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ORIGINAL RESEARCH ARTICLE

Vericiguat: A Randomized, Phase Ib, Placebo-Controlled, Double-Blind, QTc Interval Study in Patients with Chronic Coronary Syndromes

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Abstract

Background Vericiguat is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event.

Objective To investigate the effects of vericiguat on QT interval in patients with chronic coronary syndromes (CCS).

Methods This was a randomized, phase Ib, placebo-controlled, double-blind, double-dummy, multicenter study. Vericiguat once daily was up-titrated from 2.5 mg to 5 mg and then to 10 mg (treatments A, B, and C) at 14-day intervals. Positive control was moxifloxacin 400 mg (single dose on day 8 or day 50; placebo on other days [treatment D]). We evaluated the placebo-adjusted change from baseline of the Frederica-corrected QTc interval (QTcF), pharmacokinetics, safety, and tolerability of vericiguat.

Results In total, 74 patients with CCS, with mean (standard deviation) age 63.4 (8.0) years, were included and 72 patients completed the study. At each timepoint up to 7 h after administration, mean placebo-corrected change in QTcF from baseline was < 6 ms and the upper limit of the two-sided 90% confidence interval of the mean was below the 10-ms threshold for clinical relevance. Moxifloxacin confirmed the assay sensitivity. Median time of maximum concentration of vericiguat was 4.5 h post-dose. The adverse event profile of vericiguat was consistent with its mechanism of action, and the findings did not indicate any safety concerns.

Conclusions As part of an integrative risk assessment, this study demonstrated no clinically relevant corrected QT prolongation with vericiguat 10 mg once daily at steady state.

Clinical Trial Registration ClinicalTrials.gov number, NCT03504982.

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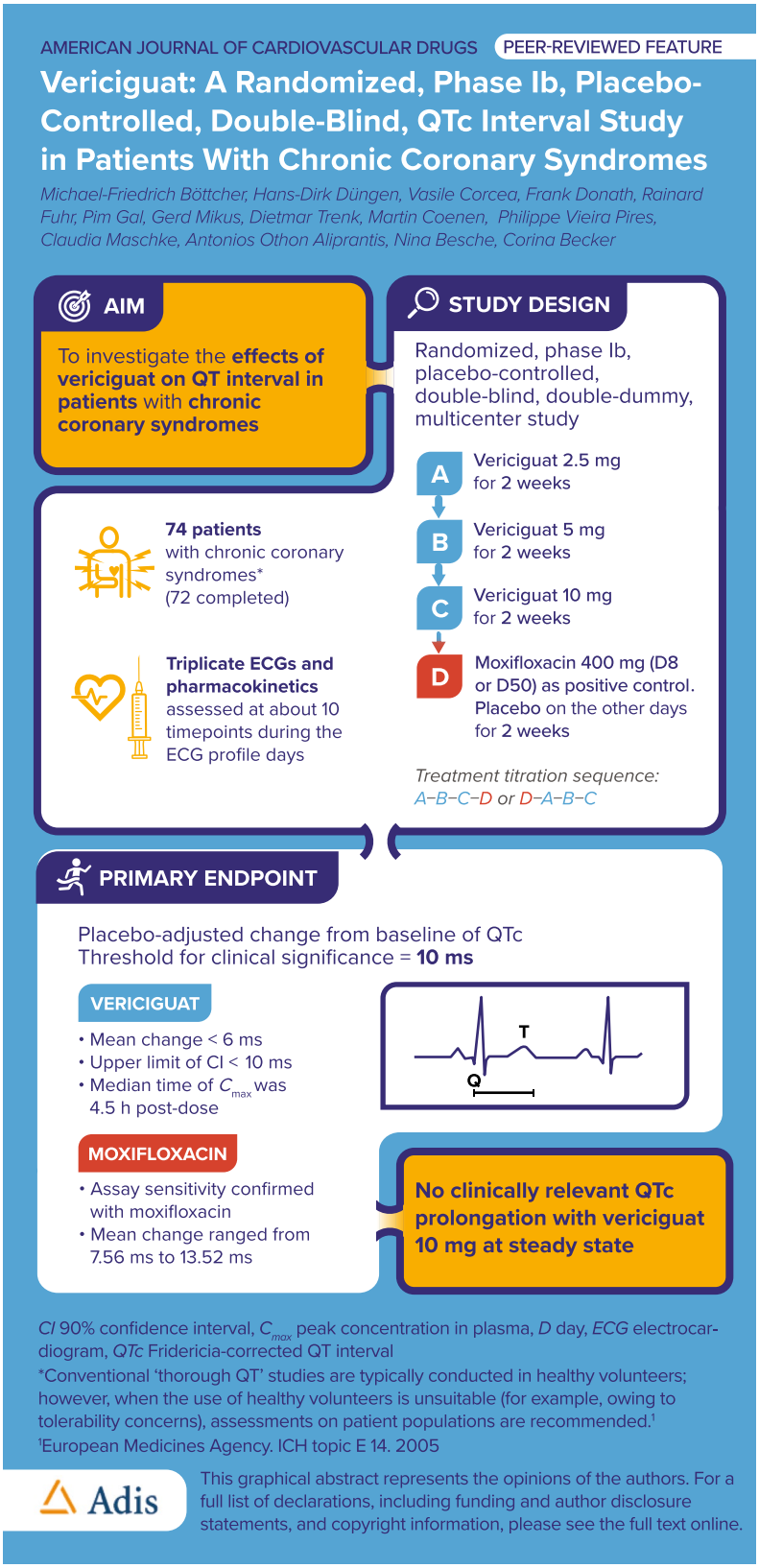
Graphical Abstract



