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RESEARCH ARTICLE

Vericiguat Global Study in Participants with Chronic Heart Failure: Design of the VICTOR trial

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Aims In the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial, the soluble guanylate cyclase stimulator vericiguat reduced the risk of hospitalization for heart failure (HHF) or cardiovascular death in patients with heart failure (HF) and reduced ejection fraction (HFrEF) with recent worsening HF. The effect of vericiguat in patients with HFrEF without recent worsening HF remains unknown. The VICTOR (Vericiguat Global Study in Participants with Chronic Heart Failure) trial was designed to assess the efficacy and safety of vericiguat in patients with ejection fraction ≤40% without recent worsening HF on a background of current foundational HFrEF therapy.

Methods The primary endpoint for VICTOR is time to first event for the composite of HHF or cardiovascular death. The trial will also assess the effect of vericiguat on time to cardiovascular death, time to HHF, total HHF, and all-cause death. As an event-driven trial, at least 1080 primary events are expected, but follow-up will continue until the targeted number of at least 590 cardiovascular deaths has been reached. Approximately 6000 participants will be randomized to vericiguat or placebo.

Conclusion VICTOR is the first large event-driven HFrEF trial performed in the contemporary era of quadruple foundational guideline-directed medical therapy, in a compensated ambulatory HF population. VICTOR will add important information to the evidence of the effects of vericiguat across the spectrum of patients with HFrEF.

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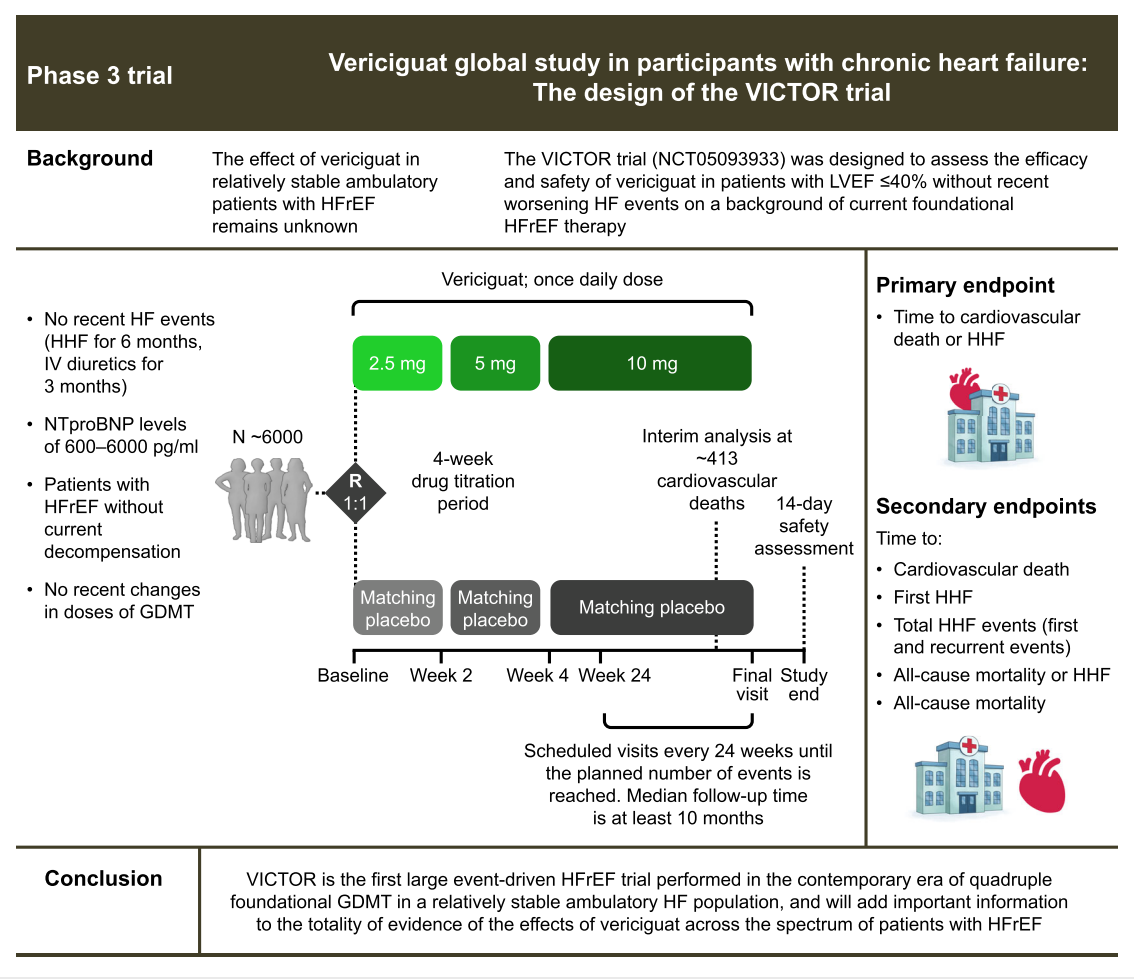
Graphical Abstract



