

ARTICLE

Vericiguat in combination with isosorbide mononitrate in patients with chronic coronary syndromes: The randomized, phase Ib, VISOR study

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Abstract

Vericiguat was developed for the treatment of symptomatic chronic heart failure (HF) in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event. Guidelines recommend long-acting nitrates, such as isosorbide mononitrate, for angina prophylaxis in chronic coronary syndromes (CCS), common comorbidities in HF. This study evaluated safety, tolerability, and the pharmacodynamic (PD) interaction between co-administered vericiguat and isosorbide mononitrate in patients with CCS. In this phase Ib, double-blind, multicenter study, patients were randomized 2:1 to receive vericiguat plus isosorbide mononitrate ($n = 28$) or placebo plus isosorbide mononitrate ($n = 13$). Isosorbide mononitrate was uptitrated to a stable dose of 60 mg once daily, followed by co-administration with vericiguat (uptitrated every 2 weeks from 2.5 mg to 5 mg and 10 mg) or placebo. Thirty-five patients completed treatment (vericiguat, $n = 23$; placebo, $n = 12$). Mean baseline- and placebo-adjusted vital signs showed reductions of 1.4–5.1 mmHg (systolic blood pressure) and 0.4–2.9 mmHg (diastolic blood pressure) and increases of 0.0–1.8 beats per minute (heart rate) with vericiguat plus isosorbide mononitrate. No consistent vericiguat dose-dependent PD effects were noted. The incidence of adverse events (AEs) was 92.3% and 66.7% in the vericiguat and placebo groups, respectively, and most were mild in intensity. Blood pressure and heart rate changes observed with vericiguat plus isosorbide mononitrate were not considered clinically relevant. This combination was generally well-tolerated. Concomitant use of vericiguat with isosorbide mononitrate is unlikely to cause significant AEs beyond those known for isosorbide mononitrate.

Trial registration number: Clinicaltrials.gov: NCT03255512.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Vericiguat is indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient intravenous diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated the impact of co-administration of vericiguat and long-acting nitrates. The combination of vericiguat with isosorbide mononitrate was generally well-tolerated, and the adverse event profile was in line with the mode of action of both drugs.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

There is limited experience with vericiguat in combination with long-acting nitrates and these data provide information to guide prescribers.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These data support that there is no clinically relevant pharmacodynamic interaction between vericiguat and the long-acting nitrate isosorbide mononitrate in patients with chronic coronary syndromes.

INTRODUCTION

Heart failure (HF) is a significant and growing public health concern that places a substantial burden not just on patients but also on healthcare systems worldwide.^{1,2} The complex physiology of HF means that three subtypes have been categorized according to ejection fraction: HF with preserved ejection fraction (HFpEF; left ventricular ejection fraction [LVEF] $\geq 50\%$); HF with mid-range ejection fraction (LVEF 40–49%); and HF with reduced ejection fraction (HFrEF; LVEF $< 40\%$).³

Approximately one in six patients with HFrEF develop worsening chronic HF (WCHF) within 18 months of diagnosis.⁴ Patients with WCHF exhibit progressive signs and symptoms of HF requiring intensification of therapy or hospitalization.⁴ Despite the availability of current HF therapies, the residual risk of WCHF, mortality, and re-hospitalization remains high.^{5,6}

Coronary artery disease (CAD) is a major risk factor for HF,⁷ and angina pectoris is a common symptom in patients with HFrEF and CAD.^{3,8} In the recently updated European Society of Cardiology (ESC) guidelines, patients with CAD have been categorized as having either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS) to reflect the different evolutionary phases of CAD.⁹ In the present report, the definition of CCS will be used henceforth when referring to patients with CAD in this trial. Long-acting nitrates, such as isosorbide mononitrate, are recommended as second-line therapy for angina prophylaxis in CCS when initial

therapy with a beta blocker or non-dihydropyridine calcium channel blocker is contraindicated or insufficient to manage symptoms.⁹

Soluble guanylate cyclase (sGC)-derived production of the molecular messenger cyclic guanosine monophosphate (cGMP) is essential for normal cardiac and vascular function.^{10–12} Owing to reduced nitric oxide (NO) bioavailability, the functionality of sGC is impaired in HF, resulting in a loss of cGMP production that may contribute to the progression of cardiovascular disease.^{11,13} Therefore, addressing the sGC impairment and deficiency in cGMP represents an untapped therapeutic approach for the treatment of WCHF.^{11,14} Vericiguat is an orally administered sGC stimulator developed for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring intravenous therapy.^{15–17}

Vericiguat and isosorbide mononitrate may be co-administered to patients with HF, but as they act on the same NO–sGC–cGMP pathway, it is important to understand their potential pharmacodynamic (PD) interactions. The phase Ib Vericiguat Nitroglycerin Clinical Interaction (VENICE) study (NCT02617550) investigated the co-administration of vericiguat with the short-acting nitrate nitroglycerin in patients with CAD.¹⁸ In this paper, we report the results from the phase Ib Vericiguat ISOsoRbide mononitrate interaction (VISOR) study (NCT03255512¹⁹; EudraCT number: 2016-005178-36). The study investigated the hemodynamic effects of vericiguat co-administered with isosorbide mononitrate in patients with CCS, and

whether concomitant administration would be well-tolerated without clinically significant adverse effects beyond those known for isosorbide mononitrate.

METHODS

VISOR was a phase Ib, multicenter, randomized, placebo-controlled, double-blind, group comparison study that enrolled patients with stable CCS with or without HF. The study was performed across six study centers in Germany (Table S1). At each center, the principal investigator was responsible for the study. Participants gave written informed consent to participate before entering the study. The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonisation guideline E6: Good Clinical Practice. The protocol and all amendments were reviewed and approved by each study site's Independent Ethics Committee before the start of the study.

