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Safety and tolerability of a 5 mg starting dose of vericiguat among patients with heart failure: The VELOCITY study

Introduction

To maximally improve patient outcomes, clinical guidelines for heart failure (HF) with reduced ejection fraction (HFrEF) recommend that disease-modifying medications be titrated to target doses derived from landmark clinical trials, as tolerated.[1,2] Nonetheless, in routine clinical practice, the majority of patients with HFrEF do not achieve target doses and few patients have doses increased over time.[3,4] These gaps in medication titration are seen even in cohorts with relatively robust blood pressure 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 dosing.[3–5]

To overcome challenges with clinical inertia and effective care delivery, simplifying the number of medication titration steps may improve implementation of guideline-directed medical therapy (GDMT) in clinical practice and increase likelihood of patients reaching the target dose. Vericiguat, a soluble guanylate cyclase stimulator, demonstrated a dose-dependent effect on N-terminal pro-B-type natriuretic peptide reduction among patients with HF with ejection fraction (EF) <45% in the SOCRATES-REDUCED trial (Soluble Guanylate Cyclase Stimulator in Heart Failure with Reduced Ejection Fraction Study), with 10 mg daily identified as the effective target dose for the subsequent phase III VICTORIA trial (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction).[6,7] Based on VICTORIA, vericiguat is now approved for the treatment of worsening HF (WHF) with EF <45%, with current labelling recommending initiation of vericiguat at 2.5 mg daily, increasing to 5 mg daily at 2 weeks, and further increasing to the target dose 10 mg daily at 4 weeks.[7] If the initial 2.5 mg step could be removed, while maintaining patient safety, it could facilitate more patients in clinical practice reaching the 10 mg daily target dose. The VELOCITY study (NCT06195930) examined whether bypassing the 2.5 mg step for vericiguat, and initiating therapy at 5 mg daily, would be a safe and well tolerated approach for patients with HF and EF <45%.

Methods

Study design

VELOCITY was a multinational prospective, 2-week, single-arm, open-label phase 2b study that enrolled patients with chronic HF with EF <45%, with or without a recent WHF event. The trial was approved by the local institutional review boards or ethics committees at all study sites, and all patients signed informed consent. Participants underwent a screening visit to assess eligibility, with eligible patients then returning 2 weeks later for Visit 1. At Visit 1, participants were initiated on vericiguat 5 mg daily, and this dose was continued as tolerated for a 2-week treatment period until Visit 2, which was the final study visit (online supplementary *Figure S1*).

Participants

Eligible patients were adults aged ≥18 years with chronic HF and left ventricular EF <45% (by most recent assessment and within 12 months before Visit 1), New York Heart Association class II–IV symptoms, and systolic blood pressure (SBP) ≥100 mmHg at screening and Visit 1. Eligible patients were stratified by presence or absence of a recent WHF event, defined as HF hospitalization ≤6 months prior to screening or outpatient intravenous or subcutaneous diuretic use ≤3 months prior to screening. Patients were required to have had no changes in background GDMT or oral diuretics for either 2 weeks (if recent WHF event) or 4 weeks (if no recent WHF event) prior to screening. Key exclusion criteria included symptomatic hypotension 4 weeks prior to screening, estimated glomerular filtration rate <15 ml/min/1.73 m^2 or chronic dialysis, or concurrent use of vericiguat or another soluble guanylate cyclase stimulator. Full eligibility criteria are detailed in online supplementary *Table S1*.

Study endpoints

The primary endpoint was tolerability of the 5 mg vericiguat starting dose, defined as completion of the 2-week 5 mg dose with maximum 1-day interruption and without moderate–severe symptomatic hypotension. A pre-specified sensitivity analysis definition of the primary tolerability endpoint increased the maximum allowable interruption to 2 days. Secondary safety and tolerability endpoints included completion of 2-week study period without an adverse event (AE) related to vericiguat, and completion of 2-week study period with either continued adherence to vericiguat or able to restart after any temporary discontinuation.

Statistical analysis

Analyses were descriptive and no hypothesis testing was planned or performed. All analyses were performed on the safety analysis set (SAF) of all patients who started study treatment. Proportions for participants meeting study endpoints assessing safety and tolerability were calculated using the number of participants who met the endpoint definition as the numerator and the total number of participants in the SAF as the denominator.

To further contextualize results in the current single-arm study, HF patients initiated on vericiguat 2.5 mg daily in the VICTORIA trial of patients with chronic HF with EF <45% and recent WHF were analysed for the VELOCITY study endpoints.[7] Tolerability endpoints for the 2 weeks following initiation of vericiguat 2.5 mg daily (VICTORIA) versus vericiguat 5 mg daily (VELOCITY) were compared.