Design of the vericiguat global study in participants with chronic heart failure (VICTOR) trial. GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Vericiguat • Heart failure with reduced ejection fraction

Introduction

Vericiguat, a soluble guanylate cyclase stimulator, is approved in many countries for the treatment of worsening heart failure (HF) with reduced ejection fraction (HFrEF). In the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial, vericiguat reduced the risk of hospitalization for heart failure (HHF) or cardiovascular death in patients with HFrEF and a left ventricular ejection fraction (LVEF) <45% with recent worsening HF.[1] Worsening HF was defined as either a recent HHF or need for urgent intravenous diuretic therapy in the outpatient setting. Consistent with the population studied, short-term event rates in VICTORIA were high, leading to a median follow-up of only 10.8 months at the time the required number of events had accrued in the trial, which limited evaluation of more prolonged drug exposure on cardiovascular mortality.[2] In keeping with clinical practice at the time of enrolment, baseline use of an angiotensin receptor–neprilysin inhibitor (ARNI) was modest, and use of sodium–glucose cotransporter-2 inhibitors (SGLT2i) was negligible in VICTORIA. Furthermore, since VICTORIA exclusively included a worsening HF population, the effect of vericiguat in more compensated ambulatory patients with HFrEF remains unknown. This is relevant as analyses from VICTORIA suggested that efficacy was potentially greater among less sick patients.[3,4]

The VICTOR (Vericiguat Global Study in Participants with Chronic Heart Failure) trial is designed to address existing knowledge gaps by assessing the safety and efficacy of vericiguat on the risk of HHF or cardiovascular death among contemporary

lower-risk patients with HFrEF who have not experienced recent worsening HF. The VICTOR trial will assess the impact of vericiguat in the background of expected higher use of ARNI and SGLT2i at baseline. Since vericiguat works by restoring impaired nitric oxide signalling by soluble guanylate cyclase stimulation with potential vascular and myocardial remodelling benefits that are not targeted by existing therapies, it is anticipated that vericiguat will have incremental efficacy on top of contemporary guideline-directed medical therapy. The VICTOR trial is therefore well positioned to address the unresolved impact of vericiguat on cardiovascular mortality, while expanding the evidence for vericiguat to cover the entire spectrum of risk in HFrEF.

Methods

Study design

VICTOR (NCT05093933) is a double-blind, placebo-controlled, parallel group, 1:1 randomized, event-driven trial testing the effects of oral vericiguat at a target dose of 10 mg versus placebo in ambulatory patients with HFrEF and no recent worsening HF episode. As an event-driven trial, the study is designed to assess the primary endpoint but is also designed to ensure adequate power to assess the impact of vericiguat on cardiovascular deaths in the non-worsening HF population recruited. Therefore, the follow-up will continue until the targeted number of cardiovascular deaths are reached. A steering committee will provide guidance and make recommendations on the operational aspects of the study. In addition, a data monitoring committee will monitor unblinded interim data from the study and make recommendations to the sponsor's executive oversight committee. The target dose and titration regimen for VICTOR are identical to VICTORIA[1] where vericiguat was well tolerated with ~90% of participants receiving the target dose of 10 mg once daily at 1 year.

Eligibility

The eligibility criteria for VICTOR are shown in *Table 1*. Consistent with the aim of testing vericiguat in an ambulatory HFrEF population without recent worsening HF, there are important differences in eligibility criteria between the VICTOR and VICTORIA trials. VICTOR will exclude patients with a recent event of HF worsening, with HF worsening defined as either a HF event that required hospitalization in the last 6 months or urgent outpatient diuretic use in the last 3 months. Indeed, the higher short-term risks of recurrent HHF or cardiovascular death decreases within the first 6 months after a worsening HF event (*Figure 1*).[5,6] For example, in the EMPEROR trials, the rates of HHF or cardiovascular death per 100 person-years was 26.7 with hospitalization within 3 months, 18.1 between 3 and 6 months, 13.7 between 6 and 12 months and 2.8 when HHF was over 12 months prior to enrolment.[6]

