A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator

The VICTORIA Trial

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ABSTRACT

This trial sought to evaluate whether vericiguat, a novel oral soluble guanylate cyclase (sGC) stimulator, was superior to placebo, on a background of standard of care, in increasing the time to the first occurrence of the composite endpoints of cardiovascular (CV) death and heart failure (HF) hospitalization in patients with HF with reduced ejection fraction (HFrEF). Deficiency in sGC-derived cyclic guanosine monophosphate (cGMP) causes both myocardial dysfunction and impaired endothelium-dependent vasomotor regulation that includes the myocardial microcirculation. Experimental studies have suggested multiple potential benefits of sGC stimulators including prevention, or even reversal, of left ventricular hypertrophy and fibrosis, as well as reduction of ventricular afterload through both systemic and pulmonary vasodilation. Hence, restoration of sufficient nitric oxide (NO)-sGC-cGMP signaling has been proposed as an important treatment target in HF. Vericiguat has been shown to directly stimulate sGC and enhance sGC sensitivity to endogenous NO. Available phase IIb data in HFrEF patients indicate vericiguat is safe and well-tolerated, and exploratory analyses indicate that it results in a dose-dependent, clinically significant reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) at the highest tested dose. VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) is a randomized, placebo-controlled, parallel group, multicenter, double-blind, event-driven phase 3 trial of vericiguat in subjects with HFrEF. Approximately 4,872 subjects will be randomized to evaluate the efficacy and safety of vericiguat compared with placebo on a background of standard of care. After a screening phase of up to 30 days, eligible subjects will be treated until the required number of cardiovascular deaths is observed. The estimated median follow-up duration is approximately 18 months. All subjects will be followed until study completion to assess for the occurrence of endpoint events. VICTORIA will establish the efficacy and safety of vericiguat on cardiovascular death and HF hospitalization in patients with HFrEF. (A Randomized Parallel-Group, Placebo-Controlled, Double-Blind, Event-Driven, Multi-Center Pivotal Phase III Clinical Outcome Trial of Efficacy and Safety of the Oral sGC Stimulator Vericiguat in Subjects With Heart Failure With Reduced Ejection Fraction [HFrEF]—VerICiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction [VICTORIA]; NCT02861534) (J Am Coll Cardiol HF 2018;6:96–104) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Heart failure (HF) with reduced ejection fraction (HFrEF) constitutes a major global public health challenge. Not only does HF represent a substantial cause of morbidity and mortality, but it also imposes a major economic burden on the health care system. Although advances in care have reduced mortality and morbidity, the prognosis for these patients remains poor. It is estimated that only 50% of patients survive 5 years beyond their initial diagnosis. Moreover, repeated hospitalizations and the need for supplemental parenteral emergent therapy provoked by frequent exacerbations signal both an impaired quality of life and an even worse prognosis. Notwithstanding the optimal use of evidence-based HFrEF therapy, these clinical realities represent both unmet needs and opportunities for advancements in care. Hence, as articulated in the 2013 American College of Cardiology/American Heart Association guidelines, “Future research will need to focus on novel pharmacological therapies, especially for hospitalized HF” (1).