Plain Language Summary

Vericiguat is approved for treating worsening heart failure with reduced ejection fraction. As part of the safety evaluation of vericiguat, this study assessed its effect on the QT interval of the electrocardiogram. An electrocardiogram measures electrical activity of the heart. The QT interval is the time from the start of the Q wave to the end of the T wave. A longer than normal QT interval indicates an increased chance for abnormal heart rhythms. Usually, a QT study is conducted at high doses in healthy volunteers. Previous studies indicated that high doses of vericiguat may cause increased changes in blood pressure in healthy volunteers. Therefore, this study was performed in patients at a normal therapeutic dose. Patients with chronic coronary syndromes were enrolled rather than patients with heart failure with reduced ejection fraction, because they have fewer electrocardiogram abnormalities. The starting dose of vericiguat was 2.5 mg once daily, and the dose was increased to 5 mg and then to 10 mg at 14-day intervals. Placebo was tested for comparison and moxifloxacin (400 mg), a drug known to increase the QT interval, was tested to confirm that the study could detect a change in the QT interval. An increase in the QT interval of more than 10 ms was considered clinically relevant. Of 74 patients included, 72 completed the study. At each timepoint (up to 7 h after dosing), the difference between the QT change for vericiguat and placebo was less than 10 ms; therefore, vericiguat does not prolong the QT interval to a clinically relevant extent.

Key Points

Guidelines recommend that the safety evaluation of a new pharmaceutical agent should include characterization of its effects on the heart rate-corrected QT interval to assess its proarrhythmic potential.

Vericiguat is a soluble guanylate cyclase stimulator for the treatment of adult patients with symptomatic chronic heart failure with reduced left ventricular ejection fraction who are stabilized after a recent decompensation event requiring intravenous therapy.

A dedicated corrected QT study of vericiguat at therapeutic doses was conducted in patients with chronic coronary syndromes, in line with recommendations for corrected QT evaluations when 'thorough QT' studies in healthy volunteers are inappropriate.

Vericiguat was not associated with a clinically relevant corrected QT prolongation.

This study forms part of an integrative corrected QT assessment that indicates a low proarrhythmic potential of vericiguat.

1 Introduction

Vericiguat is a soluble guanylate cyclase stimulator developed for the treatment of adult patients with symptomatic chronic heart failure (HF) with reduced left ventricular ejection fraction (HFrEF) who are stabilized after a recent decompensation event requiring intravenous therapy [1, 2]. The European Society of Cardiology recommends that vericiguat may be considered in patients with HFrEF in New York Heart Association class II–IV who have had worsening HF despite standard treatment [3]. This recommendation is based on the findings of the pivotal phase III study VICTORIA, which established the clinical benefits of vericiguat in this patient group; vericiguat titrated up to 10 mg reduced the primary composite outcome of death from cardiovascular causes or first hospitalization for HF (hazard ratio, 0.90) in patients with HF and ejection fraction (EF) < 45% who had a recent worsening HF event [4].

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH E14 guideline) specifies that safety evaluation of a new pharmaceutical agent should include characterization of its effects on the heart rate-corrected QT (QTc) interval [5]. Prolongation of the QTc interval on the electrocardiogram (ECG) is associated with increased susceptibility to cardiac arrhythmias, most notably torsade de pointes [5, 6]. A negative study is one in which the upper bound of the 95% one-sided confidence interval (CI) for the largest time-matched mean effect of the drug on the QTc interval is below 10 ms [5].

Guidelines on QTc studies recommend evaluation of investigational drugs at higher concentrations than the anticipated therapeutic dose. These conventional 'thorough QT' studies are typically conducted in healthy volunteers; however, when the use of healthy volunteers is unsuitable (e.g., owing to tolerability concerns), assessments on patient populations are recommended [5].

In this article, we report the findings of a study on the effect of vericiguat on QTc prolongation. The aim of the study was to evaluate any potential risk of QTc prolongation following administration of oral vericiguat 2.5 mg, 5 mg, and 10 mg once daily at the initiation of each dose level and at steady state, using a placebo-adjusted change from baseline of the Fridericia-corrected QT (QTcF) interval. As vericiguat at supratherapeutic exposures may cause exaggerated orthostatic reactions in healthy volunteers [7], we conducted a dedicated QTc study using the therapeutic

range of vericiguat in patients, in line with QTc study recommendations for special cases when studies in healthy volunteers are inappropriate [8]. Current guidelines categorize coronary artery disease as either acute or chronic coronary syndromes (CCS) [9]. We chose to conduct the study in patients with CCS because this population was expected to be more hemodynamically stable, with fewer confounders, such as pacemakers, atrial fibrillation, and left bundle branch block, than the worsening HF population studied in VICTORIA. Moreover, it is reasonable to assume that the relationship between vericiguat concentration and QTc is similar between this study population and that of the population enrolled in the VICTORIA trial. Moxifloxacin 400 mg, which has been shown to prolong the QTc interval by ~6 ms [10], was administered as a positive control to establish the sensitivity of the assay, as recommended by the ICH E14 guidelines [5].