The LVEF inclusion criterion in VICTORIA was <45%, whereas VICTOR will limit enrolment to patients with LVEF ≤40%.[7] This threshold is consistent with the universal definition of HFrEF.[8] In VICTORIA, those with baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in the lower three quartiles (≤5314 pg/ml) derived the greatest benefit from vericiguat with benefit attenuating in those in the highest quartile.[3,4] Consistent with the study aim of evaluating vericiguat in more compensated patients with HFrEF, participants with NT-proBNP >6000 pg/ml are excluded. The lower-limit

Table 1 Inclusion and exclusion criteria for VICTOR

Inclusion criteria
New York Heart Association class II to IV chronic heart failure on guideline-directed medical therapy
No events of heart failure hospitalization within 6 months or outpatient intravenous diuretic use within 3 months
Adults ≥18 years of age
Screening N-terminal pro-B-type natriuretic peptide within 30 days before randomization between 600 and 6000 pg/ml if the patient is in sinus rhythm, or between 900 and 6000 pg/ml if the patient is in atrial fibrillation
Left ventricular ejection fraction ≤40% within 12 months before randomization
Exclusion criteria
Systolic blood pressure <100 mmHg or symptomatic hypotension
Awaiting heart transplantation or receiving continuous intravenous inotropic therapy
Amyloidosis, sarcoidosis, hypertrophic cardiomyopathy, myocarditis, or stress cardiomyopathy
Tachycardia cardiomyopathy or uncontrolled tachyarrhythmia
Constrictive pericarditis or endocarditis
Has acute coronary syndrome or undergone coronary artery bypass grafting or percutaneous coronary intervention within 3 months
Has estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation of <15 ml/min/1.73 m^2 within 30 days before randomization or is on chronic dialysis
Severe hepatic insufficiency
Any discontinuation or dose modification of guideline-directed medical therapy within 4 weeks before randomization
Has primary valvular heart disease requiring intervention or has undergone valvular intervention within 3 months
Has symptomatic carotid stenosis, transient ischaemic attack, or stroke within 3 months
Complex congenital heart disease, or simple congenital heart disease with residual haemodynamic lesions
Prior heart transplantation
Malignancy or other non-cardiac condition limiting life expectancy to <3 years
Continuous home oxygen or interstitial lung disease
Concurrent or anticipated use of phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil) or other soluble guanylate cyclase stimulators (riociguat) during the study

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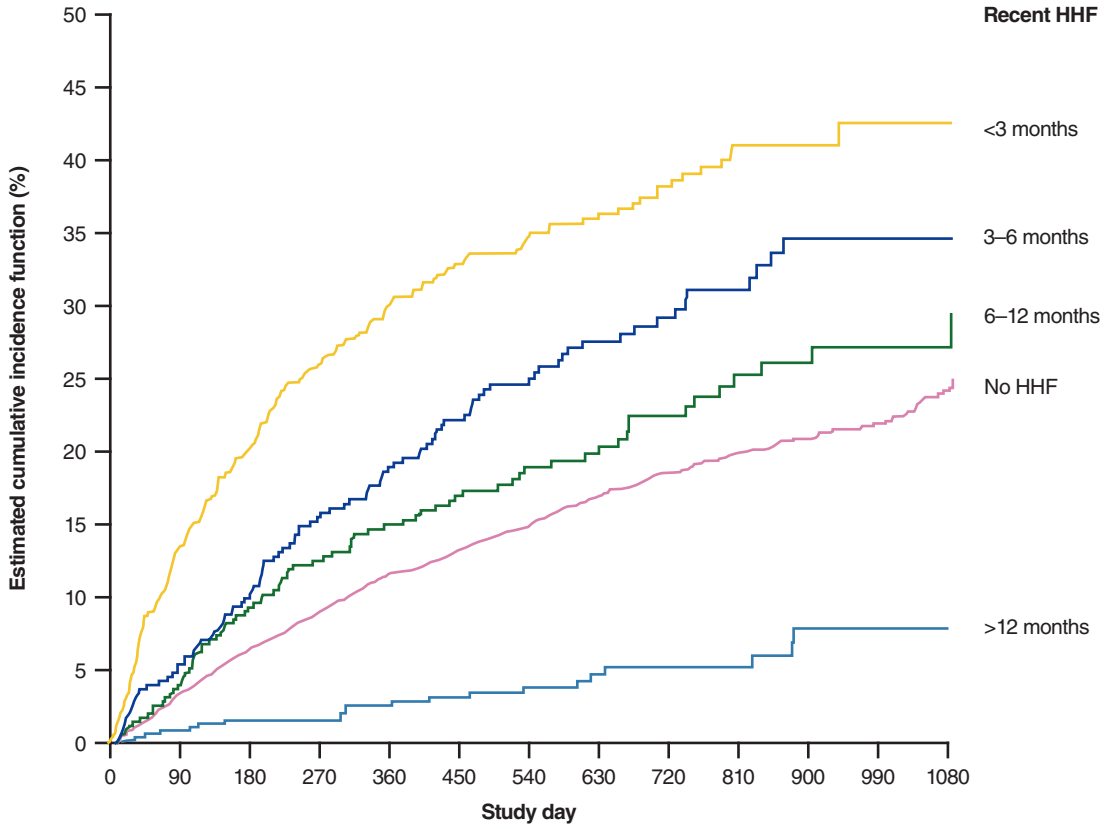

