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CADTH Reimbursement Review

Vericiguat (Verquvo)

Sponsor: Bayer Inc.

Therapeutic area: Heart failure

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Abbreviations

6MWT	6-minute walk test
ACEi	angiotensin-converting enzyme inhibitor
AE	adverse event
ARB	angiotensin receptor blocker
ARNi	angiotensin receptor–neprilysin inhibitor
ASaT	all subjects as treated
BIA	budget impact analysis
BNP	brain natriuretic peptide
CEC	Clinical Events Committee
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CrI	credible interval
CV	cardiovascular
eGFR	estimated glomerular filtration rate
EQ-5D-3L	3-Level EQ-5D
EQ-5D-5L	5-Level EQ-5D
EQ VAS	EQ visual analogue scale
GDMT	guideline-directed medical therapy
HF	heart failure
HHF	hospitalization for heart failure
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention to treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LS	least squares
LVEF	left ventricular ejection fraction
MCID	minimal clinically important difference
MI	myocardial infarction
MID	minimal importance difference
MRA	mineralocorticoid receptor antagonist
NMA	network meta-analysis
NO	nitric oxide
NP	natriuretic peptide

NT-proBNP	N-terminal pro–B-type natriuretic peptide
NYHA	New York Heart Association
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SF-36	36-item Short Form Survey
sGC	soluble guanylate cyclase
SGLT2	sodium-glucose cotransporter-2
SOC	standard of care

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Vericiguat (Verquvo), 2.5 mg, 5 mg, 10 mg, orally administered, film-coated tablets
Indication	Verquvo (vericiguat) is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent heart failure decompensation event requiring hospitalization and/or IV diuretic therapy. Verquvo should be used in combination with standard-of-care therapy for heart failure.
Reimbursement request	For the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent heart failure decompensation event requiring hospitalization and/or IV diuretic therapy. Vericiguat should be used in combination with standard-of-care therapy for heart failure. Initiation criteria: • In adult patients with chronic heart failure of NYHA class II, III, or IV • Other heart failure therapies include an ACEi, ARB, or ARNi, a beta-blocker, and, if tolerated, an MRA • Vericiguat should be initiated under the supervision of a health care professional who is experienced in the management of heart failure.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	April 28, 2023
Sponsor	Bayer Inc.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor and neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; NOC = Notice of Compliance; NYHA = New York Heart Association.

Introduction

Heart failure (HF), sometimes referred to as congestive heart failure, is a clinical condition in which the heart is unable to adequately pump blood throughout the body to maintain the metabolic needs of tissues and organs. HF results from structural or functional impairment of ventricular filling or ejection of blood.[1,2] HF is classified based on the percentage of blood that is being pumped out of the left ventricle, otherwise known as the left ventricular ejection fraction (LVEF).[2] HF with reduced ejection fraction is defined as HF with an LVEF of 40% or less, whereas having an LVEF of 50% or greater is termed HF with preserved ejection fraction. There are an estimated 669,000 people in Canada older than 40 years with HF, with an age-standardized prevalence of 3.5%.[3] Between 2001 and 2013, the age-standardized incidence rate of HF in Canada declined, as did the age-standardized all-cause mortality rate among people living with HF.[3] However, people in Canada older than 40 years with HF are 6 times more likely to die than those without a HF diagnosis.[3] The economic burden due to HF is substantial, with costs associated with health care services, medications, and lost productivity.

Common symptoms of HF include dyspnea (breathlessness) and fatigue, exercise intolerance, and fluid build-up, which in turn may lead to pulmonary congestion and peripheral edema (mainly in the feet, ankles, or legs) that can have a significant effect on a patient's quality of life.[1] Depending on symptom severity, HF may go unnoticed, only causing minor symptoms, but patients with advanced HF may find it difficult to carry out normal everyday activities.[4] HF leads to a progressive decline in cardiac function over time, with persistent signs and symptoms interspersed with acute episodes of decompensation. Acute decompensated HF is a sudden worsening of the signs and symptoms of HF that often lead to hospitalization or an emergency department visit.[5] Worsening HF and hospitalization for heart failure (HHF) portend a poor prognosis and are associated with an increased risk of mortality and hospital readmission.[6] Hospitalizations due to HF are frequent, with 83% of patients hospitalized at least once and 43% hospitalized 4 or more times after a diagnosis of HF.[7] It is generally accepted that hospitalization for acute decompensated HF is a powerful predictor of readmission and death after discharge in patients with chronic HF, with postdischarge mortality rates as high as 20%.[5,8] The current foundational pharmaceutical management of HF with reduced ejection fraction encompasses combination therapy (in the absence of contraindications), including 1 evidence-based medication from each of the following categories: (1) sacubitril-valsartan, either as first-line therapy or switching from an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), (2) beta-blockers, (3) mineralocorticoid receptor antagonists (MRAs), and (4) sodium-glucose cotransporter-2 (SGLT2) inhibitors.[6] Recently, new therapies have emerged, such as soluble guanylate cyclase (sGC) stimulators or ivabradine (a sinus node inhibitor), that are taken in conjunction with well-established therapies and have shown benefit in patients with HF with reduced ejection fraction.[6]

Vericiguat is a stimulator of sGC. HF is associated with impaired nitric oxide (NO) synthesis and decreased activity of its receptor, sGC. Vericiguat restores the relative deficiency in this signalling pathway by directly stimulating sGC, independently and synergistically with NO, to increase the level of intracellular cyclic guanosine monophosphate (cGMP), which may improve both myocardial and vascular function. According to the proposed Health Canada indication, vericiguat is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy. Vericiguat should be used in combination with standard-of-care (SOC) therapy for HF. Vericiguat should be initiated under the supervision of a health care professional who is experienced in the management of HF. The recommended starting dose of vericiguat is 2.5 mg administered orally once daily, followed by doubling the dose every 2 weeks to the target maintenance dose of 10 mg, as tolerated by the patient.[9]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of vericiguat 10 mg once daily to reduce the risk of cardiovascular (CV) death and HHF in adults with symptomatic chronic HF and an ejection fraction of less than 45% who are stabilized after a recent worsening HF event in combination with other HF therapies.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, the HeartLife Foundation and the Heart Function Clinic in Vancouver General Hospital, St. Paul's Hospital, British Columbia, provided input for the review of vericiguat. The HeartLife Foundation is a patient-driven federal charity whose mission is to transform the quality of life for people living with HF by engaging, educating, and empowering a global community to create lasting solutions and build healthier lives. The input was informed by interviews with 3 HF specialists (British Columbia, Ontario, and Quebec), 1 researcher (Alberta), and 2 patients with HF (British Columbia and Ontario), as well as a review of study material and online literature.

The HeartLife Foundation indicated that patients with HF experience a wide range of physical, social, and emotional challenges. Symptoms include shortness of breath, extreme fatigue, low blood pressure, dizziness, edema, bloating, palpitations, and arrhythmia. The HeartLife Foundation highlighted that access to care, medical therapies, and support services vary widely across Canada, and that every individual's experience with HF is unique. Two patient interviews (aged 33 and 44 years; 1 male and 1 female) highlighted the impact of HF on their quality of life, including being unable to pursue their desired career or exercise regularly. A recurring theme in the 2 patient interviews was the need to find a "new normal" for life following their diagnosis of HF. The Heart Function Clinic highlighted the following gaps in the treatment of HF: not all patients respond to available treatments and patients become refractory to existing treatment options. The HeartLife Foundation indicated that patients with HF seek to improve their quantitative and qualitative outcomes. The HeartLife Foundation further emphasized that it is imperative to provide equitable access to high-quality care and services for all patients with HF, including access to diagnostics, medical therapy, mental health support, cardiac rehabilitation, and advanced care. The HeartLife Foundation advocated for vericiguat to be approved for the indication under review and suggested that vericiguat will help alleviate the gaps in current therapy.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH for this review indicated that HF with reduced ejection fraction is still associated with increased rates of death and need for hospitalization despite standard therapy. The clinical expert noted that not all patients are eligible for the standard quadruple therapy due to side effects or comorbidities. It was further highlighted by the clinical expert that some patients who experience disease progression while on standard therapy may require de-escalation of therapy to become restabilized. The clinical expert consulted indicated that vericiguat can be added to foundational quadruple HF therapy, as its mechanism of action differs from that of the foundational treatment. However, the impact or role of vericiguat in the context of current quadruple therapy is unknown because the VICTORIA trial was designed and completed before the current therapeutic paradigm, which now includes SGLT2 inhibitors, was widely adopted. The clinical expert consulted indicated that patients included in the VICTORIA trial received foundational therapy and generally tended to be "sicker" than those included in HF trials with other therapies. The clinical expert noted that the response to therapy in clinical practice is assessed based on the reduction in burden of symptoms, the need for escalation of diuretic therapy, hospitalization, or death. The clinical

expert indicated that vericiguat should be prescribed by a practitioner with expertise in the management of HF in specialty clinics with a focus on the assessment and management of HF. It was further mentioned by the clinical expert that the addition of this medication is expected to have a positive impact on the management of these patients.

Clinician Group Input

The clinician group input was obtained from 3 clinician groups, including Oakville Cardiologists, represented by 9 clinicians; 1 clinician from the Division of Cardiology, University of Alberta; and 1 clinician representing the North Shore Heart Centre in Vancouver. The clinician from the Division of Cardiology, University of Alberta, identified the following as key goals of new therapies for HF: reducing recurrent symptoms and the need for hospitalization or emergency department visits. All clinician groups agreed that morbidity and mortality rates remain high in patients with HF with reduced ejection fraction despite advancements in therapies, and many patients cannot be titrated to the optimal doses of the medications due to hypotension, hyperkalemia, bradycardia, or renal dysfunction. The clinician groups agreed that vericiguat represents an additional approach to the treatment of HF with reduced ejection fraction, which is not targeted by current guideline-directed medical therapy (GDMT). The clinician from the Division of Cardiology, University of Alberta, also suggested that because vericiguat does not cause hyperkalemia or impair renal function, patients who cannot tolerate angiotensin receptor–neprilysin inhibitors (ARNis) or ACEis (e.g., patients with diabetes or renal impairment) would be good candidates for vericiguat. The clinical groups pointed out several reasons that may lead to the discontinuation of vericiguat, including a decline in the glomerular filtration rate to less than 15 mL/min/1.73 m^2, severe hypotension, and syncope. The Oakville Cardiologists indicated that physician assessment of clinical stability and patient-reported symptoms continue to be the cornerstone of evaluating response to therapy in patients with HF with reduced ejection fraction in the outpatient setting. The clinical groups advocated for vericiguat to be an accessible treatment option in the high-risk HF patient population, as it is safe, well tolerated, and taken once daily.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially affect the implementation of a CADTH recommendation for vericiguat:

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing therapy
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The VICTORIA trial was a phase III, randomized, multicentre, double-blind, event-driven, placebo-controlled trial designed to assess the efficacy and safety of vericiguat versus placebo as an adjunct to SOC therapy in adults with symptomatic chronic HF and an ejection fraction of less than 45% who are stabilized after a recent worsening HF event. Previous HF decompensation (or worsening) was defined as HHF within 6 months before randomization or the use of an IV diuretic for HF (without hospitalization) within 3 months before randomization. A total of 5,050 patients with symptomatic chronic HF with reduced ejection fraction were enrolled across 694 sites in 42 countries in North America (560 patients), Eastern Europe, Western Europe, the Asia-Pacific region, and Latin and South America. The primary efficacy end point was the time to first event of the adjudicated CV death or HHF; the key secondary end points were time to CV death, time to first event of HHF, time to total events (first and recurrent) of HHF, time to first event of all-cause mortality or HHF, and time to all-cause mortality events. Health-related quality of life (HRQoL) was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EQ-5D instrument. Futility and efficacy interim analyses were planned for the time when approximately 75% (587 events) of the planned number of CV death events were reached and data safety monitoring board could recommend early termination of the trial for overwhelming efficacy or futility. The database lock was executed on October 31, 2019.

Overall, baseline characteristics were well balanced between treatment groups in the VICTORIA trial. The mean age of all randomized patients in the VICTORIA trial was 67.3 years (standard deviation [SD] = 12.2 years). A total of 76.1% of patients were male, and 24.0% were female. About 64.1% of patients were white, while 27.0% were Asian or multiracial. A total of 81.4% of patients were non-Hispanic or non-Latino, and 16.1% were Hispanic or Latino. The mean LVEF was 28.9% (SD = 8.30%), and nearly half of patients had an LVEF of less than 30% (49.3%). Most patients had a New York Heart Association (NYHA) functional class II or III (98.6%) at baseline. The mean N-terminal probrain natriuretic peptide (NT-proBNP) was 4,741.90 pg/mL (SD = 6,845.60 pg/mL), the mean brain natriuretic peptide (BNP) was [redacted] pg/mL (SD = [redacted] pg/mL), and the mean estimated glomerular filtration rate (eGFR) was 61.5 mL/min/1.73 m^2 (SD = 27.2 mL/min/1.73 m^2). Approximately 70% of patients had HHF within 3 months before randomization, 17.2% had HHF within 3 to 6 months, and 15.9% had outpatient treatment with IV diuretics for worsening HF within 3 months before hospitalization. A total of 91.2% of patients received 2 or more HF medications, and only 60% of patients received triple therapy, including ACEis or ARBs, beta-blockers, and MRAs.

Efficacy Results

A summary of the results for the main efficacy and safety outcomes of the VICTORIA trial is presented in Table 2.

Time to First Event of CV Death or HHF

A composite of time to first event of adjudicated CV death or HHF occurred in 897 patients (35.5%) in the vericiguat group and 972 patients (38.5%) in the placebo group. The annual event rate was lower in the

vericiguat group compared with the placebo group (33.6% and 37.8%, respectively), with a hazard ratio (HR) of 0.90 (95% confidence interval [CI], 0.82 to 0.98; P = 0.019) in favour of the vericiguat group. The median follow-up duration was 11.1 months in the vericiguat group and 10.4 months in the placebo group. The proportion of HHF as the first event was lower in the vericiguat group (27.4%) compared with the placebo group (29.6%), whereas proportion of CV death was similar between the treatment groups (8.2% versus 8.9% in the vericiguat and placebo groups, respectively).

Table 2: Summary of Key Results From Pivotal Study

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Time to first event of CEC-confirmed CV death or HHF		
Patients with event, n (%)	897 (35.5)	972 (38.5)
HHF as first event, n (%)	691 (27.4)	747 (29.6)
CV death as first event, n (%)	206 (8.2)	225 (8.9)
Annual rate, %[a]	33.6	37.8
KM% (95% CI) at 2 years[b]	43.9 (41.5 to 46.4)	46.9 (44.4 to 49.4)
HR (95% CI)[c]	0.90 (0.82 to 0.98)	
P value[d]	0.019	Reference
Time to CEC-confirmed CV death		
CV death, n (%)	414 (16.4)	441 (17.5)
Heart failure	165 (6.5)	191 (7.6)
Myocardial infarction	10 (0.4)	11 (0.4)
Stroke	7 (0.3)	16 (0.6)
Other cardiovascular event	13 (0.5)	9 (0.4)
Sudden cardiac death	107 (4.2)	113 (4.5)
Undetermined cause of death	112 (4.4)	101 (4.0)
Annual event rate,[a] %	12.9	13.9
KM% (95% CI) at 2 years[b]	22.0 (20.0 to 24.2)	23.7 (21.6 to 26.0)
HR (95% CI)[c]	0.93 (0.81 to 1.06)	
P value[d,e]	0.269	Reference
Time to CEC-confirmed all-cause mortality		
All-cause mortality, n (%)	512 (20.3)	534 (21.2)
Annual event rate,[a] %	16.0	16.9
KM% (95% CI) at 2 years[b]	26.6 (24.4 to 28.9)	28.3 (26.0 to 30.7)
HR (95% CI)[c]	0.95 (0.84 to 1.07)	
P value[d]	0.377	Reference

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Time to CEC-confirmed all-cause mortality or HHF		
Patients with event, n (%)	957 (37.9)	1,032 (40.9)
All-cause mortality as first event, n (%)	266 (10.5)	285 (11.3)
HHF as first event, n (%)	691 (27.4)	747 (29.6)
Annual event rate,[a] %	35.9	40.1
KM% (95% CI) at 2 years[b]	46.1 (43.6 to 48.6)	49.3 (46.9 to 51.9)
HR (95% CI)[c]	0.90 (0.83 to 0.98)	
P value[d]	0.021	Reference
Time to CEC-confirmed CV hospitalization		
CV hospitalization, n (%)	[redacted]	[redacted]
Annual event rate,[a] %	[redacted]	[redacted]
KM% (95% CI) at 2 years[b]	[redacted]	[redacted]
HR (95% CI)[c]	[redacted]	
P value[d,e]	[redacted]	[redacted]
Time to first event of CEC-confirmed HHF		
HHF, n (%)	691 (27.4)	747 (29.6)
Annual event rate,[a] %	25.9	29.1
KM% (95% CI) at 2 years[b]	35.1 (32.7 to 37.6)	37.5 (35.0 to 40.0)
HR (95% CI)[c]	0.90 (0.81 to 1.00)	
P value[d,e]	0.048	Reference
Time to total events of CEC-confirmed HHF		
Total HHF,[a] n	1,223	1,336
Patients with only 1 event	415	431
Patients with only 2 events	160	179
Patients with only 3 events	55	75
Patients with ≥ 4 events	61	62
Annual rate,[b] %	38.3	42.4
HR (95% CI)[c]	0.91 (0.84 to 0.99)	
P value[d]	0.023	Reference
Change from baseline in KCCQ scores at week 32		
KCCQ overall summary score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Change from baseline mean (SD)		
LS mean (95% CI)		
Difference in LS means[f] (95% CI)		
P value[e]		
KCCQ total symptom score		
Baseline, mean (SD)		
Week 32, mean (SD)		
Change from baseline mean (SD)		
LS mean (95% CI)		
Difference in LS means[f] (95% CI)		
P value[e]		
KCCQ clinical summary score		
Baseline, mean (SD)		
Week 32, mean (SD)		
Change from baseline mean (SD)		
LS mean (95% CI)		
Difference in LS means[f] (95% CI)		
P value[e]		
Change from baseline in the EQ-5D-5L UK index score at week 32		
Baseline, mean (SD)		
Week 32, mean (SD)		
Change from baseline mean (SD)		
LS mean (95% CI)		
Difference in LS means[f] (95% CI)		
P value[e]		
Change from baseline in the EQ-5D-5L US index score at week 32		
Baseline, mean (SD)		
Week 32, mean (SD)		
Change from baseline mean (SD)		
LS mean (95% CI)		
Difference in LS means[f] (95% CI)		
P value[e]		

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Change from baseline in EQ VAS score at week 32		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means[f] (95% CI)	[redacted]	
P value[e]	[redacted]	[redacted]
Harms		
Patients with ≥ 1 AE, n (%)	2,027 (80.5)	2,036 (81.0)
Patients with ≥ 1 SAE, n (%)	826 (32.8)	876 (34.8)
Patients who died due to AE,[g] n (%)	83 (3.3)	85 (3.4)
Withdrawal due to AE, n (%)	167 (6.6)	158 (6.3)
Withdrawal due to SAE, n (%)	71 (2.8)	87 (3.5)
Patients with ≥ 1 AE leading to dose modification,[h] n (%)	653 (25.9)	606 (24.1)
Notable harms, n (%)		
Symptomatic hypotension	229 (9.1)	198 (7.9)
Syncope	101 (4.0)	87 (3.5)
Patients with any hepatic AE, n (%)	23 (0.9)	13 (0.5)

AE = adverse event; CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; EQ VAS = EQ-5D visual analogue scale; EQ-5D-5L = 5-Level EQ-5D; HHF = hospitalization for heart failure; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; KM = Kaplan-Meier; LS = least squares; SAE = serious adverse event; SD = standard deviation.

Notes: For patients with multiple events, only the first event contributing to the composite end point is counted in the table.

Based on data up to the primary completion date (June 18, 2019).

[a]Total events per 100 patient-years at risk.

[b]KM estimate and CI at 2 years.

[c]HR (vericiguat over placebo) and CI from Cox proportional hazard model, controlled for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race.

[e]P value was not adjusted for multiplicity.

[f]Based on a longitudinal analysis of the covariance model, with change in score as the dependent variable, including categorical terms for stratification factor, week, treatment group, and week-by-treatment-group interaction, with the baseline value as a continuous covariate and including all postrandomization time points through week 96. For baseline and week 32, N is the number of patients with nonmissing assessments at the specific time point. For change from baseline, N is the number of patients with nonmissing assessment in both baseline and week 32.

[g]Includes AEs associated with a fatal outcome but does not reflect all deaths reported in the study.

[h]Defined as a dose reduction, drug interruption, or drug withdrawal.

Source: Clinical Study Report for VICTORIA.[10]

Time to CV Death

This secondary outcome was tested in a nonhierarchical sequence without adjustments for multiplicity and was exploratory in nature. The number of CV death events was 414 (16.4%) in the vericiguat group and 441 (17.5%) in the placebo group. The proportion of patients who died of HF was 6.5% and 7.6% in the vericiguat

and placebo groups, respectively; sudden cardiac event 4.2% and 4.5% in the vericiguat and placebo groups, respectively; and undetermined cause of death 4.4% and 4.0% in the vericiguat and placebo groups, respectively. The HR for time to CV death was 0.93 (95% CI, 0.81 to 1.06; P = 0.269).

Time to All-Cause Mortality

A total of 512 (20.3%) patients in the vericiguat group and 534 (21.2%) patients in the placebo group died of any cause. The annual event rate was similar between the treatment groups (16.0% and 16.9% in the vericiguat and placebo groups, respectively), with an HR of 0.95 (95% CI, 0.84 to 1.07; P = 0.377).

Time to First Event of All-Cause Mortality or HHF

A composite of time to first event of all-cause mortality or HHF occurred in 957 patients (37.9%) in the vericiguat group and 1,032 patients (40.9%) in the placebo group. The annual event rate was 35.9% and 40.1% in the vericiguat and placebo groups, respectively, with an HR of 0.90 (95% CI, 0.83 to 0.98; P = 0.021). This difference was likely driven primarily by a lower proportion of HHF events, although individual components of this composite end point were not formally tested for significance.

Time to CV Hospitalization

This secondary outcome was tested in a nonhierarchical sequence without adjustments for multiplicity and was exploratory in nature. A total of [redacted] in the vericiguat group and [redacted] in the placebo group had CV hospitalizations. The annual event rate was lower in the vericiguat group ([redacted]) compared with the placebo group ([redacted]), with an HR of [redacted].

Time to First Event of HHF

This secondary outcome was tested as a component of the primary composite end point in a nonhierarchical sequence without adjustments for multiplicity and was exploratory in nature. The number of patients with HHF events was 691 (27.4%) in the vericiguat group and 747 (29.6%) in the placebo group. The annual event rate was 25.9% in the vericiguat group and 29.1% in the placebo group, with an HR of 0.90 (95% CI, 0.81 to 1.00; P = 0.048).

Time to Total Events (First and Recurrent) of HHF

The total number of HHF events was lower in patients who received vericiguat (n = 1,223) compared with those who received placebo (n = 1,336). The annual event rate was 38.3% in the vericiguat group and 42.4% in the placebo group, with an HR of 0.91 (95% CI, 0.84 to 0.99; P = 0.023).

Health-Related Quality of Life

No strong conclusions could be drawn about the effect of vericiguat compared with placebo on HRQoL due to an increased risk of type I error and a high risk of attrition bias.

KCCQ Score

For the analysis of the KCCQ score based on the intention-to-treat (ITT) population, week 32 data were missing for [redacted] of patients in the vericiguat group and for [redacted] of patients in the placebo group. No clinically meaningful differences were found between treatment groups in change from baseline in KCCQ scores at week 32 (less than minimally important difference [MID] of 5 or more points).

KCCQ Overall Summary Score: The KCCQ overall summary score combines the physical limitation, total symptom, social limitation, and HRQoL domains into a single score. The analysis showed a slight improvement from baseline of [redacted] (SD = [redacted]) in the vericiguat group and [redacted] points (SD = [redacted]) in the placebo group in the KCCQ overall summary score at week 32, with a least squares (LS) mean difference of [redacted].

KCCQ Total Symptom Score: The KCCQ total symptom score combines the symptom burden and symptom frequency domains into a single score. The analysis showed a slight improvement from baseline of [redacted] in the vericiguat group and [redacted] in the placebo group in the KCCQ total symptom score at week 32, with an LS mean difference of [redacted].

KCCQ Clinical Summary Score: The KCCQ clinical summary score combines the physical limitation and total symptom domains into a single score. The analysis showed a slight improvement from baseline of [redacted] in the vericiguat group and [redacted] in the placebo group in the KCCQ clinical summary score at week 32, with an LS mean difference of [redacted].

5-Level EQ-5D

For the analysis of the 5-Level EQ-5D (EQ-5D-5L) index score based on the ITT population, week 32 data were missing for [redacted] of patients in the vericiguat and placebo groups, respectively. No difference was found between the 2 treatment groups in mean change from baseline in EQ-5D-5L score at week 32. For the EQ-5D-5L UK and US index scores, the LS mean differences at week 32 for vericiguat versus placebo were [redacted] and 0.01 (95% CI, −0.01 to 0.03; P = 0.257), respectively.

Harms Results

A total of 2,027 (80.5%) patients in the vericiguat group and 2,036 (81.0%) patients in the placebo group experienced 1 or more adverse events (AEs). The most common AEs that occurred in the vericiguat or placebo groups were hypotension (15.4% and 14.1%, respectively), cardiac failure (8.9% and 9.9%, respectively), anemia (7.6% and 5.7%, respectively), and pneumonia (6.4% and 7.2%, respectively). A total of 653 (25.9%) patients in the vericiguat group and 606 (24.1%) patients in the placebo group experienced 1 or more AEs leading to dose modification. The proportion of fatal AEs during the double-blind treatment phase was similar between the treatment groups (3.3% and 3.4% in the vericiguat and placebo groups, respectively). A total of 826 (32.8%) patients in the vericiguat group and 876 (34.8%) in the placebo groups experienced 1 or more serious adverse event (SAE). Withdrawal of study treatment due to AEs was required in 167 (6.6%) patients in the vericiguat group and 158 (6.3%) patients in the placebo group. The most common reasons for discontinuation in the vericiguat and placebo groups were hypotension (1.9% and 1.3%, respectively), chronic kidney disease (0.3% and 0.6%, respectively), pneumonia (0.1% and 0.2%, respectively), cardiac failure (0.2% and 0.2%, respectively), and dyspepsia (0.2% and 0.1%, respectively). In the VICTORIA trial, symptomatic hypotension was the most commonly reported notable AE (9.1% and 7.9% in the vericiguat and placebo groups, respectively), followed by syncope (4.0% and 3.5% in the vericiguat and placebo groups, respectively), and hepatic AEs (0.9% and 0.5% in the vericiguat and placebo groups, respectively).

Critical Appraisal

Internal Validity

The VICTORIA trial used accepted methods for blinding, allocation concealment, and randomization with stratification by race and geographic region. An Interactive Voice Response System and Integrated Web Response System methodology was used, and randomization with stratification was performed centrally, which typically has a low risk of bias. The baseline demographic and disease characteristics of patients were generally balanced between the treatment groups, so randomization was successful. A relatively high proportion of patients prematurely discontinued the trial medication (38.7%), but the cause of discontinuations occurred at a similar frequency between the treatment groups. The clinical expert consulted by CADTH for this review noted that the main reason for treatment discontinuation was fatal events, reflecting the natural course of HF. In accordance with the exclusion criteria, patients in the trial were randomized starting 24 hours after IV diuretic treatment, which may not be enough time to achieve clinically stability after a worsening HF event and may lead to an underestimation or overestimation of the treatment effect. Furthermore, there was no run-in period in the trial to initiate or maintain optimal doses of HF medications to achieve clinical stability after worsening HF. However, the clinical expert consulted noted that sometimes only 1 dose of a diuretic is required to achieve clinical stability, and sometimes it takes several days or weeks before the patient becomes stable.

An independent blinded Clinical Events Committee (CEC) performed an adjudication of efficacy and safety end points a priori. The clinical expert consulted indicated that the primary and key secondary outcomes were appropriate for the disease setting. The analyses of primary and key secondary outcomes were conducted using the ITT population, which maintains randomization and minimizes the risk of bias by comparing groups with similar prognostic factors. Both interim and final analyses were planned a priori and adequately described; however, the decision was made to cancel the interim analysis because there were more than expected CV death events. Given the potential misclassification of CV deaths, which may overestimate the true incidence of CV death events, as they include undetermined causes of death, there is a possibility that the trial was stopped earlier than planned. Therefore, there is a risk that the effect of vericiguat, compared to placebo, is overestimated, but the presence and extent of any estimation in uncertain.[11-13] The median primary composite end point, all-cause survival, total HHF, and a composite of all-cause mortality and HHF was not estimable because insufficient follow-up time had elapsed for these outcomes; thus, the long-term efficacy of vericiguat is unknown. Subgroup analyses were not adjusted for multiplicity and may not have been powered to detect a treatment difference; as such, any inferences or interpretations based on subgroups should be made with caution. Although improvement in HRQoL was of primary importance for both patients and physicians, this was an exploratory outcome and was tested outside the statistical testing hierarchy. The KCCQ is generally a valid and reliable questionnaire for HF, but there is no evidence for the validity or reliability of the EQ-5D instrument in patients with HF. Clinical experts consulted indicated that these tools are not commonly used in clinical practice. No strong conclusions could be drawn about the effect of vericiguat, compared with placebo, on HRQoL due to an increased risk of type I error and a high risk of attrition bias, especially with longer follow-up.

External Validity

In general, the clinical expert consulted by CADTH for this review confirmed that the population of the VICTORIA trial was similar to patients seen in Canadian clinics, and the study results would be generalizable to patients with HF in Canada with some limitations. CADTH was unable to draw conclusions about patients with NYHA class I or IV HF because the VICTORIA trial excluded patients who had NYHA class I HF and only included a very small proportion of patients who had NYHA class IV HF (1.1%). Furthermore, the clinical expert consulted indicated that patients with NYHA class IV HF are more likely to be clinically unstable than those with NYHA class II or class III HF. About 26.4% of patients in the trial did not pass the screening, predominantly because the NT-proBNP level of those patients was below the prespecified threshold. According to the clinical expert consulted, NT-proBNP testing is not widely available in Canada because some jurisdictions have limited access to it; thus, this patient selection criterion would be difficult to implement in clinical practice. The clinical expert further noted that the enrolment of patients with elevated NT-proBNP levels likely created an enriched population in the trial because these patients appeared to be sicker and more likely to benefit from treatment with vericiguat than the population in the real-world setting. The clinical expert consulted indicated that the population in the VICTORIA trial was younger than the typical adult population in Canada with symptomatic chronic HF with reduced ejection fraction (mean age is 75 to 77 years). Most patients were white and non-Hispanic or non-Latino, and only 11% of patients were recruited from North America. The clinical expert consulted noted that the lack of representation of Canadian patients does not reduce the generalizability of the results to Canadian clinical practice.

About 91% of patients in the trial received 2 or more background HF treatments, and only 60% of patients received triple therapy for HF, representing a large majority of patients whose treatment was suboptimal. In addition, a small proportion of patients (14.4%) received sacubitril-valsartan and none of the patients received SGLT2 inhibitors for the treatment of HF. According to the clinical expert consulted, SGLT2 inhibitors became available for the treatment of chronic HF with reduced ejection fraction after the VICTORIA trial was conducted (between 2016 and 2019). Therefore, it is unclear whether the population included in the VICTORIA study is reflective of the population that would be eligible for treatment with vericiguat in current Canadian clinical practice. The clinical expert consulted indicated that vericiguat may be added to foundational quadruple HF therapy (including ACEis or ARBs, beta-blockers, MRAs, and SGLT2 inhibitors), as its mechanism of action is different from quadruple therapy medications. However, the cumulative benefit of vericiguat added to quadruple therapy remains unknown. According to the clinical expert consulted by CADTH for this review, most clinicians will choose to prescribe SGLT2 inhibitors over vericiguat in combination with triple HF therapy unless contraindicated,[6] and only after failure of standard quadruple therapy would they prescribe vericiguat to patients who are stabilized after worsening HF.

Indirect Comparisons

No sponsor-submitted network meta-analysis (NMA) was identified for this review. A focused literature search for indirect treatment comparisons dealing with HF was run in MEDLINE All (1946–) on November 9, 2022. No limits were applied to the search. The literature search identified 7 potential citations, of which 4 were included for consideration for the following reasons: in the VICTORIA trial, vericiguat was compared to placebo plus standard triple therapy; only 14% of patients in the VICTORIA trial received sacubitril-valsartan;

and none of the patients received SGLT2 inhibitors for HF treatment because they became available only after completion of the VICTORIA trial. The 4 studies identified through the literature search aimed to compare the efficacy of vericiguat in the treatment of patients with HF with reduced ejection fraction with SGLT2 inhibitors, sacubitril-valsartan, ivabradine, and a standard triple therapy, which were considered to be comparators in the systematic review protocol.

Aimo et al. (2021) NMA

The NMA by Aimo et al. (2021)[14] was identified from the literature. The objective of the analysis was to compare vericiguat with sacubitril-valsartan and with SGLT2 inhibitors in the treatment of patients with HF with reduced ejection fraction. Databases, including PubMed, Embase, and clinicaltrials.gov, were searched for articles of interest on September 25, 2020. The systematic review included 6 studies for analysis that compared sacubitril-valsartan, vericiguat, or SGLT2 inhibitors with SOC therapy. A random-effects NMA with the DerSimonian-Laird estimator and a fixed-effects model were performed separately for the primary and secondary outcomes of interest. The primary end point of interest was a composite of CV death and HHF, and the secondary end points included CV death alone and HHF alone.

The pooled results of the NMA showed for a composite of CV death and HHF, the HR for SGLT2 inhibitors versus vericiguat and sacubitril-valsartan was 0.83 (95% CI, 0.73 to 0.94) and 0.92 (95% CI, 0.88 to 1.24), respectively. For CV death, the HR for SGLT2 inhibitors versus vericiguat and sacubitril-valsartan was 0.88 (95% CI, 0.63 to 1.22) and 1.04 (95% CI, 0.88 to 1.24), respectively. For HHF, the HR for SGLT2 inhibitors versus vericiguat and sacubitril-valsartan was 0.77 (95% CI, 0.66 to 0.89) and 0.87 (95% CI, 0.75 to 1.02), respectively.

De Marzo et al. (2022) NMA

The NMA by De Marzo et al. (2022)[15] was identified from the literature The objective of the analysis was to compare the efficacy of vericiguat, ivabradine, and SGLT2 inhibitors in the treatment of patients with HF with reduced ejection fraction. Databases, including PubMed, Embase, SCOPUS, and the Cochrane Library, were searched for articles of interest on November 30, 2020. The NMA comprised both a fixed-effects model and a random-effects model within a Bayesian framework. The primary end point of interest was all-cause death, and the secondary end points included CV death, HHF, and all-cause hospitalization. The systematic review included 69 randomized controlled trials (RCTs) for all-cause death, 56 RCTs for CV death, 45 RCTs for HHF, and 26 RCTs for all-cause hospitalization.

The results of the NMA showed that for the primary end point of all-cause death, the HR for ivabradine and SGLT2 inhibitors versus vericiguat was 0.97 (95% credible interval [CrI], 0.60 to 1.60) and 0.94 (95% CrI, 0.62 to 1.40), respectively. For CV death, the HR for ivabradine and SGLT2 inhibitors versus vericiguat was 1.00 (95% CrI, 0.61 to 1.50) and 0.94 (95% CrI, 0.61 to 1.50). For HHF, the HR for ivabradine and SGLT2 inhibitors versus vericiguat was 0.89 (95% CrI, 0.50 to 1.70) and 0.88 (95% CrI, 0.56 to 1.60). The results for all-cause hospitalizations were not reported, as this information was not available in 63% of the RCTs examined.

Luo et al. (2022) NMA

The NMA by Luo et al. (2022)[16] was identified from the literature. The objective of the analysis was to compare sGC stimulators, ARNis, and SGLT2 inhibitors in the treatment of patients with HF with reduced ejection fraction. Databases, including PubMed, Embase, the Cochrane Library, and Web of Science, were searched for articles of interest on September 1, 2021. A random-effects model was constructed based on frequency theory. The efficacy outcomes included HF rehospitalization, all-cause mortality, CV death, and CV death or HF rehospitalization. A total of 15 RCTs were included for HF rehospitalization, 14 RCTs for all-cause mortality, 12 RCTs for CV death, and 16 RCTs for CV death or HF rehospitalization.

The results of the NMA for HF rehospitalization, the odds ratio (OR) for SGLT2 inhibitors versus sGC stimulators was 0.79 (95% CI, 0.68 to 0.93), whereas the OR for ARNis versus sGC stimulators was 0.87 (95% CI, 0.75 to 1.01). For all-cause mortality, the OR for SGLT2 inhibitors versus sGC stimulators was 0.98 (95% CI, 0.70 to 1.38), whereas for ARNis versus sGC stimulators was 0.87 (95% CI, 0.61 to 1.25). For CV death, the OR for SGLT2 inhibitors versus sGC stimulators was 0.96 (95% CI, 0.74 to 1.25), whereas for ARNis versus sGC stimulators was 0.88 (95% CI, 0.68 to 1.15). For CV death or HF rehospitalization, the OR for SGLT2 inhibitors versus sGC stimulators was 0.87 (95% CI, 0.76 to 1.00), whereas for ARNis versus sGC stimulators was 0.88 (95% CI, 0.77 to 1.01).

Pagnesi et al. (2022) NMA

The NMA by Pagnesi et al. (2022)[17] was identified from the literature .The objective of the analysis was to compare vericiguat with SGLT2 inhibitors in the treatment of patients with HF with reduced ejection fraction. Databases, including PubMed, Embase, Google Scholar, and the Cochrane Central Register of Controlled Trials, were searched for articles of interest on March 18, 2021. A random-effects NMA was performed on the cumulative event rates for primary and secondary end points based on a frequentist approach with the DerSimonian-Laird estimator. The primary end point was the composite of CV death and HHF, and secondary end points were CV death, all-cause death, and HHF. The systematic review included 7 studies for the composite of CV death and HHF, 10 studies for CV death, 12 studies for all-cause mortality, and 10 studies for HHF.

The results of the NMA For a composite of CV death or HHF, the relative risk (RR) for SGLT2 inhibitors versus vericiguat was 0.84 (95% CI, 0.75 to 0.96). For all-cause mortality, the RR for SGLT2 inhibitors versus vericiguat was 0.90 (95% CI, 0.77 to 1.04). For CV death, the RR for SGLT2 inhibitors versus vericiguat was 0.91 (95% CI, 0.91 to 0.96). For HHF, the RR for SGLT2 inhibitors versus vericiguat was 0.79 (95% CI, 0.69 to 0.91).

Critical Appraisal of Published NMA Articles

The results of the NMA are highly uncertain, given the heterogeneity across the studies included in the networks, heterogeneity in the baseline characteristics of patients within the included trials, and limited information related to definitions of end points. Furthermore, ivabradine and vericiguat were restricted to selected patients who were stabilized after an episode of worsening HF. Results in efficacy estimates were imprecise (i.e., wide CIs including HR = 1) in many comparisons and end points, which adds to the uncertainty in the effect estimates. Therefore, no definitive conclusions can be drawn from the published

NMAs for many outcome comparisons due to methodological limitations and impression in the effect estimates. Furthermore, safety outcomes were not analyzed in the published NMAs, and no justification was provided, which precludes a balanced judgment of comparative benefits relative to comparative harms. Outcomes important to patients, such as HRQoL, were also not analyzed in the published NMAs.

Other Relevant Evidence

No other relevant evidence was identified for this review.

Conclusions

Based on data from the VICTORIA trial, vericiguat demonstrated a statistically significant and clinically meaningful benefit compared to placebo in reducing the hazard rates of first event of CV death or HHF, occurrence of first and recurrent HHF, and the composite of all-cause mortality and HHF in adult patients with symptomatic chronic HF with reduced ejection fraction. The median composite primary end point, total events of HHF, and composite of all-cause mortality and HHF were not estimable in either treatment group because insufficient follow-up time had elapsed for these outcomes; thus, the longer-term efficacy of vericiguat is unknown. In addition, the estimates of the benefit of vericiguat may be overestimated because of the possibility that the trial was stopped earlier than planned due to the potential misclassification of CV death; however, the presence and extent of any overestimation is uncertain. Strong conclusions could not be drawn about the effect of vericiguat on HRQoL due to the high risk of attrition bias and increased risk of type I error in the analyses of these outcomes. No new safety signals were identified in patients with HF with reduced ejection fraction. Owing to its superiority over placebo, vericiguat may be another treatment option for patients with HF with reduced ejection fraction who are stabilized after a recent HF decompensation event. According to the clinical expert consulted by CADTH, vericiguat may be added to foundational quadruple HF therapy (including ACEis or ARBs, beta-blockers, MRAs, and SGLT2 inhibitors); however, the cumulative benefit of vericiguat added to the current model of quadruple therapy remains unknown. No conclusions could be drawn from the published NMAs about the efficacy of vericiguat relative to SGLT2 inhibitors, ivabradine, and sacubitril-valsartan for the treatment of patients with HF with reduced ejection fraction due to methodological limitations and imprecision in the effect estimates.