Study population

Only subjects with CCS (with or without HF) aged between 30 and 80 years were eligible for the study if they fulfilled all inclusion criteria and none of the exclusion criteria (Table S2). Subjects must have been clinically stable for at least 3 months prior to the first screening examination, and existing chronic medication had to have been stable for at least 2 months before initiating treatment and during the conduct of the study. The use of phosphodiesterase type 5 (PDE5) inhibitors (from 14 days before screening to study end), or other nitrate medications or

riociguat (both from 3 months before screening to study end), was not permitted.

At the end of the last screening visit, eligible patients were sequentially assigned to a unique number in ascending order. Each number was randomly assigned to a treatment (active or placebo, ratio 2:1) according to computer-generated randomization envelopes provided by the Bayer Randomization Management Department.

Study design

A detailed study schedule is shown in Figure 1. Patients were randomized to vericiguat plus isosorbide mononitrate ($n = 28$) or placebo plus isosorbide mononitrate ($n = 13$). In the run-in phase, patients received isosorbide mononitrate 30 mg extended-release tablets once daily (q.d.) for 1 week and 60 mg extended-release tablets q.d. for 1 week, with the option to reduce back to 30 mg if 60 mg was not tolerated during the titration phase until day -1 . The main treatment phase included co-administration of isosorbide mononitrate 60 mg, administered 30 min before breakfast, with vericiguat/placebo, administered after breakfast. The protocol specified continuation of the study with administration of isosorbide mononitrate 30 mg q.d. in those who could not tolerate the higher dose of 60 mg. The dose of oral vericiguat was uptitrated from 2.5 mg q.d. to 5 mg q.d. and 10 mg q.d., with each dose administered for 14 ± 3 days.

Study objectives

The primary objective was to evaluate the PD drug–drug interaction between isosorbide mononitrate and vericiguat by monitoring the effects of their co-administration

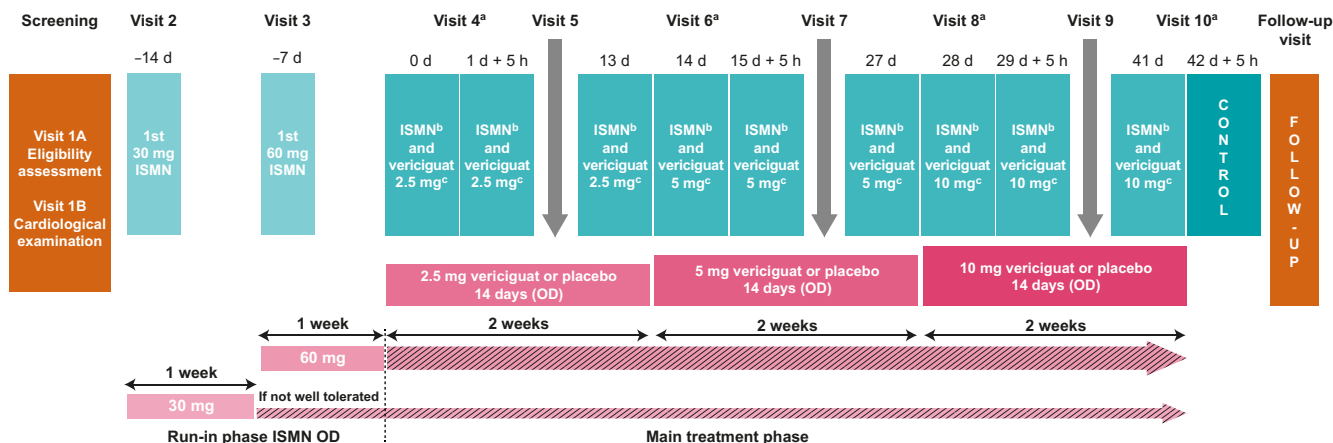


FIGURE 1 VISOR study design. ^aIn-house phases; ^b30 min before breakfast; ^cAfter breakfast. Visits 5, 7, and 9 were ambulatory visits at day 7, day 21, and day 35 ± 2 days, respectively. ER, extended release; ISMN, isosorbide mononitrate; OD, once daily

on blood pressure (BP) and heart rate (HR). The secondary objective was to evaluate the safety and tolerability of the co-administration of isosorbide mononitrate and vericiguat.

Study end points

Figure 2 shows the time points at which BP and HR measurements were taken relative to isosorbide mononitrate and vericiguat/placebo administration. Supine BP and HR were measured regularly from 45 min before isosorbide mononitrate administration until 255 min after vericiguat/placebo administration. Hemodynamic measurements were performed after 2 min in the upright position at given time points to test orthostatic tolerability.

Safety and tolerability assessments included the number of patients with adverse events (AEs) and serious AEs (SAEs), clinically relevant findings in vital signs, standard safety laboratory parameters, clinical measurements, and electrocardiographic and echocardiographic measurements (e.g., interventricular septal wall thickness, posterior wall thickness, left ventricular diameter, left ventricular volume, and ejection fraction).