Patients at risk

No HHF	3180	3043	2928	2746	2541	2233	1844	1546	1224	979	690	466	275
>12 months	434	426	420	387	364	317	249	199	157	124	88	65	40
6–12 months	360	346	325	293	271	237	185	157	121	90	65	44	29
3–6 months	362	338	314	275	252	225	181	151	111	85	60	47	24
<3 months	522	450	411	350	307	266	218	178	145	109	79	61	32

Figure 1 Cumulative incidence of hospitalization for heart failure (HHF) or cardiovascular death by recency of hospitalization in placebo arms of the EMPEROR trials. With shorter duration from recent HHF at time of enrolment, there are higher early event rates that decline with increasing duration from prior HHF. Reproduced from Ferreira *et al.*[6] under the terms of the CC BY 4.0 license.

NT-proBNP entry criterion is 600 pg/ml in patients with sinus rhythm and 900 pg/ml in those with atrial fibrillation.[9,10] Enrolment of participants with an estimated glomerular filtration rate (eGFR) between 15 and 30 ml/min/1.73 m^2 will be limited to ~15% of the total study population.

Despite exclusion of participants at highest risk for events, it is expected that substantial residual risk will remain in enrolled patients despite contemporary therapy. This risk is evident in trials using broadly similar entry criteria including lower-limit natriuretic peptide inclusion thresholds. The annualized event rate for time to HHF or cardiovascular death in DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and PARADIGM-HF (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitors with Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) was 11.4% in the dapagliflozin arm and 10.5% in the sacubitril/valsartan arm, respectively, underscoring the unmet need for novel therapies to decrease this residual risk.[9,10]

Randomization and visits

After a screening period of up to 30 days, ~6000 participants will be randomized 1:1 to receive vericiguat titrated to 10 mg daily or placebo. Randomization will be stratified by baseline New York Heart Association class (II vs. III/IV). Participants will start with a 2.5 mg oral dose of blinded vericiguat or matching placebo once daily. The dose will be titrated to 5 mg vericiguat at the next study visit scheduled at 14 ± 4 days, and the second titration to 10 mg vericiguat at the following study visit at 28 ± 4 days after randomization. Dose titration will depend on systolic blood pressure and the presence of symptoms of hypotension (*Table 2*). Following this 4-week drug titration period (*Graphical Abstract*), participants will return for scheduled visits every

Table 2 Systolic blood pressure criteria for study drug modification

Systolic blood pressure	Dose modification
≥100 mmHg and not on 10 mg target dose	Increase
≥100 mmHg and on 10 mg target dose or ≥90 mmHg and <100 mmHg	Maintain
<90 mmHg, asymptomatic	If currently on 5 or 10 mg, decrease If currently on 2.5 mg, interrupt
<90 mmHg, symptomatic	Interrupt

24 weeks until study completion. After the end of the treatment period, all participants will have a follow-up evaluation at day 14 for safety assessment.

Background therapy

In contrast to VICTORIA, the VICTOR trial is conducted following the establishment of SGLT2i as recommended therapy in HFrEF based on the DAPA-HF[10] and the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction)[11] trials. Although the results of PARADIGM-HF[9] demonstrating benefit with ARNI were available during VICTORIA enrolment, the use of ARNI was modest (<20%) at baseline in VICTORIA.[12] With recent trials[13] and guideline updates[8] now endorsing ARNI as first-line therapy for HFrEF, it is anticipated that a higher baseline use of ARNI in VICTOR will be seen. VICTOR is the first large, randomized outcome trial in the modern era of quadruple therapy in HFrEF (*Table 3*).[1,6,9–11,14–16] By recruiting a compensated well treated population with persistent left ventricular dysfunction, high rates of implantable cardioverter defibrillator use are also expected. Since ARNI, SGLT2i and defibrillator therapies all decrease sudden death rates,[17,18] cardiovascular death rates may be lower in VICTOR than in previous trials. Therefore, VICTOR will provide contemporary estimates of residual risk for HHF and cardiovascular death in an ambulatory HFrEF population.