Vericiguat (Central Illustration) is a novel soluble guanylate cyclase (sGC) stimulator optimized for once-daily dosage in development for chronic HF. Beyond its vasodilatory properties, low-dose sGC stimulation in preclinical models has been shown to also have direct antifibrotic effects, improving myocardial remodeling and diastolic relaxation in the absence of any hemodynamic effects. The sGC is the intracellular receptor for its endogenous ligand nitric oxide (NO). NO is generated in endothelial cells upon physiologic stimuli such as laminar blood flow shear forces as well as within the endocardium. NO diffuses to neighboring tissues such as vascular or cardiac muscle cells and stimulates sGC to generate cyclic guanosine monophosphate (cGMP) in these cells (2). The sGC-mediated production of cGMP is essential for normal cardiac and vascular function (3-5). In HF patients, endothelial dysfunction and reactive oxygen species have been shown to reduce NO bioavailability, resulting in relative sGC deficiency and a reduction in cGMP synthesis (2). Reduced sGC activity associated with coronary microvascular dysfunction, cardiomyocyte stiffness, interstitial fibrosis, and ultimately, myocardial dysfunction has been suggested as a driving factor behind the progression of myocardial dysfunction in HF (6-8). These mechanisms are not directly addressed by currently established therapies that modulate neurohumoral blockade and afterload reduction. Direct NO-independent sGC stimulation is hypothesized to offer a novel approach to address the relative cGMP deficit in HF, and the sGC stimulator, vericiguat, was developed for this purpose (9). Preclinical and clinical studies with other sGC stimulators have suggested that vericiguat is well suited for development as an HF agent based on its direct vasodilatory properties, as well as on its targeting myocardial compliance, diastolic function, endothelial function to improve vasotonal regulation, ventricular-arterial coupling, and cardiac reserve in HF (10). Clinical support for the concept of the sGC stimulator mechanism in HFrEF was established with riociguat in the LEPHT (Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial) study (11), which showed that sGC stimulators are both well tolerated in patients with advanced systolic left ventricular dysfunction and secondary pulmonary hypertension due to HF and improve cardiac index, quality of life, and pulmonary and systemic vascular resistance at 16 weeks of treatment. These hemodynamic improvements occurred in the absence of changes in heart rate, blood pressure, and the primary endpoint pulmonary...
Endothelial dysfunction due to oxidative stress and inflammation reduces nitric oxide bioavailability leading to insufficient activation of sGC. The resulting cGMP deficiency is associated with myocardial dysfunction and impaired endothelium-dependent vasomotor regulation (orange). Vericiguat directly stimulates sGC in a NO-independent manner and by sensitizing the enzyme to endogenous NO (green). cGMP = cyclic guanosine monophosphate; HF = heart failure; NO = nitric oxide; sGC = soluble guanylate cyclase.

Evidence supporting the current study emanates from the phase IIb dose-finding study (SOCRATES-REDUCED [SOluble guanylate Cyclase stimulatorR in heArt failure]) in subjects with HFrEF. In that study, vericiguat was added to standard of care in patients with worsening chronic HF requiring hospitalization or intravenous (IV) diuretic treatment and increased B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) (14). Whereas the pre-specified primary endpoint analysis comparing the impact of the 3 pooled higher dose groups on NT-proBNP to placebo did not reach statistical significance, an exploratory analysis showed a clinically significant reduction of NT-proBNP at the highest dose group. Although not powered for clinical endpoints, exploratory analysis also revealed numerical trends in both cardiovascular (CV) death and HF hospitalization, as well as improved New York Heart Association (NYHA) functional class in the 2 highest dose groups along with concurrent improvement in left ventricular EF with the highest target vericiguat dose (14). Overall, vericiguat was safe and well tolerated relative to placebo, except for treatment-emergent syncope and hypotension that was more common in the 10-mg group (although this tended to occur within the first 2 weeks of randomization while receiving the 2.5-mg dose). These findings provide the rationale for this phase III clinical outcome trial in HFrEF. By contrast, in another phase 2 study of HFpEF patients, vericiguat did not modify NT-proBNP concentration but did demonstrate improvement in quality of life metrics (15).

Bayer and Merck Sharp & Dohme (Whitehouse Station, New Jersey) are supporting the co-development of vericiguat in collaboration with academic partners at the Canadian Virtual Coordinating Global Collaborative Cardiovascular Research Centre at the University of Alberta and the Duke Clinical Research Institute to conduct the VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial.

**STUDY OBJECTIVES**

The primary objective of the VICTORIA trial is to determine whether vericiguat is superior to placebo on a background of standard of care in increasing the time to the first occurrence of the composite endpoint of CV death or HF hospitalization in patients with HFrEF.

Secondary objectives are to determine whether vericiguat is superior to placebo in increasing the time to CV death, time to first and subsequent HF hospitalizations, time to first occurrence of the composite of all-cause mortality or HF hospitalization, and time to all-cause mortality and to assess the safety and tolerability of vericiguat.

