difference to AEs of mild intensity (5.7% vs. 1.7%, respectively), which is reassuring. The Applicant provided the definition of mild, moderate and severe hypotension, which is the same as classification of AEs in general. Mild hypotension can be considered as minimally clinically relevant.

Issue resolved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 3

Of the patients who did not meet the primary endpoint treatment tolerability, the reason for treatment discontinuation was not clear for all patients (VELOCITY) or for any of the patients (VICTORIA). The Applicant is requested to compare and discuss the reason for discontinuation for the patients who did not meet the primary endpoint between the studies.

Summary of the MAH's response

Table 12 provides an overview of the reasons why participants did NOT meet the VELOCITY primary endpoint in vericiguat-treated VICTORIA participants, in the overall VELOCITY population and in two subgroups (with or without recent WHF event). To allow a balanced comparison between VICTORIA and VELOCITY datasets, only data collected within 14 days of treatment initiation are displayed for the VICTORIA population. Please note that the proportion of VICTORIA study participants meeting the VELOCITY primary endpoint is reported as 97.2% in the Clinical Overview (VICTORIA, Module 2.5), while the table below reports a slightly lower proportion (96.3%). This difference reflects the derivation of dose interruptions and discontinuations in the VICTORIA data from the dose modification assessment CRF page (96.3%) rather than the exposure CRF page (97.2%). This method uses as source a CRF built specifically to record changes in study medication and was therefore preferred in this analysis for capturing the VELOCITY-like endpoint in that dataset.

As discussed in the Clinical Overview, the difference between the proportion of participants reaching the VELOCITY primary endpoint in VICTORIA and in the VELOCITY group with WHF < 6 months prior to treatment initiation was modest (96.3 vs. 90.6%). The discontinuations and the temporary interruptions due to symptomatic hypotension were higher in this VELOCITY subgroup compared to VICTORIA (3.8% vs. <0.1% and 1.9% vs. <0.1%, respectively). In VELOCITY, the discontinuations were due to an event of symptomatic hypotension of moderate intensity (requiring discontinuation as per protocol-defined criterion) in one participant and to an event of mild symptomatic hypotension in another participant who had a concurrent SAE of upper gastrointestinal bleeding. Despite the numerical difference between the two groups, the proportion of participants that required either a discontinuation or a temporary interruption of the 5 mg vericiguat dose remains low.

Table 12: Participants that did NOT meet the VELOCITY (at Day 14) primary endpoint in VICTORIA and VELOCITY – safety analysis set

	VICTORIA	VELOCITY		
	Vericiguat (n=2519) (100%)	**Overall (n=106) (100%)**	**With WHF <6 months n=53 (100%)**	**Without WHF <6 months n=53 (100%)**
Participants that met the VELOCITY primary endpoint	2426 (96.3)	99 (93.4)	48 (90.6)	51 (96.2)
Participants that did NOT meet the VELOCITY primary endpoint	93 (3.7)	7 (6.6)	5 (9.4)	2 (3.8)
Reasons for not meeting the endpoint				
Discontinuation due to symptomatic hypotension	2 (<0.1)	2 (1.9)	2 (3.8)	0
Discontinuation due to hypotension	1 (<0.1)	-	-	-
Discontinuation due to other AEs	11 (0.4)	2 (1.9)	1 (1.9)	1 (1.9)
Discontinuation due to other reasons	46 (1.8)			
Symptomatic hypotension within 14 days without discontinuation	13 (0.5)	-	-	-
Temporary interruption ≥ 2 days due to symptomatic hypotension without discontinuation	2 (<0.1)	1 (1.9%)	1 (1.9%)	0
Temporary interruption ≥ 2 days without discontinuation	18 (0.7)	2 (1.9%)	1 (1.9%)	1 (1.9)