Introduction

Disease Background

HF, sometimes referred to as congestive HF, is a clinical condition in which the heart is unable to adequately pump blood throughout the body to maintain the metabolic needs of tissues and organs. HF results from structural or functional impairment of ventricular filling or ejection of blood.[1,2] HF is classified based on the percentage of blood that is being pumped out of the left ventricle, otherwise known as the LVEF.[2] HF with reduced ejection fraction is defined as HF with an LVEF of 40% or less, whereas HF with preserved ejection fraction is defined as an LVEF of 50% or greater. HF with an LVEF in the range of 41% to 49% is defined as HF with midrange LVEF, which may represent a variety of phenotypes, including patients transitioning to and

from HF with preserved ejection fraction.[2] There is uncertainty regarding management strategies, including surveillance, treatment, and prognosis, for patients with HF with midrange ejection fraction.[2] Additionally, HF with "recovered" or "improved" ejection fraction is defined as an LVEF of more than 40% but with a previously documented LVEF of less than 40%.[18] Assessment of LVEF is a routine part of the diagnosis and management of HF and can be carried out using a variety of techniques, the most common being 2D echocardiography, as well as nuclear medicine, angiography, and MRI; however, LVEF estimates may vary depending on the patient, technical factors, and clinical deterioration.[2] Natriuretic peptide (NP) tests may be useful in identifying individuals at increased risk of developing HF in whom preventive strategies have been studied.[2] In addition, the monitoring of NP levels can provide important information about response to therapy and residual risk.[19,20] Another common classification system is the NYHA functional classification, which is based on HF symptoms and a patient's ability to perform physical activities. Patients with NYHA class I HF have no symptoms (asymptomatic), and those with class IV HF have symptoms at rest or with any minimal activity.[2]

There are an estimated 669,000 people in Canada older than 40 years with HF, with an age-standardized prevalence of 3.5%.[3] Between 2001 and 2013, the age-standardized incidence rate of HF in Canada declined, as did the age-standardized all-cause mortality rate among people living with HF.[3] However, people in Canada older than 40 years with HF are 6 times more likely to die than those without a HF diagnosis.[3] The economic burden due to HF is substantial, with costs associated with health care services, medications, and lost productivity. Common symptoms of HF include dyspnea (breathlessness) and fatigue, exercise intolerance, and fluid build-up, which in turn may lead to pulmonary congestion and peripheral edema (mainly feet, ankles, or legs), which significantly affect patients' quality of life.[1] Other possible symptoms include a rapid heartbeat, frequent urination at night, difficulties concentrating, weight gain, and a dry cough, although these symptoms are present in other conditions, making it difficult to distinguish HF from other medical conditions, particularly during the early stages.

Depending on symptom severity, HF may go unnoticed or cause only minor symptoms; however, patients with advanced HF may find it difficult to carry out normal everyday activities.[4] HF leads to a progressive decline in cardiac function over time, with persistent signs and symptoms interspersed with acute episodes of decompensation. Acute decompensated HF is a sudden worsening of the signs and symptoms of HF that often lead to hospitalization or an emergency department visit.[5] Worsening HF and hospitalization for HF portend a poor prognosis and are associated with an increased risk of mortality and readmissions.[6] Hospitalizations due to HF are frequent, with 83% of patients hospitalized at least once and 43% of patients are hospitalized 4 or more times after a diagnosis of HF.[7] Approximately half of patients with HF have a reduced ejection fraction; it is in this population that the evidence base regarding treatment is well established.[7] It is generally accepted that hospitalization for acute decompensated HF is a powerful predictor of readmission and death after discharge in patients with chronic HF; postdischarge mortality rates are as high as 20%.[5,8] Patients with HF are often afflicted with multiple comorbid conditions, such as hypertension, atrial fibrillation, renal disease, and diabetes mellitus, which contribute to increased morbidity and mortality rates and an impaired quality of life.[21]

Standards of Therapy

The current foundational pharmaceutical management of HF with reduced ejection fraction encompasses combination therapy (in the absence of contraindications), including 1 evidence-based medication from each of the following categories: (1) sacubitril-valsartan, either as first-line therapy or switching from ACEis or ARBs, (2) beta-blockers, (3) MRAs, and (4) SGLT2 inhibitors.[6] These drug classes, individually and together, have shown improvement in clinical outcomes, including worsening, rehospitalizations and mortality, in patients with HF with reduced ejection fraction. In addition to this standard quadruple therapy, complementary medications benefit important subgroups of patients with HF with reduced ejection fraction, and should be initiated and titrated when indicated.[6] Recently, new therapies that have emerged, such as sGC stimulators and ivabradine (a sinus node inhibitor), are taken in conjunction with well-established therapies and have shown benefit in HF with reduced ejection fraction.[6] Other potential therapies for HF with reduced ejection fraction, depending on the situation, include diuretics, digoxin, temporary inotropic therapy, cardiac resynchronization therapy, and implantable cardioverter defibrillators.[2,6] Nonpharmacological measures include lifestyle recommendations for HF with reduced ejection fraction, such as fluid restriction, avoiding salt and alcohol, and regular exercise.[2,6] In general, patients with HF with reduced ejection fraction benefit from lifestyle changes, cardiac rehabilitation attendance, coordinated management with a multidisciplinary team, and pharmacotherapy. According to the clinical expert and clinician groups consulted by CADTH, the goal of HF therapy is to reduce the risk of CV death and HHF, and to improve quality of life.

Drug

Vericiguat is an sGC. HF is associated with impaired NO synthesis and decreased activity of its receptor, sGC. sGC catalyzes the synthesis of intracellular cGMP, an important signalling molecule that regulates critical physiological processes, such as cardiac contractility, vascular tone, and cardiac remodelling. Deficiency in cGMP derived from sGC contributes to myocardial and vascular dysfunction. Vericiguat restores the relative deficiency in this signalling pathway by directly stimulating sGC, independent from and synergistically with NO, to increase the level of intracellular cGMP, which may improve both myocardial and vascular function. Thus, the complementary cardiovascular benefits of vericiguat in patients with HF are associated with the active restoration of the deficient NO-sGC-cGMP pathway.

The vericiguat dossiers were submitted to CADTH as a pre–Notice of Compliance submission, with an anticipated Notice of Compliance date of April 10, 2023. Verquvo (vericiguat) underwent a standard review at Health Canada and obtained a Notice of Compliance on April 28, 2023, for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy. Vericiguat should be used in combination with SOC therapy for HF. Vericiguat should be initiated under the supervision of a health care professional who is experienced in the management of HF.[9] The sponsor's requested reimbursement criteria for vericiguat are generally aligned with the Health Canada–proposed indication; however, the sponsor added the following initiation criteria to the reimbursement request: in adult patients with chronic HF with NYHA class II to class IV HF; other patients taking other HF therapies that include ACEis or ARNis, ARBs, beta-blockers, and MRAs, if tolerated; and vericiguat should be initiated under the supervision of a health

care professional who is experienced in the management of HF.[22] Vericiguat is available as 2.5 mg, 5 mg, and 10 mg tablets. The recommended starting dose of vericiguat is 2.5 mg, followed by a doubling of the dose every 2 weeks up to the target maintenance dose of 10 mg administered orally once daily, as tolerated by the patient.[9]

Vericiguat received approval from the FDA in January 2021 to reduce the risk of CV death and HHF after hospitalization for heart failure or the need for outpatient IV diuretics in adults with symptomatic chronic HF and an ejection fraction less than 45%.[23] Vericiguat received approval from the European Medicines Agency in May 2021 for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy.[24]

Key characteristics of commonly used medical treatments for HF are presented in Table 3.

Table 3: Key Characteristics of Pharmacotherapies for HF (by Drug Class)

Characteristic	sGC stimulator	SGLT2 inhibitor	ARNi	ACEi	ARB	Ivabradine
Mechanism of action	Stimulates sGC, catalyzes the synthesis of intracellular cGMP	Inhibits SGLT2	Inhibits the breakdown of peptides by neprilysin and blocks the binding of angiotensin II to the AT1 receptor	Inhibits the conversion of angiotensin I to angiotensin II, thereby inhibiting the RAAS	Selectively blocks the binding of angiotensin II to the AT1) receptor, thereby inhibiting the RAAS	Reduces heart rate by blocking the HCN channel, which is responsible for the I_f current
Indication[a]	Verquvo (Vericiguat) is indicated for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy. Verquvo should be used in combination with SOC therapy for HF	Empagliflozin: treatment of adults with chronic HF as an adjunct to SOC therapy Dapagliflozin: treatment of HF with reduced ejection fraction to reduce the risk of CV death, HHF, and urgent HF visit, as an adjunct to SOC therapy	Treatment of HF with reduced ejection fraction in patients with NYHA class II or III HF	Treatment of symptomatic congestive HF, essential hypertension	Treatment of chronic HF, essential hypertension	Treatment of stable chronic HF with reduced ejection fraction (≤ 35%) in patients with NYHA class II or III HF in sinus rhythm and heart rates ≥ 77 bpm in combination with optimal standard of treatment of HF
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral
Recommended dose	Vericiguat: 2.5 mg once daily, followed by a doubling of the dose every 2 weeks up to the target maintenance dose of 10 mg	Empagliflozin: 10 mg daily Dapagliflozin: 10 mg daily	Sacubitril 24 mg plus valsartan 26 mg to sacubitril 97 mg plus valsartan 103 mg twice daily	Captopril: 50 mg 3 times daily Enalapril: 10 mg to 20 mg twice daily Fosinopril: 40 mg daily Lisinopril: 20 mg to 40 mg daily Perindopril: 8 mg to 16 mg daily Quinapril: 20 mg twice	Candesartan: 32 mg daily Losartan: 50 mg to 150 mg daily Valsartan: 160 mg twice daily	7.5 mg twice daily

Characteristic	sGC stimulator	SGLT2 inhibitor	ARNi	ACEi	ARB	Ivabradine
				daily Ramipril: 10 mg daily Trandolapril: 4 mg daily		
Serious adverse effects or safety issues	Hypotension, anemia, pneumonia, dyspepsia, nausea, headache, syncope, symptomatic hypotension, and predefined alterations in liver function tests Contraindicated with concomitant use of other sGC stimulators Caution with markedly elevated NT-proBNP, symptomatic hypotension Concomitant use with PDE-5 inhibitors is not recommended	Female genital mycotic infections, hypotension, hypoglycemia, urinary tract infections, and renal impairment Contraindicated in patients on dialysis, patients with type 2 diabetes with severe renal impairment, and patients with end-stage renal disease Caution with diabetic ketoacidosis in patients with diabetes and with patients at risk for volume depletion, hypotension and/or electrolyte imbalances	Hypotension, renal dysfunction, hyperkalemia, angioedema Contraindicated with ACEis, ARBs, or aliskiren, and in patients with symptomatic hypotension, history of angioedema, or pregnancy Caution in patients with renal artery stenosis	Hypotension, renal dysfunction, hyperkalemia, angioedema, cough, neutropenia/ agranulocytosis, impaired liver function Contraindicated with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate-to-severe renal impairment, patients with history of angioedema, pregnancy Caution in patients with renal artery stenosis	Hypotension, renal dysfunction, hyperkalemia, angioedema Contraindicated with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate-to-severe renal impairment, patients with history of angioedema, pregnancy Caution in patients with renal artery stenosis	Hypotension, renal impairment, eye disorders (phosphenes, visual disturbances), cardiac arrhythmias, bradycardia
Other	NA	NA	36-hour washout period required between ACEi and ARNi therapy	NA	Generally reserved for use in patients who cannot tolerate ACE inhibitors	NA

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor and neprilysin inhibitor; AT1 = angiotensin type 1; bpm = beats per minute; cGMP = cyclic guanosine monophosphate; CV = cardiovascular; HCN = hyperpolarization and cyclic nucleotide; HF = heart failure; HHF = hospitalization for heart failure; I_f = pacemaker current; NA = not applicable; NT-proBNP = N-terminal probrain natriuretic peptide; NYHA = New York Heart Association; PDE-5 = phosphodiesterase type 5; RAAS = renin-angiotensin-aldosterone system; SGLT2 = sodium-glucose cotransporter-2; SOC = standard of care; sGC = soluble guanylate cyclase.

[a]Health Canada–approved indication.

Sources: Product monographs for Verquvo (Bayer Inc.),[9] Jardiance (Boehringer Ingelheim Ltd.),[25] Forxiga (Novartis),[26] Entresto,[27] Lancora,[28] and Canadian Pharmacists Association.[29,30]

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full original patient inputs received by CADTH have been included in the stakeholder section at the end of this report.

Two patient groups, the HeartLife Foundation and the Heart Function Clinic in Vancouver General Hospital, St. Paul's Hospital, British Columbia, provided input for the review of vericiguat. The HeartLife Foundation is a patient-driven federal charity whose mission is to transform the quality of life of people living with HF by engaging, educating, and empowering a global community to create lasting solutions and build healthier lives. The input was informed by interviews with 3 HF specialists (British Columbia, Ontario, and Quebec), 1 researcher (Alberta), and 2 patients with HF (British Columbia and Ontario), as well as the review of study material and online literature.

The HeartLife Foundation indicated that patients with HF experience a wide range of physical, social, and emotional challenges. Symptoms include shortness of breath, extreme fatigue, low blood pressure, dizziness, edema, bloating, palpitations, and arrhythmia. Moreover, HF is associated with comorbidities, including anxiety, depression, and a decline in cognitive function, that can have a negative impact on mental health. The HeartLife Foundation highlighted that access to care, medical therapies, and support services vary widely across Canada, and that every individual's experience with HF is unique.

Two patient interviews (ages 33 and 44 years; 1 male and 1 female) highlighted the impact of HF on their quality of life, including being unable to pursue their desired career and exercise regularly. A recurring theme in the 2 patient interviews was the need to find a "new normal" for life after their diagnosis of HF. The HeartLife Foundation stated that there is currently no cure for HF and, if left untreated, the condition will progress over time; however, medical therapies and lifestyle changes can help patients manage their HF. The Heart Function Clinic highlighted the following gaps in the treatment of HF: not all patients respond to available treatments and patients become refractory to existing treatment options. Respondents from the HeartLife Foundation noted that the current standard therapy includes ARNis (as first-line therapy or after ACEi or ARB titration), beta-blockers, MRAs, and SGLT2 inhibitors.

An interview with 1 patient whose HF treatment included a medication plan (beta-blocker, Lasix, and Entresto), a healthy diet, and cardiac rehabilitation, reported that his HF worsens 40% of the time. The patient expressed a desire to be stable 100% of the time and avoid the 40% of the time he feels unwell and has to be hospitalized. No patient interviewees reported experience with vericiguat. The HeartLife Foundation indicated that patients with HF seek to improve their quantitative and qualitative outcomes. The HeartLife Foundation further emphasized that it is imperative to provide equitable access to high-quality care and services for all patients with HF, including access to diagnostics, medical therapy, mental health support, cardiac rehabilitation, and advanced care. The HeartLife Foundation advocated for vericiguat to be approved for the indication under review and suggested that vericiguat will help alleviate the gaps in current therapy.

Clinician Input

Input From Clinical Expert Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of HF.

Unmet Needs

The clinical expert consulted by CADTH for this review indicated that HF with reduced ejection fraction is associated with increased rates of death and the need for hospitalization even with standard quadruple therapy. The clinical expert highlighted that not all patients are eligible for standard quadruple therapy due to side effects, contraindications, or comorbidities, and some patients who experience disease progression while on standard therapy may require de-escalation of therapy to become restabilized.

Place in Therapy

The clinical expert consulted indicated that vericiguat can be added to foundational quadruple HF therapy, as its mechanism of action differs from that of the foundational medications. It was further noted by the clinical expert that the impact or role of vericiguat in the context of current quadruple therapy is unknown because the VICTORIA trial was designed and completed before the current therapeutic paradigm, such as SGLT2 inhibitors, was widely adopted.

Patient Population

The clinical expert consulted indicated that patients included in the VICTORIA trial received background dual or triple HF therapy and generally tended to be “sicker” than those included in HF trials with other therapies. The clinical expert noted that patients with more advanced disease may benefit the most.

Assessing Response to Treatment

The clinical expert indicated that the response to therapy in clinical practice is assessed based on reduction in burden of symptoms, need for IV diuretic therapy, hospitalization, or death.

Discontinuing Treatment

The clinical expert identified the following factors to consider when deciding to discontinue treatment with vericiguat: symptomatic hypotension and disease progression (need for transplant, left ventricular assist device [LVAD], or palliation).

Prescribing Conditions

The clinical expert indicated that vericiguat should be prescribed by a practitioner with expertise in the management of HF in specialty clinics with a focus on the assessment and management of HF.

Additional Considerations

The clinical expert noted that although the role of vericiguat in the management of HF with reduced ejection fraction in patients receiving quadruple therapy is uncertain, given the mechanism of action of vericiguat, the addition of this medication is expected to have a positive impact on the management of patients who have worsened while taking foundational quadruple therapy.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by the clinician group. The full original clinician group inputs received by CADTH have been included in the stakeholder section at the end of this report.

The clinician group input was obtained from 3 sources: Oakville Cardiologists, represented by 9 clinicians; 1 clinician from the Division of Cardiology, University of Alberta; and 1 clinician representing the North Shore Heart Centre in Vancouver. The Oakville Cardiologists is a cardiology group practising in Oakville, Ontario, that meets regularly to share best practices and collaborate on research and educational projects to improve the care of patients with cardiovascular disease.

The Oakville Cardiologists and the clinician from the Division of Cardiology, University of Alberta, indicated that patients with HF with reduced ejection fraction should be treated with 4 standard therapies: ARNis either as first-line therapy or switching from ACEis or ARBs; beta-blockers; MRAs; and SGLT2 inhibitors. This GDMT is indicated to reduce morbidity and mortality, as well as improve quality of life. The clinician groups agreed that for patients with HF with reduced ejection fraction who are in sinus rhythm (heart rate greater than 70 beats per minute) and remain symptomatic despite treatment with GDMT, ivabradine is also prescribed to prevent CV death and HHF. In addition, 2 nonpharmacologic interventions are often considered for patients with HF with reduced ejection fraction, including implantable cardioverter defibrillator therapy and cardiac resynchronization therapy.

The clinician from the Division of Cardiology, University of Alberta, identified the following as key goals of new therapies in HF: reducing recurrent symptoms and the need for hospitalization or emergency department visits. All clinical groups agreed that morbidity and mortality rates remain high in patients with HF with reduced ejection fraction despite advancements in therapies, and many patients cannot be titrated to the optimal doses of the medications due to hypotension, hyperkalemia, bradycardia, and renal dysfunction. The clinical groups agreed that vericiguat represents an additional approach to the treatment of HF with reduced ejection fraction, which is not targeted by the current GDMT. The clinician from the Division of Cardiology, University of Alberta, also suggested that because vericiguat does not cause hyperkalemia or impair renal function, patients who cannot tolerate ARNis or ACEis (e.g., patients with diabetes or renal impairment) would be good candidates for vericiguat.

The clinician groups consulted noted that vericiguat would be prescribed for patients with HF with reduced ejection fraction on optimal therapy who develop worsening symptoms or who needed HHF in the past 6 months to reduce CV death or first HHF; this was identified as a high-risk patient population by the clinician groups. The clinician groups pointed out several reasons that may lead to the discontinuation of vericiguat,

including a decline in the glomerular filtration rate to less than 15 mL/min/1.73 m^2, severe hypotension, and syncope. The Oakville Cardiologists indicated that physician assessment of clinical stability and patient-reported symptoms continue to be the cornerstone of evaluating response to therapy in patients with HF with reduced ejection fraction in the outpatient setting. The clinical groups advocated for vericiguat to be an accessible treatment option for the high-risk HF patient population, as it is safe, well tolerated, and taken once daily.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical expert consulted by CADTH are summarized in Table 4.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
1. Issues with the choice of comparator in the submitted trial The pivotal phase III VICTORIA trial demonstrated that Verquvo had a significant reduction in CV death and HHF, with a comparable safety profile to placebo on top of background therapy. The background therapy included an ACEi, ARB, or ARNi, a beta-blocker, and/or an MRA, which represent the SOC at the time of trial conclusion and continue to represent fundamental pillars of the new SOC. The Canadian Cardiovascular Society defines 4 key therapeutic drug classes as standard therapy for most patients: ARNi (as first-line therapy or after ACEi or ARB titration); beta-blockers; MRAs; and SGLT2 inhibitors. How can vericiguat be integrated into the current treatment paradigm with drugs such as dapagliflozin, empagliflozin, or ivabradine?	Vericiguat may be added to foundational quadruple HF therapy, as its mechanism of action is different from quadruple therapy medications. However, given SGLT2 inhibitors are also now an option, the cumulative benefit of vericiguat added to quadruple therapy remains unknown. Not all patients are eligible for standard quadruple therapy due to side effects, contraindications, or comorbidities, and vericiguat could be a treatment option for these patients.
Considerations for initiation of therapy	
1. Disease diagnosis, scoring, or staging for eligibility In the VICTORIA trial, evidence of worsening HF was categorized based on the timing of the HF decompensation: those hospitalized within 3 to 6 months before randomization; or those receiving IV diuretics for HF, without hospitalization, within the previous 3 months. How is worsening HF defined in clinical practice?	HF decompensation event or progressive HF is most commonly defined as worsening symptoms while on conventional therapy, resulting in treatment escalation and hospitalization or outpatient IV diuretic treatment. The laboratory and diagnostic tests to define worsening HF include elevated BNP or NT-proBNP, or reduction in ejection fraction.
2. Eligibility for re-treatment What is the expected treatment duration for vericiguat?	HF is a chronic disease, and given the mechanism of action of vericiguat, the duration of treatment is indefinite.

Drug program implementation questions	Clinical expert response
Considerations for prescribing of therapy	
1. Dosing, schedule or frequency, dose intensity The recommended starting dose of Verquvo is 2.5 mg administered orally once daily, followed by doubling the dose every 2 weeks to the target maintenance dose of 10 mg, as tolerated by the patient.	No response required. For CDEC consideration.
2. Consistency with prescribing criteria associated with other drugs reviewed by CADTH in the same therapeutic space Per the indication and sponsor request, vericiguat "should be initiated under the supervision of a health care professional who is experienced in the management of HF."	No response required. For CDEC consideration.
System and economic issues	
1. Concerns regarding the anticipated budget impact and sustainability The list price of Verquvo 2.5 mg, 5 mg, and 10 mg is anticipated to be $4.83 per tablet in Canada, which corresponds to a total cost of $4.83 per day (once daily dosage). BIA estimate that listing Verquvo will lead to an incremental budget impact of [redacted] in year 1, [redacted] in year 2, and [redacted] in year 3, for a total of [redacted] million over 3 years.	No response required. For CDEC consideration.
2. Presence of confidential negotiated prices for comparators Negotiated prices for Inspra (eplerenone), Entresto (sacubitril-valsartan) and Forxiga (dapagliflozin) for HF. Generics are available for other comparators.	No response required. For CDEC consideration.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor–neprilysin inhibitor; BIA = budget impact analysis; BNP = brain natriuretic peptide; CDEC = CADTH Canadian Drug Expert Committee; CV = cardiovascular; HF = heart failure; HHF = hospitalization for heart failure; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-brain natriuretic peptide; SGLT2 = sodium-glucose cotransporter-2; SOC = standard of care.

Clinical Evidence

The clinical evidence included in the review of vericiguat is presented in 2 sections. The first section, the Systematic Review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as studies that were selected according to an a priori protocol. The second section includes indirect evidence selected from the literature that met the selection criteria specified in the review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

A systematic review was performed to assess the beneficial and harmful effects of vericiguat 10 mg once daily when used to reduce the risk of CV death and HHF in adults with symptomatic chronic HF and an ejection fraction of less than 45% who are stabilized after a recent worsening HF event, in combination with other HF therapies.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 5: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Adults with symptomatic chronic HF and an ejection fraction of less than 45% Subgroups: • LVEF • NYHA class • Renal function • Background treatments for HF • BNP level • NT-proBNP level • History of atrial fibrillation • History of type 2 diabetes • Baseline systolic blood pressure • Prior hospitalization[a] vs. IV diuretic treatment for HF[b]
Intervention	Vericiguat added on to other HF therapies: • 2.5 mg orally once daily to start, followed by a doubling of the dose every 2 weeks up to the target maintenance dose of 10 mg orally once daily
Comparators	Standard HF regimens that include combinations of the following: • ACEi or ARB • Beta-blocker • Sacubitril-valsartan • SGLT2 inhibitor • Ivabradine • MRA
Outcomes	Efficacy outcomes: • CV death • All-cause mortality • CV hospitalization • HHF • All-cause hospitalization • Change in BNP level • Change in NT-BNP level • Change in ejection fraction • Functional status • CV events (e.g., MI)

Criteria	Description
	• HRQoL • Change in renal function Harms outcomes: AEs, SAEs, WDAEs, mortality, notable harms and harms of special interest (syncope, symptomatic hypotension, anemia, hepatic insufficiency [acute hepatic failure, increased aspartate aminotransferase, alanine transaminase, or bilirubin]), acute kidney injury, hyperkalemia
Study design	Published and unpublished phase III and IV RCTs

ACEi = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; CV = cardiovascular; HF = heart failure; HHF = hospitalization for heart failure; HRQoL = health-related quality of life; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal probrain natriuretic peptide; NYHA = New York Heart Association; RCT = randomized controlled trial; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2; WDAE = withdrawal due to adverse event.

[a]HF hospitalization within 6 months before randomization.

[b]IV diuretic treatment for HF (without hospitalization) within 3 months before randomization.

The literature search was performed by an information specialist using a peer-reviewed search strategy in accordance with the PRESS Peer Review of Electronic Search Strategies checklist.[31]

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in Endnote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Verquvo (vericiguat) and heart failure. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

If filters were used, CADTH-developed search filters were applied to limit retrieval to RCTs or controlled clinical trials. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on November 10, 2022. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on March 22, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist.[32] Included in this search were the websites of regulatory agencies (FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Findings From the Literature

A total of 195 studies were identified from the literature for inclusion in the systematic review (Figure 1). A total of 3 reports[10,33,34] of 1 study were included in the systematic review. The included studies are summarized in Table 6. A list of excluded studies is presented in Appendix 2.

Table 6: Details of the VICTORIA Trial

Detail	VICTORIA
Designs and populations	
Study design	Phase III, multicentre, randomized, double-blind, placebo-controlled, event-driven, trial
Locations	Patients enrolled across 694 sites in 42 countries worldwide (including North America [560 patients], Latin and South America, Eastern Europe, Western Europe, and the Asia-Pacific region)
Patient enrolment dates	From September 20, 2016, to June 18, 2019
Randomized (N)	5,050 patients
Inclusion criteria	• ≥ 18 years of age • History of chronic HF (NYHA class II to class IV) on standard therapy before qualifying HF decompensation • Previous HHF within 6 months before randomization[a] or IV diuretic treatment for HF (without hospitalization) within 3 months before randomization[b] • BNP[c] or NT-proBNP levels within 30 days before randomization, as follows: ◦ for patients with sinus rhythm ▪ NT-proBNP ≥ 1,000 pg/mL ▪ BNP ≥ 300 pg/mL ◦ for patients with atrial fibrillation ▪ NT-proBNP ≥ 1,600 pg/mL ▪ BNP ≥ 500 pg/mL • LVEF of less than 45% assessed within 12 months before[c] to randomization by any method • Female who is not of reproductive potential or of reproductive potential and agrees to avoid becoming pregnant
Exclusion criteria	• Clinically unstable at the time of randomization as defined by: ◦ administration of any IV treatment within 24 hours before randomization, and/or ◦ SBP < 100 mm Hg or symptomatic hypotension • Concurrent or anticipated use of long-acting nitrates or nitric acid donors[d] • Concurrent use or anticipated use of PDE5 inhibitors • Receiving IV inotropes • Having or anticipating receiving implantable LV assist device • Awaiting heart transplant • Having cardiac comorbidity: ◦ primary valvular heart disease requiring surgery or intervention or is within 3 months after valvular surgery or intervention ◦ hypertrophic obstructive cardiomyopathy

Detail	VICTORIA
	◦ post–heart transplant cardiomyopathy ◦ acute myocarditis, amyloidosis, sarcoidosis, tachycardia-induced cardiomyopathy, symptomatic carotid stenosis, TIA ◦ acute coronary syndrome, including unstable angina, NSTEMI or STEMI, or coronary revascularization (CABG or PCI) within 60 days before randomization, or indication of revascularization at time of randomization ◦ complex congenital heart disease, active endocarditis, or constrictive pericarditis • Having noncardiac comorbidity: ◦ estimated eGFR < 15 mL/min/1.73 m^2 or chronic dialysis[e] ◦ severe hepatic insufficiency ◦ malignancy or other noncardiac condition limiting life expectancy to < 3 years ◦ requiring continuous home oxygen for severe pulmonary disease ◦ interstitial lung disease ◦ females of reproductive age not using an acceptable form of contraception or who are pregnant or breastfeeding[f]
Drugs	
Intervention	Vericiguat tablet of 2.5 mg, followed by doubling the dose every 2 weeks to the target maintenance dose of 10 mg, administered orally once daily
Comparator(s)	Matching placebo tablet of 2.5 mg, followed by doubling the dose every 2 weeks to the target dose of 10 mg, administered orally once daily
Duration	
Phase	
Screening[g]	30 days
Double-blind[h]	Event-driven trial
Follow-up[i]	14 days
Outcomes	
Primary end point	Time to first event of CV death or HHF
Secondary and exploratory end points	Secondary: • time to CV death • time to first event of HHF • time to total events (first and recurrent) of HHF • time to first event of all-cause mortality or HHF • time to all-cause mortality Exploratory: • time to first HF event, defined as composite of HHF or urgent HF visit (not meeting the criteria for HHF) • time to first CV hospitalization • total number of HHF events • change from baseline in health-related quality of life measures at week 32 (KCCQ and EQ-5D) • time to first event of CV death, MI hospitalization, or stroke hospitalization

Detail	VICTORIA
	• number of days alive and not hospitalized for HF Additional: • change from baseline in NYHA class at week 32 • change from baseline in NT-proBNP at week 32 Safety: AEs, physical examination, laboratory data, vital signs
Notes	
Publications	Armstrong et al.(2020)[33] Pieske et al. (2019)[34]

AE = adverse event; BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HHF = hospitalization for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non–ST elevation myocardial infarction, NT-proBNP = N-terminal probrain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PDE5 = phosphodiesterase type 5; SBP = systolic blood pressure; STEMI = ST elevation myocardial infarction; TIA = transient ischemic attack.

[a]No more than approximately 20% of patients will be randomized with a qualifying HF hospitalization > 3 months before randomization.

[b]BNP cannot be used to determine eligibility for inclusion in patients on sacubitril-valsartan because sacubitril-valsartan led to an increase of approximately 15% in median BNP in the PARADIGM-HF trial. NT-proBNP must be used to confirm eligibility for patients taking sacubitril-valsartan.

[c]Most recent measurement must be used to determine eligibility.

[d]Coadministration of short-acting nitrates (i.e., sublingual nitroglycerin spray as indicated for angina attacks) is allowed.

[e]No more than approximately 15% of patients will be enrolled with an eGFR in the 15 mL/min/1.73 m^2 to 30 mL/min/1.73 m^2 range.

[f]This wording is from original study.

[g]Screening could start as early as at time of hospitalization or upon IV diuretic treatment for HF. Screening visit and randomization (visit 2) could occur on the same day if the patient is clinically stable, defined as having not received IV treatment for more than 24 hours and having SBP greater than or equal to 100 mm Hg. In this case, all procedures specified for visit 2 were done after informed consent was given and replaced screening visit procedures.

[h]It was an event-driven trial and was to stop once the required number of CV death events was reached.

[i]All patients were contacted by phone within 14 days (+ 1 week) of the final visit to assess for clinical events, AEs, and vital status (if applicable).

Source: Clinical Study Report for VICTORIA.[10]

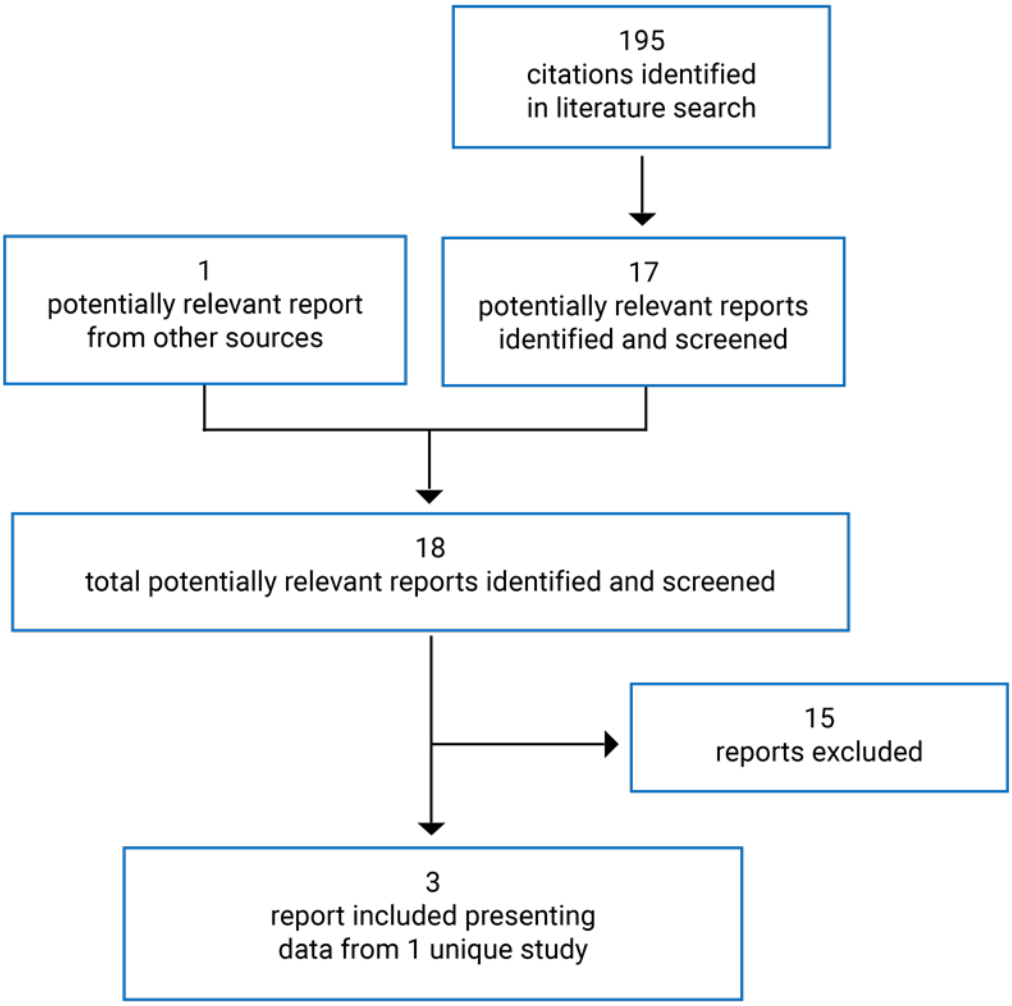
Description of the VICTORIA Trial

One sponsor-conducted trial (VICTORIA)[10] that met the CADTH review protocol criteria was included in this systematic review (Table 5). Study-specific details are included in Table 6. A schematic of the trial is presented in Figure 2.

The VICTORIA trial was a phase III, randomized, multicentre, double-blind, event-driven, placebo-controlled trial designed to assess the efficacy and safety of vericiguat versus placebo as an adjunct to SOC therapy in adults with symptomatic chronic HF and ejection fraction less than 45% who are stabilized after a recent worsening HF event. A previous HF decompensation (or worsening) event was defined as HHF within 6 months before randomization or the use of an IV diuretic for HF (without hospitalization) within 3 months before randomization. No more than 20% of patients with previous HF decompensation that occurred more than 3 months before randomization were to be enrolled in the VICTORIA trial. A total of 5,050 patients with symptomatic chronic HF with reduced ejection fraction were enrolled across 694 sites in 42 countries in North America (560 patients), Eastern Europe, Western Europe, the Asia-Pacific region, and Latin and South America. The primary efficacy end point was the time to first event of CV death or HHF, and the key secondary end points were time to CV death, time to first event of HHF, time to total events (first and recurrent) of HHF, time to first event of all-cause mortality or HHF, and time to all-cause mortality. HRQoL was assessed using the KCCQ and the EQ-5D instrument. Futility and efficacy interim analyses were planned

at the time when approximately 75% of the planned number of CV death events (587 events) was reached, and the data safety monitoring board could recommend early termination of the trial for overwhelming efficacy or futility. The database lock was executed on October 31, 2019.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



Randomization, Treatment Allocation, and Blinding

An Interactive Voice Response System and Integrated Web Response System methodology was used to randomly assign patients in a 1:1 ratio to receive vericiguat at a dose of 2.5 mg, 5.0 mg, or 10 mg once daily (N = 2,526) or to receive matching placebo (N = 2,524). Randomization was stratified by geographic region and race. The stratification variable race was nested within the North America region as North America (Black) and North America (non-Black). As a result of the combination of these 2 stratification variables, patients were randomized into 6 different strata, as follows: Eastern Europe (including Israel and South Africa), Western Europe, North America (Black), North America (non-Black), Latin and South America, and the

Asia-Pacific region (including Australia). Both patients and investigators were blinded to the study treatments administered during the trial.

Study Phases

Screening Phase

In the VICTORIA trial, patients were randomized within 30 days of the screening period. The screening visit could begin at the time of hospitalization (or after IV diuretic treatment for HF without hospitalization) and up to 30 days before randomization (visit 2). The screening visit and randomization (visit 2) could occur on the same day if the patient was clinically stable, defined as not receiving IV treatment for more than 24 hours and having systolic blood pressure greater than or equal to 100 mm Hg. In addition, evidence was provided that LVEF was less than 45% within 12 months before randomization (the most recent measurement should be used).

Treatment Phase

The VICTORIA trial was an event-driven trial and was to stop once the required number of CV death events was reached. Thus, the duration of the double-blind treatment phase was different for each patient. After the 4-week titration phase, during which the starting dose (2.5 mg) of the study medication was up-titrated to the target dose of 10 mg, patients were assessed at week 16 and then every 4 months until the end of the trial. The final visit was conducted for all patients when the planned number of CV death events was reached and the efficacy cut-off was announced. If applicable, patients continued to take the study medication until the final visit and were asked to stop taking the study drug medication during that visit. An independent data and safety monitoring committee was responsible for reviewing the safety and efficacy data approximately every 3 to 6 months throughout the trial. Discontinuation visits were conducted at the time of permanent treatment discontinuation to collect information on clinical events, AEs, and other clinical and laboratory procedures.

Follow-Up Safety Phase

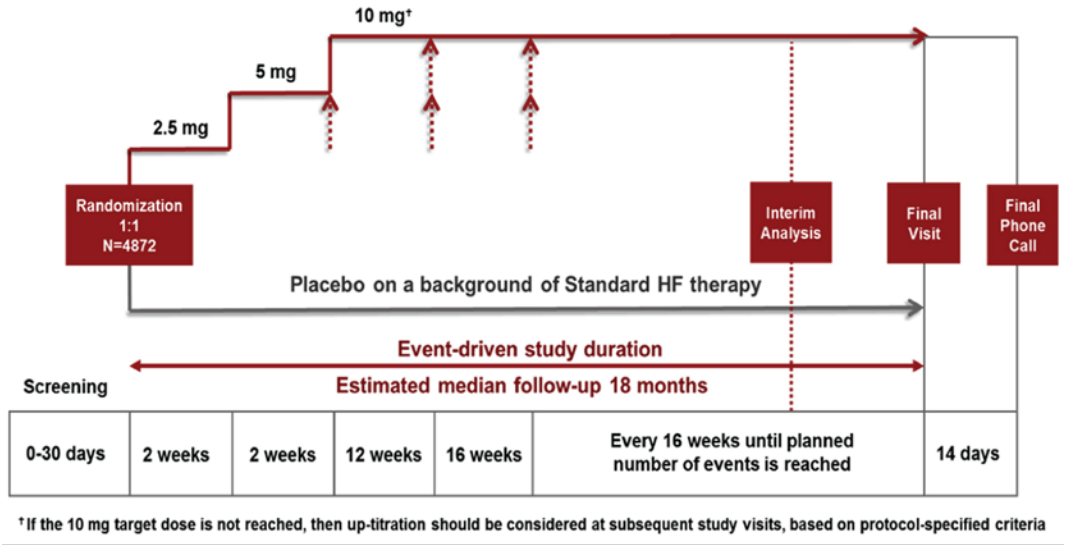
Within 14 days after the last dose of study medication, all patients who discontinued the study drug prematurely had an in-clinic safety follow-up visit. Thus, patients who permanently discontinued the study drug were still followed up for clinical events and vital status until study completion. If the patients did not attend the study visit, a telephone contact would be made to collect information on protocol-defined end point events.

Protocol Amendments

Several modifications were made to the study protocol after the start of patient recruitment that were documented in the Clinical Study Report. The amendments dated June 15, 2016, included: exclusion of patients with intestinal lung disease, exclusion of patients who are breastfeeding or plan to breastfeed during the course of the trial, and addition of echocardiography and cardiac MRI assessments. The amendments dated December 20, 2017, included: addition of the indication that futility analysis would be performed at 75% of CV death events, revision of the futility analysis approach and bounds, addition of the minimal NP cut-off points for sinus rhythm and atrial fibrillation, clarification of the inclusion and exclusion criteria related to

pregnancy, addition of the Canadian Cardiovascular Society functional classification of angina to trial flow chart, and addition of instruction regarding the pulse rate assessment at the randomization visit.