Results

Patients

From April 2024 through July 2024, 125 patients were screened across 28 sites and 7 countries (online supplementary *Table S2*, *Appendix S1*). In total, 106 patients were deemed eligible and initiated on vericiguat 5 mg, of whom 53 (50.0%) had a recent WHF event and 53 (50.0%) had no recent WHF event (online supplementary *Figure S2*).

Overall, mean ± standard deviation age was 66.9 ± 11.3 years, and 30 (28.3%) patients were women (*Table 1*). Rates of background GDMT at baseline were high, including 81.1%

Table 1 Baseline patient characteristics

	Overall ($n = 106$)	Recent WHF ($n = 53$)	No recent WHF ($n = 53$)
Age (years)	66.9 ± 11.3	67.2 ± 11.4	66.6 ± 11.3
Female sex, *n* (%)	30 (28.3)	16 (30.2)	14 (26.4)
Race, *n* (%)			
White	102 (96.2)	51 (96.2)	51 (96.2)
Black or African/American	3 (2.8)	2 (3.8)	1 (1.9)
Not reported	1 (0.9)	0 (0)	1 (1.9)
Baseline vital signs, laboratories			
Systolic blood pressure (mmHg)	125.5 ± 16.8	125.8 ± 16.3	125.2 ± 17.4
Diastolic blood pressure (mmHg)	75.9 ± 10.9	74.7 ± 11.1	77.1 ± 10.7
Heart rate (bpm)	70 ± 11	70 ± 11	69 ± 10
eGFR (ml/min/1.73 m^2)[a]	65 ± 23	58 ± 22	72 ± 22
Body mass index (kg/m^2)[a]	29.5 ± 6.0	28.7 ± 6.2	30.3 ± 5.8
Past medical history, *n* (%)			
Hypertension	81 (76.4)	43 (81.1)	38 (71.7)
Coronary artery disease	24 (22.6)	13 (24.5)	11 (20.8)
Chronic kidney disease	27 (25.5)	19 (35.8)	8 (15.1)
Type 2 diabetes	39 (36.8)	21 (39.6)	18 (34.0)
Atrial fibrillation	36 (34.0)	22 (41.5)	14 (26.4)
Cerebrovascular accident	8 (7.5)	3 (5.7)	5 (9.4)
Chronic obstructive pulmonary disease	15 (14.2)	7 (13.2)	8 (15.1)
Background medications, *n* (%)			
Loop diuretic	72 (67.9)	45 (84.9)	27 (50.9)
ACEI/ARB/ARNI	99 (93.4)	47 (88.7)	52 (98.1)
ARNI	57 (53.8)	24 (45.3)	33 (62.3)
Beta-blocker	100 (94.3)	50 (94.3)	50 (94.3)
MRA	87 (82.1)	46 (86.8)	41 (77.4)
SGLT2i	86 (81.1)	43 (81.1)	43 (81.1)
Both ARNI and SGLT2i	50 (47.2)	21 (39.6)	29 (54.7)
No ARNI and no SGLT2i	13 (12.3)	7 (13.2)	6 (11.3)

Data are reported as mean ± standard deviation or *n* (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor; WHF, worsening heart failure.
[a]Value at time of screening.

of patients treated with a sodium–glucose cotransporter 2 inhibitor (SGLT2i), 53.8% of patients treated with an angiotensin receptor–neprilysin inhibitor (ARNI), and 47.2% treated with both SGLT2i and ARNI. Patients with and without a recent WHF event were similar with respect to demographics and blood pressure, but patients with recent WHF had higher rates of baseline chronic kidney disease, were more likely to be prescribed a loop diuretic, and less likely to be prescribed ARNI.

Primary and secondary endpoints

Overall, the primary tolerability endpoint was met in 93.4% of patients, including 90.6% of patients in the WHF group and 96.2% of patients in the non-WHF group. Findings were generally consistent for the pre-specified sensitivity analysis definition of the primary endpoint, and secondary endpoints (*Figure 1*, *Table 2*). Findings were also generally consistent among patients prescribed background SGLT2i or ARNI therapy (online supplementary *Table S3*).

Safety

Treatment-emergent AEs occurred in 14 participants (13.2%). There was one severe AE (i.e. facial angioedema). All other AEs were mild/moderate intensity, of which one participant experienced a serious treatment-emergent AE assessed as not related to study intervention (i.e. upper gastrointestinal bleed) (online supplementary *Table S4*). There were no deaths during the study.

Overall, 4 (3.8%) participants discontinued treatment due to an AE, with two discontinuations due to symptomatic hypotension (1.9%) (online supplementary *Table S5*). In total, six patients had episodes of symptomatic hypotension, with five judged by investigators as mild severity and one judged as moderate severity (online supplementary *Table S6*). There was a modest decrease in blood pressure from baseline to Day 14 (Visit 2) (mean ± standard deviation −3.2 ± 12.8 mmHg for systolic and −2.4 ± 7.9 mmHg for diastolic).