Statistical analysis

A sample size of 24 patients (vericiguat, $n = 16$; placebo, $n = 8$) has 91% power to detect a difference of 10 mmHg isosorbide mononitrate-induced decrease in systolic BP (SBP), assuming an isosorbide mononitrate-induced decrease in SBP of 5 mmHg after placebo treatment. The common SD was assumed to be 6.65 mmHg, in line with a previous phase I study in healthy volunteers²⁰ (EudraCT number: 2012-000953-30) after multiple doses of vericiguat 10 mg q.d. for all SBP measurements within a 4-h time window after dosing, including a hemodynamic profile. This sample size estimation is applicable for a 1-way analysis of covariance (ANCOVA) with significance level $\alpha = 0.05$ and an unbalanced 1:2 randomization in favor of the vericiguat arm. The calculation was conducted using SAS 9.2 PROC POWER. No adjustment for multiplicity was performed.

All variables were analyzed by descriptive statistical methods. The number of data available and missing data, mean, SD, minimum, median, and maximum were calculated for metric data. Frequency tables were generated for categorical data. All planned statistical analyses were exploratory. All patients who received at least one dose of study medication (vericiguat, isosorbide mononitrate, or placebo) were included in the safety analysis set. All patients

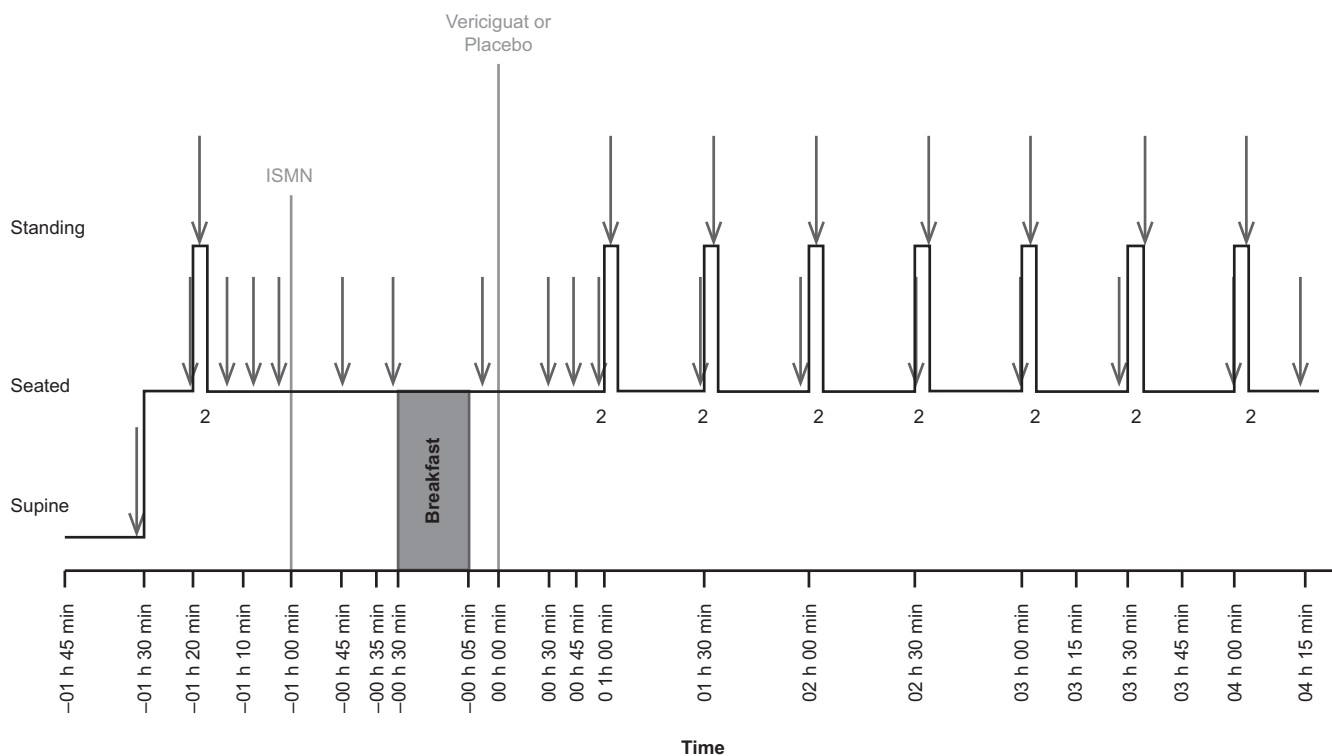


FIGURE 2 Hemodynamic profile time points. Axis is time in minutes. Black arrows represent time points at which hemodynamic measurements were taken. ISMN, isosorbide mononitrate

who received at least one dose of study medication and for whom evaluable PD data were available were included in the PD analysis set (PDS). Missing data were not replaced.

Changes in seated SBP, diastolic BP (DBP), and HR after isosorbide mononitrate dose of the vericiguat treatment group were analyzed assuming normally distributed data using ANCOVA, including treatment (vericiguat plus isosorbide mononitrate or placebo plus isosorbide mononitrate), time, and treatment-by-time effects with the baseline value of SBP, DBP, or HR as covariates. The analysis was conducted for data from hemodynamic profiles on each profile day (days 0, 13, 14, 27, 28, and 41). Point estimates (least squares mean [LSM]) and exploratory 90% confidence intervals (CIs) for the difference between vericiguat plus isosorbide mononitrate and placebo plus isosorbide mononitrate were calculated. In addition, two ANCOVAs, one including treatment (vericiguat 2.5 mg plus isosorbide mononitrate and vericiguat 5 mg plus isosorbide mononitrate), time, and treatment-by-time effects, and the second including treatment (vericiguat 2.5 mg

plus isosorbide mononitrate and vericiguat 10 mg plus isosorbide mononitrate), time, and treatment-by-time effects, both with the baseline value of SBP, DBP, or HR as covariates, were performed. Based on these ANCOVAs, LSM and exploratory 90% CIs for the difference between vericiguat 5 mg plus isosorbide mononitrate on day 27 versus vericiguat 2.5 mg plus isosorbide mononitrate on day 13, and for the difference between vericiguat 10 mg plus isosorbide mononitrate on day 41 versus vericiguat 2.5 mg plus isosorbide mononitrate on day 13 were calculated.