Other exploratory objectives include comparison of vericiguat with placebo regarding the time to first occurrence of the composite of HF hospitalizations or urgent HF visits, time to first CV hospitalizations, total number of HF hospitalizations, and changes in quality of life health-related summary measurements (using Kansas City Cardiomyopathy Questionnaire and EuroQol Group 5-Dimensional surveys) from baseline. The relationships among treatment effect, baseline biomarkers, and genetic variation will also be examined.
METHODS

STUDY DESIGN. This is a randomized, placebo-controlled, parallel-group, multicenter, double-blind, event-driven trial of vericiguat in subjects with HFrEF, to be conducted in conformance with Good Clinical Practice. Approximately 4,872 subjects will be randomized in a 1:1 ratio to compare the efficacy and safety of vericiguat with those of placebo on a background of standard of care. After a screening phase of up to 30 days, eligible subjects will be treated until the required number of CV deaths is observed. The estimated median follow-up duration is approximately 18 months. All subjects will be followed until study completion to assess for the occurrence of endpoint events.

STUDY INTERVENTION. As shown in Figure 1, after randomization, the protocol is initiated with a 2.5-mg dose of vericiguat or matching placebo. Subjects will then be up-titrated in a blinded fashion to 5 mg and subsequently to the target dose of 10 mg of vericiguat or matching placebo. This titration criterion is based on evaluation of mean systolic blood pressure and clinical symptoms at 2-week intervals. Following the 4-week titration phase, subjects will be evaluated every 4 months until study completion. In order to maximize the likelihood of titration to the 10-mg target dose, additional efforts (at the discretion of the investigator) will be undertaken at every subsequent visit throughout the study to consider upward titration in those subjects not reaching the target dose, based on mean systolic blood pressure measurement and safety considerations.

STUDY POPULATION. The population includes subjects ≥18 years of age with chronic HF (NYHA functional classes II to IV) and reduced EF of <45% receiving standard of care, guided by European Society of Cardiology and American Heart Association/American College of Cardiology heart failure guidelines, as well as country specific guidelines (where they exist). Inclusion and exclusion criteria are described in Table 1 and reflect experience in the SOCRATES-REDUCED trial (14). While a similar population is being targeted in this phase III trial, the inclusion window has been extended from 4 weeks to 6 months post-discharge to include a broader HF population ranging from those initially stabilized after hospitalization or IV diuretic treatment to long-term stable patients after their most recent HF event. This temporal window in the context of worsening HF is meant to provide a broader and more representative HF patient population. Additionally, given a lack of meaningful influence of vericiguat on blood pressure in the SOCRATES-REDUCED trial, the minimal systolic blood pressure exclusion criterion has been lowered from 110 to 100 mm Hg.
STATISTICAL CONSIDERATIONS. The sample size estimation is based on a 1:1 randomization. The overall study-wise type I error will be controlled at 0.025 (1-sided). The study is event-driven, and accrual is planned to occur over 30 months with a follow-up of 9 months after the last subject is enrolled. The sample size calculation is determined by the CV death component of the composite primary endpoint; the expected event rate of CV death in the placebo group is 11% after 12 months. The relative risk reduction with vericiguat is assumed to be 20%, relating to a hazard ratio (HR) of 0.8. Using the log-rank test, 782 deaths confirmed by a Clinical Events Committee (CEC) will be required to achieve 80% power. For the placebo arm, the event rate of the composite endpoint, that is, first HF hospitalization or CV death, is expected to be 23% after 12 months. The relative risk reduction with vericiguat is also assumed to be 20%, relating to an HR of 0.8. With a sample size of 4,872 subjects, it is anticipated that 1,951 subjects will experience a composite primary endpoint event resulting in an expected power of approximately 98%. The time point of final analysis will be based on the number of CV deaths. The median treatment duration will be approximately 480 days. If the CV death event rate is higher than anticipated, such that the median follow-up time is <10 months when 782 CV death events have been observed, the study will continue until a median follow-up time of 10 months has been reached.