Comparison with initiation of vericiguat 2.5 mg in VICTORIA

When comparing patients starting vericiguat 2.5 mg daily in VICTORIA with those starting vericiguat 5 mg daily in VELOCITY, treatment was overall well-tolerated between Day 1 and Day 14 in both studies. Overall, 97.2% of patients initiated on vericiguat 2.5 mg in VICTORIA met the 2-week primary tolerability endpoint specified in VELOCITY. By comparison, 93.4% of patients initiated on vericiguat 5 mg in VELOCITY met the VELOCITY primary endpoint (*Figure 1*).

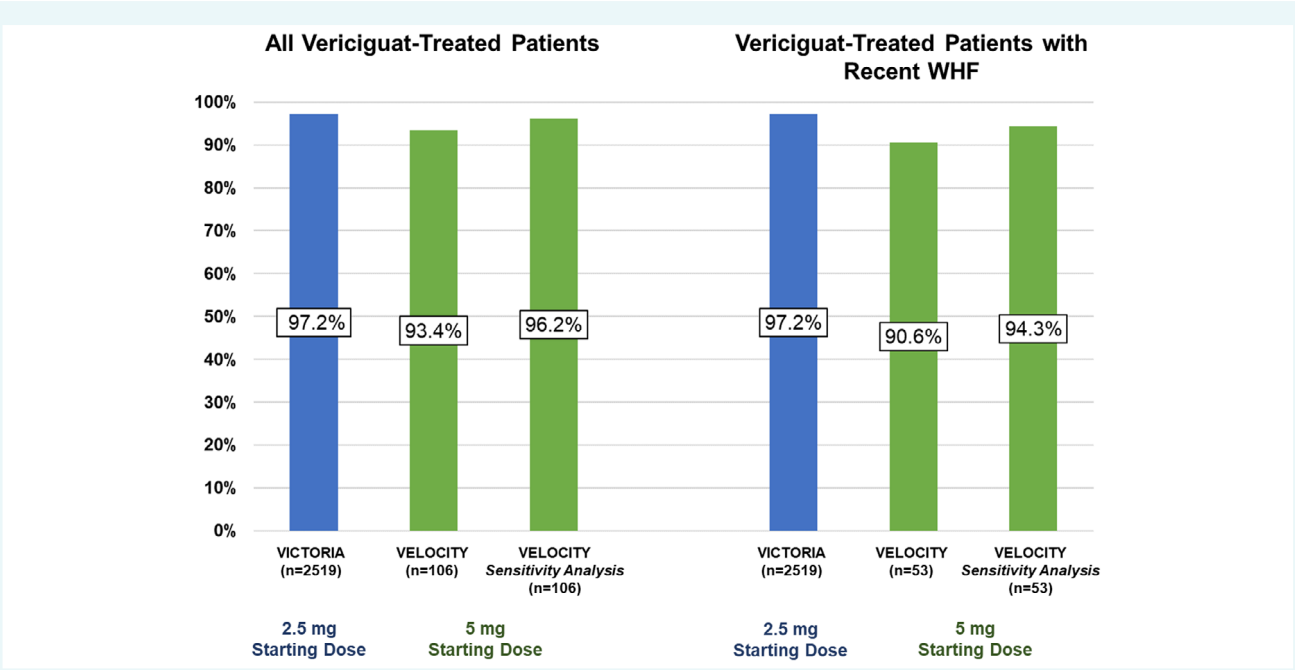

Figure 1 Proportion of vericiguat-treated patients achieving primary tolerability endpoint. Patients in VELOCITY initiated on vericiguat 5 mg daily were compared with patients in VICTORIA initiated on vericiguat 2.5 mg daily. The primary endpoint was completion of 2-week study period with maximum 1-day interruption and without symptomatic hypotension of moderate to severe intensity. The sensitivity analysis of the primary endpoint was completion of 2-week study period with maximum 2 days of interruption and without symptomatic hypotension of moderate to severe intensity. WHF, worsening heart failure.