VELOCITY and VICTORIA: Primary endpoint: 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 or first two weeks of treatment. Interruptions were identified from the dose modification assessment CRF page.
Source: VICTORIA 16493_ema, Table 3 / 1; VELOCITY 21683_ema, Table 3 / 1

Assessment of the MAH's response

The Applicant provided an overview of patients' reasons for discontinuation in VICTORIA and VELOCITY. The proportion of patients who did not meet the primary endpoint defined in VELOCITY was higher in the VELOCITY patients with WHF <6 months (9.4%) compared with the VICTORIA patients (3.7%). The primary reason for discontinuation in these patients was symptomatic hypotension (2 patients, 3.8%) compared with 2 patients (<0.1%) in VICTORIA. In VELOCITY, the discontinuations were due to an event of symptomatic hypotension of moderate intensity (requiring discontinuation as per protocol-defined criterion) in one participant and to an event of mild symptomatic hypotension in another participant who had a concurrent SAE of upper gastrointestinal bleeding. Overall, although a higher percentage of patients discontinued due to hypotension in the VELOCITY study compared with the VICTORIA study, the numbers were small and the events were mild or moderate in severity, which is reassuring and do not raise concerns on the newly proposed dosing titration strategy.

Issue resolved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 4

The HOVER study could be used as useful information in this application as a large cohort of patients did not show an increased risk of syncope or hypotension in the higher dosage regimens with a starting dose of 5 mg and 10 mg compared to 2.5 mg which could point to the tolerability of higher dosages. No other factors were associated with the outcome. There was strong evidence that hypotension at baseline was associated with an increased likelihood of hypotension/syncope (first event) during follow-up in addition to anaemia and usage of calcium channel blockers. However, the trial does not seem to be entirely balanced between subgroups as it is stated that a history of hypotension or syncope was more frequent in the subgroup starting with the 2.5 mg dosage, compared to the higher dosage groups. The study results have not been published, and as this is a study sponsored by the Applicant, it would be of high relevance if the Applicant could state if confounding could be an issue seen for the results of the 2.5 mg and 5 mg starting dose comparison in incidence of syncope or if the measure could be reliable.

Summary of the MAH's response

The HOVER study was an observational, retrospective database-study, conducted in a large cohort of patients (n=1361) starting treatment with vericiguat in the US. There was no signal of a higher risk of hypotension or syncope in patients starting with a higher dose (5 mg or 10 mg daily) compared to those starting at 2.5 mg daily. Factors associated with hypotension (history of hypotension, anaemia, use of calcium channel blockers at baseline) are in-line with published literature and have been described previously among general risk factors for hypotension in patients with HF, unrelated to any vericiguat intake (4). Differences in baseline variables were present (e.g. less frequent history of hypotension and higher ARNI intake in the 5 mg group) but these were adjusted by a multivariate Cox-model.

Some limitations of the study should nevertheless be considered. There is no systematic blood pressure monitoring in a real-world setting and hypotension episodes are probably under-recorded. However, there is no indication that any specific dosage group is disproportionately affected by this under-recording. A further limitation pertains to the identification of the vericiguat starting dose. In the database used, as in most such general healthcare databases, medication start during a hospitalization is not recorded and we could only use ambulatory prescriptions to identify drug intake. To mitigate this possible bias, we excluded all patients with 5 mg or 10 mg as first recorded dosage who had a HF hospitalization within the four weeks before the first ambulatory prescription. In a sensitivity analysis we applied this criterion also to the 2.5 mg starting dose, to have the same restriction in all dosage groups, but results did not materially change.

As in all observational studies, residual confounding or unmeasured confounding needs to be considered. We adjusted the estimates for the available potential confounders at baseline by using a multivariate Cox-regression model. However, some clinically relevant information, e.g. on severity of HF, left ventricular ejection fraction or NT-proBNP measurements were not available in the data and therefore could not be adjusted for.