Figure 2: Study Schema for the VICTORIA Trial



HF = heart failure.
Source: Clinical Study Report for VICTORIA.[10]

There were several modifications to the statistical analysis plan for the study that were documented in the statistical analysis plan amendments. The amendments dated March 8, 2017, included addition of the days alive and out of HHF as an additional exploratory end point, addition of subgroup analyses for CV death and HHF, and addition of baseline ejection fraction as a subgroup. The amendments dated October 22, 2019, included addition of the exploratory end point of time to the first occurrence of the composite of CV death, myocardial infarction (MI) hospitalization, and stroke hospitalization; addition of a subsection to describe intention to withdraw analysis; addition of a subsection to discuss the approaches for randomization errors; addition of the censoring rule for time-to-event end points; addition of the imputation rule for partial death dates; addition of a description of on-treatment analysis of efficacy end points; and removal of subsections related to interim analysis approaches.

Populations

Inclusion and Exclusion Criteria

The key inclusion and exclusion criteria applied to the VICTORIA trial are summarized in Table 6. Briefly, patients eligible for enrolment in the VICTORIA trial were adults with symptomatic chronic HF with reduced ejection fraction; NYHA class II, class III, or class IV HF; and receipt of guideline-recommended SOC therapy. Patients were also required to have elevated levels of NPs (i.e., NT-proBNP ≥ 1,000 pg/mL or BNP ≥ 300 pg/mL for patients in sinus rhythm), previous HF decompensation defined as HHF within 6 months before randomization or receiving IV diuretic therapy for HF within 3 months before randomization. No more than 20% of patients were to be randomized with a qualifying HHF more than 3 months before randomization.

Patients were excluded from the VICTORIA trial if they were clinically unstable within 24 hours before randomization, defined as the administration of any IV treatment and/or systolic blood pressure less than 100 mm Hg, or symptomatic hypotension. Patients with cardiac comorbidities (i.e., hypertrophic obstructive or post–heart transplant cardiomyopathy, acute coronary syndrome) or noncardiac comorbidities (i.e., chronic dialysis, hepatic insufficiency, malignancy) were excluded from the VICTORIA trial.

Baseline Characteristics

A summary of baseline characteristics is presented in Table 7. Baseline characteristics were well balanced between the treatment arms. The mean age of all randomized patients in the VICTORIA trial was 67.3 years (SD = 12.2 years). A total of 76.1% of patients were male, and 24.0% were female. About 64.1% of patients were white, and 27.0% were Asian or multiracial. A total of 81.4% of patients were non-Hispanic or non-Latino, and 16.1% were Hispanic or Latino. The mean LVEF was 28.9% (SD = 8.30%), and nearly half of patients had an LVEF of less than 30% (49.3%). Most patients had NYHA functional class II and class III HF (98.6%) at baseline. The mean NT-proBNP was 4,741.90 pg/mL (SD = 6,845.60 pg/mL), the mean BNP was [redacted] pg/mL (SD = [redacted] pg/mL), and the mean eGFR was 61.5 mL/min/1.73 m^2 (SD = 27.2 mL/min/1.73 m^2). Approximately 70% of patients had HHF within 3 months before randomization, 17.2% had HHF within 3 to 6 months before randomization, and 15.9% received outpatient treatment with IV diuretics for worsening HF within 3 months before hospitalization. The mean time from a diagnosis of HF to randomization was 4.8 years (SD = 5.4 years), and the mean time from the index event (hospitalization or use of an IV diuretic for HF) to randomization was 50.2 days (SD = 46.57 days). Patients received the following previous HF medications at the start of the VICTORIA trial: ACEis or ARBs (73.4%), beta-blockers (93.1%), MRAs (70.3%), and sacubitril-valsartan (14.5%). A total of 91.2% of patients received 2 or more HF medications, and only 60% of patients received triple therapy, including ACEis or ARBs, beta-blockers, and MRAs. Almost half of the patients were diagnosed with diabetes mellitus (46.9%) at baseline, and about 52.8% had a history of atrial fibrillation or flutter.

Table 7: Summary of Baseline Characteristics — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Demographic characteristics		
Mean age, years (SD)	67.5 (12.2)	67.2 (12.2)
Median age, years (range)	69.0 (24 to 98)	68.0 (23 to 97)
Age groups, n (%)		
≤ 50 years	223 (8.8)	247 (9.8)
51 to 60 years	446 (17.7)	427 (16.9)
61 to 70 years	758 (30.0)	753 (29.8)
71 to 80 years	737 (29.2)	778 (30.8)
≥ 81 years	362 (14.3)	319 (12.6)
Sex, n (%)		

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Male	1,921 (76.0)	1,921 (76.1)
Female	605 (24.0)	603 (23.9)
Race, n (%)		
American Indian or Alaska Native	24 (1.0)	28 (1.1)
Asian	571 (22.6)	561 (22.2)
Multiracial	123 (4.9)	126 (5.0)
Native Hawaiian or other Pacific Islander	183 (7.2)	180 (7.1)
White	1,621 (64.2)	1,618 (64.1)
Not reported	3 (0.1)	11 (0.4)
Ethnicity, n (%)		
Hispanic or Latino	410 (16.2)	403 (16.0)
Non-Hispanic or non-Latino	2,044 (80.9)	2,065 (81.8)
Unknown	33 (1.3)	27 (1.1)
Not reported	39 (1.5)	29 (1.1)
Geographic region, n (%)		
Eastern Europe	848 (33.6)	846 (33.5)
Western Europe	443 (17.5)	446 (17.7)
Asia-Pacific	592 (23.4)	591 (23.4)
Latin and South America	362 (14.3)	362 (14.3)
North America	281 (11.1)	279 (11.1)
Race in North America, n (%)		
Black	62 (2.5)	61 (2.4)
Non-Black	219 (8.7)	218 (8.6)
Outside North America	2,245 (88.9)	2,245 (88.9)
Patient and disease characteristics		
Body mass index, kg/m^2		
Mean (SD)	27.7 (5.8)	27.9 (6.1)
Median (range)	26.8 (14.2 to 55.6)	26.9 (15.1 to 63.0)
BNP level (pg/mL)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
NT-proBNP level (pg/mL)		
Mean (SD)	4,803 (7,549.4)	4,679.6 (6,053.6)

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Median (range)	2,803.5 (10.0 to 175,000.0)	2,821.0 (70.0 to 86,155.0)
eGFR (mL/min/1.73 m^2)		
Mean (SD)	61.3 (27.0)	61.7 (27.3)
Median (range)	58.4 (11.0 to 225.5)	58.3 (11.1 to 226.8)
eGFR category (mL/min/1.73 m^2), n (%)		
≤ 30	259 (10.3)	247 (9.8)
31 to 60	1,054 (41.7)	1,064 (42.2)
> 60	1,161 (46.0)	1,174 (46.5)
Missing	52 (2.1)	39 (1.5)
Index event, n (%)		
HHF within 3 months	1,673 (66.2)	1,705 (67.6)
HHF 3 to 6 months	454 (18.0)	417 (16.5)
IV diuretic[a] for HF within 3 months	399 (15.8)	402 (15.9)
Time of primary diagnosis of HF to randomization (year)		
Mean (SD)	4.7 (5.5)	4.8 (5.4)
Median (range)	2.9 (0.0 to 57.8)	2.9 (0.0 to 48.4)
NYHA class, n (%)		
I	0 (0.0)	2 (0.1)
II	1,478 (58.5)	1,497 (59.3)
III	1,010 (40.0)	993 (39.3)
IV	35 (1.4)	31 (1.2)
Ejection fraction (%)		
Mean (SD)	29.0 (8.26)	28.8 (8.34)
Median (range)	30.0 (6.0 to 45.0)	29.0 (5.0 to 45.0)
Ejection fraction (%) category, n (%)		
< 30	1,210 (47.9)	1,280 (50.7)
30 to 34	515 (20.4)	461 (18.3)
35 to 39	433 (17.1)	417 (16.5)
40 to 45	358 (14.2)	362 (14.3)
Missing	10 (0.4)	4 (0.2)
CCSA class, n (%)		
No angina	2,148 (85.0)	2,147 (85.1)
CCSA class 1	203 (8.0)	202 (8.0)

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
CCSA class 2	121 (4.8)	123 (4.9)
CCSA class 3	51 (2.0)	51 (2.0)
CCSA class 4	3 (0.1)	1 (0.0)
Time from index event to randomization (days)		
Mean (SD)	50.9 (46.08)	49.5 (47.05)
Median (range)	33.0 (2.0 to 343.0)	31.0 (2.0 to 621.0)
SOC treatment for HF		
Patients with 1 or more SOC HF treatment, n (%)	2,517 (99.8)	2,513 (99.8)
Use of sacubitril-valsartan, n (%)		
Yes	360 (14.3)	371 (14.7)
No	2,161 (85.7)	2,148 (85.1)
Use of beta-blockers, n (%)		
Yes	2,349 (93.2)	2,342 (93.0)
No	172 (6.8)	177 (7.0)
Use of ACEi or ARB, n (%)		
Yes	1,847 (73.3)	1,853 (73.6)
No	674 (26.7)	666 (26.4)
Use of MRA, n (%)		
Yes	1,747 (69.3)	1,798 (71.4)
No	774 (30.7)	721 (28.6)
Patients with 2 or more SOC HF treatment, n (%)	2,300 (91.2)	2,309 (91.7)
MRA and ACEi or ARB, n (%)	1,480 (58.7)	1,529 (60.7)
Beta-blocker and ACEi or ARB, n (%)	569 (22.6)	532 (21.1)
MRA and beta-blocker, n (%)	160 (6.3)	148 (5.9)
MRA and beta-blocker and ACEi or ARB, n (%)	1,480 (58.7)	1,529 (60.7)
SOC device, n (%)		
No device	1,708 (67.8)	1,717 (68.2)
ICD only	443 (17.6)	433 (17.2)
Biventricular pacemaker only	117 (4.6)	99 (3.9)
ICD and biventricular pacemaker	253 (10.0)	270 (10.7)
Comorbid conditions, n (%)		
1 or more conditions	2,517 (99.6)	2,518 (99.8)
Diabetes	1,226 (48.5)	1,143 (45.3)

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Atrial fibrillation	1,102 (43.6)	1,173 (46.5)
Atrial flutter	180 (7.1)	213 (8.4)
Hypertension	2,003 (79.3)	1,993 (79.0)
Coronary artery disease	1,514 (59.9)	1,436 (56.9)
Hyperlipidemia	1,476 (58.4)	1,419 (56.2)
Myocardial infarction	1,103 (43.7)	1,025 (40.6)

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP = brain natriuretic peptide; CCSA = Canadian Cardiovascular Society Functional Classification of Angina; eGFR = estimated glomerular filtration rate; HF = heart failure; HHF = hospitalization for heart failure; ICD = implantable cardioverter defibrillator; ITT = intention to treat; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; SOC = standard of care.

[a]IV diuretic for HF (without hospitalization).

Source: Clinical Study Report for VICTORIA.[10]

Interventions

All eligible patients were randomized in a 1:1 ratio to receive vericiguat or matching placebo, administered orally once daily with food. The vericiguat and placebo tablets were identical in packaging and labelling. Treatment was started with a starting dose of 2.5 mg, followed by 2 dose doublings every 2 weeks to the target dose of 10 mg. In the phase IIb SOCRATES-REDUCED trial,[35] vericiguat doses from 1.25 mg up to a target dose of 10 mg were examined in patients with worsening chronic HF with reduced ejection fraction. Vericiguat at a dose of 1.25 mg was confirmed as a "no effective dose" and had an overall profile comparable to placebo. Vericiguat at a dose of 2.5 mg was associated with a first-dose systolic blood pressure–lowering effect of approximately 3 mm Hg, and was defined as the "minimally effective dose." The 10 mg target dose of vericiguat reduced NT-proBNP level and was well tolerated, compared to placebo.[35] The blood pressure criterion for dose up-titration was a systolic blood pressure greater than or equal to 100 mm Hg. The titration steps included a sham titration in the placebo group. Dose assessments were performed at all scheduled and unscheduled visits when blood pressure was assessed. Dose modifications were based on mean systolic blood pressure, the absence of symptoms indicative of hypotension, and the investigator's discretion (Table 8). Reasons for dose modifications were recorded at all scheduled and unscheduled visits. All attempts were made to resume the study treatment after a temporary interruption (during the titration phase or after 28 days) and to reach and maintain the target dose of the study treatment when deemed medically appropriate by the investigator. There was no defined maximum time limit for temporary treatment interruption.

Table 8: SBP Criteria for Study Treatment Dose Modification

Blood pressure assessment	Dose modification
SBP ≥ 100 mm Hg and not on 10 mg target dose	Increase dose
SBP ≥ 100 mm Hg and not on 10 mg target dose SBP between 90 and < 100 mm Hg	Maintain dose
SBP < 90 mm Hg, asymptomatic	If currently on 5 mg or 10 mg, decrease dose If currently on 2.5 mg, interrupt dose
SBP < 90 mm Hg, symptomatic	Interrupt dose

SBP = systolic blood pressure.
Source: Clinical Study Report for VICTORIA.[10]

All patients should receive guideline-recommended SOC therapy for HF, including beta-blockers, ACEis, ARBs, MRAs, sacubitril-valsartan, and cardiac device therapies, such as implantable cardioverter defibrillators and biventricular pacemakers. Prohibited concomitant treatments included long-lasting nitrates or NO donors (i.e., isosorbide 5-mononitrate, pentaerythritol tetranitrate), phosphodiesterase type 5 (PDE5) inhibitors (i.e., vardenafil, tadalafil, or sildenafil), and sGC stimulators (i.e., riociguat).

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 9. These end points are also further summarized subsequently. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Efficacy Outcomes

The primary composite end point of the VICTORIA trial was the time to first event of adjudicated CV death or HHF.

The CEC performed an adjudication of the following outcomes occurring after randomization: reported death (CV and non-CV death), CV hospitalizations, and urgent HF visits.

CV death included:

- death due to HF, which refers to a death associated with clinically worsening symptoms and/or signs of HF, regardless of HF etiology
- death due to acute MI, which refers to a death from any CV mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) at least 30 days after an MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. Death resulting from a procedure to treat an MI, (e.g., percutaneous coronary intervention, coronary artery bypass grafting) or to treat a complication resulting from an MI was also considered a death due to acute MI.
- sudden cardiac death, which refers to a death
  - occurring without new or worsening symptoms

    - witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
    - witnessed and attributed to an identified arrhythmia
    - after unsuccessful resuscitation from cardiac arrest
    - after successful resuscitation from cardiac arrest and without identification of a specific cardiac or noncardiac etiology
    - unwitnessed death in a person seen alive and clinically stable at least 24 hours before being found dead without any evidence supporting a specific non-CV cause of death.
- death due to stroke, which refers to a death after a stroke that is either a direct consequence of the stroke or a complication of the stroke
- other CV causes, which refer to a CV death not included in the previous categories but with a specific, known cause
- undetermined cause of death, which refers to a death not attributable to any of the previous categories of CV death or to a non-CV cause.

Secondary end points in the VICTORIA trial included time to CV death, time to first event of HHF, time to total (first and recurrent) HHF events, time to all-cause mortality or HHF, and time to all-cause mortality.

Non-CV death was defined as any death with a specific cause that is not thought to be CV in nature.

CV hospitalization: The duration of the patient's stay in the hospital or emergency department was at least 24 hours and was unplanned. If death occurred within 24 hours after hospitalization, that event was considered a death and not a hospitalization.

CV hospitalization was defined as an event that met all the following criteria:

- HHF
    - the patient was admitted to the hospital or emergency department with a primary diagnosis of HF
    - the patient's length of stay in hospital or emergency department extended for at least 24 hours
    - the patient exhibited new or worsening symptoms due to HF on presentation
    - the patient had objective evidence of new or worsening HF, consisting of at least 2 physical examination findings or 1 physical examination finding and at least 1 laboratory criterion
    - the patient received initiation or intensification of treatment specifically for HF (i.e., IV diuretic, mechanical or surgical intervention).
- Hospitalization for MI, defined as a patient demonstrating at least 1 biochemical indicator of myocardial necrosis.
- Hospitalization for stroke, defined as an acute episode of focal or global neurologic dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction —
    - ischemic stroke
    - hemorrhagic stroke

- undetermined stroke.
- Other CV hospitalizations, defined as urgent and unscheduled hospitalization for CV causes that do not meet the criteria for the specific events listed here.

Table 9: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	Outcome level
Time to first event of CV death or HHF	Primary
Time to CV death	Secondary
Time to first HHF	Secondary
Time to total events (first and recurrent) of HHF	Secondary
Time to first event of all-cause mortality or HHF	Secondary
Time to all-cause mortality	Secondary
Change from baseline in health-related quality of life measures (KCCQ and EQ-5D)	Exploratory
Time to first CV hospitalization	Exploratory
Total number of HHF	Exploratory
Time to first HF event, defined as composite of HHF and urgent HF visit (not meeting the criteria for HHF)	Exploratory
Change in NYHA class	Additional
Change in NT-proBNP	Additional

CV = cardiovascular; HF = heart failure; HHF = hospitalization for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire, NT-proBNP = N-terminal probrain natriuretic peptide; NYHA = New York Heart Association.

Source: Clinical Study Report for VICTORIA.[10]

Patient-Reported Outcomes

In addition to the clinical end points, HRQoL was measured in the VICTORIA trial using the KCCQ and EQ-5D instrument.

Kansas City Cardiomyopathy Questionnaire

The KCCQ is a self-administered, 23-item, disease-specific questionnaire used to measure HRQoL in patients with HF over a 2-week recall period. Items are categorized into the following 7 domains: symptom frequency; symptom burden; symptom stability; physical limitations; social limitations; quality of life; and self-efficacy. The questionnaire is scored by assigning each item an ordinal value, beginning with 1 as the lowest level of functioning, then summing all items within each domain and transforming the value to a 0- to 100-point scale. Missing values are assigned the average score of the answered items in the same domain.[36] Lower scores indicate greater symptom severity and limitations, whereas a score of 100 would indicate no symptoms, no limitations, and excellent HRQoL. Additionally, the KCCQ scores can be summarized in 25-point health status ranges, where 0 to 24 represent very poor to poor, 25 to 49 represent poor to fair, 50 to 74 represent fair to good, and 75 to 100 represent good to excellent health status.[37] To improve the interpretation of the questionnaire results, summary scores were developed. The KCCQ total symptom score comprises the symptom frequency and symptom severity domains. The KCCQ clinical summary score

comprises the physical limitation, symptom frequency, and symptom severity domains. The KCCQ overall summary score comprises the physical limitation, symptom frequency, symptoms severity, HRQoL, and social limitation domains.[36,37]

The KCCQ questionnaire is generally a valid, reliable, and responsive instrument for CV diseases, including HF. Convergent validity was demonstrated in patients with HF with reduced ejection fraction (defined as an LVEF of less than 40%) (N = 129).[36] The Spearman's rank correlation coefficient for the KCCQ physical limitation domain ranged from 0.48 for the 6-minute walk test (6MWT) to 0.84 for the 36-Item Short Form Survey (SF-36) physical limitation domain; for the KCCQ quality-of-life domain, the correlation ranged from 0.45 for the SF-36 general health perception domain to −0.64 for NYHA class; for the KCCQ social limitation domain, the correlation was −0.57 for NYHA class and 0.62 for the SF-36 social functioning domain.[36] Construct validity of the KCCQ physical limitation domain in patients with HF was demonstrated by the correlation coefficient that ranged from 0.48 for the 6MWT to 0.84 for the SF-36 physical functioning domain, and for the KCCQ social limitation domain, the correlation coefficient was 0.59 to 0.62 for the SF-36 social functioning domain.[38] For internal consistency, the Cronbach alpha was 0.62 for the KCCQ self-efficacy score, 0.78 for the KCCQ quality-of-life score, 0.86 for the KCCQ social limitation score, 0.88 for the KCCQ total symptoms score, 0.90 for the KCCQ physical limitation score, 0.93 for the KCCQ clinical summary score, and 0.95 for the KCCQ overall summary score in patients with HF with reduced ejection fraction (defined as an LVEF of less than 40%) (N = 39).[36] For test-retest reliability, no differences were found in the mean domain or summary scores between baseline and 3-month follow-up.[36] Guyatt's responsiveness statistic was 0.62 for the KCCQ social limitation domain, 0.83 for the KCCQ self-efficacy domain, 0.86 for the KCCQ quality-of-life score, 1.48 for the KCCQ physical limitation score, 1.74 for the KCCQ overall summary score, 2.62 for the KCCQ symptom stability score, 2.77 for the KCCQ clinical summary score, and 3.19 for the KCCQ symptom frequency and severity domain.[36]

The relationship between KCCQ and 6MWT and peak oxygen consumption (VO_2) in patients with HF with reduced ejection fraction (defined as LVEF of less than 35%) (N = 2,331) was assessed in Flynn et al. (2009).[39] The authors of that study by Flynn et al. (2009)[39] concluded that the results generally supported the need for a 5-point difference in the KCCQ between patients to be clinically meaningful. In another study, Spertus et al. (2005)[40] described the relationship between measures of disease status, and clinically observed changes in patients with HF with reduced ejection fraction (defined as LVEF of less than 40%) using clinical change assessed by a cardiologist on a 15-point Likert scale, which ranged from extremely worse to extremely better, and grouped into categories of change (N = 476).[40] When the KCCQ overall summary score was assessed at baseline and at 6 weeks, a mean improvement of 5.7 points (SD = 16) was associated with a small improvement in HF, and a mean decline of 5.3 points (SD = 11) was associated with a small deterioration in HF.[40]

5-Level EQ-5D Instrument

The EQ-5D-5L is a generic self-reported HRQoL outcome measure that can be applied to a variety of health conditions and treatments. The EQ-5D-5L was developed by the EuroQol Group as an improvement to the 3-Level EQ-5D (EQ-5D-3L) to measure small and medium health changes and reduce ceiling effects.[39] The

instrument comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on 5 levels: level 1 "no problems," level 2 "slight problems," level 3 "moderate problems," level 4 "severe problems," and level 5 "extreme problems" or "unable to perform."[41,42] A total of 3,125 unique health states are possible, with 55555 representing the worst health state and 11111 representing the best state. The corresponding scoring of EQ-5D-5L health states is based on a scoring algorithm derived from preference data obtained from interviews using choice-based techniques (e.g., time trade-off) and discrete choice experiment tasks.[41,42] The lowest and highest scores vary depending on the scoring algorithm used. Scores less than 0 represent health states that are valued by society as being worse than dead, whereas scores of 0 and 1.00 are assigned to the health states "dead"' and "'perfect health," respectively. As an example, a Canadian scoring algorithm results in a score of −0.148 for health state 55555 (worst health state) and a score of 0.949 for health state 11111 (best health state).[41,42] Another component of the EQ-5D-5L is a visual analogue scale (EQ VAS), which asks respondents to rate their health on a visual scale from 0 (worst health imaginable) to 100 (best health imaginable).

The literature search completed by CADTH did not find any evidence on the validity, reliability, responsiveness, and MID of the EQ-5D-5L questionnaire in patients with HF, although a Canadian-specific MID of 0.037 has been reported for the EQ-5D-5L.[41,42]

Harms

The safety outcomes assessed in the VICTORIA trial were:

- AEs
- SAEs
- AEs leading to discontinuation of the investigational drug
- AEs of special interests, including syncope, symptomatic hypotension, and elevated aspartate aminotransferase and alanine transaminase values
- pharmacokinetic and pharmacodynamic measurements.

Statistical Analysis

The statistical analysis of efficacy end points conducted in the VICTORIA trial is summarized in Table 9.

Sample Size Calculations

In the VICTORIA trial, the sample size calculation was driven by the CV death component of the composite primary end point. At least 782 CEC-confirmed CV death events in the ITT population were required to achieve an 80% power at a study-wise 1-sided significance level of 0.025. The sponsor estimated that at least 4,872 patients needed to be enrolled to achieve the required number of events, assuming a yearly CV death event rate in the placebo group of 11%,[43] an accrual period of approximately 30 months, and a median follow-up period of 10 months. With this sample size, 1,561 patients with a primary end point event were expected to be followed, with a power of approximately 98%, to test the primary hypothesis. The yearly dropout rate was assumed to be 2%. In addition, approximately 10% of patients per year were expected to discontinue the study drug, but they could be followed after discontinuation of treatment for the primary end

point. A true HR of 0.8 between vericiguat and placebo was considered to be a clinically relevant treatment effect for the primary composite end point in the planned high-risk population.

Interim and Final Analyses

One futility interim analysis to assess lack of efficacy was to be performed approximately 27 months after the start of the study, when approximately 50% (781 events) of the planned number of primary end point events was observed. One efficacy interim analysis was to be performed approximately 33 months after the start of the study, with a median follow-up of 10 months, when approximately 75% of the planned number of CV death events (587 events) as a component of the composite primary end point was observed. The Hwang, Shih, and DeCani alpha spending function was to be used to assess the superiority of vericiguat. However, the decision was made to cancel the interim analysis because the number of CV death events was higher than expected. Accordingly, no multiplicity adjustment for the interim analysis was applied, and a 1-sided significance level of 0.025 was used for all hypothesis testing at the final analysis. A final analysis was to be performed approximately 39 months after the start of the study, with a median follow-up of 10 months, when approximately 782 CV deaths were observed.

Analysis of Outcomes

Primary Outcome

In the VICTORIA trial, the analysis of the composite end point of time to first event of CV death or HHF was performed using a 1-sided stratified log-rank test, stratified by geographic region and race considered for randomization. Only the adjudicated and confirmed events were included in the primary analysis. This analysis was based on the ITT population (described subsequently), comprised of all randomized patients. The overall study-wise 1-sided type I error rate was controlled at 0.025. Kaplan-Meier estimates of the primary composite end point (95% CI) survival curves were presented for each treatment group. HR, RR reduction, and corresponding 95% CIs were estimated using a Cox proportional hazards model, controlled by stratification factors (geographic region and race). The proportional hazards assumption between treatments in the models were assessed with ZPH tests for nonproportional hazards, and no evidence of any nonproportional hazard of treatments was found for any of the transitions. The number and proportion of patients with CV death or HHF events and rates per 100 patient-years were provided by treatment group. The time to event was derived from the date of randomization. A patient with at least 1 event (CV death or HHF) was considered to have an event, and the date of the first event was used for the composite end point analysis. Patients without a specific end point event were censored based on the date of their non-CV death, last available information for the primary end point event, or the primary completion date (June 18, 2019), whichever was earliest. The component of the primary end point was also summarized. If a patient's first HHF and CV death occurred on the same day, the CV death was considered to be the component that contributed to the primary end point.

Of the subgroups listed in the CADTH review protocol, the following subgroups were prespecified in the VICTORIA trial:

- ejection fraction (LVEF < 35% versus ≥ 35%, and LVEF < 40% versus ≥ 40%)
- NYHA class (class I or II or class III or IV)

- renal function (eGFR ≤ 30 mL/min/1.73 m^2 versus eGFR between 31 and 60 mL/min/1.73 m^2 and versus eGFR > 60 mL/min/1.73 m^2)
- index event (IV diuretic within 3 months of randomization versus hospitalization within 3 months of randomization, and versus hospitalization within 3 to 6 months before randomization)
- prior use of sacubitril-valsartan (yes versus no)
- baseline NT-proBNP by quartiles.

The subgroup analyses for the primary composite end point and its components, time to CV death and time to first HHF, were performed using a Cox proportional hazards model. There were no adjustments made for multiplicity; as such, all subgroup analyses are exploratory in nature. A between-group treatment effect with a nominal 95% CI for these end points was estimated within each category. Forest plots were created, including interaction P values for treatment-by-subgroup interactions.

Sensitivity Analysis

On-treatment analyses were performed on the primary composite end point, as approximately half of the patients were no longer receiving the study drug by the end of the trial. This analysis included all randomized patients who received the study drug. Efficacy measurement or follow-up from the date of first dose of the study drug to 14 days after the last dose of the study drug was included in the on-treatment analysis.

Secondary Outcomes

The secondary end points were separated into 2 families. The first family included the time to CV death and time to first HHF, and these were tested without multiplicity adjustment.

The end points of the second family, including time to total events (first and recurrent) of HHF, time to first event of all-cause mortality or HHF, and time to all-cause mortality, were analyzed using a 1-sided stratified log-rank test. The time to total events of HHF was analyzed using the Andersen-Gill model, and treatment group and the stratification factors used for randomization were included in the model as fixed effects. In addition, the marginal approach of Wei, Lin, and Weissfeld method was used for analysis of the time to total events of HHF, including all patients included in the ITT analysis, assuming each patient is simultaneously at risk for each type of event (sensitivity analysis). A Cox regression model with covariates for treatment and stratification factors was used to estimate the HR for each type of event. Subgroup analyses were carried out; however, there were no adjustments made for multiplicity. The sensitivity on-treatment analysis of the secondary outcomes included all randomized patients who received the study drug.

For end points defined as time to a nonfatal event or composite end points defined as time to both fatal and nonfatal events, censoring time was the date of last study follow-up (excluding follow-up for vital status only). If a patient died during the study but the death was not part of the end point (i.e., non-CV death for the primary end point), and the death occurred in the 4 months after the last study follow-up (excluding vital status only follow-up), the date of the non–end point death was considered as the last follow-up date. If the non–end point death occurred more than 4 months after the last study follow-up (excluding vital status only follow-up), the date of follow-up before death was considered as last follow-up date. For end points defined

as time to a fatal event, the censoring time was the date of the last study follow-up, including follow-ups for vital status only.

A fixed-sequence hierarchical resting approach was used to test the secondary end points from the second family to control the study-wise type I error. In particular, the secondary end points were only tested if the primary composite end point was significant. The time to total events of HHF was tested only if the primary composite end point was significant, the time to the first event of all-cause mortality or HHF was only tested if the time to total events of HHF was significant, and the time to all-cause mortality was tested only if the time to the first event of all-cause mortality or HHF was significant (Figure 3).

Exploratory Outcomes

In the VICTORIA trial, end points listed as exploratory were tested in a nonhierarchical fashion without adjustments for multiplicity. The following time-to-event end points were analyzed using a Cox proportional hazard model, as they were in the primary outcome analysis: time to first HF event (defined as a composite of HHF or urgent HF visit, time to first CV hospitalization, and total number of HHFs, and time to the first event of CV death, MI hospitalization, or stroke hospitalization.

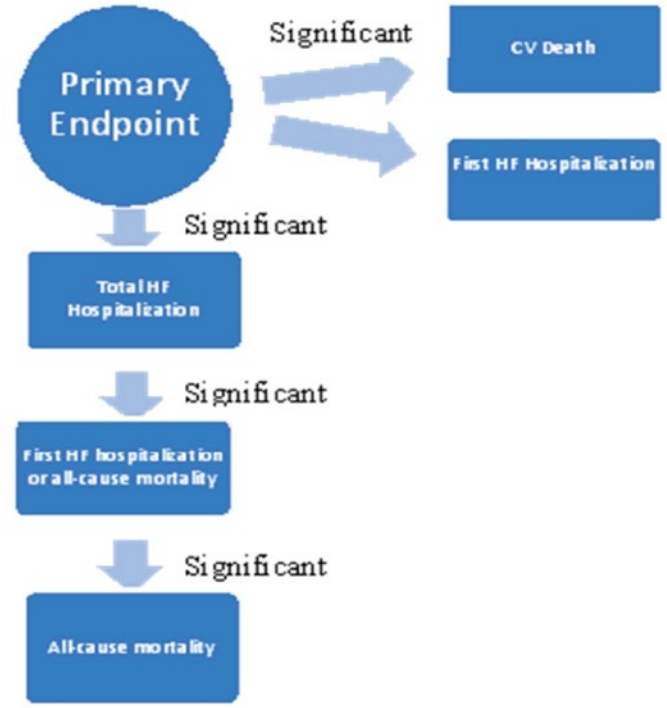
In the VICTORIA trial, the changes from baseline in KCCQ physical limitation score, KCCQ symptom frequency score, KCCQ total symptom score, KCCQ clinical summary score, KCCQ overall summary score, EQ-5D-5L index, and EQ-5D VAS score at week 32 were analyzed in the ITT population using a repeated-measures covariance model with region, study group, stratification factors, study visit, and the interaction between study visit and study treatment group as covariates. For patients who died during the trial, the worst score (0) was used for each of these scores from the time of death onward (Table 10).

Missing Data

In the VICTORIA study, patients who discontinued study treatment early were followed up for further data collection; thus, the amount of missing data was expected to be minor. Because the analysis of the primary end point is the time-to-event analysis, patients with missing follow-up data were included in the analysis, with time to event censored at the last visit date with full assessment of efficacy end points. Lost follow-up time was calculated as the time from the last visit with full evaluation of efficacy end points to the last visit in the study.

In addition, missing follow-up data on the primary end point were planned to simulate based on the assumption that the time to first primary event will have similar survival distribution pattern as the observed data and would include 2 scenarios: missing at random and missing not at random. The time-to-event analysis on the combined data (observed plus imputed) using the same 1-sided log-rank test for primary efficacy analysis was planned; however, it was not conducted because the amount of missing follow-up data was low.

Figure 3: Summary of Hierarchical Testing



CV = cardiovascular; HF = heart failure.

Sources: Clinical Study Report for VICTORIA,[10] Statistical Analysis Plan.[44]

Table 10: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Sensitivity analysis[a]
Time to the first event of CV death or HHF	Stratified long-rank test Cox proportional regression model	Treatment group and stratification factors: region and race	On-treatment analysis
Time to CV death	Stratified long-rank test Cox proportional regression model	Treatment group and stratification factors: region and race	On-treatment analysis
Time to first event of HHF	Stratified long-rank test Cox proportional regression model	Treatment group and stratification factors: region and race	On-treatment analysis
Time to total events of HHF (first and recurrent)	Andersen-Gill model	Treatment group and stratification factors (region and race) as fixed effects	On-treatment analysis Marginal approach of Wei, Lin, and Weissfeld method
Time to first event of all-cause mortality or HHF	Stratified long-rank test Cox proportional regression model	Treatment group and stratification factors: region and race	On-treatment analysis
Time to all-cause mortality	Stratified long-rank test Cox proportional regression model	Treatment group and stratification factors: region and race	On-treatment analysis
Time to first HF event, defined as composite of HHF and urgent HF visit	Stratified long-rank test Cox proportional regression model	Treatment group and stratification factors: region and race	On-treatment analysis

End point	Statistical model	Adjustment factors	Sensitivity analysis[a]
Time to first CV hospitalization	Stratified long-rank test Cox proportional regression model	Treatment group and stratification factors: region and race	On-treatment analysis
Change in KCCQ scores from baseline to week 32[b]	Repeated-measures analysis of covariance	Region, study treatment group, stratification factors, study visit, and interaction between study visit and study treatment group	On-treatment analysis
Change in EQ-5D-5L index and EQ VAS scores from baseline to week 32	Repeated-measures analysis of covariance	Region, study treatment group, stratification factors, study visit, and interaction between study visit and study treatment group	On-treatment analysis
Change in NYHA class	Descriptive analysis	None	None
Change in NT-proBNP	Longitudinal analysis of covariance model	Region, race, study treatment group, and week-by-treatment interaction	None

CV = cardiovascular; EQ-5D-5L = 5-Level EQ-5D; EQ VAS = EQ visual analogue scale; HF = heart failure; HHF = hospitalization for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-termina probrain natriuretic peptide; NYHA = New York Heart Association.

[a]On-treatment analysis helped to establish the treatment effect for patients who remained on the study drug. This analysis included all randomized patients who received the study drug. Efficacy measurement or follow-up from the date of first dose of study drug to 14 days after the last dose of study drug was included in the on-treatment analysis.

[b]KCCQ scores include KCCQ physical limitation score, KCCQ symptom frequency score, KCCQ total symptom score, KCCQ clinical summary score, and KCCQ overall summary score.

Source: Clinical Study Report for VICTORIA.[10]

Harms

The CEC reviewed each suspected clinical end point event without unblinding treatment. All safety end points were reported using descriptive statistics and were carried out on the safety (or all subjects as treated [ASaT]) population, including patients who had received at least 1 dose of the trial medication. Separate summaries were provided for the 2 most notable safety end points: syncope, and symptomatic hypotension. The incidence of these end points was analyzed by treatment, as well as by subgroups.

Analysis Populations

All patient populations were defined and documented before the database lock.

The ITT population (N = 5,050) consisted of all randomized patients. Patients were analyzed according to their randomized group. Unless otherwise specified, all efficacy end points were summarized and analyzed using the ITT population.

The ASaT, or safety, population (N = 5,034) consisted of all randomized patients who received at least 1 dose of the study drug. Patients were analyzed according to their randomized group. The summary for the safety analysis set was based on subjects “as treated.” A total of 7 patients, 4 of whom were randomized to the placebo group, received both placebo and vericiguat during the trial and were analyzed according to their planned treatment.

Results

Patient Disposition

As of the primary completion date (June 18, 2019), 6,857 individuals were screened, of whom 1,807 (26.4%) did not pass screening. The main reason was not meeting eligibility criteria, predominantly because patients' NT-proBNP levels were below the prespecified thresholds at screening (59.7%), patients were clinically unstable (14.7%), or patients withdrew consent (10.6%). In total, 5,050 patients were randomized in the treatment period (Table 11). Vital status for the primary end point was known for 2,524 (99.9%) patients in the vericiguat group and 2,520 (99.8%) patients in the placebo group. Of the 5,034 patients treated with the study medication, 38.2% of patients in the vericiguat group and 37.4% of patients in the placebo group discontinued treatment. The most frequently reported reasons for discontinuation were AEs (7.0% and 6.3% in the vericiguat and placebo groups, respectively), death (14.0% and 15.0% in the vericiguat and placebo groups, respectively), and withdrawal by patient (7.7% and 7.6% in the vericiguat and placebo groups, respectively).

Table 11: Patient Disposition — ITT Population

Patient disposition	Vericiguat	Placebo
Screened, N	[redacted]	
Randomized, n	[redacted]	[redacted]
Final vital status known,[a] n (%)	[redacted]	[redacted]
Complete follow-up for primary end point,[b] n (%)	[redacted]	[redacted]
Prematurely discontinued from study, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]
Status not recorded, n (%)	[redacted]	[redacted]
Started treatment, n (%)	[redacted]	[redacted]
Completed treatment, n (%)	[redacted]	[redacted]
Prematurely discontinued from treatment, n (%)	[redacted]	[redacted]
Reason for treatment discontinuation, n (%)		
Adverse event	177 (7.0)	159 (6.3)
Death	353 (14.0)	376 (15.0)
Lost to follow-up	9 (0.4)	11 (0.4)
Noncompliance with study medication	48 (1.9)	49 (1.9)
Physician decision	173 (6.9)	154 (6.1)
Protocol deviation	8 (0.3)	2 (0.1)
Withdrawal by patient	195 (7.7)	190 (7.6)

Patient disposition	Vericiguat	Placebo
Status not recorded, n (%)	[redacted]	[redacted]
ITT population, N (%)	[redacted]	[redacted]
ASaT (safety) population, N (%)	[redacted]	[redacted]

ASaT = all subjects as treated; ITT = intention to treat.
Note: Based on data up to the primary completion date (June 18, 2019).
[a]Complete follow-up for vital status was defined as meeting either of the following criteria:
• the patient died during the study
• the patient's last known vital status was on or after the primary completion date.
[b]Complete follow-up for the primary end point was defined as meeting any of the following criteria:
• the patient had a primary end point event before the primary completion date
• the patient died during the study
• the patient's last follow-up date occurred on or after the primary completion date.
Source: Clinical Study Report for VICTORIA.[10]

Exposure to Study Treatments

Treatment compliance was assessed based on the amount of study drug returned at the end of the treatment period. Compliance with the study treatment regimen was high and similar across the treatment groups. Most patients (86.8% and 85.6% in the vericiguat and placebo groups, respectively) were between 90% and 100% compliant with the study medications during the trial.

As of the primary completion date (June 18, 2019), the mean duration of exposure to any dose of vericiguat was 375.5 days (range = 1 to 964 days), and to vericiguat at a dose of 10 mg was 362.0 days (range = 1 to 935 days) (Table 12). The mean duration of exposure to any dose of placebo was 374.7 days (range = 1 to 966 days). The mean dose of the study intervention was similar between the vericiguat and placebo groups (7.8 mg and 8.0 mg, respectively). A total of 218 (8.9%) of patients in the vericiguat group required a dose decrease at 1 or more visits, compared to 181 (7.4%) patients in the placebo group (Table 12). The proportion of patients requiring a study drug dose interruption was similar in the vericiguat and placebo groups (17.0% and 16.4%, respectively).

Protocol Deviation

Protocol deviations in the VICTORIA trial are summarized in Table 13. Overall, 114 (11.3%) patients had at least 1 major protocol deviation, with similar frequencies across the treatment groups. A total of 75 (3.0%) patients in the vericiguat group and 71 (2.8%) in the placebo group had at least 1 clinically important protocol deviation. The most common were related to safety reporting (1.4%), study intervention (0.9%), and inclusion or /exclusion criteria (3.8%).

Table 12: Treatment Exposure — ASaT Population

Treatment exposure	Vericiguat	Placebo
Any dose,[a] n	2,519	2,515
Mean duration of exposure (range),[b] days	375.5 (1 to 964)	374.7 (1 to 966)
≤ 2 weeks, n	78	81
> 2 to 4 weeks, n	81	58
> 4 to 16 weeks, n	268	252
> 16 to 32 weeks, n	412	369
> 32 weeks to 1 year, n	561	595
> 1 to 2 years, n	810	837
> 2 to 3 years, n	309	323
2.5 mg, n	2,517	—
Mean duration of exposure (range), days	35.0 (1 to 918)	—
5 mg, n	2,285	—
Mean duration of exposure (range), days	48.2 (1 to 861)	—
10 mg, n	2,063	—
Mean duration of exposure (range), days	362.0 (1 to 935)	—
Mean study drug dose (SD), mg	7.8 (2.5)	8.0 (2.4)
Median study drug dose (range), mg	9.2 (2.1 to 12.7)	9.2 (2.5 to 13.8)
Dose decrease or interruption at 1 or more visits, n (%)	570 (23.2)	535 (21.8)
Dose decrease at 1 or more visits, n (%)	218 (8.9)	181 (7.4)
Dose interruption at 1 or more visits, n (%)	419 (17.0)	403 (16.4)

ASaT = all subjects as treated; SD = standard deviation.