A futility interim analysis to assess lack of efficacy is planned when approximately 50% of the primary events are observed. An efficacy interim analysis is planned to test for the primary endpoint and the secondary endpoint of time to CV death at the time when approximately 75% of the CV death events are observed. In accordance with this interim analysis, the nominal 1-sided significance level will be 0.0241 at the final analysis (Figure 2).

Analysis of the primary efficacy endpoint will follow the intention-to-treat principle on all subjects randomized. This analysis will be based on results from centrally performed blinded adjudication and will test whether the time to the first occurrence of the composite endpoint is prolonged in the vericiguat as compared to that in the placebo group. Subgroup analysis according to standard prognostically relevant baseline factors will be performed and also include the following: baseline NT-proBNP concentration by quartiles, EF of <35% versus ≥35%, and use of sacubitril/valsartan therapy. Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory tests, and vital signs. Based on the aforementioned analyses, an independent Data Safety Monitoring Board (DSMB) supported by a statistical group external to the trial will make recommendations to the Executive Steering Committee chairman to continue under the current protocol, amend the current protocol, or terminate the study. The DSMB will function under prespecified guidelines and procedures, as described in a separate charter.

Table 1: VICTORIA Trial Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Main Exclusion Criteria</th>
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<tr>
<td>Ejection fraction of &lt;45% assessed within 12 months prior to randomization</td>
<td>Clinically unstable</td>
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<tr>
<td>Elevated natriuretic peptide levels within 30 days prior to randomization; for patients in sinus rhythm, BNP ≥300 pg/ml and for NT-proBNP ≥1,000 pg/ml; for those in atrial fibrillation, BNP &lt; 500 pg/ml; and for NT-proBNP ≥1,600 pg/ml*</td>
<td>Systolic blood pressure &lt;100 mm Hg</td>
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<td>Prior HF hospitalization within 6 months (those ≥3 months limited to 20%) or outpatient IV diuretic therapy for HF within 3 months prior to randomization</td>
<td>Concurrent or anticipated use of long-acting nitrates of sGC stimulator</td>
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<td></td>
<td>PDE5 inhibitors</td>
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<td>Receiving IV inotropes, an implantable LV assist device or awaiting heart transplantation</td>
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<td></td>
<td>Correctable, complex, or clinically active cardiac comorbidity</td>
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<td></td>
<td>Prior cardiac valve intervention &lt;3 months or coronary revascularization &lt;60 days</td>
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<td></td>
<td>Unable to provide informed consent</td>
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<td></td>
<td>Females of reproductive age not using an acceptable form of contraception</td>
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*For those subjects receiving sacubitril/valsartan, NT-proBNP criteria will be applied.

BNP = brain natriuretic peptide; HF = heart failure; IV = intravenous; LV = left ventricle; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PDE5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase; VICTORIA = Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction.
Consortium, Austin, Texas) and as prespecified in the CEC charter. Data adjudicated by the CEC will be used in the final safety and efficacy analysis, unless otherwise stated.

ADVERSE EVENTS OF SPECIAL INTEREST OR EVENTS OF CLINICAL INTEREST. Clinical investigator reports of “symptomatic hypotension” and “syncope” (nonserious and serious adverse events) will be followed as prespecified adverse events of special interest (also known as an “event of clinical interest”), using accelerated reporting timelines. Furthermore, following available standard regulatory guidance, significant laboratory elevations of liver enzymes (alanine aminotransferase or aspartate aminotransferase $\geq 3 \times$ upper limit of normal) and total bilirubin ($\geq 2 \times$ upper limit of normal in the absence of alkaline phosphatase $\geq 2 \times$ upper limit of normal) will be followed as events of clinical interest (Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation; U.S. Food and Drug Administration, Rockville, Maryland).