2 Methods

This was a randomized, phase Ib, placebo-controlled, double-blind, double-dummy, multicenter study (NCT03504982) in patients with CCS. Patients were eligible for inclusion if they had CCS for at least 3 months prior to the first screening examination, were 30–80 years of age, and had a body mass index of 18.0–36.0 kg/m^2. CCS was defined as the presence of coronary artery stenosis in any of the main coronary vessels of ≥ 50%, as documented by coronary angiography within the previous 36 months, or a history of myocardial infarction that was clinically stable for at least 3 months. Patients with EF < 30% at screening, a recent myocardial infarction, or unstable angina (< 6 months), recent worsening progressive angina, or coronary intervention (< 3 months) or current relevant coronary stenosis ≥ 90% in any of the main three coronary vessels without bypass graft were excluded. Specific ECG exclusion criteria included the presence of clinically significant and persisting cardiac ischemia, as assessed by the investigator based on medical history and available clinical data (including past angiograms or pre-existing or current exercise testing with any imaging technique, such as dobutamine stress echocardiography, adenosine or dobutamine stress cardiac magnetic resonance imaging, scintigraphy, or exercise ECG) and QRS prolongation > 120 ms (e.g., in the presence of a complete bundle branch block).

Patients were randomized to one of two treatment sequences, comprising four treatments each (A*, B, C, D or D, A, B, C*; Fig. 1). Oral vericiguat (test drug) was administered once daily, initially at a dose of 2.5 mg (treatment A and A*) and was up-titrated to 5 mg (treatment B) and then to 10 mg (treatment C and C*) at 14 (± 3)-day intervals for a total treatment duration of 42 days. Moxifloxacin (treatment D) was administered as a positive control for assay sensitivity testing regarding QTc prolongation. A single dose of moxifloxacin 400 mg on day 8 (± 3 days) or day 50 (± 3 days) with vericiguat placebo administered on other days was administered as a positive control. For treatment A* and treatment C*, moxifloxacin placebo was administered on day 8 or day 50, respectively, to maintain blinding. Study treatment was administered in the fed state (after a standard breakfast). No washouts between doses of vericiguat were performed, as the regimen for active treatment was an up-titration followed, or preceded, by placebo.

2.1 Pharmacodynamic Evaluation

Triplicate ECGs were recorded at screening (within 28 days before first dosing) and pre-dose and 1.5, 2, 2.5, 3, 3.5, 4, 4.5,

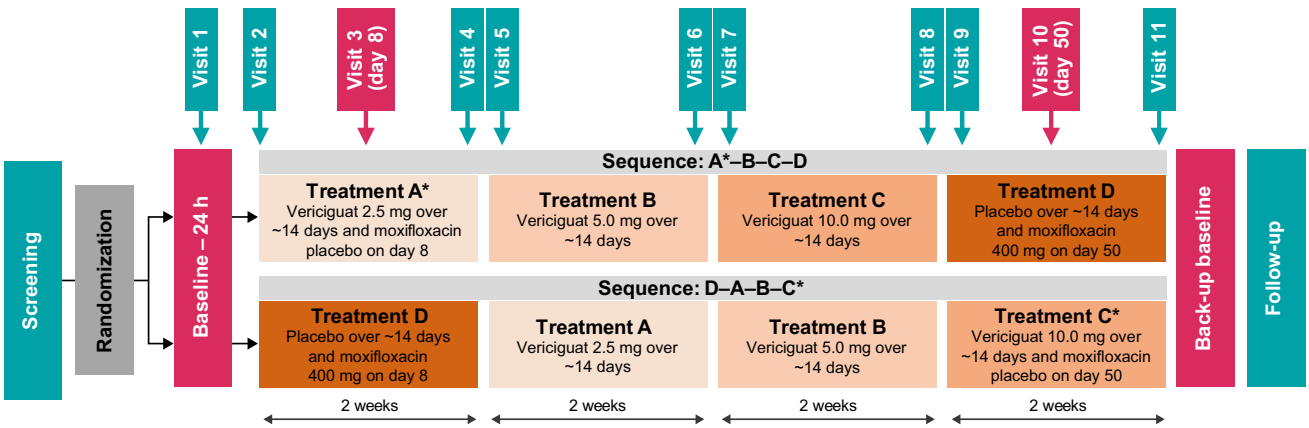


Fig. 1 Corrected QT study design. Blinding concept: vericiguat 2.5-mg and 5.0-mg tablets were the same size and shape; therefore, the same matching placebo tablet was administered. The vericiguat 10-mg tablet was larger in size than the 2.5-mg and 5.0-mg tablets; thus, a different matching placebo tablet was administered. Therefore, two tablets (one small and one larger) containing placebo or vericiguat were always administered to maintain blinding to the respective sequence. *Moxifloxacin placebo was administered on day 8 or day 50

5, and 7 h after dosing on visits 1–11 (Fig. 1) and at the follow-up visit. Two baseline profiles were measured: 'baseline' at visit 1 (day −1) and a 'back-up baseline' at follow-up (day 63; ~ 7 days after visit 11). Baseline for placebo ECG profiles was that closest to first placebo administration (treatment D). For sequence A*, B, C, D, 'back-up baseline' at day 63 was used, and, for sequence D, A, B, C*, 'baseline' at day −1 was used for placebo ECG profiles. Baselines for vericiguat/moxifloxacin ECG profiles were those closest to the vericiguat block (A, B, C* or A*, B, C). For sequence A*, B, C, D, 'baseline' day −1 was used; for sequence D, A, B, C*, 'back-up baseline' day 63 was used for vericiguat/moxifloxacin ECG profiles.