Endpoints

The primary hypothesis of VICTOR is that vericiguat is superior to placebo in reducing the risk of the composite endpoint of HHF or cardiovascular death. The effect of vericiguat on cardiovascular death alone will be assessed as a secondary endpoint. Additional secondary efficacy endpoints include time to first HHF, time to total (first and recurrent) HHF, time to first HHF or all-cause death and time to all-cause death (*Table 4*). Exploratory endpoints include time to first urgent HF visit or HHF, time to first cardiovascular hospitalization, total number of HHF, eGFR slope and change in health-related quality of life. Quality of life will be measured by the Kansas City Cardiomyopathy Questionnaire, and EuroQol 5-dimension 5-level scores at baseline, week 24 and then every 48 weeks to determine their change from baseline to capture treatment effects on patient-reported outcomes.

Endpoint adjudication

All primary and secondary endpoint components will be adjudicated by an independent clinical endpoint committee. This will include death, cardiovascular hospitalization (including HHF) and urgent HF visits. Adjudication of all events will utilize pre-specified endpoint criteria and clinical experience. HHF adjudication criteria will require hospitalization for at least 24 h with objective evidence of symptoms, physical examination and laboratory evidence of HF with initiation or intensification of treatment for HF. HF endpoints otherwise meeting these objective criteria in the emergency department (<24-h stay) or an unscheduled office visit will be classified as urgent HF visits.

Statistical analysis

All time-to-event endpoints will be performed following the intention to treat principle using a stratified log-rank test. The total HHF analysis will use the Andersen–Gill method with robust standard errors to account for possible correlation among patients who had recurrent events.[19] Testing will be performed using a one-sided type I error rate of 0.025 all endpoints tested. The components of the primary composite endpoint (time to cardiovascular death and time to first HHF) will each be tested only if the null hypothesis is rejected for the primary endpoint, but will not otherwise be controlled for multiplicity. The other secondary endpoints, addressing time to total HHF, time to first HHF or all-cause mortality, and time to all-cause mortality will be controlled for multiplicity using a hierarchical testing approach (*Figure 2*). The secondary endpoints will be tested in order if the null hypothesis of the primary composite endpoint is rejected, stopping at the first endpoint that does not achieve significance. Subgroup analyses for the primary endpoint will be performed to evaluate for consistency of treatment effect across age, sex, race, geographic region, eGFR, New York Heart Association class, baseline ARNI use, SGLT2i use, implanted defibrillator, NT-proBNP quartile and median LVEF. Safety analyses, including descriptive statistics of non-serious adverse events, serious adverse events and events of clinical interest will include all randomized participants who received at least one dose of study drug.

Event rate assumption

The assumed placebo event rates for the primary endpoint and for cardiovascular death for VICTOR were based on data from recent HF trials. In PARADIGM-HF, the incidence of HHF or cardiovascular death was 10.5 and 13.2 per 100 patient-years, and cardiovascular death 6 and 7.5 per 100 patient-years, in the sacubitril/valsartan and enalapril arms, respectively.[20] In DAPA-HF, the incidences for HHF or cardiovascular death were 11.4 and 15.3 per 100 patient-years and for cardiovascular death were 6.5 and 7.9 per 100 patient-years, in the dapagliflozin and placebo arms, respectively.[10] Considering these event rates in the context of exclusion of recent worsening HF and anticipated high use of both ARNI and SGLT2i in VICTOR, the event rate for HHF or cardiovascular death in the placebo arm of VICTOR is estimated to be 11.5 per 100 patient-years and for cardiovascular death 6 per 100 patient-years.

Sample size and power calculation

The sample size calculation was based on the above estimated event rates, ensuring adequate power to assess cardiovascular death in the recruited non-worsening HF cohort. Assuming a hazard ratio of 0.80 for the cardiovascular death endpoint and using a one-sided alpha of 0.025, 590 cardiovascular deaths will provide 80% power for cardiovascular death, conditional on a positive primary endpoint. Based on the expected placebo incidence rate presented above, a sample size of approximately ~6000 participants is expected to yield

Table 3 **Characteristics of contemporary heart failure with reduced ejection fraction trials**