RESULTS

Patient disposition and baseline characteristics

Across six centers in Germany between August 17, 2017, and February 7, 2018, a total of 59 patients with CCS were enrolled and screened. Of the 59 individuals enrolled, 41

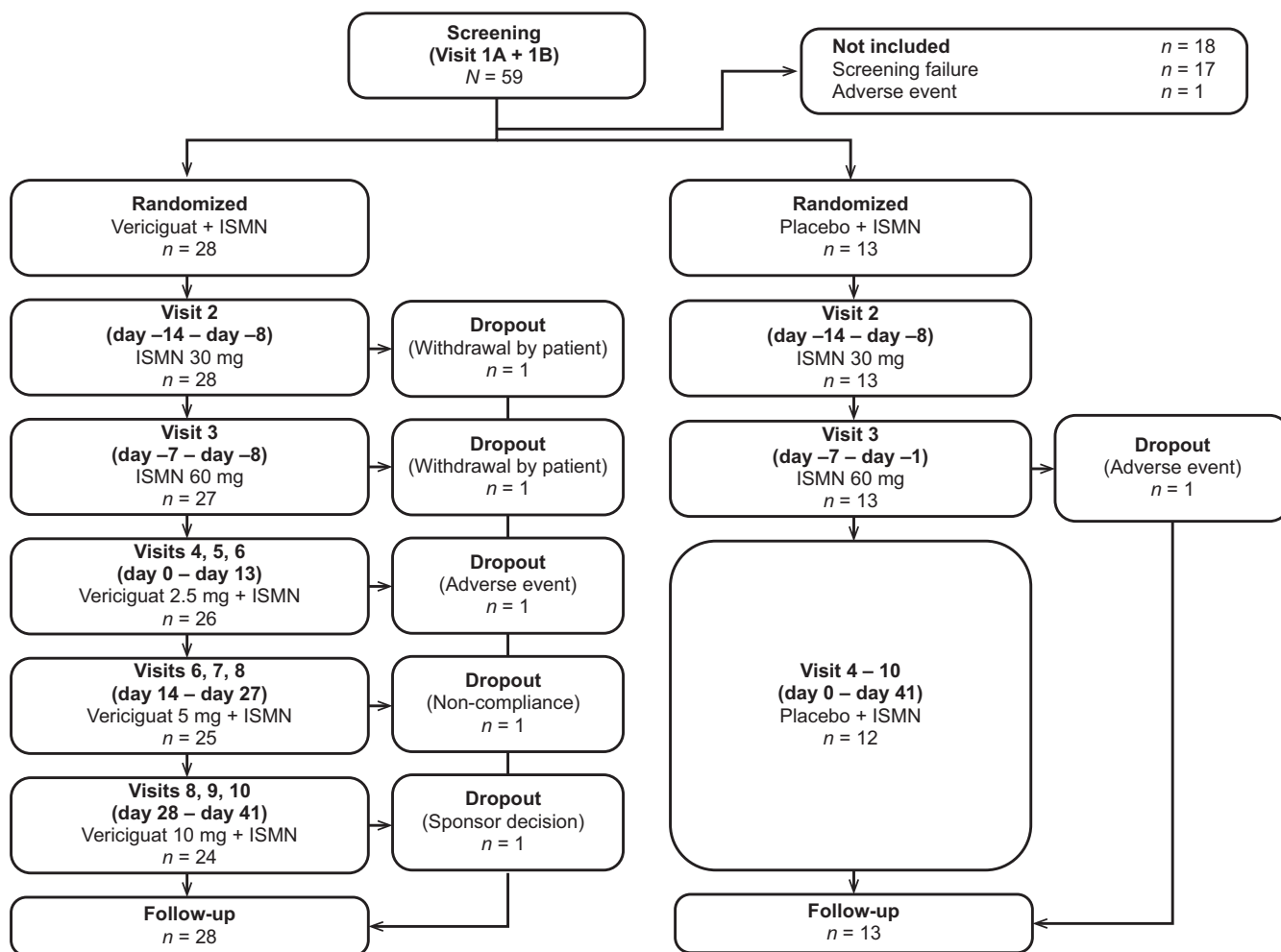


FIGURE 3 Patient disposition. ISMN, isosorbide mononitrate

patients (36 men and 5 women) aged 49–79 years (mean 64.6 years) were randomized to treatment with either vericiguat plus isosorbide mononitrate ($n = 28$) or placebo plus isosorbide mononitrate ($n = 13$). Thirty-five patients completed the study ($n = 23$ and $n = 12$ for the vericiguat and placebo groups, respectively; [Figure 3](#)). Of the six patients who did not complete the study, three dropped out during the run-in phase (one owing to AEs and two withdrew consent for personal reasons unrelated to study treatment), and three during the main treatment phase (all were in the vericiguat group: one discontinued owing to an AE, one owing to noncompliance with the study drug regimen, and one based on a sponsor decision).

All 41 patients were included in the safety analysis set and PDS. Baseline demographics and disease characteristics were generally comparable across study treatment groups ([Table 1](#)). All patients were able to tolerate a daily dose of isosorbide mononitrate 60 mg from day -7 to day 41, without reducing the dose back to 30 mg.