At all timepoints, triplicate ECGs were recorded using modified Goldberger/Einthoven leads, according to Mason/Likar, and standard chest leads, according to Wilson, after the patient was supine for 15 min. The triplicate ECGs were recorded within a time span of 2–6 min. All standard 10-s ECGs were recorded using tested digital ECG machines (approved by the European Union [CE marking] and the US Food and Drug Administration) provided by the ECG core laboratory (nabios GmbH, Munich, Germany). Prior to the start of the study, the study personnel were trained in the use of the ECG machines and transfer of the digital ECG data to the central core laboratory. The machines automatically measured and calculated heart rate, PR(PQ) interval, QRS duration, QT interval, and QTcF.

2.2 Pharmacokinetic Evaluation

Pharmacokinetics of vericiguat was assessed from blood samples collected pre-dose and at 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 h after dosing on ECG profile days (except 'baseline' and 'back-up baseline' days). Blood samples for the moxifloxacin assay were collected on day 8 and day 50. Quantitative analysis of vericiguat and moxifloxacin in plasma was performed with liquid chromatography-mass spectrometry assays (vericiguat: lower limit of quantification, 1 µg/L and upper limit of quantification, 1000 µg/L; moxifloxacin: lower limit of quantification, 10 µg/L and upper limit of quantification, 5000 µg/L; Syneos Health Clinique, Québec, QC, Canada).

2.3 Safety and Tolerability

The safety and tolerability profile of vericiguat was evaluated by assessment of adverse events (AEs), safety laboratory parameters, blood pressure, heart rate, and ECG findings.

2.4 Statistical Analysis

A minimum sample size of 59 patients was required for adequate statistical power to show non-inferiority of 10 mg of vericiguat at steady state compared with placebo, with a non-inferiority margin of 10 ms. Randomization of a minimum of 72 patients was planned, to allow for 13 patients (18%) to drop out or have invalid results.

The primary endpoint was the time-matched, placebo-corrected change from baseline in QTcF after vericiguat 10 mg at steady state, corresponding to the highest exposure of vericiguat. A clinically relevant effect was defined as a QTcF change from the time-matched baseline of > 10 ms relative to placebo. Analysis of covariance was performed on the primary endpoint separately for each timepoint, including the factors period and treatment (vericiguat 10 mg [day 14 of treatment C and C*] and placebo [day 14 of treatment D]) as fixed effects, the factor subject (sequence) as random effect, and the baseline value as covariate. Based on these analyses, point estimates (least squares [LS] means) and confirmatory two-sided 90% CIs of the true mean difference (vericiguat 10 mg at steady state [day 14 of treatment C and C*] − placebo [day 14 of treatment D]) were calculated for each timepoint on day 14 of treatment C and C* for vericiguat 10 mg. The intra-individual comparison of vericiguat 10 mg at steady state versus placebo was performed as a non-inferiority test. The purpose of this test was to show that vericiguat does not prolong the QTc time by more than 10 ms, as recommended in the ICH guideline E14 on the clinical evaluation of QT/QTc interval prolongation [5]. The upper limit of the two-sided 90% CI of the mean difference in treatment had to be below this threshold for each timepoint. Secondary objectives included assessment of the QTc interval prolongation potential of vericiguat during up-titration, pharmacokinetic evaluation of vericiguat during the QTc observation interval, and assessment of the safety and tolerability of vericiguat.

Assay sensitivity was assessed by evaluating the effect of moxifloxacin on change in QTcF at four pre-specified timepoints (2, 3, 3.5, and 4 h post-dose) during treatment D (day 8 or day 50 depending on the treatment sequence). Assay sensitivity for moxifloxacin was confirmed by the lower limit of the two-sided 90% CI of the time-matched, baseline-adjusted mean difference to placebo exceeding 5 ms at > 1 of the pre-specified timepoints.

3 Results

A total of 74 patients (66 men, eight women) with CCS were randomized; 72 completed the study and were evaluated in the pharmacodynamic analysis (Fig. S1 of the Electronic Supplementary Material [ESM]). Two patients (one in each randomization sequence) discontinued because of treatment-emergent AEs (TEAEs). Patient demographic and baseline data are summarized in Table 1 and were generally similar between treatment sequences. Mean (standard