	PARADIGM-HF[9]	DAPA-HF[10]	EMPEROR-Reduced[11]	GALACTIC-HF[14]	VICTORIA[1]
Intervention	Sacubitril/valsartan	Dapagliflozin	Empagliflozin	Omecamtiv mecarbil	Vericiguat
Sample size, *n*	8399	4744	3730	8232	5050
Key eligibility criteria	EF <40%; NYHA II–IV	EF <40%; NYHA II–IV	EF <40%; NYHA II–IV	EF <35%; NYHA II–IV	EF <45%; NYHA II–IV
Eligibility based on proximity of recent worsening for HF	Resolved recent worsening HF allowed regardless of proximity to enrolment	Worsening HF <4 weeks prior excluded	Worsening HF <1 week prior excluded	Mandatory presence of either (i) current HHF or (ii) HHF/urgent HF in past year	Mandatory presence of either (i) HHF <6 months or (ii) intravenous diuretic <3 months
Recent HHF <6 months (%)	31[15]	16[16]	23[6]	80[16]	84
NT-proBNP criteria, pg/ml	600; 400 if HHF in last year	600 sinus rhythm; 400 sinus rhythm and HHF in last year; 900 if AF regardless of HHF	600 with EF ≤30% or prior HHF (1200 if AF); 1000 with EF 31–35% (2000 if AF); 2500 with EF 36–40% (5000 if AF)	400 sinus rhythm, 1200 if AF	1000 sinus rhythm, 1600 if AF
NT-proBNP pg/ml, median (IQR)	1594 (886–3305)	1446 (857–2641)	1926 (1153–3525)	2025 (1000–4105)	2821 (1548–5206)
Background therapy – control group	BB (93%), MRA (57%), ACEi (100%)	BB (96%), MRA (71%), ACEi/ARB (83%), ARNI (11%)	BB (95%), MRA (73%), ACEi/ARB (69%), ARNI (21%)	BB (94%), MRA (78%), ACEi/ARB (68%), ARNI (19%), SGLT2i (3%)	BB (93%), MRA (70%), ACEi/ARB (74%), ARNI (14%)
ICD/CRT (%/%)	15/7	26/7	31/12	32/14	28/15
Primary endpoint (time to first event)	Cardiovascular death or first HHF	Cardiovascular death, HHF or urgent HF visit	Cardiovascular death or first HHF	Cardiovascular death, HHF or urgent HF visit	Cardiovascular death or HHF
n events	2031	888	823	3130	1869
HR (95% CI)	0.80 (0.73–0.87)	0.74 (0.65–0.85)	0.75 (0.65–0.86)	0.92 (0.86–0.99)	0.90 (0.82–0.98)
Cardiovascular death, *n* events	1251	500	389	1606	855
HR (95% CI)	0.80 (0.71–0.89)	0.82 (0.69–0.98)	0.92 (0.75–1.12)	1.01 (0.92–1.11)	0.93 (0.81–1.06)
First HHF, *n* events	1195	549	588	2321	1438
HR (95% CI)	0.79 (0.71–0.89)	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.95 (0.87–1.03)	0.90 (0.81–1.00)
Mortality, *n* events	1546	605	515	2132	1046
HR (95% CI)	0.84 (0.76–0.93)	0.83 (0.71–0.97)	0.92 (0.77–1.10)	1.00 (0.92–1.09)	0.95 (0.84–1.07)

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CI, confidence interval; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Table 4 Study endpoints in VICTOR

Primary endpoint
Time from randomization to the first event of cardiovascular death or heart failure hospitalization
Secondary endpoints
Time from randomization to cardiovascular death
Time from randomization to the first event of heart failure hospitalization
Time from randomization to total heart failure hospitalization events (first and recurrent events)
Time from randomization to the first event of all-cause mortality or heart failure hospitalization
Time from randomization to all-cause mortality

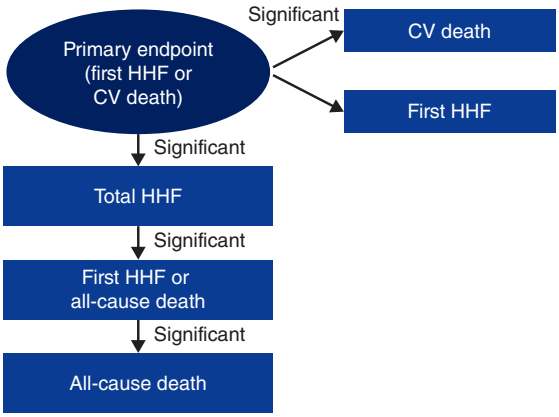

Figure 2 Hierarchical testing approach. If the primary endpoint (time to first hospitalization for heart failure [HHF] or cardiovascular [CV] death) is statistically significant, testing for secondary endpoints will proceed sequentially from (i) total HHF to (ii) time to first HHF or all-cause mortality to (iii) time to all-cause mortality based on achievement of statistical significance at each secondary endpoint. Testing for the individual components of the primary endpoint of (i) time to CV death and (ii) time to first HHF will be tested only if the primary endpoint is significant but will not otherwise be controlled for multiplicity.