Notes: Each patient is counted once in each specific dose category row, corresponding to the actual dose(s) received.

Based on data up to the primary completion date (June 18, 2019).

[a]Each patient who received at least 1 dose of vericiguat (including doses other than 2.5 mg, 5 mg, or 10 mg).

[b]Duration of exposure is calculated assuming 1 day of dosing on days of exposure.

Source: Clinical Study Report for VICTORIA.[10]

Table 13: Protocol Deviations — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Patients with at least 1 major protocol deviation, n (%)	461 (18.3)	422 (16.7)
Patients with at least 1 clinically important protocol deviation, n (%)	[redacted]	[redacted]
Inclusion or exclusion criteria	[redacted]	[redacted]
Informed consent form	[redacted]	[redacted]
Prohibited medications	[redacted]	[redacted]
Safety reporting	[redacted]	[redacted]

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Study intervention	[redacted]	[redacted]
Trial procedures	[redacted]	[redacted]

ITT = intention to treat.
Source: Clinical Study Report for VICTORIA.[10]

Concomitant Medications

Reported concomitant medication use was generally balanced between treatment arms. The most frequently reported concomitant medication categories included diuretics (98.9%), beta-blocking agents (95.1%), agents acting on the renin-angiotensin system (91.2%), and antithrombotic agents (90.5%). According to the study protocol, patients requiring treatment with long-acting nitrates or NO donors were excluded from participation in the study; however, concomitant use of short-acting nitrates for the treatment of angina attacks was permitted. During the VICTORIA trial, the proportion of patients that used nitrates at 1 or more visits was similar between the vericiguat and placebo groups (10.8% and 12.9%, respectively).

Duration of Follow-Up

The median duration of follow-up for the primary end point of time to first event of adjudicated CV death or HHF in the ITT population was 11.1 months (quartile [Q]1 to Q3, 6.5 to 19.1 months) in the vericiguat group and 10.4 months (Q1 to Q3, 6.1 to 18.7 months) in the placebo group (Table 14). The median duration of follow-up for all-cause mortality in the ITT population was [redacted] in the vericiguat group and [redacted] in the placebo group. The percentage of follow-up for the primary end point and all-cause mortality, out of the total potential follow-up, was greater than 99% in both treatment groups.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported here. Refer to Appendix 3 for detailed efficacy data. Only clinical end points adjudicated by the CEC were used in the efficacy analyses.

Table 14: Follow-Up Duration — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Time to first event of adjudicated CV death or HHF		
Mean duration of follow-up (SD), months	12.7 (8.4)	12.2 (8.4)
Median duration of follow-up (Q1 to Q3), months	11.1 (6.5 to 19.1)	10.4 (6.1 to 18.7)
Total patient-years of follow-up[a]	2,668.9	2,572.0
Total potential patient-years of follow-up[b]	2,681.2	2,582.7
Follow-up proportion,[c] %	99.5	99.6
All-cause mortality		
Mean duration of follow-up (SD), months	[redacted]	[redacted]
Median duration of follow-up (Q1 to Q3), months	[redacted]	[redacted]

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Total patient-years of follow-up[a]	[redacted]	[redacted]
Total potential patient-years of follow-up[b]	[redacted]	[redacted]
Follow-up proportion,[c] %	[redacted]	[redacted]

CV = cardiovascular; HHF = hospitalization for heart failure; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation.

[a]Computed for each patient as the day of randomization to the day of death, the last available information on vital status, or the primary completion date (June 18, 2019).

[b]Computed for each patient as the day of randomization to the day of the earlier instance of death or the primary completion date (June 18, 2019)

[c]Percentage of follow-up = (patient-years of follow-up / potential patient-years of follow-up) × 100.

Source: Clinical Study Report for VICTORIA.[10]

Time to First Event of Adjudicated CV Death or HHF

The results of the primary efficacy end point are presented in Table 15. A composite of time to first event of adjudicated CV death or HHF occurred in 897 patients (35.5%) in the vericiguat group and 972 patients (38.5%) in the placebo group. The annual event rate was lower in the vericiguat group compared to placebo group (33.6% and 37.8%, respectively), with an HR of 0.90 (99.5% CI, 0.82 to 0.98; P = 0.019) in favour of vericiguat. The median follow-up duration was 11.1 months in the vericiguat group and 10.4 months in the placebo group (Table 14). The Kaplan-Meier plot of the primary composite end point for the ITT is presented in Figure 4. The proportion of HHF as the first event was lower in the vericiguat group (27.4%) than in the placebo group (29.6%), whereas the proportion of CV death as the first event was similar across the vericiguat and placebo groups (8.2% and 8.9%, respectively). The on-treatment analysis results for the primary composite end point showed that the HR was [redacted] (Appendix 3, Table 33, Figure 11).

Subgroup Analysis

The primary end point subgroup analysis is presented in Table 16. The analyses may not have been powered to detect a treatment difference and there were no adjustments made for multiplicity. Although the treatment effects for prespecified subgroups in the CADTH protocol were generally consistent with the main effect, a potential difference was noted, depending on NT-proBNP at baseline (P value for interaction < 0.05).

Time to CV Death

This secondary outcome was tested in a nonhierarchical sequence without adjustments for multiplicity and was exploratory in nature. The number of CV death events was 414 (16.4%) in the vericiguat group and 441 (17.5%) in the placebo group (Table 17). The proportion of patients who died of HF was 6.5% and 7.6% in the vericiguat and placebo groups, respectively, sudden cardiac event 4.2% and 4.5% in the vericiguat and placebo groups, respectively, and undetermined cause of death 4.4% and 4.0% in the vericiguat and placebo groups, respectively. The HR for the time to CV death was 0.93 (99.5% CI, 0.81 to 1.06; P = 0.269). The Kaplan-Meier plot of the time to CV death is presented in Figure 5. The results of the on-treatment analysis were consistent with those of the primary analysis (HR = 0.93; 95% CI, 0.78 to 1.12; P = 0.469) (Appendix 3, Table 34, Figure 12).

Table 15: Time to First Event of CEC-Confirmed CV Death or HHF — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Patients with event, n (%)	897 (35.5)	972 (38.5)
HHF as first event, n (%)	691 (27.4)	747 (29.6)
CV death as first event, n (%)	206 (8.2)	225 (8.9)
Annual rate, %[a]	33.6	37.8
KM% (95% CI) at 2 years[b]	43.9 (41.5 to 46.4)	46.9 (44.4 to 49.4)
HR (95% CI)[c]	0.90 (0.82 to 0.98)	
P value[d]	0.019	Reference

CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.

Notes: For patients with multiple events, only the first event contributing to the composite end point is counted in the table.

Based on data up to the primary completion date (June 18, 2019).

[a]Total events per 100 patient-years at risk.

[b]KM estimate and CI at 2 years.

[c]HR (vericiguat over placebo) and CI from Cox proportional hazard model, controlled for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race.

Table 16: Subgroup Analyses of the Primary Composite End Point — ITT Population

Subgroup	Vericiguat events, n (%)	Placebo events, n (%)	HR[a] (95% CI)	Interaction P[b] value
Index event				
IV diuretic < 3 months	n = 399 96 (24.1)	n = 402 120 (29.9)	0.78 (0.60 to 1.02)	0.412
Hospitalization < 3 months	n = 1,673 660 (39.5)	n = 1,705 701 (41.1)	0.93 (0.84 to 1.04)	
Hospitalization 3 to 6 months	n = 454 141 (31.1)	n = 417 151 (36.2)	0.85 (0.67 to 1.07)	
eGFR at baseline				
≤ 30	n = 259 143 (55.2)	n = 247 128 (51.8)	1.06 (0.83 to 1.34)	0.231
31 to 60	n = 1,054 392 (37.2)	n = 1,064 455 (42.8)	0.84 (0.73 to 0.96)	
> 60	n = 1,161 346 (29.8)	n = 1,174 372 (31.7)	0.92 (0.80 to 1.07)	
NYHA class				
I or II	n = 1,478 445 (30.1)	n = 1,499 484 (32.3)	0.91 (0.80 to 1.04)	0.600
III or IV	n = 1,045 451 (43.2)	n = 1,024 487 (47.6)	0.87 (0.77 to 0.99)	

Subgroup	Vericiguat events, n (%)	Placebo events, n (%)	HR[a] (95% CI)	Interaction P[b] value
Use of sacubitril-valsartan at baseline				
Yes	n = 360 134 (37.2)	n = 371 153 (41.2)	0.88 (0.70 to 1.11)	0.897
No	n = 2,161 760 (35.2)	n = 2,148 818 (38.1)	0.90 (0.81 to 0.99)	
NT-proBNP at baseline by quartiles, pg/mL				
Q1 (≤ 1,556)	n = 599 128 (21.4)	n = 604 161 (26.7)	0.78 (0.62 to 0.99)	0.001
Q2 (1,556 to 2,816)	n = 613 165 (26.9)	n = 589 201 (34.1)	0.73 (0.60 to 0.90)	
Q3 (2,816 to 5,314)	n = 586 213 (36.3)	n = 613 257 (41.9)	0.82 (0.69 to 0.99)	
Q4 (> 5,314)	n = 616 355 (57.6)	n = 585 302 (51.6)	1.16 (0.99 to 1.35)	
Ejection fraction, %				
< 40	n = 2,158 773 (35.8)	n = 2,158 851 (39.4)	0.88 (0.80 to 0.97)	0.194
≥ 40	n = 358 119 (33.2)	n = 362 117 (32.3)	1.05 (0.81 to 1.36)	

CEC = Clinical Events Committee; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier; NT-proBNP = N-terminal probrain natriuretic peptide; NYHA = New York Heart Association; Q1 = 25th percentile; Q2 = 50th percentile; Q3 = 75th percentile; Q4 = 100th percentile.

[a]HR, CI, and P value for treatment-by-subgroup interaction from Cox proportional hazard model, with covariates of the stratification factors (defined by region and race), treatment, subgroup, and treatment-by-subgroup interaction.

[b]P value was not adjusted for multiplicity.

Table 17: Time to CEC-Confirmed CV Death — ITT Population

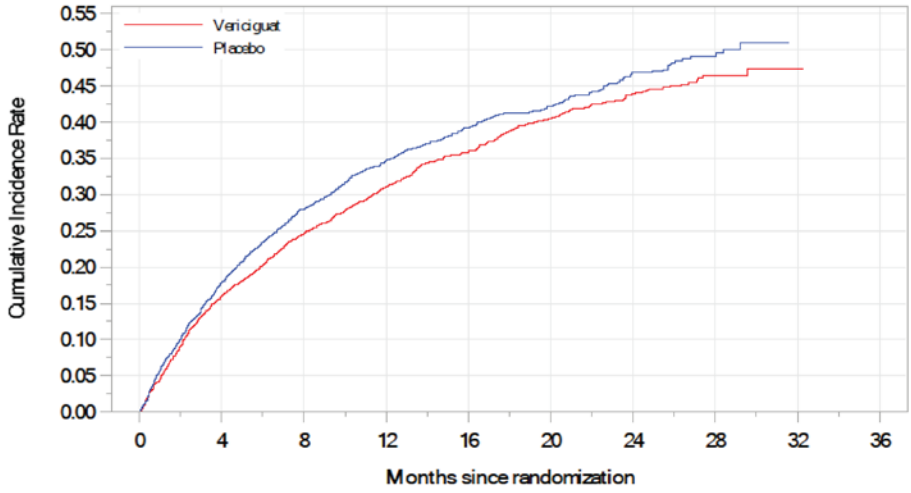
Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
CV death, n (%)	414 (16.4)	441 (17.5)
Heart failure	165 (6.5)	191 (7.6)
Myocardial infarction	10 (0.4)	11 (0.4)
Stroke	7 (0.3)	16 (0.6)
Other cardiovascular event	13 (0.5)	9 (0.4)
Sudden cardiac death	107 (4.2)	113 (4.5)
Undetermined cause of death	112 (4.4)	101 (4.0)
Annual event rate,[a] %	12.9	13.9
KM% (95% CI) at 2 years[b]	22.0 (20.0 to 24.2)	23.7 (21.6 to 26.0)
HR (95% CI)[c]	0.93 (0.81 to 1.06)	

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
P value[d]	0.269	Reference

CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.
Note: Based on data up to the primary completion date (June 18, 2019).
[a]Total events per 100 patient-years at risk.
[b]KM estimate and CI at 2 years.
[c]HR (vericiguat over placebo) and CI from Cox proportional hazard model, controlling for stratification factors (defined by region and race).
[d]From log-rank test stratified by the stratification factors, defined by region and race. P value was not adjusted for multiplicity.
Source: Clinical Study Report for VICTORIA.[10]

Source: Clinical Study Report for VICTORIA.[10]

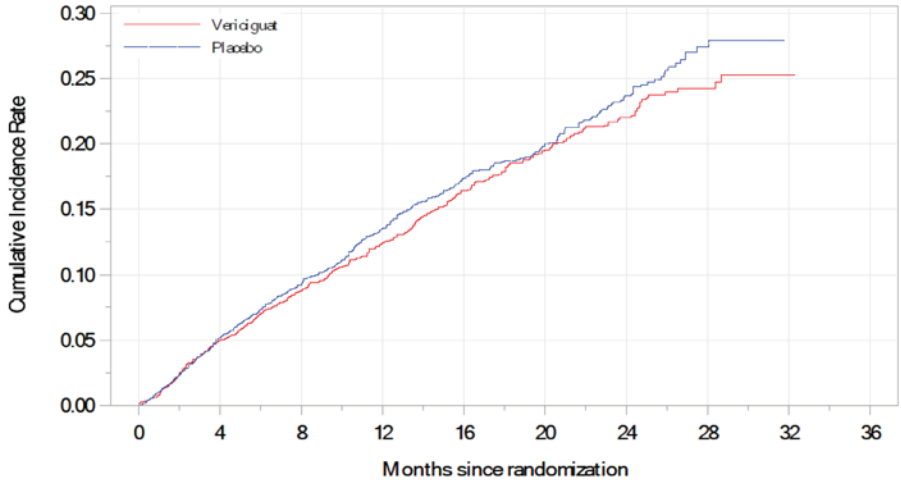
Figure 4: Kaplan-Meier Plot for CEC-Confirmed Primary Composite End Point — ITT Population



CEC = Clinical Events Committee; ITT = Intention to treat.
Note: Based on data up to the primary completion date (June 18, 2019).
Source: Clinical Study Report for VICTORIA.[10]

Subgroup analyses for time to CV death is presented in Appendix 3, Table 35. The analyses may not have been powered to detect a treatment difference and there were no adjustments made for multiplicity. The treatment effects for all prespecified subgroups in the CADTH protocol were consistent with the main effect.

Figure 5: Kaplan-Meier Plot for Time to CEC-Confirmed CV Death — ITT Population



Number of subjects at risk

Vericiguat	2526	2376	1968	1468	1070	779	487	185	1	0
Placebo	2524	2370	1951	1439	1045	768	471	157	0	0

Cumulative number of events up to the time point

Vericiguat	0	124	217	286	344	379	400	412	414	414
Placebo	0	129	228	310	366	395	424	440	441	441

CEC = Clinical Events Committee; CV = cardiovascular; ITT = intention to treat; KM = Kaplan-Meier.
Note: Based on data up to the primary completion date (June 18, 2019).
Source: Clinical Study Report for VICTORIA.[10]

Table 18: Time to CEC-Confirmed All-Cause Mortality — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
All-cause mortality, n (%)	512 (20.3)	534 (21.2)
Annual event rate,[a] %	16.0	16.9
KM% (95% CI) at 2 years[b]	26.6 (24.4 to 28.9)	28.3 (26.0 to 30.7)
HR (95% CI)[c]	0.95 (0.84 to 1.07)	
P value[d]	0.377	Reference

CEC = Clinical Events Committee; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.
Note: Based on data up to the primary completion date (June 18, 2019).
[a]Total events per 100 patient-years at risk.
[b]KM estimate and CI at 2 years.
[c]HR (vericiguat over placebo) and CI from Cox proportional hazard model, controlling for stratification factors (defined by region and race).
[d]From log-rank test stratified by the stratification factors, defined by region and race. P value was not adjusted for multiplicity.
Source: Clinical Study Report for VICTORIA.[10]

Time to All-Cause Mortality

A total of 512 (20.3%) patients in the vericiguat group and 534 (21.2%) patients in the placebo group died of any cause (Table 18). The annual event rate was similar across the treatment groups (16.0% and 16.9% in the vericiguat and placebo groups, respectively), with an HR of 0.95 (95% CI, 0.84 to 1.07; P = 0.377). The Kaplan-Meier plot of time to all-cause mortality is presented in Figure 6. Results of the on-treatment analysis of time to all-cause mortality were consistent with those of the primary analysis (HR = 0.98; 95% CI, 0.83 to 1.16; P = 0.878) (Appendix 3, Table 36, Figure 13).

Time to First Event of All-Cause Mortality or HHF

A composite of time to first event of all-cause mortality or HHF occurred in 957 patients (37.9%) in the vericiguat group and 1,032 patients (40.9%) in the placebo group (Table 19). The annual event rate was 35.9% and 40.1% in the vericiguat and placebo groups, respectively, with an HR of 0.90 (95% CI, 0.83 to 0.98; P = 0.021). This difference was likely driven primarily by a lower proportion of HHF events, although individual components of this composite end point were not formally tested for significance. The Kaplan-Meier plot of the time to all-cause mortality or HHF is presented in Figure 7. The results of the on-treatment analysis were consistent with those of the primary analysis, with an HR of 0.92 (95% CI, 0.83 to 1.01; P = 0.082) (Appendix 3, Table 37, Figure 14).

Figure 6: Kaplan-Meier Plot for Time to CEC-Confirmed All-Cause Mortality — ITT Population

Note: This figure has been redacted per the sponsor's request.

Figure 7: Kaplan-Meier Plot for Time to First Event of CEC-Confirmed All-Cause Mortality or HHF — ITT Population

Note: This figure has been redacted per the sponsor's request.

Table 19: Time to First Event of CEC-Confirmed All-Cause Mortality or HHF — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Patients with event, n (%)	957 (37.9)	1,032 (40.9)
All-cause mortality as first event, n (%)	266 (10.5)	285 (11.3)
HHF as first event, n (%)	691 (27.4)	747 (29.6)
Annual event rate,[a] %	35.9	40.1
KM% (95% CI) at 2 years[b]	46.1 (43.6 to 48.6)	49.3 (46.9 to 51.9)
HR (95% CI)[c]	0.90 (0.83 to 0.98)	
P value[d]	0.021	Reference

CEC = Clinical Events Committee; CI = confidence interval; HHF = hospitalization for heart failure; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.

Notes: Based on data up to the primary completion date (June 18, 2019).

For patients with multiple events, only the first event contributing to the composite end point is counted in the table.

[a]Total events per 100 patient-years at risk.

[b]KM estimate and CI at 2 years.

[c]HR (vericiguat over placebo) and CI from Cox proportional hazard model, controlling for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race.

Source: Clinical Study Report for VICTORIA.[10]

This secondary outcome was tested in a nonhierarchical sequence without adjustments for multiplicity and was exploratory in nature. A total of [redacted] in the vericiguat group and [redacted] in the placebo group had CV hospitalizations (Table 20). The annual event rate was lower in the vericiguat group [redacted] compared to the placebo group [redacted], with an HR of [redacted]. The Kaplan-Meier plot of time to CV hospitalization is presented in Figure 8. The results of the on-treatment analysis for CV hospitalizations were consistent with those of the primary analysis [redacted]

Table 20: Time to First Event of CEC-Confirmed CV Hospitalization — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
CV hospitalization, n (%)	[redacted]	[redacted]
Annual event rate,[a] %	[redacted]	[redacted]
KM% (95% CI) at 2 years[b]	[redacted]	[redacted]
HR (95% CI)[c]	[redacted]	
P value[d]	[redacted]	[redacted]

CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.

Notes: For patients with multiple events, only the first event contributing to the composite end point is counted in the table.

Based on data up to the primary completion date (June 18, 2019).

[a]Total events per 100 patient-years at risk.

[b]KM estimate and CI at 2 years.

[c]HR (vericiguat over placebo) and CI from Cox proportional hazard model, controlling for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race. P value was not adjuster for multiplicity.

Source: Clinical Study Report for VICTORIA.[10]

Figure 8: Kaplan-Meier Plot for Time to First Event of CEC-Confirmed CV Hospitalization — ITT Population

Note: This figure has been redacted per the sponsor's request.

Time to First Event of HHF

This secondary outcome was tested as a component of the primary composite end point in a nonhierarchical sequence without adjustments for multiplicity and was exploratory in nature. The number of patients with HHF events was 691 (27.4%) in the vericiguat group and 747 (29.6%) in the placebo group (Table 21). The annual event rate was 25.9% in the vericiguat group and 29.1% in the placebo group, with an HR of 0.90 (0.81 to 1.00; P = 0.048). The Kaplan-Meier plot for time to the first event of HHF is presented in Figure 9. The results of the on-treatment analysis for this end point were consistent with those of the primary analysis (HR = 0.89; 95% CI, 0.81 to 0.97; P = 0.012) (Appendix 3, Table 39, Figure 16). Although the treatment effects of vericiguat on the HHF for prespecified subgroups in the CADTH protocol were generally consistent with the main effect, a potential difference was noted depending on NT-proBNP at baseline (P value for interaction < 0.05) (Appendix 3, Table 40).

Table 21: Time to First Event of CEC-Confirmed HHF — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
HHF, n (%)	691 (27.4)	747 (29.6)
Annual event rate,[a] %	25.9	29.1
KM% (95% CI) at 2 years[b]	35.1 (32.7 to 37.6)	37.5 (35.0 to 40.0)
HR (95% CI)[c]	0.90 (0.81 to 1.00)	
P value[d]	0.048	Reference

CEC = Clinical Events Committee; CI = confidence interval; HHF = hospitalization for heart failure; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.

Note: Based on data up to the primary completion date (June 18, 2019).

[a]Total events per 100 patient-years at risk.

[b]KM estimate and CI at 2 years.

[c]HR (vericiguat over placebo) and CI from Cox proportional hazard model, controlling for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race. P value was not adjuster for multiplicity.

Source: Clinical Study Report for VICTORIA.[10]

Figure 9: Kaplan-Meier Plot for Time to CEC-Confirmed HHF — ITT Population

Note: This figure has been redacted per the sponsor's request.

Time to Total Events (First and Recurrent) of HHF

The total number of HHF events was lower in patients who received vericiguat (n = 1,223) compared to those who received placebo (n = 1,336) (Table 22). The annual event rate was 38.3% in the vericiguat group and 42.4% in the placebo group, with an HR of 0.91 (95% CI, 0.84 to 0.99; P = 0.023). The results of the sensitivity analysis using the Wei, Lin, and Weissfeld method and supportive on-treatment analyses were consistent with those of the primary analysis (Appendix 3, Table 41 and Table 42).

Table 22: Time to Total Events of CEC-Confirmed HHF — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Total HHF,[a] n	1,223	1,336
Patients with only 1 event	415	431
Patients with only 2 events	160	179
Patients with only 3 events	55	75
Patients with ≥ 4 events	61	62
Annual rate,[b] %	38.3	42.4
HR (95% CI)[c]	0.91 (0.84 to 0.99)	
P value[d]	0.023	Reference

CEC = Clinical Events Committee; CI = confidence interval; HHF = hospitalization for heart failure; HR = hazard ratio; ITT = intention to treat.

Note: Based on data up to the primary completion date (June 18, 2019).

[a]Total number of HHFs (first and recurrent).

[b]Total events per 100 patient-years of follow-up.

[c]Calculated based on the Andersen-Gill model, controlling for stratification factors (defined by region and race). Robust standard errors are used to account for correlations of event times for a patient.

[d]Calculated based on Andersen-Gill model controlling for stratification factors (defined by region and race). Robust standard errors are used to account for correlations of event times within a subject.

Source: Clinical Study Report for VICTORIA.[10]

Change From Baseline in NT-proBNP

This additional outcome was tested in a nonhierarchical sequence without adjustments for multiplicity and was exploratory in nature. The reduction in NT-proBNP from baseline to week 32 was greater in the vericiguat

group compared to placebo group, with a of geometric mean ratio LS means of 0.90 (95% CI, 0.85 to 0.96; P = 0.001) (Table 23).

Change From Baseline in NYHA Class

The number of patients with NYHA class I to class IV HF and the net change from baseline in NYHA class at week 32 in the vericiguat and placebo groups are presented in Table 24.

Time to First Event of CV Death, MI Hospitalization, or Stroke Hospitalization

This exploratory outcome was tested in a nonhierarchical sequence without adjustments for multiplicity. The number of patients with a composite end point was [redacted] in the vericiguat group and [redacted] in the placebo group (Table 25). The annual event rate was [redacted] in the vericiguat group and [redacted] in the placebo group, with an HR of [redacted]. The Kaplan-Meier plot for time to CV death, MI, or stroke hospitalization is presented in Figure 10. The results of the on-treatment analysis were consistent with those of the primary analysis (Appendix 3, Table 46, Figure 17).

Table 23: Change From Baseline in NT-proBNP at Week 32— ITT Population

Characteristic	Vericiguat	Placebo
Baseline, n	2,414	2,391
Geometric mean (SD)	2,928.44 (2.65)	2,886.77 (2.64)
Week 32, n	1,755	1,749
Geometric mean (SD)	1,747.79 (3.43)	1,913 (3.46)
GMR at week 32 vs. baseline		
LS mean (95% CI)	0.69 (0.66 to 0.72)	0.76 (0.73 to 0.80)
GMR LS means (95% CI)[a]	0.90 (0.85 to 0.96)	
P value[b]	0.001	Reference

CI = confidence interval, GMR = geometric mean ratio; ITT = intention to treat; LS = least squares, NT-proBNP = N-terminal probrain natriuretic peptide; SD = standard deviation (back-transformed from SD of log of NT-proBNP value).

Notes: Based on data up to the primary completion date (June 18, 2019).

For baseline and week 32, N is the number of patients with nonmissing assessments at the specific time point. For change from baseline, N is the number of patients with nonmissing assessment in both baseline and week 32.

[a]Based on a longitudinal analysis of the covariance model, with the change from baseline in log-transformed value as the dependent variable, including categorical terms for stratification factor, week, treatment group, and the week-by-treatment group interaction, with the log-transformed baseline value as a continuous covariate, and including all postrandomization time points through week 96.

[b]P value was not adjusted for multiplicity.

Source: Clinical Study Report for VICTORIA[10]

Table 24: Change From Baseline in NYHA Class at Week 32 — ITT Population

Characteristic	Vericiguat	Placebo
Baseline, n	[redacted]	[redacted]
Class I, n (%)	[redacted]	[redacted]
Class II, n (%)	[redacted]	[redacted]
Class III, n (%)	[redacted]	[redacted]
Class IV, n (%)	[redacted]	[redacted]
Week 32, n	[redacted]	[redacted]
Class I, n (%)	[redacted]	[redacted]
Class II, n (%)	[redacted]	[redacted]
Class III, n (%)	[redacted]	[redacted]
Class IV, n (%)	[redacted]	[redacted]
Net change from baseline, n	[redacted]	[redacted]
−3, n (%)	[redacted]	[redacted]
−2, n (%)	[redacted]	[redacted]
−1, n (%)	[redacted]	[redacted]
0, n (%)	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]

HF = heart failure; ITT = intention to treat; NYHA = New York Heart Association.

Notes: Percentages are computed based on the number of patients with nonmissing assessments at the specific time point.

Based on data up to the primary completion date (June 18, 2019).

Source: Clinical Study Report for VICTORIA.[10]

Table 25: Time to First Event of CEC-Confirmed CV Death, MI, or Stroke Hospitalization — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Exploratory composite end point, n (%)	[redacted]	[redacted]
CV death	[redacted]	[redacted]
MI hospitalization	[redacted]	[redacted]
Stroke hospitalization	[redacted]	[redacted]
Annual rate, %[a]	[redacted]	[redacted]
KM% (95% CI) at 2 years[b]	[redacted]	[redacted]
HR (95% CI)[c]	[redacted]	

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
P value[d]	[redacted]	[redacted]

CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier; MI = myocardial infarction.
Notes: For patients with multiple events, only the first event contributing to the composite end point is counted in the table.
Based on data up to the primary completion date (June 18, 2019).
[a]Total events per 100 patient-years at risk.
[b]KM estimate and CI at 2 years.
[c]HR (vericiguat over placebo) and CI from Cox proportional hazard model, controlling for stratification factors (defined by region and race).
[d]From log-rank test stratified by the stratification factors defined by region and race. P value was not adjuster for multiplicity.
Source: Clinical Study Report for VICTORIA.[10]

Figure 10: Kaplan-Meier Plot for Time to First Event of CEC-Confirmed CV Death, MI, or Stroke Hospitalization — ITT Population

[redacted]

Note: This figure has been redacted per the sponsor's request.

[redacted]

Health-Related Quality of Life

HRQoL was tested in a nonhierarchical sequence without adjustments for multiplicity and was exploratory in nature.

KCCQ Score

The results for change from baseline in KCCQ scores are presented in Table 26. For the analysis of the KCCQ score based on the ITT population, week 32 data were missing for [redacted] of patients in the vericiguat group and for [redacted] of patients in the placebo group. No clinically meaningful differences were found between treatment groups in change from baseline in KCCQ scores at week 32 (less than MID of at least 5 points).

KCCQ Overall Summary Score: The KCCQ overall summary score combines the physical limitation, total symptom, social limitation, and quality-of-life domains into a single score with a range of 0 to 100, where larger scores represent a better outcome. The analysis showed a slight improvement from baseline of [redacted] points (SD = [redacted]) in the vericiguat group and [redacted] points (SD = [redacted]) in the placebo group in the KCCQ overall summary score at week 32, with an LS mean difference of [redacted] ([redacted]).

KCCQ Total Symptom Score: The KCCQ total symptom score combines the symptom burden and symptom frequency domains into a single score with a range of 0 to 100, where larger scores represent a better outcome. The analysis showed a slight improvement from baseline of [redacted] points (SD = [redacted]) in the vericiguat

group and [redacted] points (SD = [redacted]) in the placebo group in the KCCQ total symptom score at week 32, with an LS mean difference of [redacted] ([redacted]).

KCCQ Clinical Summary Score: The KCCQ total symptom score combines the physical limitation and total symptom domains into a single score with a range of 0 to 100, where larger scores represent a better outcome. The analysis showed a slight improvement from baseline of [redacted] points ([redacted]) in the vericiguat group and [redacted] points (SD = [redacted]) in the placebo group in the KCCQ clinical summary score at week 32, with an LS mean difference of [redacted] ([redacted]).

Table 26: Change From Baseline in KCCQ Scores at Week 32 — ITT Population

Characteristic	Vericiguat	Placebo
KCCQ overall summary score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
KCCQ total symptom score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
KCCQ clinical summary score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
KCCQ physical limitation score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]

Characteristic	Vericiguat	Placebo
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
KCCQ quality of life score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
KCCQ symptom burden score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
KCCQ self-efficacy score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
KCCQ symptom frequency score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
KCCQ social limitation score		
Baseline, mean (SD)	[redacted]	[redacted]

Characteristic	Vericiguat	Placebo
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
KCCQ symptom stability score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]

CI = confidence interval; ITT = intention to treat; KCCQ = Kansas City Cardiomyopathy Questionnaire; LS = least squares; SD = standard deviation.

Notes: Patients who died during the study were assigned the worst possible score for all post-death visits until the primary completion date.

Based on data up to the primary completion date (June 18, 2019).

[a]Based on a longitudinal analysis of the covariance model, with the change score as the dependent variable, including categorical terms for stratification factor, week, treatment group, and the week-by-treatment group interaction, with the baseline value as a continuous covariate, and including all postrandomization time points through week 96. For baseline and week 32, N is the number of patients with nonmissing assessments at the specific time point. For change from baseline, N is the number of patients with nonmissing assessments at both baseline and week 32.

[b]P value was not adjusted for multiplicity.

Source: Clinical Study Report for VICTORIA.[10]

5-Level EQ-5D

For the analysis of the EQ-5D-5L index score based on the ITT population, week 32 data were missing for [redacted] and [redacted] of patients in the vericiguat and placebo groups, respectively. No difference was found between the 2 treatment groups for mean changes in EQ-5D-5L index and EQ VAS scores from baseline at week 32. (Table 27). For the EQ-5D-5L UK and US index scores, the LS mean differences at week 32 for vericiguat versus placebo were [redacted] and 0.01 (95% CI, −0.01 to 0.03; P = 0.257), respectively.

Table 27: Change From Baseline in EQ-5D-5L US Score at Week 32 — ITT Population

Characteristic	Vericiguat	Placebo
EQ-5D-5L UK index score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]

Characteristic	Vericiguat	Placebo
EQ-5D-5L US index score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]
EQ VAS score		
Baseline, mean (SD)	[redacted]	[redacted]
Week 32, mean (SD)	[redacted]	[redacted]
Change from baseline mean (SD)	[redacted]	[redacted]
LS mean (95% CI)	[redacted]	[redacted]
Difference in LS means,[a] (95% CI)	[redacted]	
P value[b]	[redacted]	[redacted]

CI = confidence Interval; EQ VAS = EQ visual analogue scale; EQ-5D-5L = 5-Level EQ-5D; ITT = intention to treat; LS = least squares, SD = standard deviation.

Notes: Patients who died during the study were assigned the worst possible score for all postdeath visits until the primary completion date.

Based on data up to the primary completion date (June 18, 2019).

[a]Based on a longitudinal analysis of the covariance model, with the change score as the dependent variable, including categorical terms for stratification factor, week, treatment group, and the week-by-treatment group interaction, with the baseline value as a continuous covariate, and including all postrandomization time points through week 96. For baseline and week 32, N is the number of patients with nonmissing assessments at the specific time point. For change from baseline, N is the number of patients with nonmissing assessments at both baseline and week 32.

[b]P value was not adjusted for multiplicity.

Source: Clinical Study Report for VICTORIA.[10]

All-Cause Hospitalization

All-cause hospitalization was not measured or reported in the VICTORIA trial.

Change From Baseline in BNP

Change from baseline in BNP was not measured or reported in the VICTORIA trial.

Harms

Only those harms identified in the review protocol are reported here. Refer to Table 28 for detailed harms data.

Adverse Events

A total of 2,027 (80.5%) patients in the vericiguat group and 2,036 (81.0%) patients in the placebo group experienced 1 or more AE (Table 27). Common AEs by the preferred term are summarized in Table 29. The most common AEs occurring in the vericiguat and placebo groups were hypotension (15.4% and 14.1%, respectively), cardiac failure (8.9% and 9.9%, respectively), anemia (7.6% and 5.7%, respectively), and pneumonia (6.4% and 7.2%, respectively). A total of 653 (25.9%) patients in the vericiguat group and 606

(24.1%) patients in the placebo group experienced 1 or more AE leading to dose modification (Table 28). The proportion of fatal AEs during the double-blind treatment phase was similar in the vericiguat and placebo groups (3.3% and 3.4%, respectively).

Serious Adverse Events

A total of 826 (32.8%) patients in the vericiguat group and 876 (34.8%) patients in the placebo group experienced 1 or more SAE (Table 29). The most common SAEs occurring in the vericiguat and placebo groups were pneumonia (4.0% and 4.5%, respectively), cardiac failure (93.2% and 4.4%, respectively), acute kidney injury (2.5% and 2.0%, respectively), and syncope (1.7% and 1.3%, respectively).

Withdrawals Due to Adverse Events

In the VICTORIA trial, withdrawal of study treatment due to AEs was required in 167 (6.6%) patients in the vericiguat group and 158 (6.3%) patients in the placebo group (Table 28). The most common reasons for discontinuation were hypotension (1.9% and 1.3% in the vericiguat and placebo groups, respectively), chronic kidney disease (0.3% and 0.6% in the vericiguat and placebo groups, respectively), pneumonia (0.1% and 0.2% in the vericiguat and placebo groups, respectively), cardiac failure (0.2% and 0.2% in the vericiguat and placebo groups, respectively), and dyspepsia (0.2% and 0.1% in the vericiguat and placebo groups, respectively).

Notable Harms

In the VICTORIA trial, symptomatic hypotension was the most commonly reported notable AE (9.1% and 7.9% in the vericiguat and placebo groups, respectively), followed by syncope (4.0% and 3.5% in the vericiguat and placebo groups, respectively), and hepatic AEs (0.9% and 0.5% in the vericiguat and placebo groups, respectively).

Table 28: Summary of Harms — ASaT Population

AE category[a]	Vericiguat (N = 2,519)	Placebo (N = 2,515)
Patients with ≥ 1 AE, n (%)	2,027 (80.5)	2,036 (81.0)
Patients with ≥ 1 SAE, n (%)	826 (32.8)	876 (34.8)
Patients who died due to AE[a], n (%)	83 (3.3)	85 (3.4)
Withdrawals due to AE, n (%)	167 (6.6)	158 (6.3)
Withdrawals due to SAE, n (%)	71 (2.8)	87 (3.5)
Patients with ≥ 1 AE leading to dose modification,[b] n (%)	653 (25.9)	606 (24.1)

AE = adverse event; ASaT = all subjects as treated; SAE = serious adverse event.

Notes: Based on data up to the primary completion date (June 18, 2019).

Includes events and/or measurements from the day of the first dose of the study drug to 14 days after the last dose of the study drug.

[a]Includes AEs associated with a fatal outcome but does not reflect all deaths reported in the study.

[b]Defined as a dose reduction, drug interruption, or drug withdrawal.

Source: Clinical Study Report for VICTORIA.[10]

Table 29: AEs Reported in at Least 2% of Patients in Either Treatment Arm — ASaT Population

Preferred term	Vericiguat (N = 2,519)	Placebo (N = 2,515)
Patients with any 1 AE, n (%)	2,027 (80.5)	2,036 (81.0)
AEs reported in ≥ 2% of patients in any treatment group, n (%)		
Hypotension	388 (15.4)	354 (14.1)
Cardiac failure	224 (8.9)	250 (9.9)
Anemia	192 (7.6)	143 (5.7)
Pneumonia	161 (6.4)	180 (7.2)
Hyperkalemia	111 (4.4)	140 (5.6)
Diarrhea	130 (5.2)	124 (4.9)
Dizziness	169 (6.7)	150 (6.0)
Acute kidney injury	134 (5.3)	127 (5.0)
Upper respiratory tract infection	120 (4.8)	115 (4.6)
Atrial fibrillation	89 (3.5)	96 (3.8)
Ventricular tachycardia	42 (1.7)	60 (2.4)
Constipation	74 (2.9)	77 (3.1)
Dyspepsia	67 (2.7)	27 (1.1)
Nausea	96 (3.8)	67 (2.7)
Vomiting	56 (2.2)	45 (1.8)
Asthenia	47 (1.9)	58 (2.3)
Chest pain	59 (2.3)	74 (2.9)
Peripheral edema	98 (3.9)	95 (3.8)
Bronchitis	87 (3.5)	112 (4.5)
Cellulitis	50 (2.0)	42 (1.7)
Influenza	74 (2.9)	57 (2.3)
Nasopharyngitis	121 (4.8)	127 (5.0)
Urinary tract infection	89 (3.5)	98 (3.9)
Syncope	101 (4.0)	88 (3.5)
Dyspnea	133 (5.3)	129 (5.1)
Accidental overdose	62 (2.5)	46 (1.8)
Fall	62 (2.5)	59 (2.3)
Blood creatinine increase	52 (2.1)	50 (2.0)
Gamma-glutamyl transferase increase	49 (1.9)	66 (2.6)
Diabetes mellitus	43 (1.7)	53 (2.1)

Preferred term	Vericiguat (N = 2,519)	Placebo (N = 2,515)
Gout	83 (3.3)	96 (3.8)
Hyperuricemia	77 (3.1)	72 (2.9)
Hypokalemia	94 (3.7)	87 (3.5)
Arthralgia	49 (1.9)	57 (2.3)
Back pain	60 (2.4)	68 (2.7)
Headache	86 (3.4)	61 (2.4)
Insomnia	33 (1.3)	52 (2.1)
Acute kidney injury	134 (5.3)	127 (5.0)
Chronic kidney disease	88 (3.5)	90 (3.6)
Renal failure	92 (3.7)	89 (3.5)
Renal impairment	67 (2.7)	66 (2.6)
Chronic obstructive pulmonary disease	76 (3.0)	58 (2.3)
Cough	111 (4.4)	105 (4.2)
Epistaxis	37 (1.5)	59 (2.3)
Hypertension	51 (2.0)	67 (2.7)

AE = adverse event, ASaT = all subjects as treated; SAE = serious adverse event.
Source: Clinical Study Report for VICTORIA.[10]

Table 30: SAEs and Notable Harms — ASaT Population

Preferred term	Vericiguat (N = 2,519)	Placebo (N = 2,515)
Patients with any SAE, n (%)	826 (32.8)	876 (34.8)
Pneumonia	101 (4.0)	112 (4.5)
Cardiac failure	80 (3.2)	110 (4.4)
Acute kidney injury	64 (2.5)	51 (2.0)
Hypotension	33 (1.3)	44 (1.7)
Renal failure	23 (0.9)	30 (1.2)
Chronic kidney disease	38 (1.5)	31 (1.2)
Syncope	43 (1.7)	32 (1.3)
Atrial fibrillation	14 (0.6)	29 (1.2)
Notable harms, n (%)		
Symptomatic hypotension	229 (9.1)	198 (7.9)
Syncope	101 (4.0)	87 (3.5)
Any hepatic AE	23 (0.9)	13 (0.5)

AE = adverse event; ASaT = all subjects as treated; SAE = serious adverse event.
Source: Clinical Study Report for VICTORIA.[10]

Critical Appraisal

Internal Validity

The VICTORIA trial used accepted methods for blinding, allocation concealment, and randomization with stratification by race and geographic region. An Interactive Voice Response System and Integrated Web Response System methodology was used, and randomization with stratification was performed centrally, which typically has a low risk of bias. The baseline demographic and disease characteristics of patients were generally balanced between the treatment groups, so randomization was successful. Although the VICTORIA trial was double-blinded and the investigators were blinded to treatment assignment, risk of bias from unblinding of treatment assignment cannot be ruled out. In the vericiguat group, about 80.5% of patients experienced at least 1 AE, which may have made the investigators and/or patients aware of the treatment assignment. Knowledge of the assigned treatment could have led to bias in the reporting and measurement of subjective outcomes, including patient-reported outcomes (i.e., HRQoL) and subjective AEs. However, the extent and direction of bias due to treatment knowledge is uncertain. A relatively high proportion of patients prematurely discontinued the trial medication (38.7%), although causes of discontinuation occurred at a similar frequency in the treatment groups. The main reason for treatment discontinuation was a fatal event, which, according to the clinical expert consulted by CADTH for this review, reflects the natural course of HF. In addition, patients who withdrew from the study and those who discontinued the study medication early continued to be followed and were included in outcome analyses. Protocol deviations were reported in 17% to 18% of patients in the 2 treatment groups, and the proportion of protocol deviations was comparable between groups and identified before the database lock.