Table 1 Demographic and baseline values in the safety analysis population

Parameter	Treatment sequence		Total ($N = 74$)
	A[a]-B-C-D ($N = 37$)	D-A-B-C[a] ($N = 37$)	
Sex, *n* (%)			
Male	34 (91.9)	32 (86.5)	66 (89.2)
Female	3 (8.1)	5 (13.5)	8 (10.8)
Age, years			
Mean ± SD	63.4 ± 9.0	63.4 ± 6.9	63.4 ± 8.0
Range	31–79	48–76	31–79
Weight, kg			
Mean ± SD	85.78 ± 13.84	85.85 ± 14.08	85.81 ± 13.87
Range	54.0–109.2	65.0–119.0	54.0–119.0
Height, cm			
Mean ± SD	172.46 ± 8.11	172.12 ± 6.27	172.29 ± 7.20
Range	153.0–189.0	159.0–185.0	153.0–189.0
Body mass index, kg/m^2			
Mean ± SD	28.84 ± 4.28	28.87 ± 3.63	28.86 ± 3.94
Range	18.3–35.9	22.0–36.5	18.3–36.5
Race, *n* (%)			
White	37 (100)	37 (100)	74 (100)
Cardiac disorder, *n* (%)	37 (100)	37 (100)	74 (100)
Ischemic coronary artery disorder	36 (97.3)	35 (94.6)	71 (95.9)
Heart failure	15 (40.5)	14 (37.8)	29 (39.2)
Mitral valvular disorders	6 (16.2)	6 (16.2)	12 (16.2)
Myocardial disorders NEC	6 (16.2)	6 (16.2)	12 (16.2)
Supraventricular arrhythmias	3 (8.1)	0	3 (4.1)
At least one concomitant medication, *n* (%)	37 (100)	37 (100)	74 (100)
Antithrombotic agents	34 (91.9)	37 (100)	71 (95.9)
Lipid-modifying agents	27 (73.0)	27 (73.0)	54 (73.0)
Antihypertensive agents, *n* (%)			
RAAS agents	27 (73.0)	29 (78.4)	56 (75.7)
Beta-blockers	27 (73.0)	31 (83.8)	58 (78.4)
Calcium channel blockers	8 (21.6)	4 (10.8)	12 (16.2)
Diuretics	10 (27.0)	8 (21.6)	18 (24.3)

NEC not elsewhere classified, *RAAS* renin-angiotensin-aldosterone system, *SD* standard deviation

[a]Moxifloxacin placebo was administered on day 8 or day 50

deviation) age was 63.4 (8.0) years and 89.2% of the study population were male. All had cardiac disease, as defined by the inclusion criteria; for most (95.9%), the primary cardiac finding was an ischemic coronary artery disorder (Table 1). Prior and concomitant medication included antihypertensive drugs, antithrombotic agents (mainly acetylsalicylic acid), and serum lipid-reducing agents, which were taken by most patients.

3.1 Pharmacodynamics

The baseline-corrected LS mean differences to placebo (and two-sided 90% CIs) of QTcF are given for treatment with vericiguat 10 mg steady state and moxifloxacin 400 mg single dose at each timepoint in Table 2. At each timepoint following the administration of vericiguat, the LS mean difference between vericiguat and placebo in QTcF change from baseline was < 6 ms (range 0.58–5.68 ms) and the upper limit of the two-sided 90% CI of the mean was below the 10-ms threshold for clinical significance. The greatest LS

Table 2 Change from baseline in QTcF (ms) for vericiguat 10 mg (steady state) and for moxifloxacin (single dose) versus placebo, respectively ($N = 72$)

Timepoint post-dose	Vericiguat 10 mg (steady state)		Moxifloxacin 400 mg (single dose)
	LS mean difference (vericiguat–placebo) [90% CI]	Upper limit of 90% CI < 10 ms	LS mean difference (moxifloxacin – placebo) [corrected 90% CI]
1 h 30 min	2.58 [−0.97, 6.12]	Yes	–
2 h 00 min	0.58 [−2.90, 4.05]	Yes	7.56[a] [4.95, 10.17]
2 h 30 min	5.68 [1.78, 9.59]	Yes	–
3 h 00 min	3.68 [0.04, 7.33]	Yes	**12.10[a] [8.96, 15.23]**
3 h 30 min	2.10 [−1.70, 5.90]	Yes	11.97[a] [8.97, 14.98]
4 h 00 min	3.83 [0.15, 7.50]	Yes	13.52[a] [10.23, 16.80]
4 h 30 min	**4.30 [0.75, 7.85]**	Yes	–
5 h 00 min	3.72 [0.67, 6.78]	Yes	–
7 h 00 min	1.46 [−1.60, 4.51]	Yes	–

Values marked in bold represent the LS mean difference in QTcF (vericiguat–placebo) at T_{max} for vericiguat (4.5 h) and moxifloxacin (3.0 h)

CI confidence interval, *LS* least squares, *QTcF* Fridericia-corrected QT interval, T_{max} time taken to reach the maximum concentration

[a]Timepoints for the evaluation of the moxifloxacin effect were restricted and Hochberg's step-up method was applied to preserve the overall alpha level at 0.05 for hypothesis testing

mean difference in QTcF change from baseline between vericiguat 10 mg at steady state and placebo was 5.68 ms (90% CI 1.78–9.59 ms) at 2.5 h after dosing (Table 2). The data revealed little evidence of a relationship between vericiguat exposure and a change in QTc interval (Fig. S2 of the ESM).

Analysis of the secondary endpoints showed that after administration of vericiguat 2.5 mg, 5 mg, or 10 mg on day 1 and vericiguat 2.5 mg and 5 mg on day 14 (steady state), the upper limit of the two-sided 90% CIs remained below the threshold of 10 ms at each timepoint (Table S1 of the ESM).

The lower limits of the two-sided 90% CI of the LS mean differences between moxifloxacin and placebo in QTcF change from baseline were > 5 ms at three of the four pre-specified timepoints (3, 3.5, and 4 h; Table 2); thereby confirming the sensitivity of the assay for the detection of a QTcF effect. The largest difference in change from baseline at the pre-specified timepoints was 13.52 ms (10.23–16.80 ms) observed at 4 h post-dose.