TRIAL ORGANIZATION. VICTORIA is co-sponsored by Bayer and Merck Sharp & Dohme (Whitehouse Station, New Jersey) and conducted in collaboration with the Canadian Virtual Coordinating Global Collaborative Cardiovascular Research Centre (Edmonton, Alberta, Canada) and the Duke Clinical Research Institute (Durham, North Carolina). An executive committee supported by national leaders from participating countries/regions, a DSMB, and a CEC will oversee all aspects of the VICTORIA study (membership provided in Online Appendix A). The executive committee consists of international academic thought leaders as well as lead representatives from the joint sponsors. The independent DSMB and external DSMB statistician(s) will have access to all data and randomization codes throughout the trial. The sponsors and executive committee will have equal access to and possession of the data once it is unblinded. The executive committee will be primarily responsible for the creation, review, and submission of publications and presentations relating to the major aspects of the study. The executive committee will encourage and support other manuscript(s) for publication and presentations of similar material by the national leaders and/or study investigators as determined appropriate.

ANCILLARY STUDIES. Additional studies will be performed in conjunction with the VICTORIA trial, including baseline and serial blood sampling for vericiguat pharmacokinetics and their relationship to efficacy. The VICTORIA biomarkers and pharmacogenomics substudies are designed with the pre-specified goal of distinguishing genomic variants and soluble protein biomarkers that modulate and predict the safety and efficacy of vericiguat in the treatment of
patients with chronic systolic HF. Pharmacogenomic analyses will be executed using a genome-wide association study that will identify genomic loci that modulate individual response to vericiguat, distinguish certain populations with heightened sensitivity (either positive or negative) to the agent, and determine whether certain populations may benefit more preferentially from vericiguat therapy based on their ancestral origin. The biomarker analyses will provide insights into the potential mechanisms of therapeutic effect in HF beyond what is currently understood about how vericiguat affects cellular function. These analyses will include assessment of biomarkers that assess inflammation (high-sensitivity interleukin-6, high-sensitivity C-reactive protein, and growth differentiation factor-15), cardiac injury (high-sensitivity cardiac troponin T), myocardial stress/stretch (NT-proBNP, somatostatin receptor type 2), remodeling (galectin-3), and the cardio-renal axis (cystatin C, creatinine).

Comprehensive ancillary imaging studies will be performed before first drug exposure and after 8 months, following standardized imaging manuals and operational procedures. To this end, all participating sites will be trained and certified. Centralized echocardiography analyses (n = 900) will include standard parameters of cardiac structure and function, including volumes and left ventricular ejection fraction. Additional parameters, such as strain, measurements of right ventricle (RV) function, and estimated pulmonary artery systolic pressure will be assessed. Cardiac magnetic resonance imaging analyses (n = 180) will include 3-dimensional (3D) quantification of LV mass, as well as focal (scar) and diffuse fibrosis (extracellular volume). The key aim of the ancillary imaging substudy is to assess the effects of 8 months’ therapy, using vericiguat versus placebo on cardiac structure and function. Further details are provided in Table 2.

An economic and quality-of-life study will be performed in subjects enrolled in North America. Working groups in conjunction with executive committee oversight will conduct these studies.

**DISCUSSION**

Mortality and morbidity remain particularly high in patients with HFREF who require hospitalization or IV diuretic treatment for HF. Moreover, temporary intravenous application of novel drugs upon hospitalization when added to accepted therapy for worsening HF have failed to improve long-term outcomes (15). Hence, continued long-term treatment with novel compounds such as sacubitril/valsartan added to available standard of care for patients with HFREF show promise by improving outcomes in these patients (17). In HF there is disruption of NO-sGC-cGMP signaling related in part to impaired production of NO or its excessive degradation (18). Further negative repercussions modulated through a different pathway relate to inadequate release of atrial and B-type natriuretic peptides or release of their abnormal derivatives as ligands of extracellular pGC, thereby exacerbating HF. To overcome the presumed deficiency in sGC-derived cGMP in HF, generation of cGMP by guanylate cyclases has been previously attempted through the addition of nitrates or indirectly by inhibition of phosphodiesterase type-5 (PDE5), slowing the degradation of cGMP.