In accordance with the exclusion criteria, patients in the VICTORIA trial were randomized starting 24 hours after IV treatment, which may not have been long enough to achieve clinical stability after acute treatment for worsening HF, and could have led to an underestimation or overestimation of the treatment effect. In addition, there was no run-in period in the trial to initiate or maintain optimal doses of HF medications to achieve clinical stability after worsening HF. However, the clinical expert consulted noted that although sometimes only 1 dose of a diuretic is required to achieve clinical stability, it can take several days or weeks to regain stability. The clinical expert further indicated that stable HF lacks a consensus definition, and, in clinical practice, it reflects the physician's perception of the patient's condition. According to the Canadian Cardiovascular Society, the term “stable HF” is not considered to be clinically appropriate, given the inherent risk for future clinical events related to a progressive disease.[2]

An independent CEC performed an adjudication of CV death, HHF, and urgent HF visit events based on criteria defined a priori. The clinical expert consulted indicated that the primary and key secondary outcomes were appropriate for the disease setting. The primary composite outcome in the trial was the time to the first event of CV death or HHF. The FDA-issued guidance for industry for Multiple Endpoints in Clinical Trials[45] indicated that a composite end point may be needed when more than 1 clinical end point in a clinical trial is important and when treatment is expected to affect all outcomes. However, although the overall statistical analysis of the primary outcome indicates a benefit of treatment, it is important to analyze the individual components of the composite end point for a greater depth of understanding of the treatment’s effects.[45] In the VICTORIA trial, CV death as an individual component of the primary composite end point

(which was defined based on time to first event) was not formally tested, whereas HHF was tested with a hierarchical testing strategy without adjustment for multiplicity and is exploratory in nature. Also, composite outcomes, although commonly used in trials of CV therapies, assume that each component has equal clinical importance, which is unlikely to be true when comparing hospitalization and death. Given that HF hospitalizations occurred at a greater frequency (and at earlier time points) than deaths in the composite outcome, the time to first event definition means that the measurement of the effect of vericiguat on CV death is likely imprecise, based on the composite outcome analysis. CV death was evaluated as a secondary outcome; however, given the criteria for interim efficacy assessment and stopping the trial prematurely, the longer-term effects of vericiguat on this outcome are difficult to determine.

Non-CV death was not considered a competing risk in the analysis of the primary composite end point, which could lead to a biased effect of vericiguat compared to placebo. In addition, the clinical expert consulted indicated that the list of criteria used to define CV deaths in the trial appeared to be too comprehensive, as it included undetermined causes of death, which could have resulted in a similar proportion of CV deaths in the 2 treatment groups. Secondary end points were separated into 2 families. The first family included time to CV death and time to HHF, which were tested in nonhierarchical sequence without adjustments for multiplicity and were exploratory in nature. The second family consisted of the end points of time to total hospitalizations for HF, time to all-cause mortality, and a composite of time to the first occurrence of the composite of HHF or all-cause mortality, and was tested hierarchically using a fixed-sequence approach to reduce the risk of type I error across these analyses.

The statistical analysis methods appear to be acceptable. The analyses of primary and key secondary outcomes were conducted using the ITT population, which maintains randomization and minimizes the risk of bias by comparing groups with similar prognostic factors. Both the interim and final analyses were planned a priori and adequately described. However, a decision was made to cancel the interim analysis because there were more CV deaths than expected. Given the potential misclassification of CV deaths, which may overestimate the true incidence of CV death events, as they include undetermined causes of death, there is a possibility that the trial was stopped earlier than planned. Therefore, there is a risk that the effect of vericiguat, compared to placebo, is overestimated, but the presence and extent of any overestimation is uncertain.[11-13] The sponsor commented on a draft version of this review report and noted that outcomes were aligned with those proposed by the Standardized Data Collection for Cardiovascular Trials Initiative and the FDA and were prespecified in the CEC charter.[46] An independent CEC blinded to treatment allocation throughout the trial assessed all reported deaths, CV hospitalizations, and urgent HF visits. The sponsor also highlighted that the inclusion of undetermined deaths as CV deaths is an accepted approach by the Standardized Data Collection for Cardiovascular Trials Initiative, is standard for large cardiometabolic trials,[47,48] and is a conservative approach to the analyses. CADTH reviewers acknowledge that the approach of classifying deaths from an undetermined cause as CV deaths has been used in other CV trials and may be a conservative approach if the criteria are applied equally to the treatment groups. The CEC charter[46] provided by the sponsor indicated that “death not attributable to CV death or to a non-CV cause” should not be used and should apply to few patients in well-run clinical trials. It is noteworthy that undetermined causes of death accounted for 25% (213 of 855) of CV deaths. Even though this approach may generally

be conservative, given the relatively high percentage of patients with deaths of undetermined cause and, as already discussed, CV deaths were used in criteria for determining early efficacy stopping decisions and that classifying patients with an undetermined cause of death as CV death may have influenced the early efficacy claims, this approach may not have been as conservative as planned because of the potentially overestimated benefit of the treatment effect, versus placebo, at an earlier point in the study's treatment period.

The clinical expert consulted noted that the results of the primary and key secondary outcomes were modest but clinically meaningful, based on the absolute event rate reduction in the selected study population. The sensitivity analysis for missing data was not performed, as about 0.4% of patients were lost to follow-up for the primary end point and vital status was known for more then 99% of patients. The median primary composite end point, all-cause survival, total HHF, and a composite of all-cause mortality and HHF was not estimable because insufficient follow-up time had elapsed for these outcomes; thus, the long-term efficacy of vericiguat is unknown. The Cox regression models were controlled for stratification factors (geographic region and race), and no rationale was provided for the lack of adjustment for important clinical variables, such as SOC therapy and comorbidities. Subgroup analyses by ejection fraction at screening, NYHA class, renal function, index event, prior use of sacubitril-valsartan, and NT-proBNP level were prespecified in the VICTORIA trial. Subgroup analyses were reported only for the primary composite end point, time to CV deaths, and time to HHF. Subgroups were not included as a stratification variable in the randomization scheme, and there may have been imbalances in the distribution of these variables within the subgroups. Subgroup analyses were not adjusted for multiplicity and may not have been powered to detect a treatment difference; as such, any inferences or interpretations based on subgroups should be made with caution.

Although improvement in HRQoL was of primary importance of both patients and physicians, this was an exploratory outcome and was tested outside the statistical testing hierarchy. HRQoL was assessed using the KCCQ and EQ-5D instruments. The KCCQ is generally a valid and reliable questionnaire for HF, but there is no evidence for the validity and reliability of the EQ-5D instrument in patients with HF. The clinical expert consulted indicated that these tools are not commonly used in clinical practice. No strong conclusions could be drawn about the effect of vericiguat, compared with placebo, on HRQoL due to an increased risk of type I error and a high risk of attrition bias, especially at longer follow-up. Because treatment discontinuation rates were relatively high in both treatment groups, there is a risk of bias, as patients who completed the questionnaires may be completely different than those who did not (e.g., differences in treatment response, AEs). Although HRQoL was measured, there were methodological issues that precluded the drawing of any strong conclusions, so there remains a knowledge gap.

External Validity

In general, the clinical expert consulted by CADTH for this review confirmed that the population in the VICTORIA trial was similar to patients seen in Canadian clinics, and the study results would be generalizable to patients with HF in Canada, with some limitations. Previous HF decompensation (or worsening) was defined as HHF within 3 to 6 months before randomization or the use of IV diuretics for HF (without hospitalization) within 3 months before randomization. The clinical expert consulted noted that the definition

of worsening HF was reflective of clinical practice. Although the proposed Health Canada indication for vericiguat is for the treatment of patients with symptomatic chronic HF with reduced ejection fraction, regardless of NYHA class, CADTH was unable to draw conclusions related to patients with NYHA class I and class IV HF, because the trial excluded patients who had NYHA class I HF and had only a very small proportion of patients who had NYHA class IV HF (1.1%). The clinical expert consulted indicated that patients with NYHA class IV HF are more likely to be clinically unstable than those with NYHA class II or class III HF. About 26.4% of patients in the trial were screening failures, predominantly because patients' NT-proBNP levels were below the prespecified threshold at screening. The clinical expert consulted indicated that NT-proBNP testing is not widely available in Canada, as some jurisdictions have limited access to it; thus, this patient selection criterion would be difficult to implement in clinical practice. The clinical expert further noted that the enrolment of patients with elevated NT-proBNP levels likely created an enriched population in the trial, with patients who appeared to be sicker and who may benefit from treatment with vericiguat more than the population in the real-world setting.

About 14% of patients had midrange LVEF (41% to 45%); however, the clinical expert consulted did not expect this to be an issue with the generalizability of the trial results to HF patients with reduced ejection fraction. According to the Canadian Cardiovascular Society, uncertainty often occurs in the measurement of LVEF, as estimates may vary, depending on the patient, technical factors, and clinical deterioration.[2] The clinical expert consulted indicated that the population in the VICTORIA trial was younger than the typical adult population in Canada with symptomatic chronic HF with reduced ejection fraction (in which the mean age is 75 to 77 years). Most patients were white, non-Hispanic or non-Latino, and only 11% of patients were recruited from North America. The clinical expert consulted noted that the lack of representation of Canadian patients does not reduce the generalizability of results to Canadian clinical practice. Protocol deviations were reported in 16.7% to 18.3% of patients in the 2 treatment groups, and the proportion of protocol deviations was comparable between groups and identified before the database lock in a blinded manner.

About 91% of patients in the trial received 2 or more background HF treatments, but only 60% of patients received triple HF therapy, representing patients whose treatment was suboptimal. In addition, a small proportion of patients (14.4%) received sacubitril-valsartan and none of the patients received SGLT2 inhibitors for the treatment of HF. The clinical expert consulted indicated that SGLT2 inhibitors became available for the treatment of chronic HF with reduced ejection fraction after the VICTORIA trial was conducted (between 2016 and 2019). Therefore, it is unclear whether the population included in the VICTORIA study is reflective of the population that would be eligible for treatment with vericiguat in current Canadian clinical practice. The clinical expert consulted indicated that vericiguat may be added to foundational quadruple HF therapy (including ACEis or ARBs, beta-blockers, MRAs, and SGLT2 inhibitors), as its mechanism of action is different from quadruple therapy medications. However, the cumulative benefit of vericiguat added to quadruple therapy remains unknown.

One of the initiation criteria in the sponsor's submitted reimbursement request indicates that vericiguat will be prescribed in combination with ACEis, ARBs, or ARNis; beta-blockers; and MRAs, if tolerated. The clinical expert consulted by CADTH for this review noted that clinicians will choose to prescribe SGLT2 inhibitors over vericiguat in combination with triple therapy unless contraindicated,[6] and only after the

failure of standard quadruple therapy will they prescribe vericiguat to patients who are stabilized after a worsening HF event.

Indirect Evidence

No sponsor-submitted NMA was identified for this review.

A focused literature search for indirect treatment comparisons dealing with HF was run in MEDLINE All (1946–) on November 9, 2022. No limits were applied to the search. The literature search identified 7 potential citations, of which 4 were included for consideration for the following reasons: in the VICTORIA trial, vericiguat was compared to placebo plus standard triple therapy, only 14% of patients received sacubitril-valsartan, and none of the patients received SGLT2 inhibitors for HF treatment, as they became available after completion of this trial. The studies identified through the literature search aimed to compare the efficacy of vericiguat for the treatment of patients with HF with reduced ejection fraction with SGLT2 inhibitors, sacubitril-valsartan, ivabradine, and triple HF therapy, which were considered comparators in the systematic review protocol.

Aimo et al. (2021) NMA

An NMA by Aimo et al. (2021)[14] was identified from the literature. The objective of the analysis was to compare vericiguat, sacubitril-valsartan, and SGLT2 inhibitors in the treatment of patients with HF with reduced ejection fraction. Databases, including PubMed, Embase, and clinicaltrials.gov, were searched for articles of interest on September 25, 2020. The systematic review included 6 studies for analysis that compared sacubitril-valsartan, vericiguat, or SGLT2 inhibitors with SOC therapy. A random-effects NMA with the DerSimonian-Laird estimator and a fixed-effects model were performed separately for the primary and secondary outcomes of interest. The primary end point of interest was a composite of CV death and HHF, and the secondary end points included CV death alone and HHF alone.

The pooled results of the NMA showed that for a composite of CV death and HHF, the HR for SGLT2 inhibitors versus vericiguat and versus sacubitril-valsartan was 0.83 (95% CI, 0.73 to 0.94) and 0.92 (95% CI, 0.88 to 1.24), respectively. For CV death, the HR for SGLT2 inhibitors versus vericiguat and versus sacubitril-valsartan was 0.88 (95% CI, 0.63 to 1.22) and 1.04 (95% CI, 0.88 to 1.24), respectively. For HHF, the HR for SGLT2 inhibitors versus vericiguat and versus sacubitril-valsartan was 0.77 (95% CI, 0.66 to 0.89) and 0.87 (95% CI, 0.75 to 1.02), respectively.

De Marzo et al. (2022) NMA

An NMA by De Marzo et al. (2022)[15] was identified from the literature. The objective of the analysis was to compare vericiguat, ivabradine, and SGLT2 inhibitors in the treatment of patients with HF with reduced ejection fraction. Databases, including PubMed, Embase, SCOPUS, and the Cochrane Library, were searched for articles of interest on November 30, 2020. The NMA comprised both a fixed-effects model and a random-effects model within a Bayesian framework. The primary end point of interest was all-cause death, and the secondary end points included CV death, HHF, and all-cause hospitalization. The systematic review included 69 RCTs for all-cause death, 56 RCTs for CV death, 45 RCTs for HHF, and 26 RCTs for all-cause hospitalization.

In the NMA for the primary end point of all-cause death, the HR for ivabradine and for SGLT2 inhibitors versus vericiguat was 0.97 (95% CrI, 0.60 to 1.60) and 0.94 (95% CrI, 0.62 to 1.40), respectively. For CV death, the HR for ivabradine and for SGLT2 inhibitors versus vericiguat was 1.00 (95% CrI, 0.61 to 1.50) and 0.94 (95% CrI, 0.61 to 1.50), respectively. For HHF, the HR for ivabradine and for SGLT2 inhibitors versus vericiguat was 0.89 (95% CrI, 0.50 to 1.70) and 0.88 (95% CrI, 0.56 to 1.60), respectively. The results for all-cause hospitalizations were not reported, as this information was not available in 63% of the RCTs examined.

Luo et al. (2022) NMA

An NMA by Luo et al. (2022)[16] was identified from the literature. The objective of the analysis was to compare sGC stimulators, ARNis, and SGLT2 inhibitors in the treatment of patients with HF with reduced ejection fraction. Databases, including PubMed, Embase, the Cochrane Library, and the Web of Science, were searched for articles of interest on September 1, 2021. A random-effects model was constructed based on frequency theory. The efficacy outcomes included rates of HF rehospitalization, all-cause mortality, CV death, and rates of CV death or HF rehospitalization. A total of 15 RCTs were included for HF rehospitalization, 14 RCTs for all-cause mortality, 12 RCTs for CV death, and 16 RCTs for rates of CV death or HF rehospitalization.

In the NMA for HF rehospitalization, the OR for SGLT2 inhibitors versus sGC stimulators was 0.79 (95% CI, 0.68 to 0.93) and the OR for ARNis versus sGC stimulators was 0.87 (95% CI, 0.75 to 1.01). For all-cause mortality, the OR for SGLT2 inhibitors versus sGC stimulators was 0.98 (95% CI, 0.70 to 1.38) and for ARNis versus sGC stimulators was 0.87 (95% CI, 0.61 to 1.25). For CV death, the OR for SGLT2 inhibitors versus sGC stimulators was 0.96 (95% CI, 0.74 to 1.25) and for ARNis versus sGC stimulators was 0.88 (95% CI, 0.68 to 1.15). For rates of CV death or HF rehospitalization, the OR for SGLT2 inhibitors versus sGC stimulators was 0.87 (95% CI, 0.76 to 1.00) and for ARNis versus sGC stimulators was 0.88 (95% CI, 0.77 to 1.01).

Pagnesi et al. (2022) NMA

An NMA by Pagnesi et al. (2022)[17] was identified from the literature. The objective of the analysis was to compare vericiguat with SGLT2 inhibitors in the treatment of patients with HF with reduced ejection fraction. Databases, including PubMed, Embase, Google Scholar, and the Cochrane Central Register of Controlled Trials, were searched for articles of interest on March 18, 2021. A random-effects NMA was performed on the cumulative event rates for primary and secondary end points based on a frequentist approach with the DerSimonian-Laird estimator. The primary end point was the composite of CV death andHHF, and the secondary end points were CV death, all-cause death, and HHF. The systematic review included 7 studies for the primary end point of CV death or HHF, 10 studies for CV death, 12 studies for all-cause mortality, and 10 studies for HHF.

The results of the NMA for a composite of CV death and HHF, the RR for SGLT2 inhibitors versus vericiguat was 0.84 (95% CI, 0.75 to 0.96). For all-cause mortality, the RR for SGLT2 inhibitors versus vericiguat was 0.90 (95% CI, 0.77 to 1.04). For CV death, the RR for SGLT2 inhibitors versus vericiguat was 0.91 (95% CI, 0.91 to 0.96). For HHF, the RR for SGLT2 inhibitors versus vericiguat was 0.79 (95% CI, 0.69 to 0.91).

Critical Appraisal of Published NMA Articles

The results of the NMAs are highly uncertain, given the heterogeneity across the studies included in the networks, the heterogeneity in the baseline characteristics of patients in the included trials, and the limited information related to definitions of end points. Furthermore, ivabradine and vericiguat were restricted to selected patients who were stabilized after an episode of worsening HF. Results in efficacy estimates were imprecise (i.e., wide CIs, including HR = 1) in many comparisons and end points, which adds to uncertainty in the effect estimates. Therefore, no definitive conclusions can be drawn from the published NMAs for many outcome comparisons due to methodological limitations and imprecision in the effect estimates. Furthermore, safety outcomes were not analyzed in the published NMAs, and no justification was provided, which precludes a balanced judgment of comparative benefits relative to comparative harms. Outcomes important to patients, such as HRQoL, were also not analyzed in the published NMAs.

Other Relevant Evidence

No other relevant evidence was identified for this review.

Discussion

Summary of Available Evidence

The VICTORIA trial[10] was a phase III, randomized, multicentre, double-blind, event-driven, placebo-controlled trial designed to assess the efficacy and safety of vericiguat versus placebo, as an adjunct to SOC therapy in adults with symptomatic chronic HF with reduced ejection fraction who are stabilized after a recent worsening HF event. The trial was initiated on September 20, 2016, at 694 sites in 42 countries in North America (560 patients), Latin and South America, Eastern Europe, Western Europe, and the Asia-Pacific region. In the VICTORIA trial, 5,050 patients were randomized in a 1:1 ratio to receive either vericiguat (N = 2,526) or placebo (N = 2,524). The mean age of all randomized patients in the VICTORIA trial was 67.3 years (SD = 12.2 years). A total of 76.1% of patients were male, and 24.0% were female. About 64.1% of patients were white, and 27.0% were Asian or multiracial. A total of 81.4% of patients were non-Hispanic or non-Latino, and 16.1% were Hispanic or Latino. The mean LVEF was 28.9% (SD = 8.30%), and nearly half of patients had an LVEF of less than 30% (49.3%).

Approximately 70% of patients had an HHF within 3 months prior randomization, 17.2% had an HHF within 3 to 6 months, and 15.9% had received outpatient treatment with IV diuretics for worsening HF within 3 months before hospitalization. A total of 91.2% of patients received 2 or more HF medications, but only 60% of patients received a triple therapy regimen that included an ACEi or ARB, a beta-blocker, and an MRA. The primary efficacy end point was the time to first event of CV death or HHF, and the secondary end points were time to CV death, time to first HHF, time to total events (first and recurrent) of HHF, time to first event of all-cause mortality or HHF, and time to all-cause mortality. HRQoL was assessed using the KCCQ and EQ-5D instruments. Harms and notable harms (identified in the CADTH systematic review protocol) were assessed.

There were 4 published NMAs identified from the literature search that aimed to compare the efficacy of vericiguat with that of SGLT2 inhibitors, sacubitril-valsartan, and ivabradine in patients with HF with reduced ejection fraction. These NMAs had significant methodological limitations, and the results were highly uncertain.

Interpretation of Results

Efficacy

The VICTORIA trial appeared to have appropriate methods for blinding, allocation concealment, randomization with stratification to minimize bias, and the type I error was adequately accounted for in the primary and key secondary outcomes. Definitive conclusions could not be drawn for HRQoL data due to the lack of adjustment for multiplicity and the high risk of attrition bias. Other key limitations of the pivotal trials include the large proportion of screening failures due to the trial's criterion that directed the inclusion of patients only with elevated NT-proBNP levels, and limited clinical evidence on the benefit of vericiguat in patients with NYHA class I and class IV HF. Thus, it is difficult to draw strong conclusions and generalize the results to all patients with symptomatic chronic HF who may be treated in a Canadian setting. Furthermore, given the potential misclassification of CV deaths, there is a possibility that the trial was stopped earlier than planned. Therefore, there is a risk that the effect of vericiguat, compared to placebo is, overestimated, but the presence and extent of any overestimation is uncertain.[11-13] Additionally, there was no run-in period in the trial to initiate or maintain optimal doses of HF medications to achieve clinical stability after worsening HF.

The superiority of vericiguat over placebo in the time to first event of CV death or HHF was demonstrated with the median follow-up duration of 10.8 months (HR = 0.90; 95% CI, 0.82 to 0.98). However, the median composite of CV death or HHF was not estimable because insufficient follow-up time had elapsed for this outcome. The clinical expert consulted noted that the results of the primary outcome were modest but clinically meaningful, based on the absolute event rate reduction of 4.2% within the selected study population. This difference was likely driven primarily by a lower proportion of HHF events in the vericiguat group compared to placebo group. However, CV death as an individual component within the primary composite end point was not formally tested, and HHF alone was tested out of the hierarchical testing strategy without adjustment for multiplicity and is exploratory in nature. Therefore, a deep understanding of which components of the primary composite end point contributed more to the overall significance remains unclear. The treatment effects for prespecified subgroups in the CADTH protocol were generally consistent with the main effect, whereas a potential difference was noted that depended on NT-proBNP at baseline.

The study demonstrated the superiority of vericiguat over placebo in terms of time to first event of HHF or all-cause mortality, with an absolute event rate reduction of 4.2%. Although individual components of this composite end point were not formally tested for significance, the difference was likely driven by a lower rate of HHF events. The median composite of all-cause mortality and HHF was not estimable because insufficient follow-up time had elapsed for this outcome. Subgroup analyses did not identify a particular group of patients who experienced a considerably higher or lower benefit from empagliflozin on the primary composite end point. The study also demonstrated the superiority of vericiguat over placebo in terms of time to total events (first and recurrent) of HHF, with an absolute event rate reduction of 4.1%. The clinical expert

consulted highlighted that the HHF is the most important outcome for assessing treatment response in patients with HF.

There were no differences between the treatment groups in the time to all-cause mortality and the time to adjudicated CV death. The time to CV death tested as part of the secondary analysis captured all CV death events observed during the trial (N = 855) and differed from CV death as a component of the primary composite end point (N = 431). The clinical expert consulted indicated that the list of criteria used to identify CV death was too comprehensive due to inclusion of undetermined causes of death, which could have resulted in the similar number of CV deaths across treatment groups. The clinical expert further noted that the mean duration of treatment exposure and the mean follow-up period were likely short to observe the beneficial effect of vericiguat on mortality, as reducing the number of hospitalizations will lead to a decrease in mortality in the long-term. Other additional end points, such as CV hospitalizations, change in NYHA class, and change in NT-proBNP, were tested as part of the exploratory outcomes. The clinical expert consulted noted that the clinical results of the trial are consistent with biochemical findings, such as change in NT-proBNP.

In their input, patients highlighted HRQoL as important outcome and important treatment goal. The clinical expert consulted indicated that quality of life is probably most important to patients with HF, as it worsens with each hospitalization. HRQoL was assessed using the KCCQ and EQ-5D-5L instruments. Although the KCCQ has been reported to be a generally valid, reliable, and responsive tool, psychometric properties of the EQ-5D-5L instrument have not been assessed in the HF population. In the VICTORIA trial, no clinically meaningful differences were found between treatment groups in change from baseline in KCCQ scores at week 32 (less than the prespecified clinically meaningful threshold of an improvement or deterioration of at least 5 points). Furthermore, for the analysis of KCCQ scores, week 32 scores were missing for about 31% of patients. The results from the EQ-5D-5L analysis showed no difference between the 2 treatment arms, suggesting that vericiguat neither improves nor impedes the HRQoL of patients with chronic HF. In addition, for the analysis of EQ-5D-5L scores, week 52 scores were missing for about 28% of patients.

Overall, the efficacy of vericiguat for use as an adjunct to standard dual or triple therapy for the treatment of adult patients with symptomatic chronic HF with reduced ejection fraction has been demonstrated. However, the generalizability to the current SOC, which includes SGLT2 inhibitors as part of a quadruple drug regimen, is currently unknown because patients enrolled in the VICTORIA trial received dual or triple therapy as background therapy. It is acknowledged that the VICTORIA trial was undertaken at the same time as trials for the recently approved SGLT2 inhibitors for HF with reduced ejection fraction, which likely prevented it from capturing the current SOC. Strong conclusions could not be drawn for HRQoL due to the high risk of attrition bias and increased risk of type I error. Four published NMAs identified from the literature search compared vericiguat with SGLT2 inhibitors, ivabradine, and sacubitril-valsartan for the treatment of patients with HF with reduced ejection fraction. No conclusion could be drawn from the published NMAs due to methodological limitations and imprecision in the effect estimates (i.e., wide 95% CIs, including HR = 1).

Harms

AE profile in the VICTORIA trial was comparable between treatment group, with similar frequencies of AEs, SAEs, and withdrawals due to AEs. Most patients in the 2 treatment groups (80.5% of patients in the vericiguat group and 81.0% of patients in the placebo group) experienced 1 or more AE. The most common AEs were hypotension, anemia, and pneumonia. The clinical expert consulted noted that hypotension would be the most expected AE related to treatment with vericiguat in clinical practice, whereas the incidence of hyperkalemia in the VICTORIA trial is slightly lower than in the real-world setting. There were no notable differences between vericiguat and placebo regarding the overall frequencies of any AE or SAE leading to treatment discontinuation. The incidence of symptomatic hypotension, syncope, and hepatic AEs were considered notable harms for this review, all of which appeared in similar frequencies in both treatment groups in the trial. The clinical experts consulted noted that more AEs would be expected in the vericiguat group compared with the placebo group, given that an additional treatment was added to the regimen in the selected study population. The clinical expert was of the opinion that vericiguat should be prescribed by specialists who have expertise in the management of HF in specialty clinics that focus on the assessment and management of HF to ensure that the drug is prescribed to appropriate patients and side effects or AEs associated with the disease or drug are prevented or managed in a timely manner. However, the sponsor highlighted that patients with HF with reduced ejection fraction in rural settings may not have access to specialty clinics, which are predominantly found in urban city centres. It was further noted by the clinical expert that treatment with vericiguat generally revealed no new safety concerns in the VICTORIA trial.

Conclusions

Based on data from the VICTORIA trial, vericiguat demonstrated a statistically significant and clinically meaningful benefit, compared to placebo, in reducing the hazard rates of the first event of CV death or HHF, occurrence of the first and recurrent HHF event, and the composite of all-cause mortality and HHF in adult patients with symptomatic chronic HF with reduced ejection fraction. The median composite primary end point, total events of HHF, and the composite of all-cause mortality and HHF were not estimable in either treatment group because insufficient follow-up time had elapsed for these outcomes; thus, the longer-term efficacy of vericiguat is unknown. In addition, the estimates of the benefit of vericiguat may be overestimated because of the possibility that the trial was stopped earlier than planned due to the potential misclassification of CV deaths; however, the presence and extent of any overestimation is uncertain. Strong conclusions could not be drawn related to the effect of vericiguat on HRQoL due to the high risk of attrition bias and increased risk of type I error in the analyses of these outcomes. No new safety signals were identified in patients with HF with reduced ejection fraction. Owing to its superiority over placebo, vericiguat may be another treatment option for patients with HF with reduced ejection fraction who are stabilized after a recent HF decompensation event. According to the clinical expert consulted by CADTH, vericiguat may be added to foundational quadruple HF therapy (which includes ACEis or ARBs, beta-blockers, MRAs, and SGLT2 inhibitors); however, the cumulative benefit of vericiguat added to the current model of quadruple therapy remains unknown. No conclusions could be drawn from the published NMAs about the efficacy of vericiguat, relative to SGLT2 inhibitors, ivabradine, or sacubitril-valsartan for the treatment of patients with HF with reduced ejection fraction due to methodological limitations and imprecision in the effect estimates.

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Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: November 10, 2022

Alerts: Biweekly search updates until project completion

Search filters applied: None

Limits:

- Conference abstracts: excluded

Table 31: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multidatabase Strategy

1. (Verquvo* or vericiguat* or BAY 102 or BAY102 or BAY 1021189 or BAY1021189 or MK-1242 or MK1242 or WHO 9805 or WHO9805 or LV66ADM269 or 5G76IGF54K).ti,ab,kf,ot,hw,rn,nm.
2. 1 use medall
3. *vericiguat/
4. (Verquvo* or vericiguat* or BAY 102 or BAY102 or BAY 1021189 or BAY1021189 or MK-1242 or MK1242 or WHO 9805 or WHO9805).ti,ab,kf,dq.
5. 3 or 4
6. 5 not (conference review or conference abstract).pt.
7. 6 use oemezd
8. 2 or 7
9. remove duplicates from 8

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- vericiguat OR verquvo OR “bay 1021189” OR bay1021189 OR “mk-1242” OR mk1242 OR “who 9805” OR who9805]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- vericiguat OR verquvo OR “bay 1021189” OR bay1021189 OR bay-1921189 OR “mk-1242” OR mk1242 OR mk 1242 OR “who 9805” OR who9805 OR who-9805]

Health Canada’s Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- vericiguat, verquvo, “bay 1021189”, bay1021189, bay-1921189, “mk-1242”, mk1242, mk 1242, “who 9805”, who9805, who-9805]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- vericiguat OR verquvo OR “bay 1021189” OR bay1021189 OR bay-1921189 OR “mk-1242” OR mk1242 OR mk 1242 OR “who 9805” OR who9805 OR who-9805]

Grey Literature

Search dates: November 2 to 11, 2022

Keywords: vericiguat, verquvo, “bay 1021189”, bay1021189, bay-1921189, “mk-1242”, mk1242, mk 1242, “who 9805”, who9805, who-9805

Limits: None

Updated: No updates

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

Appendix 2: Excluded Studies

Note that this appendix has not been copy-edited.

Table 32: Excluded Studies

Reference	Reason for exclusion
Aimo et al. (2021)[14] Armstrong et al. (2018)[49] Aziz et al. (2021)[50] Bauersachs et al. (2020)[51] Heinzl et al. (2020)[52]	Not relevant study design
Voors et al. (2021)[53]	Not relevant outcome
Armstrong et al. (2022)[54] Butler et al. (2022)[55] Ezekowitz et al. (2020)[56] Lam et al. (2021)[57] Lam et al. (2021)[58] Mentz et al. (2021)[59] Ponikowski et al. (2021)[60] Senni et al. (2022)[61] Spinar et al. (2021)[62]	Post hoc/secondary analysis

Appendix 3: Detailed Outcome Data

Note that this appendix has not been copy-edited.

Table 33: Time to First Event of CEC-Confirmed CV Death or HHF — On-Treatment Analysis

Characteristic	Vericiguat (N = 2,519)	Placebo (N = 2,515)
Patients with event, n (%)	735 (29.2)	801 (31.8)
HHF as first event, n (%)	[redacted]	[redacted]
CV death as first event, n (%)	[redacted]	[redacted]
Annual rate, %[a]	[redacted]	[redacted]
KM% (95% CI) at 2 years[b]	[redacted]	[redacted]
HR (95% CI)[c]	0.91 (0.82 to 1.01)	
P value[d]	0.063	Reference

CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; HF = heart failure; HR = hazard ratio; KM = Kaplan-Meier.

Notes: On-treatment analysis censored at 14 days after study drug discontinuation. For patients with multiple events, only the first event contributing to the composite end point is counted in the table.

Based on data up to the primary completion date (June 18, 2019).

[a]Total patients with an event per 100 person years at risk.

[b]Kaplan-Meier estimate and confidence interval at 2 years.

[c]Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race.

Source: Clinical Study Report for VICTORIA.[10]

Figure 11: Kaplan-Meier Plot for Primary Composite End Point — On-Treatment Analysis

Note: This figure has been redacted per the sponsor's request.

[redacted]

Table 34: Time to CEC-Confirmed CV Death — On-Treatment Analysis

Characteristic	Vericiguat (N = 2,519)	Placebo (N = 2,515)
CV death, n (%)		
Heart failure		
Myocardial infarction		
Stroke		
Other cardiovascular event		
Sudden cardiac death		
Undetermined cause of death		
Annual rate, %[a]		
KM% (95% CI) at 2 years[b]		
HR (95% CI)[c]		
P value[d]		

CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.

Notes: On-treatment analysis censored at 14 days after study drug discontinuation.

Based on data up to the primary completion date (June 18, 2019).

[a]Total patients with an event per 100 subject years at risk.

[b]Kaplan-Meier estimate and confidence interval at 2 years.

[c]Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors, defined by region and race.

Source: Clinical Study Report for VICTORIA.[10]

Figure 12: Kaplan-Meier Plot for Time to CEC-Confirmed CV Death — On-Treatment Analysis

Note: This figure has been redacted per the sponsor's request.

Table 35: Subgroup Analyses of the Time to CEC-Confirmed CV Death — ITT Population

Subgroup	Olaparib Events, n (%)	Placebo Events, n (%)	HR[a] (95% CI)	Interaction P value
Index event				
IV diuretic < 3 months	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalization < 3 months	[redacted]	[redacted]	[redacted]	
Hospitalization 3 to 6 months	[redacted]	[redacted]	[redacted]	
eGFR at baseline				
≤ 30	[redacted]	[redacted]	[redacted]	[redacted]
30 to 60	[redacted]	[redacted]	[redacted]	
> 60	[redacted]	[redacted]	[redacted]	
NYHA class				
I/II	[redacted]	[redacted]	[redacted]	[redacted]
III/IV	[redacted]	[redacted]	[redacted]	
Use of sacubitril-valsartan at baseline				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	
NT-proBNP at baseline by quartiles, pg/mL				
Q1 (≤ 1,556)	[redacted]	[redacted]	[redacted]	[redacted]
Q2 (1,556 to 2,816)	[redacted]	[redacted]	[redacted]	
Q3 (2,816 to 5,314)	[redacted]	[redacted]	[redacted]	
Q4 (> 5,314)	[redacted]	[redacted]	[redacted]	
Ejection fraction, %				
< 40	[redacted]	[redacted]	[redacted]	[redacted]
≥ 40	[redacted]	[redacted]	[redacted]	

CEC = Clinical Events Committee; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; NYHA = New York Heart Association; NT-proBNP = NT-proB-type natriuretic peptide; Q1 = 25th percentile; Q2 = 50th percentile; Q3 = 75th percentile; Q4 = 100th percentile.

[a]HR, confidence interval, and P value for treatment-by-subgroup interaction from Cox proportional hazard model with covariates of the stratification factors (defined by region and race), treatment, subgroup, and treatment-by-subgroup interaction.

Source: Clinical Study Report for VICTORIA.[10]

Table 36: Time to CEC-Confirmed All-Cause Mortality — On-Treatment Analysis

Characteristic	Vericiguat (N = 2,519)	Placebo (N = 2,515)
All-cause mortality, n (%)	[redacted]	[redacted]
Annual rate, %[a]	[redacted]	[redacted]
KM% (95% CI) at 2 years[b]	[redacted]	[redacted]
HR (95% CI)[c]	[redacted]	
P value[d]	[redacted]	[redacted]

CEC = Clinical Events Committee; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.
Notes: On-treatment analysis censored at 14 days after study drug discontinuation.
Based on data up to the primary completion date (June 18, 2019).
[a]Total patients with an event per 100 subject years at risk.
[b]Kaplan-Meier estimate and confidence interval at 2 years.
[c]Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
[d]From log-rank test stratified by the stratification factors, defined by region and race. P value was not adjusted for multiplicity.
Source: Clinical Study Report for VICTORIA.[10]

Table 37: Time to CEC-Confirmed All-Cause Mortality or HHF — On-Treatment Analysis

Characteristic	Vericiguat (N = 2,519)	Placebo (N = 2,515)
Patients with event, n (%)	[redacted]	[redacted]
All-cause mortality as first event	[redacted]	[redacted]
HHF as first event	[redacted]	[redacted]
Annual rate, %[a]	[redacted]	[redacted]
KM% (95% CI) at 2 years[b]	[redacted]	[redacted]
HR (95% CI)[c]	[redacted]	
P value[d]	[redacted]	[redacted]

CEC = Clinical Events Committee; CI = confidence interval; HHF = hospitalization for heart failure; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.
Notes: On-treatment analysis censored at 14 days after study drug discontinuation.
Based on data up to the primary completion date (June 18, 2019).
[a]Total patients with an event per 100 subject years at risk.
[b]Kaplan-Meier estimate and confidence interval at 2 years.
[c]Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
[d]From log-rank test stratified by the stratification factors, defined by region and race. P value was not adjusted for multiplicity.
Source: Clinical Study Report for VICTORIA.[10]

Figure 13: Kaplan-Meier Plot for Time to CEC-Confirmed All-Cause Mortality — On-Treatment Analysis

Note: This figure has been redacted per the sponsor's request.

Figure 14: Kaplan-Meier Plot for Time to CEC-Confirmed All-Cause Mortality or HHF — On-Treatment Analysis

Note: This figure has been redacted per the sponsor's request.

Table 38: Time to CEC-Confirmed CV Hospitalization — On-Treatment Analysis

Characteristic	Vericiguat (N = 2,519)	Placebo (N = 2,515)
CV hospitalization, n (%)		
Annual rate, %[a]		
KM% (95% CI) at 2 years[b]		
HR (95% CI)[c]		
P value[d]		

CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.

Notes: For patients with multiple events, only the first event contributing to the composite end point is counted in the table.

Based on data up to the primary completion date (June 18, 2019).

[a]Total patients with an event per 100 subject years at risk.

[b]Kaplan-Meier estimate and confidence interval at 2 years.

[c]Hazard ratio (Vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race. P value was not adjuster for multiplicity.

Source: Clinical Study Report for VICTORIA.[10]

Figure 15: Kaplan-Meier Plot for Time to CEC-Confirmed CV Hospitalization — On-Treatment Analysis

This figure has been redacted per the sponsor's request.

Note: This figure has been redacted per the sponsor's request.

Table 39: Time to First Event of CEC-Confirmed HHF — On-Treatment Analysis

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
HHF, n (%)		
Annual event rate, %[a]		
KM% (95% CI) at 2 years[b]		
HR (95% CI)[c]		
P value[d]		

CEC = Clinical Events Committee; CI = confidence interval; HHF = heart failure hospitalization; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.

Note: Based on data up to the primary completion date (June 18, 2019).

[a]Total events per 100 subject years at risk.

[b]Kaplan-Meier estimate and confidence interval at 2 years.

[c]Hazard ratio (Vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race. P value was not adjuster for multiplicity.

Source: Clinical Study Report for VICTORIA.[10]

Figure 16: Kaplan-Meier Plot for Time to CEC-Confirmed HHF — On-Treatment Analysis

Note: This figure has been redacted per the sponsor's request.