3.2 Pharmacokinetics

Maximum concentration of vericiguat in plasma (C_{max}) increased with increasing dose. On day 14, after administration of vericiguat 10 mg once daily, geometric mean (range) C_{max} was 322 (134–745) µg/L (Fig. 2a), with an inter-individual variability of 32.0%. Geometric median (range) time taken to reach C_{max} (T_{max}) was 4.5 (1.55–5.10) h post-dose. C_{max} was similar on days 8 and 14 following administration of vericiguat 2.5 mg (95.2 µg/L and 96.6 µg/L, respectively) and 10 mg (349 µg/L and 322 µg/L, respectively), indicating achievement of steady state after 8 days or less (pharmacokinetics was not assessed for vericiguat 5 mg on day 8).

For moxifloxacin 400 mg, the geometric mean (range) C_{max} was 1960 (969–3960) µg/L (Fig. 2b), with an inter-individual variability of 27%. Median (range) T_{max} was 3.03 (1.50–5.07) h post-dose.

3.3 Safety

The incidence of TEAEs is shown in Table 3. A total of 47 patients (63.5%) experienced at least one TEAE. Overall, 28 (37.8%) patients had TEAEs with a maximum intensity of mild and 19 (25.7%) had at least one TEAE with a maximum intensity of moderate. No deaths or drug-related serious AEs were reported. The most common TEAEs were headache and dizziness, each observed in six patients (8.1%). Supine blood pressure and heart rate were highly variable within and between patients. A trend for decreased systolic and diastolic blood pressure (~ 5 to 10 mmHg) and increased heart rate (~ 5 bpm) with increasing duration and dose of vericiguat compared with placebo and moxifloxacin was observed. The AE profile of vericiguat was consistent with its mechanism of action, and the findings did not indicate any safety concerns.

4 Discussion

In this study assessing the QT effect of vericiguat in patients with CCS, administration of vericiguat, titrated up to the clinical dose of 10 mg, was not associated with a clinically relevant QTc interval-prolonging effect.