In summary, the HOVER study provides useful information. General hypotension risk factors identified are in -line with previous knowledge and the study did not raise any suspicion that a 5 mg starting dose would be associated with a higher risk of hypotension/syncope compared to the 2.5 mg starting dose. However, considering the limitations outlined above, the study cannot be interpreted as a confirmatory trial regarding the safety of a 5 mg vericiguat starting dose.

Assessment of the MAH's response

As also pointed out by the Applicant, observational studies come with their limitations. The HOVER study is a large study in terms of sample size, but relevant baseline characteristics are only available for a subset of patients (e.g. blood pressure data is missing for 80% of patients). The reasons for some patients starting on 5mg (or even 10 mg) vericiguat remain unclear, as often the case in observational studies.

The study showed that only a quarter of included patients reached the 10 mg dose (26%) and that was largely driven by patients who already started at 10 mg. Only 1.6% of patients followed the currently recommended posology of starting with vericiguat 2.5 mg, then 5 mg and then 10 mg.

It is reassuring that hypotension during follow-up was not negatively associated with achieving the 10 mg dose, but due to the limitations of the study, this should be interpreted cautiously.

Thus, despite the limitations of the HOVER study, which are often inherent to observational studies, the study is important for demonstrating that the current vericiguat titration scheme is seldom followed in the real-world setting. The study is solely (part of) the rationale for the current variation, but not a pivotal or confirmatory study for substantiating the variation.

Issue resolved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 5

The Applicant should expand in more detail on the reasons why it has been observed that vericiguat is underdosed in the real-world setting as this is only shortly summarised in the clinical overview and the Applicant should specifically outline if there has been a signal of underdosing due to patients not tolerating higher doses of vericiguat.

Summary of the MAH's response

We acknowledge that the monitoring of SBP is a relevant factor in the titration of vericiguat, as shown by the titration guidance used in the two phase 3 randomized clinical trials conducted with vericiguat (VICTORIA and VICTOR) and by the guidance for prescribers included in the SmPC. As such, hypotension is inevitably responsible for a certain proportion of missed up-titrations. The data collected to date, however, do not suggest that intolerance is the main driver for the underdosing of vericiguat observed in the real world.

This is first shown by the VICTORIA data, submitted in response to D120 List of Questions for the Marketing Authorization (**Table 13**). In this randomized clinical trial, the proportion of study participants experiencing symptomatic hypotension while taking the 10 mg target dose was comparable in the vericiguat (5.4%) and placebo (5.2%) groups. In participants taking the 5 mg and the 2.5 mg doses, slightly higher proportions of participants with symptomatic hypotension were reported in the vericiguat groups when compared to placebo (2.1% vs. 1.5% and 3.3% vs. 2.4% for the 5 mg and 2.5 mg dose, respectively). Despite these small differences, the proportion of participants receiving the 10 mg dose

after approximately 12 months was 89.2% in the vericiguat arm. Given the comparable target dose achievement rate reported in the placebo arm (91.4%), it seems unlikely that intolerance plays an important role in preventing study participants from achieving the 10 mg dose (VICTORIA, 16493 Report PH-41322, Table 14.1-32).

Table 13: Number of subjects and events – adverse events of clinical interest symptomatic hypotension on each dose level (data through the primary completion, all subjects as treated analysis) - VICTORIA

	Vericiguat		Placebo	
	n/N (%)	Number of events	n/N (%)	Number of events
Any event	229 / 2519 (9.1%)	292	198 / 2515 (7.9%)	252
Dose/Sham				
2.5 mg	84 / 2517 (3.3%)	90	60 / 2515 (2.4%)	70
5 mg	48 / 2285 (2.1%)	58	35 / 2297 (1.5%)	37
10 mg	111 / 2063 (5.4%)	131	110 / 2114 (5.2%)	128
Interruption	13 / 1542 (0.8%)	13	17 / 1571 (1.1%)	17