Table 40: Subgroup Analyses for Frist Event of CEC-Confirmed HHF — ITT Population

Subgroup	Olaparib Events, n (%)	Placebo Events, n (%)	HR[a] (95% CI)	Interaction P value
Index event				
IV diuretic < 3 months	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalization < 3 months	[redacted]	[redacted]	[redacted]	
Hospitalization 3 to 6 months	[redacted]	[redacted]	[redacted]	
eGFR at baseline				
≤ 30	[redacted]	[redacted]	[redacted]	[redacted]
30 to 60	[redacted]	[redacted]	[redacted]	
> 60	[redacted]	[redacted]	[redacted]	
NYHA class				
I/II	[redacted]	[redacted]	[redacted]	[redacted]
III/IV	[redacted]	[redacted]	[redacted]	
Use of sacubitril-valsartan at baseline				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	
NT-proBNP at baseline by quartiles, pg/mL				
Q1 (≤ 1,556)	[redacted]	[redacted]	[redacted]	[redacted]
Q2 (1,556 to 2,816)	[redacted]	[redacted]	[redacted]	
Q3 (2,816 to 5,314)	[redacted]	[redacted]	[redacted]	
Q4 (> 5,314)	[redacted]	[redacted]	[redacted]	
Ejection fraction, %				
< 40	[redacted]	[redacted]	[redacted]	[redacted]
≥ 40	[redacted]	[redacted]	[redacted]	

CEC = Clinical Events Committee; CI = confidence interval; eGFR = estimated glomerular filtration rate; HHF = hospitalization for heart failure; HR = hazard ratio; NYHA = New York Heart Association; NT-proBNP = NT-proB-type natriuretic peptide; Q1 = 25th percentile; Q2 = 50th percentile; Q3 = 75th percentile; Q4 = 100th percentile.

[a]HR, confidence interval and P value for treatment-by-subgroup interaction from Cox proportional hazard model with covariates of the stratification factors (defined by region and race), treatment, subgroup, and treatment-by-subgroup interaction.

Source: Clinical Study Report for VICTORIA.[10]

Table 41: Time to Total Events of CEC-Confirmed HHF — On-Treatment Analysis

Characteristic	Vericiguat (N = 2,519)	Placebo (N = 2,515)
Total HHF, n[a]		
Patients with only 1 event		
Patients with only 2 events		
Patients with only 3 events		
Patients with ≥ 4 events		
Annual rate, %[b]		
HR (95% CI)[c]		
P value[c]		

CEC = Clinical Events Committee; CI = confidence interval; HHF = hospitalization for heart failure; HR = hazard ratio.

Notes: On-treatment analysis censored at 14 days after study drug discontinuation.

Based on data up to the primary completion date (June 18, 2019).

[a]Total number of hospitalizations for heart failure (first and recurrent).

[b]Total events per 100 subject years of follow-up.

[c]Calculated based on Andersen-Gill model controlling for stratification factors (defined by region and race). Robust standard errors are used to account for correlations of event times within a patient.

Source: Clinical Study Report for VICTORIA.[10]

Table 42: Time to Total Events of CEC-Confirmed HHF — ITT Population

Characteristic	Vericiguat (N = 2,519)	Placebo (N = 2,515)
Patients with first event		
Patients with second event		
Patients with third event		
Patients with fourth event		
Test of equality of HR across first 4 events		
Average HR across first 4 events		
P value		

CEC = Clinical Events Committee; CI = confidence interval; HHF = hospitalization for heart failure; HR = hazard ratio; ITT = intention to treat.

Notes: On-treatment analysis censored at 14 days after study drug discontinuation.

Based on data up to the primary completion date (June 18, 2019).

Source: Clinical Study Report for VICTORIA.[10]

Table 43: Time to First Event of CEC-Confirmed Hospitalization for MI — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
MI hospitalization, n (%)	[redacted]	[redacted]
Annual rate, %[a]	[redacted]	[redacted]
KM% (95% CI) at 2 years[b]	[redacted]	[redacted]
HR (95% CI)[c]	[redacted]	
P value[d]	[redacted]	[redacted]

CEC = Clinical Events Committee; CI = confidence interval; MI = myocardial infarction; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.
Notes: Based on data up to the primary completion date (June 18, 2019).
[a]Total events per 100 subject years at risk.
[b]Kaplan-Meier estimate and confidence interval at 2 years.
[c]Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
[d]From log-rank test stratified by the stratification factors defined by region and race. P value was not adjuster for multiplicity.
Source: Clinical Study Report for VICTORIA.[10]

Table 44: Time to First Event of CEC-Confirmed Hospitalization for Stroke — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Stroke hospitalization, n (%)	[redacted]	[redacted]
Annual rate, %[a]	[redacted]	[redacted]
KM% (95% CI) at 2 years[b]	[redacted]	[redacted]
HR (95% CI)[c]	[redacted]	
P value[d]	[redacted]	[redacted]

CEC = Clinical Events Committee; CI = confidence interval; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.
Notes: Based on data up to the primary completion date (June 18, 2019).
[a]Total events per 100 subject years at risk.
[b]Kaplan-Meier estimate and confidence interval at 2 years.
[c]Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).
[d]From log-rank test stratified by the stratification factors defined by region and race. P value was not adjuster for multiplicity.
Source: Clinical Study Report for VICTORIA.[10]

Table 45: Total Number of CEC-Confirmed HHF — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Total number of HHF, n[a]	1,223	1,336
Annual rate, %[b]	38.3	42.4
IRR (95% CI)[c]		
P value[d]		

CI = confidence interval; CEC = clinical events rate; HHF = hospitalization for heart failure; IRR = incidence rate ratio.

Notes: Based on data up to the primary completion date (June 18, 2019).

[a]Number of events in the study arm including the first event and recurrent events.

[b]Total events per 100 subject years of follow-up.

[c]Incidence rate ratio (IRR) comparing vericiguat over placebo. 95% CI is the 95% confidence interval for the estimate.

[d]P value was calculated based on negative binomial regression model with covariates for treatment and stratification factor and adjusted by subject follow-up duration.

Source: Clinical Study Report for VICTORIA.[10]

Table 46: Time to First Event of CEC-Confirmed CV Death, MI, or Stroke Hospitalization — On-Treatment Analysis

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Exploratory composite end point, n (%)		
CV death		
MI hospitalization		
Stroke hospitalization		
Annual rate, %[a]		
KM% (95% CI) at 2 years[b]		
HR (95% CI)[c]		
P value[d]		

CEC = Clinical Events Committee; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.

Notes: For patients with multiple events, only the first event contributing to the composite end point is counted in the table.

Based on data up to the primary completion date (June 18, 2019).

[a]Total events per 100 subject years at risk.

[b]Kaplan-Meier estimate and confidence interval at 2 years.

[c]Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race. P value was not adjuster for multiplicity.

Source: Clinical Study Report for VICTORIA.[10]

Figure 17: Kaplan-Meier Plot for Time to First Event of CEC-Confirmed CV Death, MI, or Stroke Hospitalization — On-Treatment Analysis

Note: This figure has been redacted per the sponsor's request.

Table 47: Number of Days Alive Outside of CEC-Confirmed HHF — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Mean (SD)	455.6 (243.64)	449.5 (240.74)
LS Mean	457.59	451.47
Difference in LS Means (95% CI)	6.11 (−7.15 to 19.38)	
P value	0.366	Reference

CI = confidence Interval; LS = least squares; SD = standard deviation.

Notes: Based on an ANOVA model with study group and stratification factors as covariates.

Based on data up to the primary completion date (June 18, 2019).

Source: Clinical Study Report for VICTORIA.[10]

Table 48: Time to First CEC-Confirmed Event of HHF or Urgent HF Visit — ITT Population

Characteristic	Vericiguat (N = 2,526)	Placebo (N = 2,524)
Composite end point, n (%)	730 (28.9)	795 (31.5)
HHF, n (%)	[redacted]	[redacted]
HF urgent visit, n (%)	[redacted]	[redacted]
Annual rate, %[a]	[redacted]	[redacted]
KM, % (95% CI)[b]	[redacted]	[redacted]
HR (95% CI)[c]	0.89 (0.81 to 0.99)	
P value[d]	0.030	Reference

CEC = Clinical Events Committee; CI = confidence interval; HF = heart failure; HHF = hospitalization for heart failure; HR = hazard ratio; ITT = intention to treat; KM = Kaplan-Meier.

Note: Based on data up to the primary completion date (June 18, 2019).

[a]Total events per 100 subject years at risk.

[b]Kaplan-Meier estimate and confidence interval at 2 years.

[c]Hazard ratio (vericiguat over placebo) and confidence interval from Cox proportional hazard model controlling for stratification factors (defined by region and race).

[d]From log-rank test stratified by the stratification factors defined by region and race. P value was not adjuster for multiplicity.

Source: Clinical Study Report for VICTORIA.[10]

Figure 18: Kaplan-Meier Plot for Time to First Event of CEC-Confirmed HHF or Urgent HF Visit — ITT Population

Note: This figure has been redacted per the sponsor's request.

Appendix 4: Description and Appraisal of Outcome Measures

Note that this appendix has not been copy-edited.

Aim

To describe the following outcome measures and review their measurement properties, including validity, reliability, responsiveness to change, and the minimal important difference (MID):

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EQ-5D-5L

Findings

The findings on the validity, reliability, and responsiveness of, and the MID in each outcome measure are summarized in Table 44.

Table 49: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
KCCQ	A self-administered, 23-item, disease-specific questionnaire used to measure HRQoL in patients with CHF based on a 2-week recall period.[36] Items are categorized into the following 7 domains: physical limitations, symptoms (further categorized into frequency, severity, and change over time), quality of life, social limitation, and self-efficacy.[36] The questionnaire is scored by assigning each item an ordinal value, then summing all items within each domain and transforming to a 0- to 100-point scale.[36] Lower scores indicate greater symptom severity and limitations, while a score of 100 would indicate no symptoms, no limitations, and excellent quality of life.[37] The KCCQ Total Symptom Score combines the symptom frequency and symptom severity domains.[36,37] The KCCQ Clinical Summary	**Validity:** Convergent validity was demonstrated in patients with HF and ejection fraction < 40% (N = 129).[36] The Spearman's correlation coefficient for the physical limitation domain ranged from 0.48 with 6MWT to 0.84 with SF-36 physical limitation domain; for the quality of life domain, the correlation ranged from 0.45 with SF-36 general health perception scale to −0.64 with NYHA class; for the social limitation domain, the correlation was −0.57 with NYHA class and 0.62 with SF-36 social functioning domain.[36] The frequency and severity symptom domains and the Clinical and Overall Summary Scores were able to differentiate between patients based on their NYHA class.[36] Construct validity of the physical limitation domain in patients with HF was demonstrated by the correlation coefficient that ranged from 0.48 with 6MWT to 0.84 with SF-36 physical functioning, and for the social limitation domain, the correlation coefficient was 0.59 to 0.62 with SF-36 social functioning.[38]	The relationship between Overall Summary Score and clinically observed change, as assessed by a cardiologist on a 15-point Likert scale, in patients with HF with reduced ejection fraction (defined as LVEF < 40%) (N = 476) was evaluated[40]: • a mean improvement of 5.7 points was associated with a small improvement, • a mean decline of 5.3 points was associated with a small deterioration. The relationship between KCCQ and 6MWT and peak VO_2 in patients with HF with reduced ejection fraction (defined as LVEF < 35%) (N = 2,331).[39] The authors concluded that the results generally supported a 5-point difference in the KCCQ, between patients, to be clinically meaningful.[39] The MCID in the KCCQ was also estimated in patients with chronic, stable HF with reduced ejection fraction and

Outcome measure	Type	Conclusions about measurement properties	MID
	Score combines the physical limitation and symptom (excludes symptom change over time) domains.[36,37] The KCCQ Overall Summary Score combines the physical limitation, symptom (excludes symptom stability), quality of life, and social limitation domains.[36,37]	No evidence of convergent validity was found for the domain and summary scores in patients who were hospitalized for decompensating HF and hemodynamically stable (N = 233).[63] **Reliability:** For internal consistency, the Cronbach alpha was 0.62 for self-efficacy, 0.78 for quality of life, 0.86 for social limitation, 0.88 for symptoms, 0.90 for physical limitation, 0.93 for the Clinical Summary Score, and 0.95 for the Overall Summary Score in patients with HF with reduced ejection fraction (defined as LVEF < 40%) (N = 39).[36] For test-retest reliability, no differences were found in the mean domain and summary scores between baseline and 3-month follow-up.[36] Internal consistency was demonstrated by the Cronbach alpha of 0.62 to 0.66 for self-efficacy, 0.78 to 0.84 for quality of life, 0.86 to 0.88 for symptoms, 0.86 to 0.90 for social limitation, and 0.90 to 0.91 for the physical domain in patients with HF.[38] For test-retest reliability, the ICC was 0.41 for self-efficacy, 0.57 for quality of life, 0.60 for symptom stability, 0.73 for social limitation, 0.78 for symptom frequency and severity, and 0.79 for the physical domain.[38] For internal consistency, the Cronbach alpha was 0.62 for symptom burden, 0.64 for self-efficacy, 0.65 for symptom frequency, 0.67 for quality of life, 0.82 for social limitation, 0.87 for physical limitation, and 0.90 for the entire KCCQ scale in patients who were hospitalized for decompensating HF and hemodynamically stable (N = 233).[63] **Responsiveness:** Responsiveness was evaluated in patients with HF with reduced ejection fraction (defined as LVEF < 40%) and whose clinical status was expected to change (N = 39). Differences were reported in the mean domain and summary scores between baseline and 3-month follow-up.[36] The Guyatt's responsiveness statistic was 0.62 for social limitation, 0.83 for	iron deficiency, with or without anemia (N = 459); PGA was the anchor.[65] The authors noted that the estimated MCID, defined as little improved vs. no change, was < 5 points in all KCCQ domain and summary scales at week 4 and in almost all of the scales at week 24, with the exception of quality of life and symptom burden domains.[65] Using anchor- (PGIS and PGIC) and distribution-based (1 SEM, and 0.2 and 0.5 SD) approaches, the authors concluded a within-patient change of ≥ 9 points in the KCCQ Total Symptom Score in patients with HF with reduced ejection fraction was considered to be clinically meaningful for improvement (N = 312).[66]

Outcome measure	Type	Conclusions about measurement properties	MID
		self-efficacy, 0.86 for quality of life, 1.48 for physical limitation, 1.74 for Overall Summary Score, 2.62 for symptom stability, 2.77 for Clinical Summary Score, and 3.19 for symptom frequency and severity.[36] The authors concluded that the KCCQ Summary Scores demonstrated the highest relative ranking (vs. EQ-5D and RAND12) across all responsiveness index and clinical criteria for classifying change in patients with HF with reduced ejection fraction (defined as LVEF < 40%) (N = 298).[64] The responsiveness statistic coefficient was 0.6 for social limitation, 0.8 for self-efficacy, 0.9 for quality of life, 1.5 for physical limitation, and 3.2 for symptoms in patients with HF.[38]	
EQ-5D-5L	A generic, self-reported measure of health status comprised of 2 parts.[67] The descriptive system consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has 5 increasing levels of severity/response. The responses are used to generate a health state profile (5-digit code) which can be converted to a summary index score based on societal preference weights. Index scores range from less than 0 to 1, with higher scores representing higher health utility.[67] Patient's perceived health status on that day is also rated using the VAS, ranging from 0 (worst imaginable health) to 100 (best imaginable health).[67]	**Validity:** Not assessed in patients with HF. **Reliability:** Not assessed in patients with HF. **Responsiveness:** Not assessed in patients with HF.	The MID in the EQ-5D-5L descriptive system for patients with HF was not assessed. The relationship between EQ VAS and 6MWT and peak VO_2 in patients with HF and ejection fraction of 35% and less (N = 2,331).[39] The authors concluded that the results demonstrated some support for a 3-point difference on the VAS, between patients, to be clinically meaningful.[39] The Canadian-specific (non-disease-specific) MID is 0.037.[41,42]

6MWT = 6-minute walk test; HF = heart failure; HF with reduced ejection fraction = HF with reduced ejection fraction; HRQoL = health-related quality of life; ICC = intraclass correlation; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MCID = minimal clinically important difference; MID = minimal important difference; NYHA = New York Heart Association; PGA = Patient Global Assessment; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SD = standard deviation; SEM = standard error of measurement; SF-36 = 36-item Short Form Survey; VAS = visual analogue scale.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

Description and Scoring

The KCCQ is a self-administered, 23-item, disease-specific questionnaire used to measure health-related quality of life (HRQoL) in patients with heart failure (HF) based on a 2-week recall period. Items are categorized into the following 7 domains: physical limitations, symptom (which is further categorized into frequency, severity [burden], and change over time [stability]), quality of life, social limitation, and self-efficacy. The questionnaire is scored by assigning each item an ordinal value, beginning with 1 as the lowest level of functioning, then summing all items within each domain and transforming the value to a 0- to 100-point scale. Missing values are assigned the average score of the answered items in the same domain.[36] Lower scores indicate greater symptom severity and limitations, while a score of 100 would indicate no symptoms, no limitations, and excellent quality of life. Additionally, the KCCQ scores can be summarized in 25-point ranges, where 0 to 24 represent very poor to poor, 25 to 49 represent poor to fair, 50 to 74 represent fair to good, and 75 to 100 represent good to excellent health status.[37]

To improve the interpretation of the questionnaire results, the following summary scores were developed. The KCCQ Total Symptom Score comprises of the symptom frequency and symptom severity domains. The KCCQ Clinical Summary Score comprises of the physical limitation, symptom frequency, and symptom severity domains. The KCCQ Overall Summary Score comprises of the physical limitation, symptom frequency, symptoms severity, quality of life, and social limitation domains.[36,37]

Validity

Green et al.[36] evaluated the validity of the KCCQ in patients with a clinical diagnosis of HF and a documented ejection fraction of less than 40%, including patients who were stable and whose clinical status was expected to change postdischarge (N = 129). Convergent validity of each domain was assessed by comparison with other measures that quantify similar concepts. The Spearman's correlation coefficient for the physical limitation domain was 0.48 with the 6-minute walk test (6MWT), −0.65 with the New York Heart Association (NYHA) classification, 0.84 with the Short Form 36 (SF-36) physical limitation domain and 0.65 with the Minnesota Living with Heart Failure Questionnaire (MLHFQ) physical domain.[36] The Spearman's correlation coefficient for the quality of life domain was 0.45 with the general health perception scale of the SF-36, −0.64 with the NYHA class, and 0.62 with the emotional domain of the MLHFQ.[36] The Spearman's correlation coefficient for the social limitation domain was 0.62 with the social functioning domain of the SF-36 and −0.57 with the NYHA class.[36] The symptom frequency and severity domain scores and the Clinical and Overall Summary Scores were able to differentiate between patients based on their NYHA class.[36] According to the authors, there was no known validated measure that could be used to validate the symptom stability (change over time) and self-efficacy domains at the time of conducting this study.[36]

Myers et al.[68] described the relationship between functional assessments, including the KCCQ, and peak VO_2 in a cohort of patients with stable, compensated HF with reduced ejection fraction (defined as LVEF < 40%) (N = 41). The correlation coefficient was 0.46 between peak VO_2 and the quality of life domain; the

correlation coefficients were not statistically significant for the physical limitation subscale (r = 0.25) and the Total Symptom and Clinical Summary Scores (r = 0.30 each).[68]

Garin et al.[38] conducted a systematic review with meta-analysis to identify and evaluate the conceptual model and metric properties of disease-specific questionnaires that measure HRQoL of patients with HF. For construct validity of the KCCQ physical limitation domain, the correlation coefficient was 0.79 to 0.84 with the SF-36 physical functioning, 0.48 with the 6MWT, and 0.65 with the NYHA class. For construct validity of the social limitation domain, the correlation coefficient was 0.59 to 0.62 with the SF-36 social functioning.[38]

The psychometric properties of the KCCQ were further examined in patients who were hospitalized for decompensating HF; note, patients were required to be hemodynamically stable (N = 233; 55 patients each [23%] were diagnosed with NYHA class III and IV). Tucker et al.[63] found no evidence of convergent validity for the KCCQ domain and summary scores with the NYHA class, brain natriuretic peptide levels, and the Charlson Comorbidity Index scores. The authors suggested that this may be due to the difference in the study population (i.e., acute) compared to previous studies evaluating convergent validity of the KCCQ.[63]

Reliability

Green et al.[36] also evaluated the reliability of the KCCQ in patients with HF with reduced ejection fraction (defined as LVEF < 40%) and who were stable (N = 39; mean NYHA class = 2.0 [SD = 0.59]). For internal consistency, the Cronbach alpha was 0.62 for self-efficacy, 0.78 for quality of life, 0.86 for social limitation, 0.88 for symptoms, 0.90 for physical limitation, 0.93 for the Clinical Summary Score, and 0.95 for the Overall Summary Score.[36] For test-retest reliability, no differences (based on P values derived from paired t-test) were observed in the mean domain and summary scales scores between baseline and 3-month follow-up (mean difference in score ranged from 0.8 to –4.0).[36]

Garin et al.[38] conducted a systematic review with meta-analysis to identify and evaluate the conceptual model and metric properties of disease-specific questionnaires that measure HRQoL of patients with HF. For internal consistency, the Cronbach alpha was 0.62 to 0.66 for self-efficacy, 0.78 to 0.84 for quality of life, 0.86 to 0.88 for symptoms, 0.86 to 0.90 for social limitation, and 0.90 to 0.91 for the physical domain. For test-retest reliability, the intraclass correlation was 0.41 for self-efficacy, 0.57 for quality of life, 0.60 for symptom stability, 0.73 for social limitation, 0.78 for symptom frequency and severity, and 0.79 for the physical domain.[38]

Tucker et al.[63] further examined the psychometric properties of the KCCQ in patients who were hospitalized for decompensating HF; patients were required to be hemodynamically stable (N = 233; 55 patients each [23%] were diagnosed with NYHA class III and IV). For internal consistency, the Cronbach alpha was 0.62 for symptom burden, 0.64 for self-efficacy, 0.65 for symptom frequency, 0.67 for quality of life, 0.82 for social limitation, 0.87 for physical limitation, and 0.90 for the entire KCCQ scale.[63]

Responsiveness

Green et al.[36] also evaluated the responsiveness of the KCCQ in patients with HF with reduced ejection fraction (defined as LVEF < 40%) and whose clinical status was expected to change (N = 39; mean NYHA class = 3.3 [SD = 0.46]). The hypothesis was that patients who were admitted to the hospital with decompensated HF would improve when surveyed 3 months later. Differences (based on P values derived from paired t-test) were observed in the mean domain and summary scales scores between baseline and 3-month follow-up (mean difference in score ranged from 15.4 to 40.4).[36] The Guyatt's responsiveness statistic was 0.62 for social limitation, 0.83 for self-efficacy, 0.86 for quality of life, 1.48 for physical limitation, 1.74 for the Overall Summary Score, 2.62 for symptom stability, 2.77 for the Clinical Summary Score, and 3.19 for symptom frequency and severity.[36]

Eurich et al.[64] compared the relative responsiveness of generic and HF-specific HRQoL instruments, including the KCCQ Clinical and Overall Summary Scores, in patients with HF with reduced ejection fraction (defined as LVEF < 40%) (N = 298; 129 patients [43%] were diagnosed with NYHA class II and 122 patients [41%] were diagnosed with NYHA class III). Classification of patients as improved, deteriorated, or unchanged were based on the 6MWT, NYHA class, and a physician global rating of change (external criteria). A total of 4 responsiveness statistics, t-test, effect size, Guyatt's responsiveness statistic, and standardized response mean, were used to evaluate the responsiveness. The authors concluded that the KCCQ Summary Scores demonstrated the highest relative ranking (versus EQ-5D and RAND12) across all responsiveness index and clinical criteria used for classifying change.[64] Note, the results should be interpreted with caution as the cohort study was conducted to evaluate the random changes observed in patients with HF and no intervention was studied during the follow-up period (i.e., responsiveness to change was not due to an intervention).

Garin et al.[38] conducted a systematic review with meta-analysis to identify and evaluate the conceptual model and metric properties of disease-specific questionnaires that measure the HRQoL of patients with HF. For responsiveness to change, the responsiveness statistic coefficient (based on inpatients 3 months postdischarge) was 0.6 for social limitation, 0.8 for self-efficacy, 0.9 for quality of life, 1.5 for physical limitation, and 3.2 for symptoms.[38]

Minimal Important Difference

Spertus et al.[40] described the relationship between measures of disease status and clinically observed change in patients with HF with reduced ejection fraction (defined as LVEF < 40%) using clinical change as assessed by a cardiologist on a 15-point Likert scale, from extremely worse to extremely better and grouped into categories of change (N = 476; 41% NYHA class II, 44% NYHA class III).[40] When the KCCQ Overall Summary Score was administered at baseline and 6 weeks, a mean improvement of 5.7 points (SD = 16) was associated with a small improvement in HF, while a mean decline of 5.3 points (SD = 11) was associated with a small deterioration in HF.[40]

Flynn et al.[39] also described the relationship between clinical and patient-reported end points using the HF-ACTION[69] trial data, which included patients with HF and ejection fraction of 35% and less and diagnosed

with NYHA class II and IV (N = 2,331). The authors considered a 1-SD difference in the 6MWT and peak VO_2 to represent a meaningful difference in patients with HF and stated that this was a more stringent criterion used for these indicators compared to previous studies.[39] After adjusting for patient characteristics, a 1-SD difference in the peak VO_2 and 6MWT was associated with a 4.75-point (95% CI, 3.78 to 5.72) and 5.92-point (95% CI, 4.98 to 6.87) difference in the Overall Summary Score, respectively. A 1-SD difference in the peak VO_2 and 6MWT was associated with a 5.41-point (95% CI, 4.56 to 6.26) and 6.37-point (95% CI, 5.51 to 7.22) difference in the KCCQ Clinical Summary Score, respectively.[39] A 1-SD difference in the peak VO_2 and 6MWT was associated with a 6.44-point (95% CI, 5.47 to 7.42) and 7.45-point (95% CI, 6.48 to 8.43) difference in the physical limitation subscale, respectively. A 1-SD difference in the peak VO_2 and 6MWT was associated with a 4.39-point (95% CI, 3.47 to 5.30) and 5.19-point (95% CI, 4.26 to 6.13) difference in the symptom subscales, respectively. A 1-SD difference in the peak VO_2 and 6MWT was associated with a 5.27-point (95% CI, 2.69 to 7.86) and 6.21-point (95% CI, 4.92 to 7.50) difference in the social limitation subscale, respectively. A 1-SD difference in the peak VO_2 and 6MWT was associated with a 0.62-point (95% CI, −0.22 to 1.47) and 0.56-point (95% CI, −0.29 to 1.42) difference in the self-efficacy subscale, respectively. A 1-SD difference in the peak VO_2 and 6MWT was associated with a 5.11-point (95% CI, 2.71 to 7.51) and 5.01-point (95% CI, 3.85 to 6.16) difference in the quality of life subscale, respectively.[39] The authors concluded that the results generally supported a 5-point difference in the KCCQ, between patients, to be clinically meaningful.[39] Note, the results should be interpreted with caution as the intervention in HF-ACTION was aerobic exercise training versus usual care.

The minimal clinically important difference (MCID) in the KCCQ was also estimated using the FAIR-HF[70] trial data and the Patient Global Assessment (PGA) of change as the clinical anchor at weeks 4 and 24.[65] The FAIR-HF trial included patients with chronic, stable heart failure with reduced ejection fraction (HF with reduced ejection fraction) and iron deficiency, with or without anemia (377 patients [82%] had NYHA class III) (N = 459).[65] For the purposes of this review, only the estimated MCID defined as little improved versus no change is summarized here. The estimated MCID in the KCCQ Overall Summary Score was 3.6 (95% CI, 1.0 to 6.2) at week 4 and 4.3 (95% CI, 0.2 to 8.4) at week 24. The estimated MCID in the Clinical Summary Score was 4.5 (95% CI, 1.8 to 7.2) at week 4 and 4.5 (95% CI, 0.5 to 8.5) at week 24. The estimated MCID in the Total Symptom Score was 4.1 (95% CI, 1.0 to 7.2) at week 4 and 4.9 (95% CI, 0.7 to 9.2) at week 24.[65] The estimated MCID in the physical limitation domain was 4.7 (95% CI, 1.4 to 8.0) at week 4 and 4.0 (95% CI, −0.9 to 9.0) at week 24. The estimated MCID in the symptom burden domain was 4.3 (95% CI, 1.0 to 7.6) at week 4 and 5.1 (95% CI, 0.5 to 9.8) at week 24. The estimated MCID in the symptom frequency domain was 3.9 (95% CI, 0.3 to 7.5) at week 4 and 4.8 (95% CI, 0.1 to 9.4) at week 24. The estimated MCID in the quality of life domain was 3.3 (95% CI, −0.3 to 6.9) at week 4 and 6.1 (95% CI, 1.2 to 11.0) at week 24. The estimated MCID in the social limitation domain was 0.9 (95% CI, −3.4 to 5.2) at week 4 and 2.0 (95% CI, −5.0 to 9.1) at week 24.[65] The investigators noted that the estimated MCID was less than 5 points in all KCCQ domain and summary scales at week 4 and in almost all of the scales at week 24, with the exception of quality of life and symptom burden domains.[65]

Butler et al.[66] estimated the within-patient clinically meaningful change in the KCCQ Total Symptom Score in patients with HF with reduced ejection fraction and NYHA class II to IV from the EMPERIAL trials[71,72]

(N = 312). For the purpose of this review, only the results pertaining to HF with reduced ejection fraction are summarized here. Both anchor- and distribution-based approaches were used; the Patient Global Impression of Severity (PGIS) was the primary anchor, and the Patient Global Impression of Change (PGIC) was the secondary anchor. A 1-category of improvement in the PGIS scale corresponded to a mean change of 12 points (SD = 17) in the KCCQ Total Symptom Score; the Spearman correlation between change from baseline to week 12 in PGIS and KCCQ Total Symptom Scores was –0.357. Based on the receiver-operating characteristic curve analysis, the authors concluded that a within-patient change of 9 points or greater in the KCCQ Total Symptom Score in patients with HF with reduced ejection fraction was considered to be the MCID for improvement. A change of at least a little better in the PGIC corresponded to a mean change of 10 points (SD = 17) in the KCCQ Total Symptom Score. Note, the Spearman correlation between the change in the PGIC and KCCQ Total Symptom scores at week 12 was 0.283 in patients with HF with reduced ejection fraction, which is less than the prespecified correlation of 0.3 that was considered to be acceptable for interpretation of the results. The distribution-based method yielded the following thresholds for a meaningful within-patient change in the KCCQ Total Symptom Score: 1 standard error of measurement corresponded to 5.83 points, 0.2 SD corresponded to 3.37 points, and 0.5 SD corresponded to 8.42 points in patients with HF with reduced ejection fraction.[66]

EQ-5D-5L

Description and Scoring

The EQ-5D-5L is a generic, self-reported measure of health status comprised of 2 parts.[67] The descriptive system assesses HRQoL in 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has 5 increasing levels of severity/response (no problems, slight problems, moderate problems, severe problems and unable to perform/extreme problems). A unique health state profile is generated as a 5-digit code (e.g., 12345 indicates no problems with mobility, slight problems with self-care, moderate problems with usual activities, severe pain or discomfort and extreme anxiety or depression). The health state can be converted to a summary index score based on societal (countries/regions) preference weights for the health state. Index scores range from less than 0 (negative values represent worse than dead, which is represented by 0) to 1 (full health), with higher scores representing higher health utility. Patient's perceived health status on that day is also rated using the visual analogue scale (VAS), ranging from 0 (worst imaginable health) to 100 (best imaginable health).[67]

Validity and Reliability

The validity and reliability of the EQ-5D-5L in patients with HF were not assessed.

Dyer et al.[73] conducted a systematic review to review the evidence on the validity and reliability of the EQ-5D-3L and EQ VAS in patients with cardiovascular disease; 2 studies that reported evidence of validity and reliability of the EQ-5D in HF were identified. When EQ-5D-3L index scores were stratified by disease severity, the mean scores decreased from 0.78 (SD = 0.18) to 0.51 (SD = 0.21) for mild to moderate and severe disease in patients with HF.[73]

Responsiveness

The responsiveness to change of the EQ-5D-5L in patients with HF was not assessed.

Eurich et al.[64] compared the relative responsiveness of generic and HF-specific HRQoL instruments, including the EQ-5D (US, UK, and VAS), in patients with HF and LVEF of less than 40% (N = 298). Classification of patients as improved, deteriorated, or unchanged were based on the 6MWT, NYHA class, and a physician global rating of change (external criteria). A total of 4 responsiveness statistics, t-test, effect size, Guyatt's responsiveness statistic, and standardized response mean, were used to evaluate responsiveness. The authors concluded that the EQ-5D was not as responsive as the RAND12 Mental Component Summary Score and the KCCQ Summary Scores. Additionally, the responsiveness of generic HRQoL measures, including EQ-5D, may be influenced by the clinical criteria used for classifying change.[64] Note, the results should be interpreted with caution as the cohort study was conducted to evaluate the random changes observed in patients with HF and no intervention was studied during the follow-up period (i.e., responsiveness to change was not due to an intervention).

Minimal Important Difference

The MID in the EQ-5D-5L for patients with HF was not identified in the literature; although a Canadian-specific MID of 0.037 has been reported for the EQ-5D-5L.[41,42]

Flynn et al.[39] described the relationship between clinical and patient-reported end points using the HF-ACTION[69] trial data, which included patients with HF and LVEF of 35% and less and diagnosed with NYHA class II and IV (N = 2,331). The authors considered a 1-SD difference in the 6MWT and peak VO_2 to represent a meaningful difference in patients with HF and stated that this was a more stringent criterion used for these indicators compared to previous studies. After adjusting for patient characteristics, a 1-SD difference in the peak VO_2 and 6MWT was associated with a 2.86-point (95% CI, 1.98 to 3.74) and 2.78-point (95% CI, 1.92 to 3.64) difference in the EQ VAS, respectively. The authors concluded that the results demonstrated some support for a 3-point difference on the VAS, between patients, to be clinically meaningful.[39] Note, the results should be interpreted with caution as the intervention in HF-ACTION was aerobic exercise training versus usual care.

Vericiguat (Verquvo)

Pharmacoeconomic Review

List of Tables

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Abbreviations

ACEi	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
ARNi	angiotensin receptor and neprilysin inhibitor
BB	beta-blocker
BIC	Bayesian information criterion
BT	background therapy
CV	cardiovascular
EF	ejection fraction
HF	heart failure
HHF	hospitalization for heart failure
HFrEF	heart failure with reduced ejection fraction
ICER	incremental cost-effectiveness ratio
LY	life-year
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
QALY	quality-adjusted life-year
SAE	serious adverse event
SGLT2	sodium-glucose cotransporter-2
SOC	standard of care
T1	transition from the alive no HHF health state to the HHF event 1 health state
T2	transition from the alive no HHF health state to death
T3	transition from an HHF event to the post-HHF health state
T4	transition from an HHF event to death
T5	transition from the post-HHF health state to death
WTP	willingness to pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Vericiguat (Verquvo), 2.5 mg, 5 mg, and 10 mg tablets
Submitted price	Vericiguat, 2.5 mg, 5 mg, or 10 mg: $4.83 per tablet
Indication	Proposed: indicated for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy. Vericiguat should be used in combination with standard-of-care therapy for HF.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	April 28, 2023
Reimbursement request	Request to be indicated for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy. Vericiguat should be used in combination with standard-of-care therapy for HF. Vericiguat should be initiated in adult patients with NYHA class II to class IV chronic HF; in combination with other HF therapies that include an ACEi, an ARB, or an ARNi, a BB, and, if tolerated, an MRA; and under the supervision of a health care professional who is experienced in the management of HF.
Sponsor	Bayer Inc.
Submission history	Previously reviewed: No

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor and neprilysin inhibitor; BB = beta-blocker; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NOC = Notice of Compliance; NYHA = New York Heart Association.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with chronic HF and EF < 45% who are stabilized after a recent HF decompensation event who: • are classified as having NYHA class II to class IV chronic HF • also receive concomitant BTs, including ACEis, ARBs, ARNis, BBs, and, if tolerated, MRAs (aligned with reimbursement request).
Treatment	Vericiguat and BTs, including ACEis, ARBs, ARNis, BBs, and MRAs
Comparator	BT alone
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	15 years

Component	Description
Key data source	VICTORIA (phase III clinical trial)
Submitted results	Requested reimbursement: ICER = $33,276 per QALY gained (incremental costs: $10,699; incremental QALYs = 0.32)
Key limitations	• Impact of vericiguat + BT on risk of first HHF event is highly uncertain. The sponsor selected joint distributions despite the fact that the VICTORIA trial presented a comparison of therapies with different mechanisms of actions. Moreover, according to clinical experts consulted for the review, all parametric distributions considered by the sponsor for vericiguat + BT yielded 5-year, 10-year, and 15- year extrapolations that were deemed optimistic relative to the most plausible extrapolation for BT alone. • Relevant variables were excluded from the risk equations used in the model to estimate the risk of first HHF event. Clinical experts consulted for the review indicated that the rate of transition to the first HHF event would differ in patients with different levels of chronic obstructive pulmonary disease, diabetes, smoking status, baseline treatments (i.e., MRAs, ARNis, devices), and cardiovascular histories. • The sponsor did not incorporate the potential for the waning of treatment effects. Based on the current literature, the efficacy of therapies used to treat HFrEF could wane as the disease progresses, unaffected by treatments. • The population considered in the economic model does not reflect the population of interest. Based on epidemiological evidence, if vericiguat were to become available in clinical practice, the average patient is likely to be 10 years older and receive a different composition of BT. As such, uncertainty exists as to whether the predicted survival benefit will be realized in the real-world setting. • The sponsor omitted SGLT2 inhibitors from the analysis, a relevant drug class for this population, as both empagliflozin and dapagliflozin are components of BT in Canadian clinical practice.
CADTH reanalysis results	• CADTH conducted reanalyses that addressed the uncertainties associated with long-term treatment efficacy by applying alternative parametric extrapolations for the risk of first HHF (gamma distribution for vericiguat + BT; Weibull distribution for BT alone), incorporating linear treatment waning that begins at 2.6 years and ends at 7.6 years, revising the starting cohort mean age to 77 years, and reducing the time horizon to 10 years. • In CADTH's reanalysis, the ICER for vericiguat + BT, compared to BT alone, is $62,778 per QALY gained (vericiguat + BT is $8,226 more expensive and yields 0.13 more QALYs) for adults with chronic HF and an EF < 45% who are stabilized after a recent HF decompensation event. A price reduction of 14% would be necessary to achieve cost-effectiveness at a willingness-to-pay threshold of $50,000 per QALY gained in the reimbursement request population. • The CADTH reanalysis estimated a smaller overall survival benefit than the sponsor's base case (0.40 incremental LYs in the sponsor's base case vs. 0.16 incremental LYs in CADTH's reanalysis), although uncertainty remains regarding the magnitude. Results should be interpreted carefully, in light of the fact that 80% of the QALY benefit was derived from the period beyond which there is observed trial data. The cost-effectiveness of vericiguat + BT was slightly sensitive to different treatment-waning assumptions.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; ARNi = angiotensin receptor and neprilysin inhibitor ; BB = beta-blocker; BT = background therapy; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICER = incremental cost-effectiveness ratio; LY = life-year; MRA = mineralocorticoid receptor antagonist; QALY = quality-adjusted life-year; SGLT2 = sodium-glucose cotransporter-2.

Conclusions

Based on data from the VICTORIA trial, the CADTH Clinical Review concluded that vericiguat demonstrated a statistically significant and clinically meaningful benefit, compared to placebo, in reducing the hazard rates

of first event of cardiovascular (CV) death or hospitalization for heart failure (HHF) (median follow-up, 11.1 months for vericiguat plus background therapy [BT] and 10.4 months for BT alone), occurrence of first and recurrent HHF, and the composite of all-cause mortality or HHF (median follow-up, ■ for vericiguat plus BT and ■ months for BT alone) in adults with symptomatic chronic heart failure (HF) with reduced ejection fraction (HFrEF). The median composite primary end point, total HHF events, and composite of all-cause mortality and HHF were not estimable in either treatment group (i.e., vericiguat plus BT or BT alone) because insufficient follow-up time had elapsed for these outcomes. As such, the long-term efficacy of vericiguat is highly uncertain. Moreover, the estimates of clinical benefit for vericiguat may be overestimated, as there is a possibility that the trial was stopped early due to the misclassification of CV deaths; however, the presence and extent of any overestimation is uncertain.

The CADTH reanalysis addressed the uncertainties associated with long-term treatment efficacy by applying alternative parametric extrapolations for the risk of first HHF (gamma distribution for vericiguat plus BT; Weibull distribution for BT alone), incorporating linear treatment waning that begins at 2.6 years and ends at 7.6 years, revising the starting cohort mean age to 77 years, and reducing the time horizon to 10 years.

CADTH estimated that the incremental cost-effectiveness ratio (ICER) for vericiguat plus BT compared to BT alone in the reimbursement request population (adult patients with symptomatic chronic HFrEF who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy) is $62,778 per quality-adjusted life-year (QALY) gained. The probability that vericiguat plus BT was cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY was 37%. A price reduction of 14% would be necessary for vericiguat plus BT to achieve cost-effectiveness, compared to BT alone, at a WTP threshold of $50,000 per QALY gained.