Prior and concomitant therapy

Baseline drug use was balanced between the groups ([Table 1](#)). The most common antihypertensive drugs taken were angiotensin-converting enzyme inhibitors, taken by 39 patients (95.1%), and beta-blocking agents, taken by 35 patients (85.4%).

Pharmacodynamic interaction between isosorbide mononitrate and vericiguat

Mean supine SBP and DBP before the start of the run-in period on day -14 were 130.7 ± 13.2 mmHg and 74.9 ± 8.9 mmHg, respectively, for the vericiguat group and 126.1 ± 10.6 mmHg and 69.7 ± 7.0 mmHg, respectively, for the placebo group. The mean values were generally around 5 mmHg higher in the vericiguat group than in the placebo group throughout the study.

Mean decreases in SBP and DBP were 0.6–14.3 mmHg and 2.4–9.9 mmHg, respectively, ~ 1 h after isosorbide mononitrate administration. An increase in HR was also noted in this period. The effects were similar in the vericiguat and placebo groups. Vericiguat had only a slightly additive BP-lowering effect: mean maximum seated SBP decreases of 25.7–32.2 mmHg in the vericiguat group and 21.0–30.2 mmHg in the placebo group were observed; mean maximum seated DBP decreases of 18.4–22.3 mmHg in the vericiguat group and 14.0–20.0 mmHg in the placebo group were noted.

In the exploratory analysis of differences between the vericiguat and placebo groups in seated SBP and DBP after isosorbide mononitrate administration, all point

TABLE 1 Baseline demographics (safety analysis set)

	ISMN + placebo ($n = 13$)	ISMN + vericiguat ($n = 28$)
Age, years (SD)	64.2 (6.7)	64.8 (7.1)
Female, n (%)	0 (0.0)	5 (17.9)
White race, n (%)	13 (100)	28 (100.0)
Weight, kg	82.6 (15.2)	87.4 (14.3)
Height, cm	173.5 (3.2)	174.8 (7.5)
Body mass index, kg/m ²	27.4 (4.4)	28.5 (3.7)
Sitting SBP, ^a mmHg	131.8 (13.4)	130.7 (13.7)
Sitting DBP, ^a mmHg	77.9 (7.9)	78.3 (8.6)
Sitting HR, ^a bpm	61.0 (8.2)	65.6 (8.6)
Medical history		
Cardiovascular disease, n (%)	12 (92.3)	28 (100.0)
CAD	10 (76.9)	26 (92.9)
Chronic HF	0 (0.0)	2 (7.1)
Acute MI	5 (38.5)	11 (39.3)
MI	5 (38.5)	14 (50.0)
Treatment at randomization, n (%)		
ACE inhibitors	12 (92.3)	27 (96.4)
Antithrombotic agents	13 (100.0)	27 (96.4)
Beta-blockers	12 (92.3)	23 (82.1)
Calcium channel blockers	2 (15.4)	6 (21.4)
Cardiac therapy	3 (23.1)	2 (7.1)
Diuretics	3 (23.1)	8 (28.6)
Lipid-lowering agents	13 (100.0)	25 (89.3)
Vasoprotectives	0 (0.0)	3 (10.7)

Note: All values are arithmetic mean (SD) unless otherwise specified.

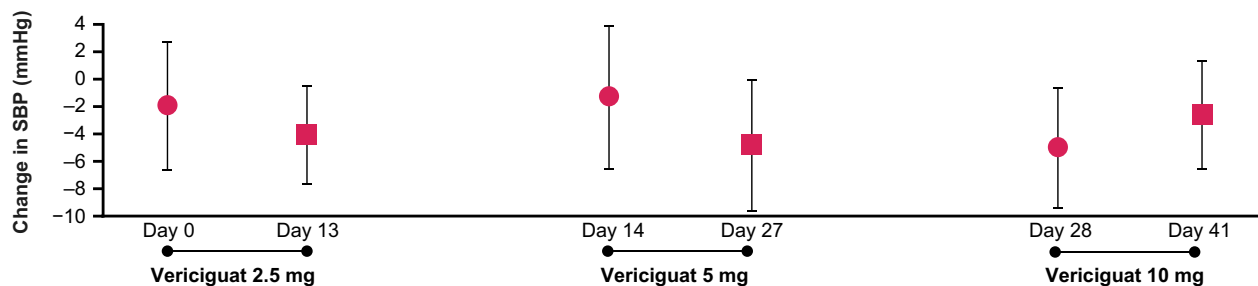
All patients included in the safety analysis set started with a daily dose of isosorbide mononitrate 30 mg, followed by a daily dose of isosorbide mononitrate 60 mg from day -7 to day 41.

Abbreviations: ACE, angiotensin-converting enzyme; CAD, coronary artery disease; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; ISMN, isosorbide mononitrate; MI, myocardial infarction; SBP, systolic blood pressure.

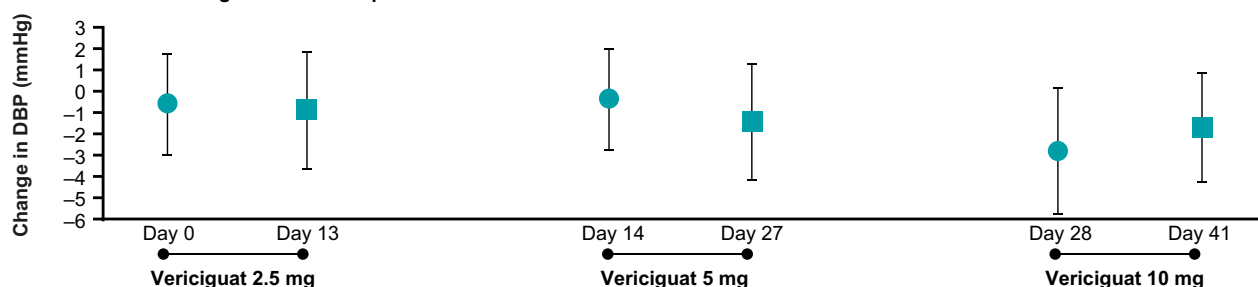
^aScreening measurement.