Given the limitations of these strategies, including the development of nitrate tolerance, the limited PDE5 expression in cardiac tissues, and the dependence on endogenous cGMP, neither have proven efficacious for the chronic treatment of HF. The mechanism of action of vericiguat is distinct from that of sacubitril’s inhibition of neprilysin. Vericiguat interacts directly with sGC, the intracellular receptor for endogenous nitric oxide, which stimulates cGMP production. In contrast, sacubitril

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**TABLE 2** Techniques and Parameters Acquired in VICTORIA Imaging Studies

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<tr>
<th>Cardiac Magnetic Resonance</th>
<th>Echocardiography</th>
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<tr>
<td>SSFP Cine imaging</td>
<td>2D Imaging</td>
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<tr>
<td>T1 Mapping (MOLLI) (pre- and post Gd-contrast)</td>
<td>3D Imaging</td>
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<tr>
<td>T2 Mapping</td>
<td>Color Doppler imaging</td>
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<tr>
<td>Delayed contrast enhancing imaging</td>
<td>Spectral Doppler imaging</td>
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<tr>
<td>Imaging Parameters</td>
<td>Tissue Doppler imaging</td>
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Gd = gadolinium; LA = left atrium; LV = left ventricular; MOLLI = Modified Look-Locker Inversion; SSFP = steady-state free precession; VICTORIA = Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction.
affects the particulate guanylate cyclase (pGC), the membrane-bound receptor for natriuretic peptides, indirectly by inhibition of the degradation of the endogenous ligand. Hence, both the receptor type as well as the molecular mode of action are different. Vericiguat has a dual mode of action to help correct the relative cGMP deficiency observed in advanced forms of HF. It sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. It also directly stimulates sGC by a different binding site, independent of NO. sGC stimulation through vericiguat leads to an increase in intracellular cGMP in cardiac myocytes and vascular smooth muscle cells affecting directly both myocardial function and vascular tone. In contrast, sacubitril inhibition primarily effects pGC receptor, resulting in an increase in extracellular cGMP, dependent on the endogenous levels of natriuretic peptides (19).

STUDY LIMITATIONS. Activators of these 2 distinct signaling pathways are expected to have nonredundant effects owing to the intracellular compartmentation of cGMP-dependent effectors (20). Preclinical studies as well as early development studies further document the additive pharmacodynamics effect of these 2 mechanisms. Therefore, although the potential for hypotension with concomitant blood pressure-lowering drugs also includes sacubitril/valsartan, the combination of vericiguat with neprilysin inhibitors is expected to be safe and well tolerated. Instead, coactivation of both distinct GCs has been postulated as potential beneficial therapeutic strategy in HF (21).

CONCLUSIONS

The VICTORIA trial constitutes a novel, major industrial and academic collaboration directed toward meeting clinical needs of high-risk HFrEF patients with progression of chronic HF despite optimized standard of care therapy. It represents the first phase III study of vericiguat, a novel sGC stimulator designed to enhance outcomes in this disorder. Additional supporting ancillary studies will help to elucidate an understanding of the clinical outcomes. A substantial international effort is now under way to recruit appropriate patients. The first patient was randomized on September 23, 2016. Study enrollment is expected to be completed before the end of 2019.

ACKNOWLEDGEMENT The authors thank Lisa Soulard for her expert editorial assistance.

REFERENCES


PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HFrEF constitutes a major global public health challenge. Deficiency in sGC-derived cGMP causes both myocardial dysfunction and impaired endothelium-dependent vasomotor regulation, and restoration of sufficient sGC-cGMP signaling has been proposed as a potentially important target in HF therapy. The VICTORIA trial will establish the efficacy and safety of vericiguat, a soluble guanylate cyclase stimulator, in increasing the time to the composite endpoint of cardiovascular death or hospitalization in patients with HFrEF.

TRANSLATIONAL OUTLOOK: Successful demonstration of the efficacy and safety of vericiguat will address a key unmet need for a new pharmacological treatment of patients with HFrEF. Additional supporting ancillary studies will help to elucidate an understanding of the observed clinical outcomes.

KEY WORDS cardiovascular, heart failure, heart failure with reduced ejection fraction, NO-sGC-cGMP, pGC

APPENDIX For a listing of the members of the VICTORIA study group, please see the online version of this paper.