This table includes treatment-emergent events, defined as events that started or worsened after start of study medication until last intake of study medication plus 14 days.
Events were identified based on investigator's assessment.
In case no sufficient time information is available to decide whether an event occurred before or after dose modification, the event was assigned to the higher dose.
Each subject was counted once in each dose level he/she passed.

n/N=Number of subjects
Source: VICTORIA, 16493_ ema Table 4 / 1

In the observational database study HOVER, several factors potentially related to achieving the 10 mg dose were investigated. While factors often associated with underdosing/lack of up-titration (e.g. older age, CKD, anaemia, history of hypotension) did not appear to limit up-titration, the strongest predictor for reaching the 10 mg target dose was a vericiguat starting dose of 5 mg/day. Furthermore, anaemia and history of hypotension were identified as risk factors for the development of hypotension in HOVER but were nevertheless not identified as factors preventing target dose achievement.

The underdosing observed for vericiguat has also been reported for other HFrEF guideline-directed medical therapies (5,6). These gaps in medication titration are seen even in cohorts with relatively robust BP and kidney function, suggesting that clinical inertia towards medication changes and/or system-based barriers, rather than true medication intolerance, may be predominant factors preventing achievement of target dose (7).

Additionally, in two single-centre observational studies conducted in Spain, more than 70% of participants followed in the real world achieved the 10 mg target dose (8,9). This seems to corroborate the idea that adequate follow-up (e.g. access to care similar to a clinical trial setting, specialty vs. primary care access to drugs) and enhanced physicians' awareness can at least in part overcome clinical inertia and lead to target dose achievement comparable to that observed in clinical trials. In this context, simplification of the dosing regimen like the one proposed for vericiguat in HFrEF can further facilitate target dose achievement in the real world.

In the post-marketing setting, no new safety concerns have been observed for vericiguat pertaining to its listed ADRs or drug intolerance when instructions of administration are followed according to the product SmPC. Very few cases reported underdose as an AE, and no safety signal of vericiguat underdosing due to drug intolerance has been identified.

Assessment of the MAH's response

Applicant has demonstrated in VICTORIA that, in the setting of a clinical trial, most patients (~90%) reached the 10 mg dose, and there were only minor differences in tolerability compared with placebo. However, as pointed out in the clinical overview, in real-world setting, these numbers are not met (see also the assessment of the response on question 4, the HOVER study).

According to the Applicant, clinical inertia (e.g. patient stable on current therapy) may explain why real-world patients do not reach target dose of vericiguat, as it has been reported for other GDMT in HF patients. It is agreed with the Applicant that clinical inertia might contribute to patients not achieving target dose.

Of note, it was striking that in the Spanish studies provided by the Applicant over 70% of patients reached target dose. As these were small, single-centre patients, it is not considered that these are more representative of current clinical practice than those studies provided in the clinical overview.

Issue resolved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

☒No need to update overall conclusion and impact on benefit-risk balance.

11. Further request for supplementary information

11.1. Major objections

Clinical aspects

None.

11.2. Other concerns

Clinical aspects

1. The Applicant is requested to remove the information on the VELOCTY study from section 5.1 of the SmPC. Please refer to the Product Information including the CHMP Rapporteur's assessment.

12. Assessment of the responses to the further request for supplementary information

12.1. Major objections

Clinical aspects

None.

12.2. Other concerns

Clinical aspects

Question 1
The Applicant is requested to remove the information on the VELOCTY study from section 5.1 of the SmPC. Please refer to the Product Information including the CHMP Rapporteur's assessment.

Summary of the MAH's response
The Applicant agrees to remove the information on the VELOCITY study from section 5.1 of the SmPC. The revised version of the SmPC is presented in Module 1.3.1.

Assessment of the MAH's response
Please refer to the assessment in the separately attached Product Information document.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

☐No need to update overall conclusion and impact on benefit-risk balance.

13. Attachments

1. Product Information including the updated CHMP Rapporteur's assessment.