estimates for the differences were negative, with SBP differences ranging between -1.4 and -5.1 mmHg, and DBP differences ranging between -0.4 and -2.9 mmHg (PDS; [Figure 4](#), [Table S3](#)). Differences between the vericiguat and placebo groups were only observed for SBP at day 13 (vericiguat 2.5 mg at steady-state), day 27 (vericiguat 5 mg at steady-state), and day 28 (first day of vericiguat 10 mg administration), as for these estimates, the 90% CIs were completely below zero. Point estimates for the difference with vericiguat versus placebo on these profile days ranged between -1.4 mmHg and -5.1 mmHg. For

(a) Difference in SBP of vericiguat + ISMN vs. placebo + ISMN with 90% CIs



(b) Difference in DBP of vericiguat + ISMN vs. placebo + ISMN with 90% CIs



(c) Difference in HR of vericiguat + ISMN vs. placebo + ISMN with 90% CIs

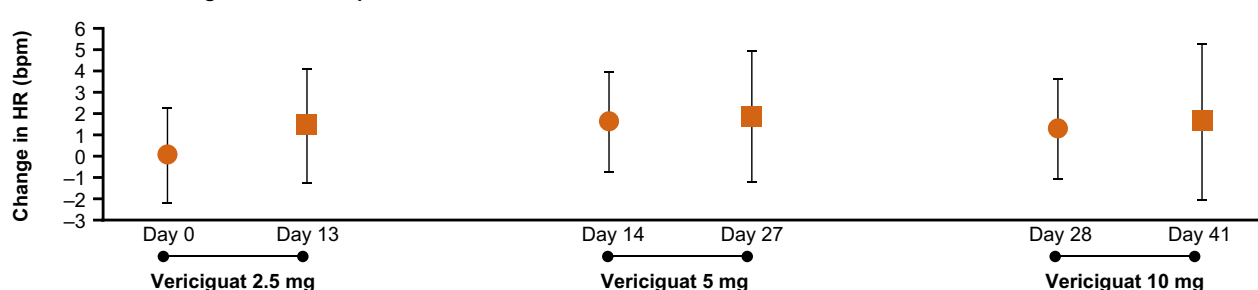


FIGURE 4 Results of the ANCOVA. Least squares mean difference ($\pm 90\%$ CI) in hemodynamic parameter between vericiguat + ISMN and placebo + ISMN: (a) SBP, (b) DBP, and (c) HR. Circles indicate first dose; squares indicate steady-state. ANCOVA, analysis of covariance; CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; ISMN, isosorbide mononitrate; SBP, systolic blood pressure

SBP on day 0 (first dose of vericiguat 2.5 mg), day 14 (first dose of vericiguat 5 mg), and day 41 (vericiguat 10 mg at steady-state), and for all DBP profiles, no differences with vericiguat versus placebo were indicated.

An additional ANCOVA comparing the three vericiguat doses at steady-state (day 13, 2.5 mg; day 27, 5 mg; and day 41, 10 mg) indicated a 2.4 mmHg higher SBP with vericiguat 5 mg than with vericiguat 2.5 mg at steady-state, and a 2.0 mmHg lower DBP with vericiguat 10 mg compared with vericiguat 2.5 mg.

Mean maximum increases in HR were 10.3–14.2 beats per minute (bpm) with vericiguat and 9.6–13.6 bpm with placebo. There were no differences in HR with vericiguat compared with placebo in the explorative ANCOVA (point estimates for differences ranging from 0 to 1.8 bpm were noted). However, increases in HR of 2.1 bpm with vericiguat 5 mg and 1.4 bpm with vericiguat 10 mg relative to vericiguat 2.5 mg were observed.

Safety and tolerability

In total, 37 patients (90.2%) had at least one treatment-emergent AE (TEAE; [Table 2](#)): 29 patients (70.7%) during treatment with isosorbide mononitrate alone in the run-in phase (overall population), and 24 patients (92.3%) in the vericiguat group and eight patients (66.7%) in the placebo group in the main treatment phase.

Under blinded conditions, TEAEs were assessed as related to vericiguat by the investigator in 21 patients (51.2%) in total; in 15 patients (57.7%) in the vericiguat group and six patients (50.0%) in the placebo group. TEAEs assessed as related to isosorbide mononitrate by the investigator were reported for 26 patients (63.4%) overall; 21 patients (51.2%) in the isosorbide mononitrate run-in phase, 14 patients (53.8%) in the vericiguat group, and five patients (41.7%) in the placebo group in the main treatment phase.