590 cardiovascular deaths within 43 months from the time of first participant enrolling until the last participant's last study contact, and median follow-up of approximately 25 months. If observed event rates are lower than anticipated, this will only prolong trial duration, but will not impact statistical power for cardiovascular death due to the event-driven nature of the trial. It is estimated that ~1080 participants will experience a primary composite event at the time of 590 cardiovascular death events, and with the placebo incidence rate presented above and a hazard ratio of 0.80, this will provide ~95% power for the primary hypothesis.

Interim analysis

A single interim analysis for efficacy is planned when approximately 413 cardiovascular deaths (70% of planned for the trial) are observed. To ensure that the study has accumulated adequate follow-up for safety assessment if stopped for efficacy, the timing of the interim analysis will require a median follow-up time of at least 10 months. At the interim analysis, the primary hypotheses will be tested. The Hwang, Shih and De Cani alpha-spending function will be used to assess superiority of vericiguat at the interim analysis. With this alpha-spending approach and a percentage of information of 70%, the nominal significance level will be approximately 0.005 (one-sided) at the interim analysis and 0.024 (one-sided) at the final analysis, respectively. This testing approach controls the one-sided alpha between the efficacy interim analysis and final analysis at 0.025. The actual alpha to be spent at the efficacy interim analysis will be determined using the number of observed cardiovascular deaths and the alpha-spending function. Cardiovascular death at the interim analysis will not be tested unless the interim success criterion for the primary endpoint is met. The study can be terminated early for success only if both the primary endpoint and the cardiovascular death endpoint reach the statistical significance level of approximately 0.005 (one-sided); otherwise, the study will continue until the pre-specified number of 590 cardiovascular deaths have accumulated. If the study can be stopped early for success, the nominal one-sided significance level of approximately 0.005 for the primary endpoint and cardiovascular death will be applied to other secondary endpoints.

Safety

The adverse event profile (including nausea and headache)[1] in VICTORIA was related to vericiguat's mechanism of action and similar to other soluble guanylate cyclase stimulators.[21] These adverse events were generally non-serious and uncommon even in the high-risk VICTORIA population. The effect of vericiguat on systolic blood pressure during the study was ~1–2 mmHg more mean reduction in participants who received vericiguat.[1,22] Based on the overall safety profile of vericiguat in VICTORIA, the VICTOR trial has been granted by the US Food and Drug Administration a more streamlined approach to adverse event monitoring by sites. Safety endpoints of clinical interest include adverse events of symptomatic hypotension, anaemia and drug-induced liver injury. Since ARNI therapy has a well-established vasodilatory effect with a larger decrease in blood pressure compared to angiotensin-converting enzyme inhibitors alone,[23,24] evaluation of safety in this subgroup is of interest. In VICTORIA there was no clear evidence of increased adverse events, dizziness or hypotension with vericiguat compared to placebo in those on background ARNI therapy[12]; however, VICTOR is expected to have a larger proportion of patients receiving this therapy. Modestly higher proportions of participants with an adverse event of anaemia were observed in the vericiguat arm (9.6%) compared with the placebo arm (7.4%) in VICTORIA.[25] Since SGLT2i have been shown to improve anaemia in HFrEF through multiple mechanisms,[26,27] the effect of vericiguat on anaemia in this population with anticipated high SGLT2i use will be evaluated.

Discussion

The VICTOR trial has several unique features that will provide novel insight. The exclusive focus on patients without recent worsening HF is unique among large outcome trials in HFrEF. Recruited patients are also anticipated to have higher rates of quadruple therapy than prior trials, thereby being more representative of the contemporary epidemiology of HFrEF following the availability of ARNI and SGLT2i. These baseline features are expected to translate into a lower cardiovascular death rate reflecting true contemporary

residual risk for a well-treated ambulatory HFrEF population. It is also likely that an alteration in the traditional composition of cardiovascular death events will be observed, with a lower sudden cardiac death rate anticipated in the setting of excellent background medical and device therapy. Recognizing these factors, VICTOR is designed as an event-driven trial where follow-up will continue until the target number of cardiovascular death events is achieved. Indeed, per protocol, the trial duration is event driven until 590 cardiovascular death events, providing sufficient statistical power to detect (or rule out) any clinically and statistically significant effect of vericiguat on cardiovascular death. VICTOR will therefore likely provide reliable estimates of the effects of vericiguat on cardiovascular death in current ambulatory patients with HFrEF who continue to have meaningful residual risk.