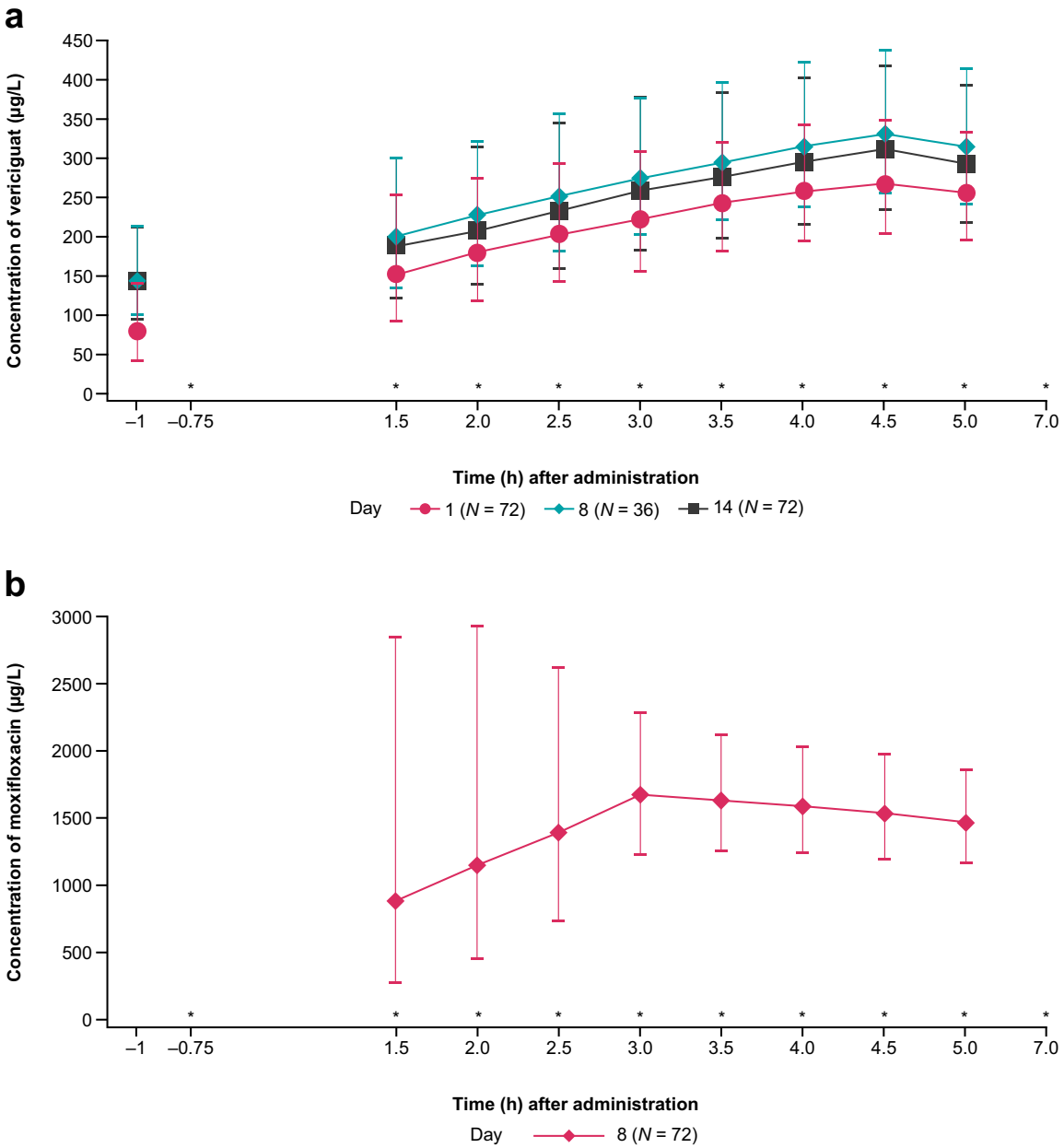


Fig. 2 Geometric mean (standard deviation) for concentration of **a** vericiguat in plasma after administration of first and multiple doses of vericiguat 10 mg and **b** moxifloxacin (pharmacokinetic analysis set, $N = 73$). *Denotes the timepoints of the electrocardiogram recordings

In the current study, we used a time-matched single-baseline approach, in which QTcF was adjusted with placebo and either 'baseline' or 'back-up baseline' QTcF on an individual basis. In a supportive 'modeled baseline' analysis, a linear mixed-effects model was used to account for individual baseline and placebo effects, such as diurnal time course [11]. Consistent with the current study, the upper limits of the two-sided 90% CIs for QTc were below the threshold of 10 ms using this concentration–QTc modeling approach [11].

Administration of the positive control, moxifloxacin 400 mg, was associated with an increase in QTc interval. It is known that food intake alters the pharmacokinetic profile of moxifloxacin, reducing C_{max} and delaying the peak effect on QTc, thereby reducing the magnitude of its effects on QTc [12]. In this study, treatment was administered after a standard breakfast. In addition, the effect of food itself results in a shortening of the QTc interval, which partially offsets the QTc effect of moxifloxacin [12]. Consequently, dosing in the fed state may have affected the evaluation of

Table 3 Summary of the number of patients with treatment-emergent AEs

	Vericiguat			Moxifloxacin	Placebo	Total
	2.5 mg ($N = 73$)	5 mg ($N = 72$)	10 mg ($N = 72$)	($N = 72$)	($N = 73$)	($N = 74$)
Any AE	27 (37.0)	16 (22.2)	19 (26.4)	4 (5.6)	21 (28.8)	47 (63.5)
Maximum intensity for any AE						
Mild	20 (27.4)	13 (18.1)	11 (15.3)	4 (5.6)	14 (19.2)	28 (37.8)
Moderate	7 (9.6)	3 (4.2)	8 (11.1)	0	7 (9.6)	19 (25.7)
Any AE leading to discontinuation of the study drug	1 (1.4)	0	0	0	1 (1.4)	2 (2.7)
Any SAE	1 (1.4)	0	1 (1.4)	0	0	2 (2.7)
SAE related to the study drug	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

Data are presented as *n* (%) of patients

AE adverse event, *SAE* serious adverse event

assay sensitivity. Still, the lower limit of the two-sided 90% CI for QTc was > 5 ms for three out of four pre-specified timepoints after administration of moxifloxacin. Therefore, the minimum requirement for demonstrating that the assay conditions were sensitive enough to permit detection of a difference in QTc between vericiguat and placebo (> 5 ms at one timepoint) was met.

The LS mean differences in QTc change from baseline between moxifloxacin and placebo ranged from 7.56 to 13.52 ms, which was greater than the expected 6-ms prolongation previously reported for moxifloxacin [10]. This did not seem to be a result of higher exposure to moxifloxacin in our study. In our study, consistent with the effect of food on the pharmacokinetics of moxifloxacin [12], C_{max} (1.96 mg/L) was lower and T_{max} (3.03 h) longer than previously reported in a study in healthy volunteers, which demonstrated a C_{max} of 3.1 ± 1 mg/L and a T_{max} of about 1 h [10]. Maximum concentration was lower than that (about 2.75 mg/L) associated with a ~ 6-ms change in QT interval in a population model for placebo-corrected moxifloxacin QT interval based on data from healthy volunteers [13]. Given that aortic stenosis and HF are risk factors for QT interval prolongation [14], the greater change in QT interval with moxifloxacin observed in our study likely reflects an intrinsically higher sensitivity to QT interval prolongation in the CCS patient population compared with healthy volunteers. Owing to this higher sensitivity for QTc prolongation, the CCS patient population may be preferred over healthy volunteers as a study population for QT interval studies.

This study forms part of an integrative assessment of the proarrhythmic potential of vericiguat along with preclinical and other clinical studies, which have consistently found that vericiguat does not prolong the QTc interval. In a preclinical study in conscious telemetered dogs, administration of single doses of vericiguat caused dose-dependent decreases in arterial blood pressure and compensatory increases in heart rate, consistent with its mode of action; however, QTc intervals were not prolonged to a clinically relevant extent [15]. In a series of in vitro electrophysiological studies, neither vericiguat nor its pharmacologically inactive M-1 metabolite inhibited cardiac ion channels (hERG, hNav 1.5, hCav 1.2, hKvLQT1/minK, and hKv 4.3) at exposure multiples of > 150-fold under conditions simulating normal and diseased physiological states [15]. Manual voltage clamp recordings at room temperature indicated a 20% threshold inhibitory concentration of ~ 1.9 µM of vericiguat (approximately 105-fold higher than the human clinical C_{max} [unbound] of 18 nmol/L at 10 mg) and a 50% threshold inhibitory concentration of 9.9 µM of vericiguat (approximately 550-fold higher than the human C_{max} [unbound]) for hERG K+ inhibition by vericiguat [15].