TABLE 2 Overall summary of number of patients with TEAEs (safety analysis set)

	ISMN alone (<i>n</i> = 41)	ISMN + placebo (<i>n</i> = 12)	ISMN + vericiguat (<i>n</i> = 26)
Any AE, <i>n</i> (%)	29 (70.7)	8 (66.7)	24 (92.3)
Vericiguat/placebo-related AE	0 (0.0)	6 (50.0)	15 (57.7)
ISMN-related AE	21 (51.2)	5 (41.7)	14 (53.8)
Procedure-related AE	3 (7.3)	2 (16.7)	4 (15.4)
AE-related deaths, <i>n</i> (%)	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE, <i>n</i> (%)	0 (0.0)	0 (0.0)	1 (3.8)
Vericiguat/placebo-related SAE	0 (0.0)	0 (0.0)	0 (0.0)
ISMN-related SAE	0 (0.0)	0 (0.0)	0 (0.0)
Procedure-related SAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations			
Of vericiguat/placebo due to AE	0 (0.0)	0 (0.0)	1 (3.8)
Of ISMN due to AE	2 (4.9)	0 (0.0)	1 (3.8)
Of vericiguat/placebo due to SAE	0 (0.0)	0 (0.0)	0 (0.0)
Of ISMN due to SAE	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; ISMN, isosorbide mononitrate; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

In 21 patients (51.2%), TEAEs with a maximum intensity of mild were reported; for 10 patients (24.4%), TEAEs with a maximum intensity of moderate were reported; and in six patients (14.6%), TEAEs with a maximally severe intensity were documented (for 2 patients, these were considered related to vericiguat [vericiguat group, *n* = 1; placebo group, *n* = 1], and for 4 patients, these were considered related to isosorbide mononitrate [isosorbide mononitrate run-in, *n* = 2; vericiguat group, *n* = 1; placebo group, *n* = 1]).

The most common AE was headache, occurring in 18 patients (43.9%) overall. The highest incidence of headache was seen after the start of the run-in treatment with isosorbide mononitrate 30 mg (day -14 to day -7), where it was reported in more than one-third of patients. Despite the introduction and uptitration of vericiguat every 2 weeks, the incidence of headache decreased following the course of treatment.

During the uptitration of vericiguat from 2.5 mg to 5 mg and to 10 mg, the overall incidence of TEAEs decreased from 69.2% to 56.0% and to 45.8%, respectively, whereas in the placebo group, rates of 33.3%, 25.0%, and 41.7% were observed for the three respective 2-week periods.

Two SAEs (ACS on day 6, and angina pectoris on day 8 after randomization) occurred in one patient (vericiguat group). Neither SAE was considered related to treatment with vericiguat or isosorbide mononitrate.

Of the six patients who did not complete the study, three discontinued during the run-in phase: one owing to an AE (intermittent headache of severe intensity) under treatment with isosorbide mononitrate 30 mg,

and two withdrew consent (one under treatment with isosorbide mononitrate 30 mg, and one under treatment with isosorbide mononitrate 30 mg). Of the two patients who withdrew consent, one experienced nausea and vomiting of mild intensity under treatment with isosorbide mononitrate 60 mg. Three patients discontinued during the main treatment phase (all were in the vericiguat group). One discontinued owing to an AE (angina pectoris during exertion) prior to intake of isosorbide mononitrate 60 mg and vericiguat 2.5 mg on day 10, which resolved without further treatment. No relationship to study drug was seen; however, the investigator decided to stop further treatment owing to the reported event. A second patient discontinued at the request of the sponsor, in liaison with the investigator, owing to poor BP control and the principal investigator's decision to split dosing of the antihypertensive drugs. This patient had experienced one AE assessed as related to vericiguat/placebo (headache of mild intensity), which occurred 2 days prior to discontinuation and resolved on the same day. The third discontinuation during the main treatment phase was a result of noncompliance with intake of study medication.

Laboratory parameters

There were no signs or trends for an impact of vericiguat or isosorbide mononitrate on any of the observed safety laboratory parameters. In general, the means for all laboratory parameters remained within the normal ranges.

Other safety parameters

A symptomatic BP drop with a SBP value below 90 mmHg with orthostatic intolerance of severe intensity was only seen for one subject during the uptitration of isosorbide mononitrate in the run-in phase of the study. For several other patients, seated and standing SBP values below 90 mmHg were commonly seen during the hemodynamic tests on profile days, but no further clinical symptoms were reported. These nonsymptomatic decreases were seen in both groups.

No effects of vericiguat or isosorbide mononitrate on any measured electrocardiographic parameter were revealed.

DISCUSSION

Results from the VISOR study showed that, in patients with CCS, the co-administration of vericiguat plus isosorbide mononitrate was found to be generally well-tolerated, and no clinically relevant PD differences between the vericiguat and placebo groups were revealed.

Co-administration of vericiguat with isosorbide mononitrate led to mean baseline- and placebo-adjusted reductions in SBP of up to 5.1 mmHg and in DBP of up to 2.9 mmHg, and an increase in HR of up to 1.8 bpm. However, based on the lack of associated symptoms, these changes were not considered to be clinically meaningful. When comparing the three vericiguat doses at steady-state, SBP was 2.4 mmHg higher with vericiguat 5 mg than with vericiguat 2.5 mg, and DBP was 2.0 mmHg lower with vericiguat 10 mg than with vericiguat 2.5 mg. No consistent vericiguat dose-dependent PD effects could be determined; the variable effects may have been related to the adaptation of patients to the combined vasodilatory effects of isosorbide mononitrate and vericiguat, especially at day 41, at which there was no difference between vericiguat 10 mg at steady-state and placebo. In addition, no differences in HR were noted between the vericiguat and placebo groups, and there was no trend toward an increase in HR with the uptitration of vericiguat from 5 mg to 10 mg. This could also be explained by tolerance to the ongoing isosorbide mononitrate treatment.

The BP decrease and HR increase observed during the standing hemodynamic profiles can be primarily attributed to the mode of action of isosorbide mononitrate and the standing BP procedure itself. As therapeutic doses of isosorbide mononitrate are known to cause hypotension and tachycardia,²¹ the results here are fully aligned with the assumption that the effects of vericiguat and isosorbide mononitrate on BP and HR are not more than additive, and the trends observed are related to the known effects of isosorbide mononitrate alone. The additional

observed changes caused by vericiguat were in a range that cannot be considered clinically relevant.