The CADTH reanalysis estimated a smaller overall survival benefit with vericiguat plus BT when compared to the sponsor's base case (0.40 incremental life-years [LYs] in the sponsor's base case versus 0.16 incremental LYs in CADTH's reanalysis), which translated to fewer overall incremental QALYs in the CADTH reanalysis. Despite CADTH's reanalyses, there remains a substantial proportion (80%) of the QALY benefit realized by patients receiving vericiguat plus BT compared to BT alone, derived from the period beyond which there is observed trial data. Given this uncertainty, additional price reductions may be warranted.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

One patient group, the HeartLife Foundation, provided input for this review. The input was informed by interviews with 2 patients with HF (British Columbia and Ontario), 3 HF specialists (British Columbia, Ontario, and Quebec), and 1 HF researcher (Alberta). Overall, patients' disease experience was influenced by a wide range of physical, social, and emotional challenges. Symptoms include shortness of breath, extreme fatigue, low blood pressure, dizziness, edema, bloating, palpitations, and arrhythmia. The most important outcomes for patients included delaying disease progression and avoiding hospitalization, with the ultimate objective of

improving survival; preserving independence to minimize the burden on caregivers; and maintaining quality of life. The HeartLife Foundation indicated that for most patients with HFrEF, the Canadian Cardiovascular Society recommends that they be treated with 4 key therapeutic drug classes as the standard-of-care (SOC) therapy early after diagnosis. These include an angiotensin receptor and neprilysin inhibitor (ARNi) as first-line or after either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor antagonist (ARB), a beta-blocker (BB), a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter-2 (SGLT2) inhibitor. Patients often experience loss of response under various treatment options, so continual treatment switching is required to achieve an adequate response until all therapeutic options are exhausted. Patient input emphasized that although quadruple therapy is available, not all patients respond to treatment and some patients become refractory to current treatment options.

Registered clinician input was received from the Oakville Cardiologists. Patient input was echoed by clinicians, who noted that the current pathway of care for patients with HFrEF consists primarily of 4 SOC therapies: ARNis, ACEis, or ARBs; BB; MRAs; and SGLT2 inhibitors. For patients with HFrEF whose heart rate is greater than 70 beats per minute and who remain symptomatic despite treatment with SOC, clinician input indicated that ivabradine tends to be prescribed for the prevention of CV death and HHF. Clinicians indicated that a treatment gap exists with current SOC, as many patients cannot be titrated to the optimal doses of the medications due to hypotension, hyperkalemia, bradycardia, or renal dysfunction. Clinician input noted that vericiguat represents an additional approach to the treatment of HFrEF because it targets neurohormonal compensatory mechanisms that are currently unaddressed by SOC. Clinicians highlighted that because vericiguat neither causes hyperkalemia nor impairs renal function, patients who may not tolerate an ARNi, ARB, or ACEi (e.g., patients with diabetes or renal impairment) would be good candidates for vericiguat. Clinician input identified that the high-risk patient population with HFrEF on optimal therapy who have worsening symptoms and HHF in the previous 6 months would be among the most suitable to receive vericiguat.

CADTH-participating drug plans highlighted implementation issues regarding vericiguat's expected place in therapy. In particular, drug plans questioned how vericiguat would be integrated in the current treatment paradigm that includes therapies such as SGLT2 inhibitors (i.e., dapagliflozin and empagliflozin). This is especially relevant given that SGLT2 inhibitors were not included in the SOC considered in the economic evaluation, as only a small proportion of patients (2.7%) were on these medications in the trial.

Several of these concerns were addressed in the sponsor's model:

- The model was informed by transitions from the alive no HHF health state to the HHF event 1 health state (T1), from the alive no HHF health state to death (T2), and from the post-HHF health state to death (T5), which were derived from trial-based CV mortality and HHF, outcomes that are valued by patients.
- The impact of disease and treatment on a patient's quality of life was captured with utility values. Serious adverse events (SAEs), including renal failure, acute kidney injury, and chronic kidney disease, were incorporated as disutilities in the analysis.

In addition, CADTH addressed some of these concerns, as follows:

- Patient and clinician input confirmed that the disease management journey for patients with HFrEF is characterized by treatment switching until all therapeutic options are exhausted. Their inputs emphasized that not all patients may respond to available SOC treatments, and that disease may progress among patients who become refractory to current treatment options. To accurately characterize natural disease progression and address concerns raised from stakeholder input, CADTH incorporated a treatment-waning assumption into the reanalysis.

CADTH was unable to address the following concern raised from stakeholder input:

- Patient, clinician, and drug plan input indicated that the SGLT2 inhibitor therapeutic class of comparators is relevant to this population, as both empagliflozin and dapagliflozin are important components of SOC prescribed in Canadian clinical practice. CADTH was unable to include SGLT2 inhibitors to the reanalysis.

Economic Review

The current review is for vericiguat (Verquvo) for adult patients with chronic HF and an ejection fraction (EF) less than 45% who are stabilized after a recent HF decompensation event who are classified as having New York Heart Association (NYHA) class II to class IV chronic HF and who are receiving concomitant BT, including ACEis, ARBs, ARNis, BBs, and, if tolerated, MRAs.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of vericiguat in combination with BT, which included an ACEi, ARB, or ARNi, a BB, and an MRA (henceforth, vericiguat plus BT) compared with BT alone.[1] Vericiguat is indicated for use as an adjunct to SOC for the treatment of symptomatic chronic HF in adult patients with reduced EF who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy. The sponsor's reimbursement request is for use as an adjunct to BT in adult patients with symptomatic chronic HFrEF who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy (where BT includes ACEis, ARBs, ARNis, BBs, and MRAs).[1] The reimbursement request population is aligned with, but is narrower than, the Health Canada–indicated population, as it does not make reference to treatment with SGLT2 inhibitors.

Vericiguat is available as a 2.5 mg, 5 mg, and 10 mg oral tablet. The recommended starting dose of vericiguat is 2.5 mg once daily.[2] Patients are up-titrated to 5 mg and then to the target dose of 10 mg of vericiguat, based on mean systolic blood pressure evaluation and clinical symptoms assessed at 2-week intervals. The submitted price of vericiguat is $4.83 per 2.5 mg, 5 mg, or 10 mg tablet, which corresponds to an annual per-patient cost of $1,763.[1] In the model, the sponsor adopted an annual cost of $804 for BT alone. This resulted in an annual per-patient cost of $2,567 for vericiguat plus BT.

The analysis was performed from the perspective of the Canadian publicly funded health care system. Costs and clinical outcomes (LYs and QALYs) were simulated over a model horizon of 15 years and discounted at an annual rate of 1.5% per annum.

Model Structure

The sponsor submitted a Markov model with 6 health states and a 1-month cycle length (Figure 1 in Appendix 3). These health states were alive no HHF, HHF event 1, post-HHF event 1, HHF event ≥ 2, post-HHF event ≥ 2, and death. Patients enter the model in the alive no HHF health state and receive treatment with vericiguat plus BT or BT alone. This health state reflects the baseline risk of patients in the VICTORIA trial, where most patients were likely to have had 1 or 2 prior HHF at the start of the trial. At the end of the cycle, patients may remain in the alive no HHF health state, experience an HHF and transition to the HHF event 1 health state, or die. Once patients experience an HHF event in the model, they enter and stay in the HHF health state for 1 cycle and subsequently enter the post-HHF state or the death state. Patients in the post-HHF event 1 health state experienced an HHF in the previous cycle, survived, and were discharged. These patients may remain in the post-HHF event 1 health state, experience another HHF and transition to the HHF event ≥ 2 or die. Once patients experience a second HHF event in the model, they enter and stay in the HHF event ≥ 2 health state for 1 cycle and subsequently enter the post-HHF event ≥ 2 state or the death state. These patients may remain in the post-HHF event ≥ 2 health state, experience another HHF and transition to the HHF event ≥ 2 or die. Patients in all health states are subject to a probability of death each cycle.

Model Inputs

Baseline patient characteristics were derived from the VICTORIA trial, a phase III, event-driven, double-blind, randomized controlled study that compared vericiguat plus BT with BT alone among adult patients with symptomatic chronic HF and an EF of less than 45% who are stabilized after a recent HF decompensation event. The average patient in the modelled cohort was age 67 years and was more likely to be male (76%). The sponsor assumed that the VICTORIA trial patient characteristics reflected those of the patient population in Canada. These characteristics were used to inform the age- and sex-specific distribution of the general population mortality risk and the length of the lifetime horizon.[1]

The primary outcome of the VICTORIA trial was a composite of time to CV death or HHF. A set of risk equations was developed to estimate the average risk of an outcome (i.e., health state transition probability) using a multistate model structure that allowed for CV mortality and HHF to be modelled independently while considering the competing risk. As such, risk equations were used to describe the transitions from alive no HHF to HHF event 1 (T1), from alive no HHF to death (T2), and from post-HHF to death (T5). A constant case fatality rate (5.78%) was used to describe the transition from an HHF event to death (T4), whereas the transition from an HHF event to post-HHF (T3) equalled 1 minus T4. Because the multistate model approach assumed a linear dependency between survival and covariates, baseline patient characteristics from the VICTORIA trial were used as independent variables to estimate the risk equations for T1, T2, and T5 transitions, and thus influence survival in each state. The covariates included in the extrapolations of T1, T2, and T5 (i.e., treatment arm, geographic region, time-varying effect of the baseline hazard, age, sex, N-terminal pro b-type natriuretic peptide [NT-proBNP], left ventricular EF, NYHA class, and an interaction term between

treatment arm and NT-proBNP) were selected based on relevance to the cost-effectiveness model and/or known clinical relevance.

Survival distributions for T1, T2, and T5 were selected based on the Bayesian information criterion (BIC) to extrapolate CV death and HHF beyond the observed period (i.e., from the end point of the observed VICTORIA data [2.6 years] to the end of the model horizon [15 years]). The sponsor selected joint log-normal, joint generalized gamma, and joint log-normal distributions to extrapolate T1, T2, and T5, respectively, beyond time points available in the trial. The comparative efficacy of vericiguat plus BT, relative to BT alone, was modelled according to the risk equations and the underlying assumption of no treatment waning over the 15-year time horizon. Each HHF event that a patient experienced was assumed to lead to a heightened risk of CV mortality and subsequent HHF events. In the model, the hazard rate of CV mortality in the HHF event ≥ 2 health state and the post-HHF ≥ 2 health state was increased by 34% (i.e., probability multiplier) based on findings from a study by Setoguchi et al. (2007)[3] that examined patients with HF patients and a first HHF between 2000 and 2004 and survival time after first and subsequent HHFs. In addition, a 33% increased risk of HHF was applied to patients in the post-HHF event 1, HHF event ≥ 2, and post-HHF ≥ 2 health states, compared to patients in the alive no HHF health state, based on findings from the study by Braga et al. (2018).[4] Mortality was modelled based on the VICTORIA risk equations for CV mortality (i.e., T2, T4, T5) and age-specific Canadian life tables that were adjusted to remove CV mortality.

Patients accrued health state–specific QALYs, as well as treatment-related and health state–specific costs, as they transitioned through changes in disease progression. Utility values were derived from an analysis of 5-Level EQ-5D index data collected in the VICTORIA trial. The model assigned utility values to each health state using pooled utility estimates across treatments. Pooled trial-based utility scores were adjusted to align estimates with those of the general population in Canada of the same age band as the VICTORIA trial population. Utilities for the HHF event 1, post-HHF event 1, and event ≥ 2 health states were assumed to be equivalent. SAEs were incorporated in the model, as observed in the VICTORIA trial, and selected based on incidence and potential impact on incremental outcomes. These included pneumonia, cardiac failure, acute kidney injury, syncope, anemia, chronic kidney disease, renal failure, ventricular tachycardia, and atrial fibrillation. The influence of SAEs was incorporated in the model using literature sources for disutility and duration. The disutility associated with SAEs and urgent HF visits was modelled using a QALY decrement approach, in which disutilities were deducted from the total sum of utilities after the model horizon. Hence, the model assumed that health state utility values excluded the impact of SAEs and urgent HF visits on quality of life.

Costs captured in the model included drug acquisition, hospitalization and monthly management of HF, management of adverse events, and end-of-life care. Drug-acquisition costs for vericiguat were based on the sponsor's submitted price.[1] Drug-acquisition costs for BT were sourced from the Ontario Drug Benefits Formulary and the Saskatchewan Drug Formulary.[5,6] The recommended daily dosage regimen for BT was based on respective product monographs. The distribution of therapies within BT was assumed to be equivalent for patients receiving vericiguat plus BT and BT alone. The composition of BT within each drug category reflected the most commonly prescribed drugs per category in the VICTORIA trial, and the use of diuretics and ivabradine was based on Canadian clinician input (Table 10 and Table 11).[1] Based on the

literature and clinical expert input, patients in the alive no HHF and post-HHF health states were assumed to have 10 and 4 follow-up visits annually with their general practitioner and cardiologist, respectively.[7] The cost for repeat consultations with medical professionals were obtained from the Ontario Schedule of Benefits for Physician Services.[8] A one-time HHF cost ($14,937) was incurred when patients entered the HHF event 1 or HHF event ≥ 2, whereas an end-of-life cost ($13,216) was incurred upon death, based on an Ontario retrospective cohort study of HHF and a study of hospital abstracts from the Canadian Institute of Health Information.[9,10] The costs for SAEs were obtained from the Ontario Schedule of Benefits. Costs associated with SAEs were predominantly derived from specialist consultation after the event, whereas pneumonia and renal failure also included hospitalization costs of $9,993 and $11,253, respectively, based on estimates derived from the Ontario Case Costing Initiative.[11] Patients who experienced urgent HF visits incurred a $741 cost, based on the mean chronic HF emergency department visit cost in Canada between 2009 and 2013 among patients aged 65 years and older.[9]

Summary of Sponsor's Economic Evaluation Results

The sponsor conducted the base case for the reimbursement request population using a probabilistic sensitivity analysis with 5,000 simulations. The deterministic and probabilistic results were similar. The probabilistic findings are presented here.

Base-Case Results

In the sponsor's requested reimbursement population, vericiguat plus BT was associated with a QALY gain of 0.32 at an additional cost of $10,699, resulting in an ICER of $33,276 per QALY gained, compared with SOC (Table 3).

The sponsor's analysis predicted that vericiguat plus BT was associated with a longer duration of life than BT alone (i.e., incremental LYs = 0.40). Given the duration of the VICTORIA trial (i.e., 2.6 years), in contrast to the model's time horizon (i.e., 15 years), it is important to note that the majority of the QALY benefit (90%) realized by patients receiving vericiguat plus BT was derived from the period beyond which there is observed trial data (i.e., extrapolated period). Most of the QALYs gained by patients receiving vericiguat plus BT (65%) and BT alone (62%) were realized in the alive no HHF health state. The key cost driver among patients receiving vericiguat plus BT was the cost of drug acquisition, accounting for 38% of the total cost. The main cost driver in the BT alone arm, which accounted for 37% of its total expected cost, was the cost of hospitalization. The sponsor's submitted analysis is based on publicly available prices for all drug treatments. Vericiguat plus BT was cost-effective at a WTP threshold of $50,000 per QALY in 72% of the iterations. Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 3.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	Total LYs	Incremental LYs	ICER vs. BT alone ($/QALY)
BT alone	$34,583	Reference	4.74	Reference	6.10	Reference	Reference
Vericiguat plus BT	$45,282	$10,699	5.06	0.32	6.50	0.40	$33,276

BT = background therapy; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[1]

Sensitivity and Scenario Analyses Results

The sponsor assessed several model parameters and assumptions in probabilistic scenario analyses, including alternate parametric distributions for the risk equations T1, T2, and T5; the assumption of independence between prior HHF and the risk of HHF and CV death; treatment-waning assumptions; modelled time horizons and utilities. Notably, the sponsor's base-case ICER was robust across scenario analyses. When assuming linear treatment waning from 3 to 15 years, the ICER increased to $39,240 per QALY. When a 10-year time horizon was selected, the ICER increased to $38,085 per QALY. All other scenarios resulted in ICERs below $37,000 per QALY.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis:

- **Impact of vericiguat plus BT on long-term transition to the first HHF event is highly uncertain.** The sponsor used risk equations to describe the transition from alive no HHF to HHF event 1 (T1). The sponsor selected joint log-normal survival distributions based on BIC to extrapolate T1 beyond the observed period (i.e., from the end point of the observed VICTORIA data [2.6 years] to the end of the model horizon [15 years]). CADTH notes that using BIC when assisting in the selection of the most appropriate functional form for a projective (i.e., extrapolated) model has questionable value. Although BIC offers a numerical measure of the match between observed data and model estimates across the available trial follow-up, they give no indication of the relative merits of competing models when used for extrapolation.[12] In using a dependent model (i.e., a single parametric model with treatment coefficient), the sponsor assumed that the hazard rates for vericiguat plus BT and BT alone would remain proportional over time. As a new treatment option that specifically targets nitric oxide-cyclic guanosine monophosphate-soluble guanylate cyclase signalling, a pathway that is currently unaddressed by available treatments for HFrEF, vericiguat represents a different class of medication with a unique mechanism of action. CADTH notes that it is not ideal to apply a dependent model to clinical trial data for 2 treatment arms when the trial offers a comparison of treatments with different mechanisms of actions and, consequently, different patterns of event hazards over time. Moreover, dependent models tend to bias the estimated survival in both arms, as the parameter estimates are necessarily compromised away from the best fit for either arm. CADTH emphasizes that the

presumption should be against the joint modelling of treatment arms unless modelling the trial arms independently reveals that functional forms and parameter estimates are closely aligned.[12]

CADTH sought clinical expert advice to validate the HHF event 1 extrapolations derived from different parametric distributions for each treatment strategy. According to clinical expert judgment, all of the parametric distributions conducted by the sponsor (with the exception of Weibull) yielded 5-year, 10-year, and 15-year HHF event 1 extrapolations for BT alone that were not deemed clinically plausible (i.e., most distributions underestimated the proportion of patients who would have experienced a first HHF). Of note, the log-normal distribution selected by the sponsor for BT alone predicted the transition probability for the first HHF in excess of 12 and 15 percentage points at 10 and 15 years, respectively, relative to clinical expert feedback. Additionally, clinical expert feedback emphasized that, relative to the most plausible extrapolation for BT alone generated by the Weibull curve, all parametric distributions conducted by the sponsor for vericiguat plus BT yielded 5-year, 10-year, and 15- year HHF event 1 extrapolations that were deemed optimistic. The log-normal distribution selected by the sponsor for vericiguat plus BT would have generated an incremental benefit in survival without HHF favouring vericiguat plus BT in excess of 9, 15, and 16 percentage points at years 5, 10 and 15, respectively. Given that a 2.5 percentage-point difference in first HHF was observed in the VICTORIA trial between vericiguat plus BT and BT alone at year 2, CADTH notes that there is no evidence to support the plausibility of parametric distributions that predict a greater and sustained long-term benefit of transition to first HHF favouring vericiguat plus BT.

  - In light of these limitations, to address uncertainty in the long term transition to first HHF event, CADTH conducted a reanalysis that incorporated alternative parametric extrapolations (Weibull distribution for BT alone; gamma distribution for vericiguat plus BT). Aligned with clinical expert feedback, this reanalysis achieved more plausible curves for T1 in the absence of long-term evidence, while still conferring a benefit with vericiguat plus BT.

- **Omission of relevant variables from the risk-equation model used to estimate the transition to first HHF event.** The sponsor used baseline patient characteristics from the VICTORIA trial as independent variables to estimate the risk equation for T1. The objective of including covariates in the risk-equation model for T1 is to adjust for the independent effect that baseline patient characteristics (as factors explaining variability in the hazard function) may have on the probability to transition from alive no HHF to HHF event 1. In selecting the Cox proportional hazards regression analysis, the sponsor may have sought to address remaining participant heterogeneity in the probability to transition to the first HHF event across treatment strategies and narrow the effect attributable to the treatment. Clinical expert feedback indicated that the rate of transition to the first HHF event would differ between patients with different levels of chronic obstructive pulmonary disease, diabetes, smoking status, baseline treatments (i.e., MRAs, ARNis, devices), and cardiovascular histories. These variables were excluded by the sponsor, citing preference for a parsimonious model structure. Decisions made by the sponsor to include (and exclude) variables in the specification of the risk equation effectively impact the estimation of the rate of transition to the first HHF event among patients receiving vericiguat plus BT, relative to BT alone. CADTH emphasizes that the core

assumption of survival modelling is that the analysis is conducted on a common population, thus ensuring that all individuals remaining at risk at a specific point in time have the same probability of progression.[13] Given that the sponsor's specification excludes relevant clinical variables that are correlated with patient outcomes, there is a high degree of uncertainty regarding the probability of transition to the first HHF event modelled by the sponsor. Furthermore, CADTH notes that the Cox regression model relies on the fundamental assumption that the hazards are proportional, which means that the relative hazard should remain constant over time with different covariate levels.[14] Upon CADTH's request, the sponsor provided evidence suggesting that the proportional hazards assumption was violated for 2 of the covariates included in the specification of the risk equation during the observed trial period: log-transformed NT-proBNP, and log-transformed estimated glomerular filtration rate.

  - CADTH could not address the omission of relevant variables from the risk-equation model for T1 owing to the structure of the model. As such, the CADTH reanalysis omits the effect that adjustment of the risk equation by these baseline patient characteristics may have on the transition probability from alive no HHF to HHF event 1.

- **Treatment waning is not incorporated in the analysis.** The efficacy of vericiguat plus BT, relative to BT alone, was modelled according to the risk equations and the underlying assumption that treatment efficacy is maintained over time (i.e., no treatment waning) and that there is no progression of disease over the 15-year time horizon. Clinical expert feedback indicated that this assumption is highly optimistic. Indeed, the accrued literature indicates that the efficacy of therapies used to treat HFrEF could wane with time as patients develop progression and mortality that is unaffected by treatments.[15] Moreover, both patient and clinician input confirmed that the disease management journey for patients with HFrEF is characterized by treatment switching until all therapeutic options are exhausted. Their inputs emphasized that not all patients may respond to available treatments, and that disease may progress among patients who become refractory to current treatment options.
  - To accurately characterize natural disease progression and address concerns raised from stakeholder input, CADTH incorporated a treatment-waning assumption in the reanalysis. Treatment waning was achieved by gradually shifting the vericiguat plus BT survival curves toward the BT alone curves, thus diminishing the treatment effect. This was modelled as linear treatment waning that begins at 2.6 years (end point of the observed VICTORIA data) and ends by year 7.6.
- **Generalizability of the modelled population.** The patient population characteristics for the starting cohort of the model were derived from the VICTORIA trial. Hence, the mean patient age of 67 years was modelled for the reimbursement request population of adult patients with symptomatic chronic HFrEF who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy. Clinical expert feedback highlighted that the average age in this patient population is expected to be higher. Indeed, a recent population-based study aiming to describe the epidemiology of HFrEF with a HF decompensation event in Alberta estimated the median age of patients to be 77 years (interquartile range = 67 to 84 years).[16] In addition, the composition of BT among patients

receiving vericiguat plus BT and BT alone modelled by the sponsor did not align with current SOC. Based on the same real-world study using population-based data from Alberta, it was estimated that 78% of patients were either on 2 (51%) or 3 (27%) of the following BTs: ACEis, ARBs, or /ARNis; BBs; and MRAs.[16] In contrast, 91% and 60% of the modelled cohort (reflecting the VICTORIA trial population) were on dual and triple therapies, respectively. Moreover, the proportion of patients receiving diuretics (60%) modelled by the sponsor underestimated that observed in real-world clinical practice (88%).[16] As such, if vericiguat were to become available in clinical practice where the average patient is likely to be 10 years older and receive a different composition of BT, there remains uncertainty regarding the presence and the magnitude of the survival benefit in the real-world setting.

  - CADTH conducted a reanalysis that incorporated the mean starting age of 77 years, per the epidemiological evidence. In tandem with the increase in mean age, CADTH considered it pertinent to decrease the model's time horizon from 15 years to 10 years. In fact, with a mean starting age of 67 years, the sponsor's base case resulted in a cohort mean age of 82 years at the end of the 15-year modelled time horizon, whereas the CADTH reanalysis that assumed a mean starting age of 77 years resulted in a cohort mean age of 87 years at the end of the 10-year modelled time horizon. The 10-year time horizon was deemed appropriate, as the life expectancy of the general population in Canada is 82 years. With the mean starting age revised to 77 years, and after accounting for age-related mortality and mortality due to HF, 21% and 18% of patients receiving vericiguat plus BT and BT alone, respectively, remained alive after the 10-year time horizon.
  - CADTH considered it relevant to maintain the composition of BT modelled by the sponsor, as it reflected the SOC received by patients treated with vericiguat plus BT and BT alone in the VICTORIA trial and is thus associated with the clinical efficacy and safety outcomes derived from the trial.

- **Exclusion of relevant BTs.** The sponsor omitted SGLT2 inhibitors (i.e., empagliflozin and dapagliflozin) from the analysis, citing significant heterogeneity between patient populations in the VICTORIA trial, the DAPA-HF trial (dapagliflozin), and the EMPEROR-Reduced trial (empagliflozin). Although the issues with data limitations are plausible, the SGLT2 inhibitor therapeutic class of comparators is relevant to this population, as both empagliflozin and dapagliflozin are important components of BT prescribed in Canadian clinical practice. Clinical expert feedback emphasized that SGLT2 inhibitors constitute an appropriate treatment option for patients with chronic HF and an EF of less than 45% who are stabilized after a recent HF decompensation event. Clinical expert input noted that dapagliflozin and empagliflozin became available for the treatment of chronic HFrEF after the VICTORIA trial was conducted (between 2016 and 2019). Therefore, it is unclear whether the population included in the trial is reflective of the population that would be eligible for treatment with vericiguat in current Canadian clinical practice. The clinical expert consulted indicated that vericiguat may be added to foundational quadruple HF therapy (which includes ACEis, ARBs, or ARNis; BBs; MRAs; and SGLT2 inhibitors), as its mechanism of action is different from quadruple therapy

medications. However, the cumulative benefit of vericiguat added to quadruple BT remains unknown. Hence, the exclusion of SGLT2 inhibitors introduces substantial uncertainty to the sponsor's analysis.
    - CADTH was unable to address this limitation.

Additionally, the key assumptions were made by the sponsor and have been appraised by CADTH (refer to Table 4).

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH's reanalysis addressed several limitations of the economic model. The CADTH base case was derived by making changes in model parameter values and assumptions, in consultation with clinical experts. The following changes were made: alternative parametric extrapolations were applied for T1 (gamma distribution for vericiguat plus BT; Weibull distribution for BT alone); linear treatment waning was incorporated that begins at 2.6 years and ends at 7.6 years; the starting cohort was revised to a mean age to 77 years, per epidemiological evidence; and the time horizon was adjusted to 10 years. These changes are summarized in Table 5.

CADTH's base-case reanalysis estimated that vericiguat plus BT was $8,226 more expensive and yielded 0.13 more QALYS than BT alone for adults with chronic HF and an EF of less than 45% who are stabilized after a recent HF decompensation event. This resulted in an ICER for vericiguat plus BT of $62,778 per QALY gained, compared to BT alone (Table 6). The probability that vericiguat plus BT was cost-effective at a WTP threshold of $50,000 per QALY gained was 37%.

Table 4: Key Assumptions of the Submitted Economic Evaluation

Sponsor's key assumption	CADTH comment
Mortality and HHF risk were influenced by the number of previous hospitalizations that a patient has experienced.	Acceptable. The literature offers evidence for the relationship between the number of hospitalizations and mortality (2, 3, 4, and ≥ 5 hospitalizations). Clinical expert feedback noted that prior hospitalizations represent a marker for worsening health outcomes associated with HF.
AEs were applied during the first model cycle for all treatments.	Acceptable. Although it is expected that AEs can occur multiple times distributed over time, the VICTORIA trial had very low rates of AEs and no significant differences were observed between treatment arms.
Risk of future events (CV death and HHF) remained constant beyond the second event.	Acceptable as a simplifying assumption.
Parametric survival models assumed a linear dependency between survival and covariates.	Acceptable. The sponsor assumed that continuous covariates had a linear form. Evidence suggesting linearity was not provided.

AE = adverse event; CV = cardiovascular; HHF = hospitalization for heart failure.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Impact of vericiguat plus BT on long-term transition to first HHF event is highly uncertain	Parametric distribution of T1 • vericiguat plus BT: log-normal • BT alone: log-normal	Parametric distribution of T1 • vericiguat plus BT: gamma • BT alone: Weibull
2. Treatment waning is not incorporated in the analysis	No treatment waning	Linear treatment waning that begins at 2.6 years and ends by year 7.6
3. Generalizability of the modelled population	• Cohort mean starting age: 67 years • Time horizon: 15 years	• Cohort mean starting age: 77 years • Time horizon: 10 years
CADTH base case	Reanalyses 1 + 2 + 3	

BT = background therapy; HHF = hospitalization for heart failure; T1 = transition from the alive no HHF to the HHF event 1 health state.

The estimated ICER was higher than the sponsor's base-case value. Adjusting the parametric distribution of T1 for vericiguat plus BT and BT alone resulted in the largest change to the sponsor's base case. This produced more plausible transition probabilities from alive no HHF to HHF event 1 for vericiguat plus BT and BT alone in the absence of long-term evidence, while still conferring a benefit with vericiguat plus BT. The majority (80%) of the QALY benefit realized by patients receiving vericiguat plus BT compared to BT alone, was derived from the period beyond which there is observed trial data (i.e., extrapolated period). Most of the QALYs gained by patients across interventions were realized in the alive no HHF health state for vericiguat plus BT (63%) and for BT alone (62%). The key cost driver among patients receiving vericiguat plus BT and BT alone was the cost of hospitalization, accounting for 34% and 43% of the total cost, respectively. Among patients receiving vericiguat plus BT, drug acquisition was the second highest cost driver (31%).

The reanalysis is based on publicly available prices of the comparator treatments.

A detailed breakdown of the disaggregated results is available in Table 12.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case	BT alone	$34,583	4.74	Reference
	Vericiguat + BT	$45,282	5.06	$33,276
CADTH reanalysis 1	BT alone	$38,297	4.48	Reference
	Vericiguat + BT	$49,446	4.72	$46,678
CADTH reanalysis 2	BT alone	$34,164	4.64	Reference
	Vericiguat + BT	$44,626	4.89	$42,831
CADTH reanalysis 3	BT alone	$30,155	3.69	Reference

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
	Vericiguat + BT	$37,898	3.89	$38,274
CADTH base case (reanalyses 1 + 2 + 3)	BT alone	$33,638	3.66	Reference
	Vericiguat + BT	$41,864	3.80	$62,778

BT = background therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
Note: Reanalyses are based on publicly available prices of the comparator treatments.

Scenario Analysis Results

CADTH undertook price-reduction analyses based on the CADTH base case. These analyses demonstrated that a price reduction of 14% would be necessary to achieve cost-effectiveness at a WTP threshold of $50,000 per QALY gained in the reimbursement request population (Table 7).

Table 7: CADTH Price-Reduction Analyses

Analysis	ICERs for vericiguat + BT vs. BT alone ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	Dominant	$58,327
10%	Dominant	$52,233
14%	NA	$50,000
20%	Dominant	Dominant

BT = background therapy; ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

CADTH conducted a series of scenario analyses to determine the impact of alternative assumptions on the cost-effectiveness of vericiguat plus BT, which are outlined as follows:

- The treatment effect of vericiguat plus BT starts to decrease at year 2.6, waning completely by year 10.
- The treatment effect of vericiguat plus BT starts to decrease at year 7, waning completely by year 10.

The results of the scenario analyses are presented in Table 13.

Given the uncertainty of treatment waning, CADTH conducted 3 scenario analyses that considered different start and end years, parametrizing the linear decrease of vericiguat plus BT's treatment effect. When the effect of vericiguat plus BT is assumed to start decreasing at year 2.6 and wane completely by year 10 (i.e., longer rate of decline relative to the CADTH base case), the ICER for vericiguat plus BT decreases to $59,149. When the effect of vericiguat plus BT is assumed to start decreasing at year 7 and wane completely by year 10 (i.e., decline starts 4.4 years later relative to the CADTH base case), the ICER for vericiguat plus BT decreases to $54,229.

Issues for Consideration

- As noted in the CADTH Clinical Review, 26% of patients in the VICTORIA trial were screening failures, predominantly due to NT-proBNP levels were below the prespecified threshold. Clinical expert feedback indicated that NT-proBNP testing is not widely available in Canada, rendering this patient-

selection criterion difficult to implement in current clinical practice. Clinical expert feedback further noted that the enrolment of patients with elevated NT-proBNP levels likely generated an enriched trial population, in which patients appeared to be sicker and more likely to benefit from treatment with vericiguat plus BT than the expected real-world population.

- Among the submitted reimbursement request criteria, the sponsor indicates that vericiguat should be prescribed in combination with an ACEi, ARB, or ARNi, a BB, and, if tolerated, an MRA. Clinical expert feedback noted that clinicians would likely opt to prescribe SGLT2 inhibitors over vericiguat in combination with triple therapy unless contraindicated.[17] Of note, clinical expert input emphasized that vericiguat would likely be prescribed only after failure of standard quadruple therapy.

Overall Conclusions

Based on data from the VICTORIA trial, the CADTH Clinical Review concluded that vericiguat demonstrated a statistically significant and clinically meaningful benefit, compared to placebo, in reducing hazard rates of the first event of CV death or HHF (median follow-up, 11.1 months for vericiguat plus BT and 10.4 months for BT alone), the occurrence of first and recurrent HHF, and the composite of all-cause mortality and HHF (median follow-up, [redacted] for vericiguat plus BT and [redacted] months for BT alone) in adults with symptomatic chronic HFrEF. The median composite primary end point, total HHF events, and composite of all-cause mortality and HHF were not estimable in either treatment group because insufficient follow-up time had elapsed for these outcomes. As such, the long-term efficacy of vericiguat is highly uncertain. Moreover, the estimates of benefit for vericiguat may be overestimated, as there is a possibility that the trial was stopped early due to misclassification of CV death; however, the presence and extent of any overestimation is uncertain.

Additionally, CADTH identified several limitations of the sponsor's economic submission. These limitations included uncertainty regarding the impact of vericiguat plus BT on the long-term risk of first HHF event, the omission of relevant variables from the risk-equation model used to estimate the transition to first HHF event, the omission of treatment waning, a lack of generalizability of the modelled population to the Health Canada–indicated population, and the exclusion of relevant BTs used in Canadian clinical practice. As part of the base-case reanalysis, CADTH addressed the uncertainties associated with long-term treatment efficacy by applying alternative parametric extrapolations for the risk of first HHF (gamma distribution for vericiguat plus BT; Weibull distribution BT alone), incorporating linear treatment waning that begins at 2.6 years and ends at 7.6 years, revising the starting cohort mean age to 77 years, and reducing the time horizon to 10 years.

In reanalysis, CADTH estimated that vericiguat plus BT was $8,226 more costly and yielded 0.13 more QALYs than BT alone in the indicated population. This resulted in an ICER for vericiguat plus BT of $62,778 per QALY gained, compared to BT alone. The probability that vericiguat plus BT was cost-effective at a WTP threshold of $50,000 per QALY was 37%. A price reduction of 14% would be necessary for vericiguat plus BT to achieve cost-effectiveness, compared to BT alone, at a WTP threshold of $50,000 per QALY gained.

The estimated ICER was highly sensitive to adjustments in the assumed parametric distribution of the time to first HHF for vericiguat plus BT and BT alone. The values used in the CADTH reanalysis produced transition probabilities from alive no HHF to HHF event 1 for vericiguat plus BT and BT alone that were

considered more plausible, according to clinical expert feedback, while still conferring a benefit with vericiguat plus BT. The cost-effectiveness of vericiguat plus BT was somewhat sensitive to different treatment-waning assumptions.

In both the sponsor's base case and in CADTH's reanalysis, treatment with vericiguat plus BT was more costly and produced more QALYs than BT alone. The CADTH reanalysis estimated a smaller overall survival benefit with vericiguat plus BT than the sponsor's base case (0.40 incremental LYs in the sponsor's base case versus 0.16 incremental LYs in CADTH's reanalysis), which translated to fewer overall incremental QALYs in the CADTH reanalysis. Despite CADTH's reanalyses, there remains a substantial proportion (80%) of the QALY benefit realized by patients receiving vericiguat plus BT compared to BT alone, derived from the period beyond which there is observed trial data. Given this uncertainty, additional price reductions may be warranted.

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Appendix 1: Cost Comparison Table

Note this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on clinical expert feedback. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Background Therapies Indicated for the Treatment of Heart Failure

Treatment	Strength / concentration	Form	Price ($)[a]	Recommended dosage[b]	Daily cost ($)	Annual cost ($)
Soluble guanylate cyclase stimulator (sGC)						
Vericiguat	2.5 mg 5 mg 10 mg	Tablet	4.8300[c] 4.8300 4.8300	10 mg once daily	4.83	1,763
Angiotensin-converting enzyme inhibitor (ACEi)						
Captopril	6.25 mg 12.5 mg 25 mg 50 mg 100 mg	Tablet	0.1237[d] 0.2120 0.3000 0.5590 1.0395	50 mg 3 times daily	1.68	612
Cilazapril	1 mg 2.5 mg 5 mg	Tablet	0.3115 0.4295 0.4989	2.5 mg once daily	0.43	157
Enalapril	2.5 mg 5 mg 10 mg 20 mg	Tablet	0.1863 0.2203 0.2647 0.3195	10 mg twice daily	0.53	193
Fosinopril	10 mg 20 mg	Tablet	0.2178 0.2619	20 mg to 40 mg daily	0.26 to 0.52	96 to 191
Lisinopril	5 mg 10 mg 20 mg	Tablet	0.1347 0.1619 0.1945	20 mg to 35 mg daily	0.19 to 0.49	71 to 179
Perindopril	2 mg 4 mg 8 mg	Tablet	0.1632 0.2042 0.2831	4 mg daily	0.20	75
Quinapril	5 mg 10 mg 20 mg	Tablet	0.4642	20 mg twice daily	0.93	339

Treatment	Strength / concentration	Form	Price ($)[a]	Recommended dosage[b]	Daily cost ($)	Annual cost ($)
Angiotensin II receptor antagonist (ARB)						
Candesartan	4 mg 8 mg 16 mg 32 mg	Tablet	0.1700 0.2281 0.2281 0.2281	32 mg daily	0.23	83
Valsartan	80 mg 160 mg 320 mg	Tablet	0.2159 0.2159 0.2098	80 mg to 160 mg twice daily	0.43	158
Angiotensin receptor and neprilysin inhibitor (ARNi)						
Sacubitril/ valsartan (Entresto)	24 mg/26 mg 49 mg/51 mg 97 mg/103 mg	Tablet	3.7060	97 mg/103 mg twice daily	7.41	2,705
Beta-blocker (BB)						
Carvedilol	3.125 mg 6.25 mg 12.5 mg 25 mg	Tablet	0.2060	3.125 mg to 25 mg twice daily	0.41	150
Mineralocorticoid receptor antagonists (MRA)						
Eplerenone	25 mg 50 mg	Tablet	2.0595	25 mg to 50 mg daily	2.06	752
Spironolactone	25 mg 100 mg	Tablet	0.0810 0.1910	100 mg to 200 mg daily	0.19 to 0.38	30 to 139
Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitor)						
Empagliflozin (Jardiance)	10 mg 25 mg	Tablet	2.7671	10 mg once daily	2.77	1,010
Dapagliflozin (Forxiga)	5 mg 10 mg	Tablet	2.7300	10 mg once daily	2.73	996
Other treatments indicated for heart failure[e]						
Bumetanide	1 mg 5 mg	Tablet	0.7907[d] 3.0184[d]	1 mg to 10 mg daily	0.79 to 6.04	289 to 2,203
Digoxin	0.0625 mg 0.125 mg 0.25 mg	Tablet	0.2177 0.2060 0.2060	0.0625 mg to 0.25 mg daily	0.21 to 0.22	75 to 79
Furosemide	20 mg 40 mg 80 mg	Tablet	0.0218 0.0327 0.0703[f]	40 mg to 80 mg daily	0.03 to 0.07	12 to 26
Ivabradine	5 mg 7.5 mg	Tablet	0.8934 1.6339	5 mg to 7.5 mg twice daily	1.79 to 3.27	652 to 1,193

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; ARNi = angiotensin receptor and neprilysin inhibitor; BB = beta-blocker; BT = background therapy; HF = heart failure; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter-2.

[a]Prices are from the Ontario Drug Benefit Formulary (November 2022) unless otherwise indicated.[5]

[b]Recommended doses are from product monographs unless otherwise indicated.[18]

[c]Sponsor's submitted price[1]

[d]Saskatchewan Drug Benefit (November 2022).[6]

[e]Treatments recommended by e-Therapeutics.[18]

[f]Alberta Health Interactive Drug Benefit life (November 2022).[19]

Appendix 2: Submission Quality

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Table 9: Submission Quality

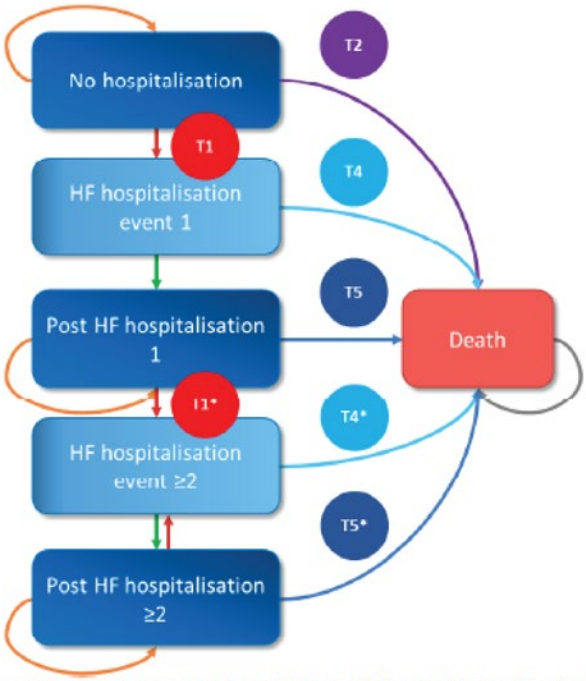
Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	The sponsor omitted SGLT2 inhibitors (i.e., empagliflozin and dapagliflozin) from the analysis citing significant heterogeneity between the patient populations in VICTORIA vs. DAPA-HF (dapagliflozin) and EMPEROR-Reduced (empagliflozin).
Model has been adequately programmed and has sufficient face validity	Yes	No comment
Model structure is adequate for decision problem	Yes	No comment
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	No comment
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	No	The risk equations used to describe the transitions from 'alive no HHF' to 'HHF event 1' (T1), from 'alive no HHF' to 'death' (T2), and from 'post-HHF' to 'death' (T5) were not transparently described. The sponsor did not provide any evidence to suggest that proportional hazards assumptions were tested.