Discussion

In this prospective multinational study of patients with chronic HF with EF <45%, initiation of vericiguat at a starting dose of 5 mg was safe and well-tolerated in >90% of patients, with minimal effect on SBP and low rates of symptomatic hypotension. These findings were generally similar regardless of patient history of a recent WHF event. Acknowledging that current regulatory labelling recommends initiation of vericiguat at a starting dose of 2.5 mg, data from VELOCITY suggests that an updated regulatory guidance including a 5 mg starting dose may be considered for eligible patients. Based on real-world experiences with other GDMTs for HF, a simplified one-step titration pathway may facilitate a higher proportion of patients achieving the 10 mg target doses of vericiguat in clinical practice.[3]

In the VICTORIA trial, initiation of vericiguat 2.5 mg resulted in an early mean reduction in SBP of ~2–3 mmHg, and 1–2 mmHg lower compared with placebo, with blood pressure returning to baseline during longer-term follow-up and subsequent dose titration.[7,8] By comparison, in the current VELOCITY study, initiation of vericiguat 5 mg was associated with a modest mean reduction in SBP of ~3 mmHg over 2 weeks. Had it been placebo-corrected, this observed decrease in SBP with vericiguat 5 mg may had been attenuated further, since early decreases in SBP are frequently seen in patients randomized to placebo in HF clinical trials, including VICTORIA.[8] In both VICTORIA and VELOCITY, any small vericiguat-induced early decrease in SBP did not translate to any significant risk of symptomatic hypotension or syncope. In VELOCITY, <4% of patients initiating vericiguat 5 mg discontinued therapy due to an adverse event, with <2% of patients discontinuing therapy due to symptomatic hypotension. This safety and tolerability of the vericiguat 5 mg starting dose was observed in the context of high background rates of other GDMTs (e.g. >80% of patients receiving SGLT2i and >50% of patients receiving ARNI). Given the known blood pressure lowering effects of select GDMTs such as ARNI, data from VELOCITY support the safety and tolerability of a 5 mg starting dose of vericiguat, in combination with prescription of other recommended HF therapies. These findings build on earlier data from VICTORIA, where vericiguat also was well-tolerated in the setting of ARNI and other GDMTs.[9]

Limitations of this study should be noted. First, this was a single-arm, open-label study without a control group. Although not a randomized comparison, to further contextualize study results, current data with initiation of vericiguat 5 mg in VELOCITY were compared with data for initiation of vericiguat 2.5 mg in VICTORIA. Additionally, the degree to which the open-label design could have impacted patient or investigator expectations and perceived tolerability of study drug is unclear. Second, study follow-up in VELOCITY was limited to 2 weeks. Although current guidance for vericiguat includes 2-week medication titration intervals as done in the VICTORIA trial, longer follow-up would be needed to detect any delayed safety or tolerability issues following initiation of a 5 mg starting dose. Third, it should be noted that by design, VELOCITY included a subset of patients without a recent WHF event. Vericiguat is not currently approved for patients with HFrEF without a prior WHF event, although a large cardiovascular outcome trial in this patient population is ongoing (NCT05093933).[10,11] Lastly, like VICTORIA, the current study required patients to have a SBP ≥100 mmHg for eligibility. The safety and tolerability of initiating vericiguat among patients with HFrEF with lower SBP is unclear. Likewise, patients with changes in background GDMT

Table 2 Safety and tolerability endpoints

Endpoint	Overall ($n = 106$)	Recent WHF ($n = 53$)	No recent WHF ($n = 53$)
Primary	99 (93.4)	48 (90.6)	51 (96.2)
Sensitivity	102 (96.2)	50 (94.3)	52 (98.1)
Secondary #1	96 (90.6)	49 (92.5)	47 (88.7)
Secondary #2	102 (96.2)	50 (94.3)	52 (98.1)

Data are presented as *n* (%). Data reflect all patients in the safety analysis set who received at least one dose of vericiguat 5 mg.
WHF, worsening heart failure.
Endpoint definitions: *Primary endpoint* = completion of 2-week study period with maximum 1-day interruption and without symptomatic hypotension of moderate to severe intensity. *Sensitivity analysis of primary endpoint* = completion of 2-week study period with maximum 2-day interruption and without symptomatic hypotension of moderate to severe intensity. *Secondary endpoint #1* = completion of 2-week study period without an adverse event related to study therapy. *Secondary endpoint #2* = completion of 2-week study period with continuous intake of study intervention or able to restart intervention after any temporary interruption.

or diuretics within the prior 2–4 weeks were excluded from VELOCITY.

In conclusion, in this prospective multinational study of patients with chronic HF with EF <45% who were well-treated with background GDMT, >9 of 10 patients safely tolerated initiation of vericiguat at a starting dose of 5 mg daily. Findings were generally consistent regardless of prior history of recent WHF. In the context of safety and tolerability data from prior vericiguat studies, the current data support a potential update in clinical guidance towards routine initiation of vericiguat at a starting dose of 5 mg, rather than 2.5 mg, among patients without recent hypotension.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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[Correction added on 03 June 2025, after first online publication: Author byline has been corrected to include "on behalf of the VELOCITY investigators" in this version.]

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