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STATE-OF-THE-ART PAPER

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 2017;■:■–■)

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ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

NO-sGC-cGMP = nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate

pGC = particulate guanylate cyclase

sGC = soluble guanylate cyclase

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 (**Figure 1**) 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 Left Ventricular

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