The most common TEAE considered to be related to isosorbide mononitrate in this study was headache. During the run-in phase with isosorbide mononitrate 30 mg, more than one-third of the patients experienced headache, tension headache, or dizziness. This can be reasonably related to its mode of action and is in line with the AEs already commonly known for isosorbide mononitrate.²¹ However, headache incidence decreased with the duration of treatment, again indicating increasing tolerance to isosorbide mononitrate.

The most commonly observed AEs for subjects receiving vericiguat were related to its pharmacological mode of action: vasodilation and decrease in peripheral resistance, accompanied by hypotension and a counter-regulatory increase in HR. However, the incidence of orthostatic hypotension in the vericiguat group was comparable to that in the placebo group and, thus, vericiguat in addition to isosorbide mononitrate was not associated with an increased risk of orthostatic hypotension. In most cases, the occurrences of hypotension could be controlled, did not require any specific therapy, and did not result in an increase in study drug discontinuation. In addition, no symptomatic decreases in BP with systolic values below 90 mmHg or symptoms of hypotension were observed with combined treatment.

Based on the findings from this study, vericiguat in combination with isosorbide mononitrate may exert therapeutic effects in patients with CCS without clinically relevant changes in BP and HR. However, whether these benefits may transfer to a broader, more severely ill population still needs to be established. There is currently limited experience with concomitant use of vericiguat and long-acting nitrates in patients with HF. Vericiguat has been evaluated in phase II studies in patients with symptomatic worsening HFrEF (SOCRATES-REDUCED; NCT01951625)²² and HFpEF (SOCRATES-PRESERVED; NCT01951638²³ and VITALITY-HFpEF; NCT03547583),^{24,25} and in the phase III VICTORIA trial (NCT02861534) in patients with symptomatic chronic HF (and LVEF <45%) who had been receiving guideline-based medical therapy and experienced a recent worsening HF event for which hospitalization or urgent treatment was warranted.¹⁵

The study population in VICTORIA included patients up to 6 months postdischarge to cover a more representative population of patients spanning a range of worsening HF, from those currently stabilized after hospitalization or intravenous diuretic treatment to more chronic stable patients after their most recent HF event.²⁶ Long-acting nitrates and other NO donors were excluded as concomitant medications in the VICTORIA study, as there is limited experience with concomitant use of vericiguat and

long-acting nitrates in patients with HF. PDE5 inhibitors were also excluded as concomitant medications in the VICTORIA study, as co-administration of vericiguat and PDE5 inhibitors, such as sildenafil, is not recommended. However, short-acting nitrates, such as sublingual nitroglycerin spray, were permitted for symptomatic relief of acute angina, as this had previously been demonstrated to be generally well-tolerated in patients with HF.¹⁶

The limitations of the VISOR study primarily relate to the small size of the study population, as there were only 35 patients who completed the study. Some slight imbalances between the groups were noted before the start of vericiguat/placebo treatment; indeed, mean supine SBP and DBP values on day -14 were ~5 mmHg higher in the vericiguat group than in the placebo group, although this was generally maintained throughout the study. Both inter- and inpatient variability may have contributed to the overall variability. In clinical trials with large sample sizes, the probability of differences in baseline characteristics may be lower. Although this study was small, the statistical design and analysis methods were optimized to address the hypothesis and the specific study population. To minimize bias, double-blind follow-up was performed; this included assessment of TEAEs by the investigator under blinded conditions.

In conclusion, overall, concomitant treatment with vericiguat and isosorbide mononitrate led to reductions in SBP and DBP, and an increase in HR, but these changes were not considered to be clinically relevant for individual patients, owing to a lack of associated symptoms. There was no obvious dose-dependent effect on BP or HR resulting from the up-titration of vericiguat compared with placebo. The combination of vericiguat with isosorbide mononitrate was generally well-tolerated, with no significant AEs beyond those known for isosorbide mononitrate, and the observed AE profile was in line with the mode of action of both drugs. These data support that there is no clinically relevant PD interaction between vericiguat and the long-acting nitrate isosorbide mononitrate in patients with CCS. In patients with HF, concomitant use with short-acting nitrates was well-tolerated, but there is limited experience with long-acting nitrates.¹⁶

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CONFLICT OF INTEREST

M.B., C.B., and D.S.-B. are employees of Bayer and may own stock in the company. J.H. is an employee of Bayer. G.M. and D.T. received speakers' fees and honoraria for advisory boards from Bayer. N.W. received travel grants from Bayer. N.B. is an employee of Chrestos Concept GmbH & Co. KG, which received funding for this analysis from Bayer AG. M.G. is a former contractor for Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. H.-D.D. has received institutional payment as an investigator and personal honoraria for advisory boards from Bayer. M.K. is supported by a Clinician Scientist Professorship Grant from the Else Kroener-Fresenius-Foundation and reports both, personal fees and grant support, from Daiichi-Sankyo, Adrenomed, Spingotec, and Vifor Pharma, all outside the submitted work. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

M.B., H.-D.D., F.D., G.M., N.W., M.K., N.B., D.S.-B., M.G., J.H., and C.B. wrote the manuscript. M.B., H.-D.D., D.T., F.D., G.M., N.W., M.K., N.B., M.G., and C.B. designed the research. H.-D.D., D.T., F.D., G.M., N.W., and M.K., performed the research. N.B., D.S.-B., M.G., J.H., and C.B. analyzed the data.

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SUPPORTING INFORMATION

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