VICTOR is the first large event-driven trial in patients with HFrEF with an expected high utilization of both ARNI and SGLT2i. The contemporary HFrEF trials that established ARNI and SGLT2i as foundational therapy included active treatment arms with either no patients on current standard of care with quadruple therapy (PARADIGM-HF[9]) or very low use of quadruple therapy (DAPA-HF,[10] EMPEROR-Reduced[11]). There is currently uncertainty about expected mortality and HF event rates in a contemporary HFrEF population with high utilization of quadruple therapy, information that is necessary to calibrate residual risk for considering additional and advanced HF therapies, including drugs and devices. In VICTOR, anticipated event rates were modelled for a contemporary stable HFrEF population by combining prior trial estimates, but the actual observed rates in VICTOR will provide the most up to date estimates of residual risk for ambulatory HFrEF with modern medical therapy. VICTOR will represent the first HFrEF trial attempting to demonstrate incremental efficacy on HF outcomes in what is likely to be the most well-treated HFrEF trial cohort to date.

Another notable feature of VICTOR is the enrolment of an ambulatory HFrEF population with intentional exclusion of those with recent worsening HF. Prior outcome trials have focused either exclusively on patients with recent worsening HF (GALACTIC-HF,[14] VICTORIA[1]), or included subsets with recent hospitalization for HF within 6 months (between 16–31% in PARADIGM-HF,[9] DAPA-HF[10] and EMPEROR-Reduced[11]) (*Table 3*). Inclusion of such patients enriches for a cohort with high short-term event rates. Although this is appealing from a trial design standpoint to decrease the trial duration, there are potential downsides to this approach. Patients with recent worsening HF have an increased early risk for HHF regardless of treatment.[6] The high early HHF events and resulting short duration of follow-up limits the ability to assess the longer term effect of novel therapy on mortality. In addition to shorter duration of randomized drug exposure, early events after recent worsening HF are dominated by recurrent worsening HF with HHF events, with proportionally lower cardiovascular death events as a component of the primary endpoint.

For reference, there was a median 27-month follow-up in a more general HFrEF cohort in PARADIGM-HF, with a higher contribution of cardiovascular death to the primary endpoint compared to first HHF events (ratio cardiovascular death/HHF for primary endpoint = 0.70)[28] (*Table 3*). In contrast, the median follow-up time for randomized drug exposure was 10.8 months in the exclusively worsening HF cohort in VICTORIA with much lower cardiovascular death events relative to first HHF events (ratio cardiovascular death/HHF for primary endpoint = 0.30).[28] Without focusing on a recent worsening HF population and with adequate median follow-up, both cardiovascular mortality and HHF were statistically significantly reduced with ARNI therapy in PARADIGM-HF. In VICTORIA however, only HHF was reduced with vericiguat, with lack of statistical significance for the effect on cardiovascular death possibly a result of the short median follow-up and high rate of early HHF in the exclusively worsening HF population studied. In another worsening HF population from the GALACTIC-HF trial, there was also a high HHF event rate relative to that for cardiovascular death (ratio cardiovascular death/HHF for primary endpoint = 0.30); however, the trial was larger with greater planned power to evaluate cardiovascular death compared to VICTORIA. This, combined with the longer 21.8 month median follow-up in GALACTIC-HF provided more confidence in the conclusion that treatment with omecamtiv mecarbil did not reduce the incidence of cardiovascular death. With enrolment of a relatively stable ambulatory HFrEF population in VICTOR, lower event rates will likely result in a longer median follow-up, and should provide definitive evidence for either the presence or absence of a meaningful effect of vericiguat on cardiovascular mortality in patients with HFrEF.

The expected longer median drug exposure in VICTOR will also address the relative risks and benefits in this well-treated ambulatory HFrEF cohort with high background ARNI and SGLT2i use. The high use of both ARNI and SGLT2i, which each independently decrease sudden cardiac death,[17,18] along with high rates of defibrillator use is likely to result in a shift in mode of cardiovascular death with a lower expected rate of sudden cardiac death. As the first large contemporary trial of patients with ambulatory HFrEF without recent worsening HF, VICTOR will provide the most robust clinical trial information on the residual risk of HF events and sudden death in patients on quadruple therapy, with high utilization of an implantable defibrillator.

The VICTORIA trial left unresolved the question of whether vericiguat reduces cardiovascular mortality in HFrEF patients. The VICTOR trial is specifically powered for the cardiovascular death component of the primary endpoint, and will continue until the planned number of cardiovascular death endpoints have been achieved. This key aspect of the trial design will allow the efficacy of vericiguat on cardiovascular death to be reliably determined. Inclusion of patients with ambulatory HFrEF in VICTOR who were excluded from VICTORIA will add valuable information to the totality of evidence of the effects of vericiguat across the spectrum of risk for patients with HFrEF.

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