In terms of the relationship between vericiguat concentration and QTc, the CCS population was assumed to be similar to that of the patient population with worsening HF enrolled in VICTORIA. This pivotal phase III VICTORIA study evaluated the efficacy and safety of vericiguat in 5050 patients with HF and EF < 45% who had a recent worsening HF event [4]. Patients were randomized to receive vericiguat 2.5 mg once daily, titrated to a target dose of 10 mg, or to placebo. The safety findings indicated no increase in the prevalence of arrhythmias in patients treated with vericiguat compared with those receiving placebo. Consistent with these findings, VITALITY, conducted in 789 patients with HF with preserved EF, did not report an increase in the prevalence of arrhythmias in patients receiving vericiguat [16]. Considering the findings of these preclinical and clinical studies together, the data support the conclusion that administration of vericiguat 10 mg is not associated with a clinically relevant QTc prolongation.

In contrast to QT studies of other HFrEF treatments (angiotensin receptor-neprilysin inhibitors, sodium-glucose co-transporter-2 inhibitors) [17–19], it was not possible to

conduct a classical QTc study of vericiguat at supratherapeutic exposures in healthy volunteers, as recommended in guidelines [5], because, based on the findings of phase I studies of vericiguat, we anticipated that exaggerated orthostatic reactions may occur at these doses [7]. Therefore, the study was performed in line with QT/QTc study recommendations for special cases when studies in healthy volunteers are inappropriate [8]. While this is a study limitation, the effect of vericiguat on QTc was assessed at its therapeutic dose at steady state (i.e., at the highest exposure in patients), and the CCS population studied appeared to be intrinsically sensitive to QT prolongation, as evidenced by the effect of moxifloxacin on QTc. As observed above, the C_{max} and T_{max} for moxifloxacin were higher in this study than previously reported in healthy volunteers [10]; however, C_{max} and T_{max} for vericiguat were in line with previously reported values [1] in patients with HF and healthy volunteers. This finding supports the assessment of vericiguat in patients with CCS for this dedicated QT study.

The study population comprised White, predominantly male (89.2%) participants. Women of childbearing potential were excluded from the study, as is standard practice during the early stages of clinical development of a drug when possible effects on female reproduction have not yet been fully investigated. This likely limited the recruitment of female participants. Race was not an inclusion or exclusion criterion; therefore, the enrollment of all White participants reflected the demographics of patients with CCS in the locations at which the study was conducted (Germany, Moldova, and the Netherlands). While the low proportion of women and the lack of inclusion of non-White participants is a limitation of the study, it is unlikely that sex or ethnic factors would introduce a large difference in QT response that would alter the findings of the study [5, 8]. The study population is in line with recommendations for conducting thorough QT studies, which do not mandate the inclusion of both sexes and different races [5, 8].

5 Conclusions

In this dedicated QTc study in patients with CCS, a placebo-corrected change from baseline in QTcF after vericiguat 10 mg at steady state did not exceed 10 ms, which supports the conclusion that therapeutic doses of vericiguat are not associated with clinically relevant QTc prolongation. The findings of this study contribute to the overall safety profile of vericiguat for the treatment of patients with HFrEF.

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Declarations

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Conflicts of interest/competing interests Corina Becker and Claudia Maschke are employees of Bayer AG. Philippe Vieira Pires was previously an employee of Bayer AG at the time of the study. Michael Böttcher is a former employee of Bayer AG, and has received within the last 36 months, salary, pension, and payment for writing and reviewing vericiguat manuscripts from Bayer AG and for lectures, exercises, and awarding and supporting bachelor and master theses. Dietmar Trenk received within the last 36 months through to the foreseeable future consulting fees/payment for lectures including service on speakers' bureaus by Amgen, AstraZeneca, Atriva, Bayer, Berlin Chemie, Bristol-Myers Squibb, Böhringer Ingelheim, Daiichi Sankyo, Ferrer, Pfizer, and Sanofi. Hans-Dirk Düngen has received institutional payment as an investigator and personal honoraria for advisory boards from Bayer. Antonios Othon Aliprantis was an employee of Merck & Co., Inc., Rahway, NJ, USA, at the time the study was conducted and held stock in the company. Rainard Fuhr is an employee of Parexel, the Clinical Research Organization that received funding from Bayer AG for the conduct of the study. Nina Besche is an employee of Chrestos Concept GmbH & Co. KG, which received funding for this analysis from Bayer AG. Martin Coenen received travel costs from Bayer AG to attend an investigator meeting related to the conduct of the study. Frank Donath, Pim Gal, Gerd Mikus, and Vasile Corcea declare no conflicts of interest.

Ethics approval The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the ICH guideline E6: Good Clinical Practice and met all local legal and regulatory requirements. During the study, all clinical data were monitored by an independent data monitoring committee [20].

Consent to participate All patients provided written informed consent before any study procedure was performed.

Consent for publication Not applicable.

Availability of data and material The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

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