SGLT2 = sodium-glucose cotransporter-2.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note this appendix has not been copy-edited.

Figure 1: Model Structure



*Multipliers are applied to account for the increased risks of HFH and CV mortality due to prior hospitalization events
Arrows of equal colour indicate the same risk equation is in use
The green arrow is always 1- T4. T4 is the Case Fatality (CF) rate of hospitalization
The orange arrow is always 1- the sum of all exit transition probabilities

Source: Sponsor's pharmacoeconomic submission.[1]

Detailed Results of the Sponsor's Base Case

Table 10: Composition of Background Therapy

Composition	Percentage	Reference
ACEi / ARB	73%	VICTORIA
Beta-Blockers	93%	VICTORIA
Diuretics	60%	Assumption
Ivabradine	5%	Assumption
ARNi	15%	VICTORIA
MRA	70%	VICTORIA

Composition	Percentage	Reference
Dual therapy	91%	VICTORIA
Triple therapy	60%	VICTORIA

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; ARNi = angiotensin receptor and neprilysin inhibitor; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist.

Note: Dual therapy was defined as 2 or more background therapies; triple therapy was defined as all 3 background therapies.

Source: Sponsor's pharmacoeconomic submission[1]

Table 11: Composition of Drugs Modelled Within Each Category

Drug category	Percentage
ACEi/ARB	
Enalapril + Enalapril Maleate	34%
Ramipril	36%
Perindopril + Perindopril Arginine + Perindopril Erbumine	18%
Lisinopril + Lisinopril Dihydrate	10%
Captopril	2%
Beta-Blockers	
Bisoprolol + Bisoprolol Fumarate	38%
Carvedilol	38%
Metoprolol Succinate + Metoprolol + Metoprolol Tartrate	23%
Atenolol	1%
Diuretics	
Furosemide + Furosemide Sodium	94%
Hydrochlorothiazide	4%
Bumetanide	3%
MRA	
Spironolactone	82%
Eplerenone	18%

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; BB = beta-blocker; MRA = mineralocorticoid receptor antagonist.

Note: The sponsor excluded ARBs within the ACEi/ARB category as these were not commonly used in the VICTORIA trial.

Source: Sponsor's pharmacoeconomic submission[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Table 12: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Vericiguat + BT	BT alone	Incremental
Discounted LYs			
Total	4.88	4.72	0.16
Alive no HHF	3.02	2.83	0.19
HHF event 1	0.05	0.05	0.00
Post HHF event 1	1.15	1.14	0.01
HHF event ≥ 2	0.03	0.03	0.00
Post HHF event ≥ 2	0.63	0.67	−0.03
Discounted QALYs			
Total	3.80	3.66	0.13
Alive no HHF	2.41	2.26	0.15
HHF event 1	0.03	0.03	0.00
Post HHF event 1	0.86	0.86	0.01
HHF event ≥ 2	0.02	0.02	0.00
Post HHF event ≥ 2	0.47	0.50	−0.02
Discounted costs ($)			
Total	$41,864	$33,638	$8,226
Drug acquisition	$12,954	$4,201	$8,753
Routine care and monitoring			
Alive no HHF	$2,626	$2,464	$162
HHF event 1	$0	$0	$0
Post HHF event 1	$1,008	$997	$11
HHF event ≥ 2	$0	$0	$0
Post HHF event ≥ 2	$553	$582	−$28
Hospitalization	$14,058	$14,472	−$414
Terminal care	$10,025	$10,181	−$156
Serious adverse event	$529	$608	−$80
Urgent HF visits	$112	$133	−$22
ICER ($/QALY)			$62,778

BT = background therapy; HF = heart failure; HHF = hospitalization for heart failure; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

Note: This table has not been copy-edited.

Detailed Results of the CADTH Base Case

Scenario Analyses

Table 13: Summary of Probabilistic Scenario Analyses Conducted on the CADTH Base Case

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
CADTH base case	BT alone	$33,638	3.66	Reference
	Vericiguat + BT	$41,864	3.80	$62,778
Scenario 1: Treatment waning begins at 2.6 years and ends by year 10	BT alone	$33,558	3.65	Reference
	Vericiguat + BT	$41,816	3.79	$59,149
Scenario 2: Treatment waning begins at 7 years and ends by year 10	BT alone	$33,528	3.64	Reference
	Vericiguat + BT	$41,860	3.79	$54,229

BT = background therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: This table has not been copy-edited.

Appendix 5: Submitted BIA and CADTH Appraisal

Note this appendix has not been copy-edited.

Table 14: Summary of Key Takeaways

Key takeaways of the BIA
• CADTH identified the following limitations in the sponsor's base case: the proportion of patients that would experience a HF decompensation event annually is underestimated, and the proportion of patients with chronic HF and EF less than 45% is uncertain. • CADTH performed a reanalysis, in line with clinician expert opinion, by increasing the proportion of patients expected to experience a HF decompensation event annually to 36.8% in accordance with the relevant literature. • Based on the CADTH reanalysis, the budget impact from the introduction of vericiguat is expected to be $2,979,718 in year 1, $6,046,031 in year 2, and $9,200,998 in year 3, with a 3-year total of $18,226,748. • CADTH conducted scenario analyses to assess the impact of different assumptions regarding the prevalence of HF with EF < 45%. This led to an increase in the estimated 3-year budget impact to $20,728,458 when assuming 58% prevalence and a decrease in the estimated 3-year budget impact to $16,082,424 when assuming 45% prevalence.

Summary of Sponsor's BIA

The sponsor submitted a budget impact analysis (BIA) to estimate the incremental 3-year budget impact of reimbursing vericiguat for the treatment of adult patients with symptomatic chronic HF and reduced EF who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy and receive BT. The analysis was performed from the perspective of the Canadian public drug plan. The sponsor estimated the budget impact by comparing 2 scenarios: a reference scenario that estimated the total costs associated with BT for the treatment of adult patients with symptomatic chronic HF and reduced EF who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy, with a new drug scenario, where vericiguat is funded as an adjunct to BT, as per its reimbursement requested criteria. The BIA assumed the following BT combinations: (1) ACEi/ARB + BB ± MRA; (2) ARNi + BB ± MRA; (3) SGLT2 inhibitor + ACEi/ARB + BB ± MRA; (4) SGLT2 inhibitor + ARNi + BB ± MRA; and (5) Ivabradine + ACEi/ARB + BB ± MRA.

The sponsor estimated the eligible population using an epidemiology-based approach, leveraging data from multiple sources in the scientific literature and assumptions based on clinical expert input. Key inputs to the BIA are documented in Table 15.

Key assumptions made by the sponsor include:

- The rate of HF in the noninsured health benefits (NIHB) population was assumed to be 28% higher than the reported rate for Ontario based on findings from a study that compared HF rates between the general population and a sample of Metis population in the province.[20]
- 30% of patients with HF and EF < 45% would experience a HF decompensation event annually based on clinical expert advice.
- 78% of patients would be on 2 or 3 of the following BTs: ACEi, ARB, ARNi, BB and MRA.

- [redacted] of eligible patients would receive vericiguat in year 1, [redacted] in year 2, and [redacted] in year 3 that it is reimbursed.
- No wastage given alignment between pack sizes and standard doses.

Table 15: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Target population	
2023 Canadian population (excluding Quebec, ≥ 40 years)	15,486,902
HF prevalence (≥ 40 years)	3.8%
HF patients with LVEF < 45%	51%
NYHA class II to IV	77%
Patients with a HF decompensation event	31%
Patients on BT (ACEi, ARB, ARNi, BB and MRA)	78%
Public drug coverage	84%
Number of patients eligible for drug under review	46,695 / 47,373 / 48,062
Market uptake (3 years)	
Uptake (reference scenario)	
BT alone	
ACEi/ARB + BB ± MRA	42.50% / 42.50% / 42.50%
ARNi + BB ± MRA	25.00% / 25.00% / 25.00%
SGLT2 inhibitor + ACEi/ARB + BB ± MRA	20.00% / 20.00% / 20.00%
SGLT2 inhibitor + ARNi + BB ± MRA	7.50% / 7.50% / 7.50%
Ivabradine + ACEi/ARB + BB ± MRA	5.00% / 5.00% / 5.00%
Uptake (new drug scenario)	
Vericiguat + BT	
Vericiguat + ACEi/ARB + BB ± MRA	[redacted]
Vericiguat + ARNi + BB ± MRA	[redacted]
Vericiguat + SGLT2 inhibitor + ACEi/ARB + BB ± MRA	[redacted]
Vericiguat + SGLT2 inhibitor + ARNi + BB ± MRA	[redacted]
Vericiguat + Ivabradine + ACEi/ARB + BB ± MRA	[redacted]
BT alone	
ACEi/ARB + BB ± MRA	[redacted]
ARNi + BB ± MRA	[redacted]
SGLT2 inhibitor + ACEi/ARB + BB ± MRA	[redacted]
SGLT2 inhibitor + ARNi + BB ± MRA	[redacted]
Ivabradine + ACEi/ARB + BB ± MRA	[redacted]
Cost of treatment (per patient)	
Annual cost of treatment	

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Vericiguat + BT	
Vericiguat + ACEi/ARB + BB ± MRA	$1,872
Vericiguat + ARNi + BB ± MRA	$4,510
Vericiguat + SGLT2 inhibitor + ACEi/ARB + BB ± MRA	$2,868
Vericiguat + SGLT2 inhibitor + ARNi + BB ± MRA	$5,507
Vericiguat + Ivabradine + ACEi/ARB + BB ± MRA	$3,065
BT alone	
ACEi/ARB + BB ± MRA	$109
ARNi + BB ± MRA	$2,747
SGLT2 inhibitor + ACEi/ARB + BB ± MRA	$1,105
SGLT2 inhibitor + ARNi + BB ± MRA	$3,744
Ivabradine + ACEi/ARB + BB ± MRA	$1,302

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; ARNi = angiotensin receptor and neprilysin inhibitor; BB = beta-blocker; BT = background therapy; EF = ejection fraction; HF = heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

Summary of the Sponsor's BIA Results

Results of the sponsor's base-case BIA suggest that the incremental expenditures associated with the reimbursement of vericiguat for the reimbursement request population of adult patients with symptomatic chronic HF and reduced EF who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy and receive BT would be [redacted] in year 1, [redacted] in year 2, and [redacted] in year 3, for a 3-year cumulative total of [redacted] under the drug plan perspective.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Proportion of patients that would experience a HF decompensation event annually is underestimated.** The sponsor estimated that 30.5% of patients with HFrEF would experience a HF decompensation event annually in Canada, represented as the average of a study conducted by Butler et al. utilizing the IBM MarketScan Commercial Database (26.8%) and a study conducted by Mentz et al. using data of Medicare beneficiaries (34.2%).[21,22] CADTH notes that the study by Butler et al. was subject to limitations of the patient population and of the data acquired from the claims databases given that (1) the identification of eligible patients via *International Classification of Diseases* (*ICD*) codes did not include a measurement of LVEF, so the actual EF values for the study population were unknown; and (2) the study population was limited to commercially insured patients aged 18 to 65 years and focused only on patients who were fully covered by private insurance.[21] Indeed, the mean age of patients with chronic HFrEF following a HF decompensation event was 56 years in the study, compared to a median age of 77 years which should be expected for this patient

population according to a recent population-based study conducted in Alberta.[16,23] CADTH favoured the use of the study by Mentz et al. to estimate the proportion of patients that would experience a HF decompensation event since the study population was aligned with the indicated population in terms of age (median: 78 years).[22] Finally, CADTH applied the cumulative risk of HF decompensation event within 12 months of the HFrEF index date while adjusting for the censoring event (36.8%), as reported in Mentz et al.

    - CADTH increased the proportion of patients that would experience a HF decompensation event annually.

- **Proportion of patients with chronic HF and EF less than 45% is uncertain.** The sponsor estimated that 51% of patients with HF would have EF less than 45% using a study from Ontario (available as an abstract), which reported that 39% of HF patients had EF < 40% and 12% had EF between 40% and 45%.[24] While patients with HF are typically categorized on the basis of LVEF, the prevalence of HFrEF (i.e., EF < 40%) varies in the literature and is reported to range from 33% to 46%.[25,26] Using the study from Petrella et al. reporting the prevalence of midrange EF (40% to 45%),[24] the literature would suggest that the prevalence of HF with EF < 45% could range between 45% and 58%. In fact, evidence from Ho et al., a study of new-onset HF cases in Framingham Heart participants between 1981 and 2008, revealed that the prevalence of HF with EF ≤ 45 to be 56%,[27] thus suggesting that the upper bound of the range is a likely estimate.
    - CADTH conducted scenario analyses to assess the impact of this assumption.

CADTH Reanalyses of the BIA

CADTH conducted reanalyses of the BIA by increasing the proportion of patients that would experience a HF decompensation event annually in accordance with the relevant literature.

The results of the CADTH step-wise reanalysis are presented in summary format in Table 17 and a more detailed breakdown is presented in Table 18. Based on the CADTH base case, the budget impact associated with vericiguat's reimbursement is expected to be $2,979,718 in year 1, $6,046,031 in year 2, and $9,200,998 in year 3, with a 3-year total of $18,226,748.

CADTH conducted additional sensitivity analyses to address remaining uncertainty, using the CADTH base case. Results are provided in Table 18.

1. Assuming 45% of patients with chronic HF have EF < 45%
2. Assuming 58% of patients with chronic HF have EF < 45%

Table 16: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Proportion of patients that would experience a HF decompensation event annually is underestimated	30.5%	36.8%
CADTH base case	Reanalysis 1	

BIA = budget impact analysis; HF = heart failure.

Table 17: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	Three-year total
Submitted base case	[redacted]
CADTH reanalysis 1	$18,226,748
CADTH base case	$18,226,748

BIA = budget impact analysis.

Table 18: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Submitted base case	Reference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	New drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CADTH base case	Reference	$72,189,944	$73,237,559	$74,301,750	$75,382,808	$295,112,061
	New drug	$72,189,944	$76,217,277	$80,347,782	$84,583,805	$313,338,808
	Budget impact	**$0**	**$2,979,718**	**$6,046,031**	**$9,200,998**	**$18,226,748**
CADTH scenario analysis 1: 14% price reduction	Reference	$72,189,944	$73,237,559	$74,301,750	$75,382,808	$295,112,061
	New drug	$72,189,944	$75,800,117	$79,501,337	$83,295,666	$310,787,064
	Budget impact	**$0**	**$2,562,558**	**$5,199,587**	**$7,912,858**	**$15,675,003**
CADTH scenario analysis 2: 45% of patients with EF < 45%	Reference	$63,697,009	$64,621,375	$65,560,368	$66,514,242	$260,392,995
	New drug	$63,697,009	$67,250,539	$70,895,102	$74,632,769	$276,475,419
	Budget impact	**$0**	**$2,629,163**	**$5,334,734**	**$8,118,527**	**$16,082,424**
CADTH scenario analysis 3: 58% of patients with EF < 45%	Reference	$82,098,368	$83,289,773	$84,500,030	$85,729,467	$335,617,638
	New drug	$82,098,368	$86,678,472	$91,375,909	$96,193,347	$356,346,096
	Budget impact	**$0**	**$3,388,699**	**$6,875,879**	**$10,463,880**	**$20,728,458**

BIA = budget impact analysis; EF = ejection fraction.

Stakeholder Input

List of Tables

Patient Input

HeartLife Foundation

About the HeartLife Foundation

An estimated 750,000 people are currently living with heart failure in Canada (Heart & Stroke Foundation, 2022). In their 2022 Report on the health of Canadians, the Heart & Stroke Foundation estimates that 100,000 Canadians are diagnosed with heart failure each year and this number is on the rise. Heart failure costs the Canadian healthcare system more than $2.8 Billion dollars per year – with the majority of those dollars being spent on acute care. Research has shown that effective patient engagement improves clinical outcomes, prevents hospitalizations, increases patient self-efficacy for managing their condition, and overall quality of life. Despite these findings, few organizations currently exist to help heart failure patients self-manage their condition, provide education and support for patients and families, and advocate for access to care and innovative treatments. The HeartLife Foundation was created in response to this need.

The HeartLife Foundation is a patient-driven charity whose mission is to transform the quality of life for people living with heart failure by engaging, educating, and empowering a global community to create lasting solutions and build healthier lives. HeartLife Foundation is Canada's first – and only – national patient-led Heart Failure organization. We are a Federal Charity aimed at raising public awareness of Heart Failure, engaging patients, families, and caregivers to provide education and support, facilitate access to the latest research, innovations, and treatments, and advocate better care for all.

Founded in June 2016 by Dr. Jillianne Code, a heart failure survivor and heart transplant recipient, and Mr. Marc Bains, a heart failure survivor and heart transplant recipient, HeartLife aims to drive healthcare innovation and transformation by adding patient voices to the heart failure conversation. In collaboration with Dr. Sean Virani, one of Canada's leading heart failure specialists and promoter of patient and family centred care, we endeavour to ensure that there is an open dialogue including patients as partners with healthcare providers, government, and industry across Canada. Our members are all patients along the heart failure continuum, their families and caregivers.

Vision: To create a better everyday life for people living with heart failure.

Mission: The HeartLife Foundation is a patient-driven charity whose mission is to transform the quality of life for people living with heart failure by engaging, educating, and empowering a global community to create lasting solutions and build healthier lives.

Website: www.heartlife.ca

Information Gathering

- Interviews with expert physicians in the Cardiovascular disease area.
- Interviews with patients living with cardiovascular disease.
- Review of study material and online literature.

Disease Experience

Heart failure (HF) is a leading cause of death and hospitalization in Canada. The Heart and Stroke Foundation estimates there are 750,000 people living with heart failure, 100,000 people are diagnosed with this incurable condition each year, and that 1 in 3 Canadians are directly or indirectly impacted by the disease (Heart and Stroke Foundation 2022).

Anique Ducharme, President of the Canadian Heart Failure Society says *"Heart failure is an epidemic. It's one of the fastest growing cardiovascular conditions in the world."*

HF is common, and on the rise in Canada. We often say all roads lead to heart failure because anything that damages the heart can lead to heart failure. As more people are surviving heart attacks and other acute heart diseases, more people are going on to develop HF. Although we don't yet have a cure for HF, medical therapies and lifestyle changes can help people living with HF to manage their condition well. Despite all we know about the disease, access to care, medical therapies, and support services varies widely from one region to the next.

Lives of patients with HF and their family carers dramatically change upon initial diagnoses. People with heart failure experience a wide range of physical, social and emotional challenges. Individual can be born with the disease, develop it throughout their adult lives, or be diagnosed in their later years. Symptoms of heart failure vary among patients. It is a condition that requires daily monitoring, adherence and vigilance on the part of the patient in order to control the delicate balance of symptoms. These symptoms include shortness of breath, extreme fatigue, low blood pressure, dizziness, edema and bloating. Many patients also have palpitations and arrhythmia as a result of the underlying etiology of the cause of their heart failure. Heart Failure has no cure and, if left untreated, will become progressively worse over time. Heart Failure is commonly associated with a variety of comorbidities, anxiety, depression, a decline in cognitive ability, and can have a negative impact on mental health.

In 2020, The HeartLife Foundation launched the Patient Journey Map and Patient Charter in Canada. The Charter was built upon the findings from the HeartLife Foundation between 2019 and 2020. HeartLife worked with patients and family carers from across the country in order to gain insight into the challenges facing Canadians directly affected by Heart Failure. HeartLife found that access to care, medical therapies, and support services varies widely from one region to the next. The overall goal of this Charter is to support establishment of high-quality care that is provided consistently across the country. The Journey Map captures and summarizes real stories, emotions, questions, and lifestyle challenges heart failure patients experience in their care continuum. By truly empathizing with and learning what heart failure patients experience today, we can highlight the current needs, pain points, and wishes on how to improve care. The Journey Map found that everyone's experience with heart failure is different. What is common is that the diagnosis and subsequent journey are the most difficult periods in people's lives. Heart failure patients must adapt to a new life journey with challenging moments, new opportunities, mixed emotions and feelings, and physical challenges.

The impact on quality of life were evident during our patient interviews. Excerpts of the interviews are below:

Patient Experience Aged 33: I was diagnosed with heart failure at the age of 18. In my perspective, I wasn't even an adult. I was in shock. I thought heart issues only effected the elderly. When I received my initial diagnosis, I was entering university, playing football, and enjoying a normal life. Thinking about it now, I had no reason to believe my heart was failing. My ejection fraction, which I came to understand was an important metric, ranged from 5%-20% throughout my journey. At first, I was depressed. I was sad that my life had stopped while my peers moved forward. After the initial impact was overcome, I decided I wanted to pursue a normal life. whatever a new normal was. It was integral for myself and my family to manage my HF and live a good quality of life. It was easier said than done. Although I am post-transplant, HF and the journey I went through continues to affect my day-to-day life. Don't get me wrong, the medications, surgeries and amazing teams propelled me to move forward and continue to live. That being said, I am still unable to work at my desired career, exercise regularly, and take part in activities I love. I have had to find a 'new normal' for life, one which I am grateful to have.

Patient Experience Aged 44: It is difficult to try and I tell all the details of my story. I could discuss about how for most of my adult life I have suffered, how at 28 heart failure literally squeezed the life out of my body, how I struggled to breathe with what felt like a vice around my chest. That despite a stroke, multiple ICD shocks, a left ventricular assist device, severe GI bleeding, countless transfusions, 13 months on the transplant list, a heart transplant, 8 days in a coma with multi organ failure, delirium, and having to learn to feed myself and walk again – that I refused to die. In the world of chronic illness, people often speak of finding your 'new normal'. Those who are in it now, will understand what I mean. But even if you have never been there I think you can probably imagine what it might be like to have something so profound happen to you that you need to readjust your horizon. Constantly needing to find a 'new normal'. 2 years after my second transplant, three years after my first transplant, 14 years after my diagnosis I still wonder at the logic of this statement. What does that even mean? What is normal, anyway?

****(Please note, these Interview were conducted for a previous submission. We believe it is relevant for this submission).**

Experiences With Currently Available Treatments

As long as patients have access to qualified care providers with an understanding of the latest developments in heart failure treatments, most often identified by the Canadian Cardiovascular Society and Canadian Heart Failure Society guidelines adopted across the country, then placing patients on optimal therapy is a matter of following the guidelines.

The Canadian Cardiovascular Society (CCS) is responsible for setting the standards for optimal heart failure care in Canada, known as "Guidelines". In 2021, the CCS updated its treatment guidelines for people living with HF with reduced ejection fraction (HF with reduced ejection fraction). These are the recommendations that health care providers and pharmacists follow to treat people with HF.

Heart Failure Guidelines recommend that people with HF with reduced ejection fraction be treated with 4 different types of medications early after diagnosis. This combination of medications is known as "guideline-

directed medical therapy", or GDMT. Additional medications may also be recommended, depending on health and risk factors.

The CCS defines 4 key therapeutic drug classes as standard therapy for most patients: an angiotensin receptor-neprilysin inhibitor (as first-line therapy or after angiotensin converting enzyme inhibitor/angiotensin receptor blocker titration); a β-blocker; a mineralocorticoid receptor antagonist; and a sodium glucose transport 2 inhibitor.

In 2021 the CCS recommended **Vericiguat** be considered for worsening HF symptoms and heart failure hospitalization in prior 6 months.

Patient Except: I currently manage my HF with a medication plan, a relatively healthy diet, and cardiac rehab. I have been doing the same thing for years. I have my ups and downs. Although I feel okay 60% of the time, 40% of the time my HF gets worse. I am on beta-blockers, Lasix, and Entresto. I know there is more out there to make me feel better or prevent me from continuing to get worse. I would rather be 'stable' 100% of the time and avoid the 40% when I am not well and end up in hospital.

Improved Outcomes

Everyone living with heart failure deserves a better expectation of care and quality of life. Patients adhering to treatment, attending therapy, and completing cardiac rehab do so to improve their quality of life. Whether a person is professional going back to work, a student trying to finish their degree, or a couple trying to build a family, people with heart failure look to improve their quantitative and qualitative outcomes. Unfortunately, Canada does not offer a universal healthcare system and access and equity of care varies across the Country.

In 2021 HeartLife launched the HF Patient and Caregiver Charter. Our heart failure patient and caregiver charter was created to support our advocacy towards the implementation of a National Standard of Care for Canadians living with heart failure and their caregivers. The aim of this Charter is to improve the overall Quality of Life for Canadians with Heart Failure (HF) throughout the care continuum. Everyone deserves the best standard of care and access to proven therapies regardless of their demographic. It is imperative to provide equitable access to high-quality care and services for all people living with HF, including access to diagnostics, medical therapy, mental health support, cardiac rehabilitation, and advanced care.

Experience With Drug Under Review

Unfortunately, none of the individuals who took part in the discussion had experience with the drug under review.

It is estimated that one in six people with HF with reduced ejection fraction develop worsening chronic HF (WCHF) within 18 months of diagnosis. Patients with worsening heart failure show progressive signs and symptoms of HF requiring more therapy or hospitalization. Despite the availability of current HF therapies, the risk of worsening HF, mortality, and re-hospitalization remains high.

The VICTORIA trial examined whether Vericiguat reduces the primary composite outcome of cardiovascular (CV) death or first HF hospitalization for patients with an NYHA II-IV classification or with recent worsening

HF requiring admission or IV diuretic. Results indicate those at high-risk who were give Vericiguat stabilized and had improved outcomes. Based on trial results the CCS recommended that Vericiguat, be considered in addition to optimal heart failure therapies for HF with reduced ejection fraction patients with worsening symptoms and hospitalization for HF in the past 6 months, to reduce the risk of subsequent heart failure hospitalization.

There is a gap in current therapy that this drug will help alleviate. Based on trial information and recommendations from CCS, the lives of patients may be improved with Vericiguat, especially those with worsening HF. We recommend that Vericiguat is approved to reduce the risk of cardiovascular death and heart failure (HF) hospitalization, in adults with symptomatic chronic HF and ejection fraction less than 45% who are stabilized after a recent worsening HF event.

Companion Diagnostic Test

Not applicable.

References:

https://ccs.ca/app/uploads/2021/04/2021-HF-Gui-PG-FINAL-WEB.pdf

https://heartfailure.ca/sites/default/files/virani_ccs_chfs_heart_failure_guidelines_workshop.pdf

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9197896/ https://pubmed.ncbi.nlm.nih.gov/30819362/

Conflict of Interest Declaration — HeartLife Foundation

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

No.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures for the HeartLife Foundation

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BI	–	–	–	X
AZ	–	–	–	X
Novartis	–	–	X	–
BMS	–	–	X	–
Bayer	–	–	X	–
Servier	–	X	–	–

Heart Function Clinic Vancouver General Hospital, St Paul's Hospital

Treatment Gaps

- Not all patients respond to available treatments
- Patients become refractory to current treatment options

Clinician Input

Single Clinician, Part of Division of Cardiology, University of Alberta

I am a cardiologist and clinician scientist with interest in heart failure (HF).

I was the Study Chairman of the VICTORIA trial which forms the basis for the request for approval. We have studied and published extensively on the efficacy and safety of verciguat (pertinent publication citations and hyperlinks are as follows):

1. Senni M, Alemayehu WG, Sim D, Edelmann F, Butler J, Ezekowitz J, Hernandez AF, Lam CSP, O'Connor CM, Pieske B, Ponikowski P, Roessig L, Voors AA, Westerhout CM, McMullan C, Armstrong PW; VICTORIA Study Group. Efficacy and safety of vericiguat in patients with heart failure with reduced ejection fraction treated with sacubitril/valsartan: insights from the VICTORIA trial. Eur J Heart Fail. 2022 Sep;24(9):1614-1622. doi: 10.1002/ejhf.2608. Epub 2022 Jul 20. PMID: 35791083.
2. Lam CSP, Giczewska A, Sliwa K, Edelmann F, Refsgaard J, Bocchi E, Ezekowitz JA, Hernandez AF, O'Connor CM, Roessig L, Patel MJ, Pieske B, Anstrom KJ, Armstrong PW; VICTORIA Study Group. Clinical Outcomes and Response to Vericiguat According to Index Heart Failure Event: Insights From the VICTORIA Trial. JAMA Cardiol. 2021 Jun 1;6(6):706- 712. doi: 10.1001/jamacardio.2020.6455. Erratum in: JAMA Cardiol. 2021 Jan 13;: Erratum in: JAMA Cardiol. 2021 Jun 1;6(6):728. Erratum in: JAMA Cardiol. 2021 Oct 6;:null. PMID: 33185650; PMCID: PMC7666431.
3. Ezekowitz JA, O'Connor CM, Troughton RW, Alemayehu WG, Westerhout CM, Voors AA, Butler J, Lam CSP, Ponikowski P, Emdin M, Patel MJ, Pieske B, Roessig L, Hernandez AF, Armstrong PW. N-Terminal Pro-B-Type Natriuretic Peptide and Clinical Outcomes: Vericiguat Heart Failure With Reduced Ejection

Fraction Study. JACC Heart Fail. 2020 Nov;8(11):931- 939. doi: 10.1016/j.jchf.2020.08.008. Epub 2020 Oct 7. PMID: 33039447.

4. Butler J, Anstrom KJ, Armstrong PW. Comparing the Benefit of Novel Therapies Across Clinical Trials: Insights From the VICTORIA Trial. Circulation. 2020 Aug 25;142(8):717-719. doi: 10.1161/CIRCULATIONAHA.120.047086. Epub 2020 Mar28. PMID: 32223438.

Current Treatments and Treatment Goals

HF with reduced ejection fraction is a major and growing clinical problem in Canada. Current therapy with beta blockers, ACE inhibitors, ARNI therapy, MRA antagonists and SGLT2 inhibitors are effective therapy but not all patients can tolerate these medicines and even amongst those that do recurrent symptoms, rehospitalization and impaired quality and quantity of life ensue in as many as 1 of 5 patients over the ensuring 2 years. The same can be said of device therapy with either ICD or CRT interventions.

Key goals of new therapy include addressing this continuing unmet need by lessening the change of recurrent symptoms and need for hospitalization or visits to the emergency room.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

Failure to tolerate current best therapy or recurrent morbidity and mortality despite its use.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

sGC activation is a novel mechanism of action not addressed by current HF with reduced ejection fraction therapy and complementary to those in use.

Because the drug is safe, easy to use as a once daily medicine and does not cause hyperkalemia or impair renal function, the substantial fraction of patients [e.g., diabetics and renal impaired patients] who cannot tolerate ACE or ARNI therapy would be good candidates for this alternative therapy.

As noted above, those patients who have recurrent symptoms despite optimizing best current therapy.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The therapy would be prescribed by physicians with expertise in HF. No other than current testing is required. In fact, the need for lab monitoring of serum potassium and renal function since this drug does not affect these parameters.

The principal caveat regarding its use is hypotension so SBP >= 100 mmHG should be present and dosing started with 2.5 mg and stepped up to 10mg as tolerated.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Conventional assessment of HF is required. Less HF worsening and possible improved survival are expected.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Severe hypotension and syncope. These are about 1.4% absolute increase over placebo.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Cardiologist or internist should initiate therapy either in hospital, ER or OP clinic.

Additional Information

This novel therapy addresses a genuine unmet need in selected Canadian pts with HF with reduced ejection fraction. It is safe, well tolerated and a once daily medicine that is easy to use. It is now available in over 60 countries and was approved for use by the FDA & EMA over 1 year ago.

Conflict of Interest Declarations — Single Clinician, Part of Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission?

None.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

As VICTORIA Study Chair, I had a team of colleagues and operational personnel helping to complete the RCT.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Declaration for Clinician 1

Name: Paul W Armstrong, OC MD

Position: Distinguished University Professor Dept. of Medicine (Cardiology), Founding Director, Canadian VIGOUR Centre University of Alberta, Edmonton, Alberta

Date: 30/10/2022

Table 2: COI Declaration for Single Clinician, Part of Division of Cardiology, U of A

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Merck (research grant or contract from this company partially supports my **research projects**)	–	–	–	X
Boehringer Ingelheim (research grant or contract from this company partially supports my **research projects**)	–	–	–	X
Bayer (research grant or contract from this company partially supports my **research projects**)	–	–	–	X
Merck (consulting or other services for this company generates **personal income**)	–	–	–	X
Boehringer Ingelheim (consulting or other services for this company generates **personal income**)	–	X	–	–
Bayer (consulting or other services for this company generates **personal income**)	–	–	–	X
Novo Nordisk (consulting or other services for this company generates **personal income**)	–	X	–	–

Note: Merck, Boehringer Ingelheim, Bayer, CSL Limited, Eli Lilli: research grant or contract from these companies generates revenue for the University of Alberta
Financial Disclosures: https://thecvc.ca/about-us/relationships-with-industry/

Oakville Cardiologists

About Oakville Cardiologists

Oakville Cardiologists represents a large cardiology group practicing in Oakville, Ontario. We participate in the management of heart failure in our region which encompasses a population of approximately 650,000 people. We care for patients living with heart failure in our clinic and in the Heart Function Clinic at Halton Healthcare. Our group of cardiologists meet regularly to share best practices and we collaborate on research and educational projects to improve the care of patients with cardiovascular disease in our region.

Information Gathering

Review of relevant literature and publications in addition to extensive background knowledge in this field.

Current Treatments and Treatment Goals

Heart Failure (HF) is one of the major chronic diseases in Canada today. It is estimated that up to 3.5% of the Canadian adult population aged 40 years and older has heart failure and the prevalence rises with age such that approximately 10% of the elderly are affected. Patients diagnosed with HF have a 30% risk of

mortality at 3 years, and those hospitalized for HF face a substantially higher risk. It is the leading cause for hospitalized Canadians in individuals older than 65 years of age.

In the current era, patients with heart failure with a reduced ejection fraction (HF with reduced ejection fraction) should be treated with 4 standard therapies. These medications include: (1) an angiotensin receptor-neprilysin inhibitor (ARNI), either as first-line therapy or switching from an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB); (2) a beta-blocker; (3) a mineralocorticoid receptor antagonist (MRA); and (4) an SGLT2 inhibitor. These four therapies are considered to be the core of guideline directed medical therapy (GDMT) for HF with reduced ejection fraction and are routinely used in clinical practice. They were endorsed in the 2021 Canadian Cardiovascular Society heart failure guidelines. These medications reduce morbidity and mortality and improve quality of life.

For patients with HF with reduced ejection fraction who are in sinus rhythm (heart rate > 70 bpm), and remain symptomatic despite treatment with GDM, ivabradine is also prescribed for the prevention of cardiovascular (CV) death and HF hospitalization. This was included in the second tier of therapy for HF with reduced ejection fraction in the 2021 Canadian Cardiovascular Society heart failure guidelines along with vericiguat.

Two non-pharmacologic interventions are often considered in patients with HF with reduced ejection fraction. The first includes ICD therapy for primary prevention to improve survival in symptomatic patients with an ejection fraction (EF) < 35% and in patients with a previous MI with EF < 30% irrespective of symptom status. The second therapy includes cardiac resynchronization for symptomatic patients on optimal GDMT with an EF < 35% and QRS duration > 130 ms with left bundle branch block (LBBB) or QRS duration > 150 ms with non-LBBB.

Despite the advancements in pharmacological and non-pharmacological therapies the morbidity and mortality remain high for patients with a diagnosis of HF with reduced ejection fraction. Additional ideal therapies should serve to reduce the risk of CV death and heart failure hospitalization.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

Heart failure is a progressive condition. Substantial evidence suggests that worsening HF, characterized by development of progressively escalating symptoms and signs of HF requiring intravenous diuretic treatment in the outpatient, emergency department, or hospitalized setting, is associated with markedly worse prognosis. In Canada, the total number of unique hospitalizations in 2016 was 50,784, with an age- sex standardized rate of 169 / 100,000 population. Approximately 50% of these patients hospitalized for HF are readmitted within 6 months of discharge, and almost 30% die within a year.

Despite recommendations from national and international guidelines, there a treatment gap exists with GDMT since many patients cannot be titrated to the optimal doses of the medications. Limitations apart from patient values and preferences include hypotension, hyperkalemia, bradycardia and renal dysfunction. It is for this reason that we require proven therapies that have minimal impact on these parameters.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

The development and progression of heart failure involves dysregulation in multiple signaling pathways, including the nitric oxide (NO), soluble guanylate cyclase (sGC), and cyclic GMP (cGMP) pathway.

Reduction in cGMP levels contribute to the progression of HF. Vericiguat directly enhances cyclic guanylate monophosphate (GMP) production and also enhances endogenous sGC sensitivity to nitric oxide. This results in a cascade of adaptive effects on the heart, blood vessels, and kidneys, providing the physiological rationale for their use in patients with HF.

Vericiguat represents an additional approach to the therapy of HF with reduced ejection fraction which is not targeted by the current GDMT therapies. In the Vericiguat Global Study in Subjects with Heart Failure With Reduced Ejection Fraction (VICTORIA) trial the efficacy and safety of vericiguat compared with standard of care was evaluated in patients with advanced functional symptoms, an LVEF < 45% and a worsening HF event characterized by HHF or elevated natriuretic peptide levels. The primary combined end point of CV death or first HHF was significantly lower (HR, 0.90 [95% CI 0.82-0.98]; P. 0.019) in the vericiguat group.

As a result of this positive findings of this study this medication was endorsed in the 2021 Canadian Cardiovascular Society heart failure guidelines for patients with worsening symptoms and HHF in the past 6 months, to reduce the risk of subsequent HF hospitalization.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As outlined in the 2021 Canadian Cardiovascular Society heart failure guidelines, vericiguat would be prescribed for patients with HF with reduced ejection fraction on optimal therapy who have developed worsening symptoms and HHF in the past 6 months. This therapy was shown to reduce CV death or first HF hospitalization in the Victoria study in this high-risk patient population on GDMT.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Physician assessment of clinical stability and patient reported symptoms (NYHA) continue to be the cornerstone of evaluating response to therapy in patients with HF with reduced ejection fraction in the outpatient setting. The GUIDE-IT study has previously demonstrated that biochemical assessments of stability (ie naturetic peptides) do not add an incremental benefit to physician evaluation and patient-reported symptoms. An assessment of response to therapy would be anticipated several weeks after each dose titration of vericiguat up to the maximal tolerated dose and then periodically thereafter (there are regional differences however this would anticipate being bi-annually for most patients in Canada).

What factors should be considered when deciding to discontinue treatment with the drug under review?

One major advantage of this medication is the positive safety / tolerability profile. It does not induce a clinically significant reduction in the blood pressure nor alter potassium levels, renal function or heart

rate. As such it will be a welcome addition to GDMT for patients with worsening HF. The major reason for discontinuation will be a decline in the GFR < 15 ml/min which was used as the parameter in the VICTORIA study.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

There are no specific restrictions with respect to the settings in which this medication could be initiated (out-patient or in-patient) in urban, suburban and rural communities. Physicians experienced in the management of HF (cardiologists and internists) would be the most likely individuals to prescribe this medication.

Additional Information

Vericiguat is a well-tolerated and safe medication for the treatment of a high-risk HF patient population. We look forward to being able to offer this therapy to our patients as my colleagues elsewhere in the world do at this time.

Conflict of Interest Declarations — Oakville Cardiologists

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission?

No.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission?

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Declaration for Clinician 1

Name: Dr. Michael Heffernan

Position: Cardiologist

Date: 15-10-2022

Table 3: COI Declaration for Oakville Cardiologists — Clinician 1

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	–	–	X	–

Declaration for Clinician 2
Name: Dr. Talha Syed

Position: Cardiologist

Date: 15-10-2022

Table 4: COI Declaration for Oakville Cardiologists — Clinician 2

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	X	–	–	–

Declaration for Clinician 3
Name: Dr. Jan Orfi

Position: Cardiologist

Date: 15-10-2022

Table 5: COI Declaration for Oakville Cardiologists — Clinician 3

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	X	–	–	–

Declaration for Clinician 4
Name: Dr. Michelle Paikin

Position: Cardiologist

Date: 15-10-2022

Table 6: COI Declaration for Oakville Cardiologists — Clinician 4

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	X	–	–	–

Declaration for Clinician 5
Name: Dr. Qin Li

Position: Cardiologist

Date: 15-10-2022

Table 7: COI Declaration for Oakville Cardiologists — Clinician 5

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	X	–	–	–

Declaration for Clinician 6
Name: Dr. Kostas Ioannou

Position: Cardiologist

Date: 15-10-2022

Table 8: COI Declaration for Oakville Cardiologists — Clinician 6

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	X	–	–	–

Declaration for Clinician 7
Name: Dr. Sean Jedrzkiewicz

Position: Cardiologist

Date: 15-10-2022

Table 9: COI Declaration for Oakville Cardiologists — Clinician 7

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	X	–	–	–

Declaration for Clinician 8
Name: Dr. David McConachie

Position: Cardiologist

Date: 15-10-2022

Table 10: COI Declaration for Oakville Cardiologists — Clinician 8

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	X	–	–	–

Declaration for Clinician 9
Name: Dr. Vera Chiamvimonvat

Position: Cardiologist

Date: 15-10-2022

Table 11: COI Declaration for Oakville Cardiologists — Clinician 9

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	X	—	—	—

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.