

# VICTORIA: Vericiguat versus Placebo in Patients with Heart Failure & Reduced EF<sup>1</sup>

Vericiguat global study in subjects with heart failure with reduced ejection fraction

## SUMMARY

- In **VICTORIA**, **recently decompensated** HF-rEF patients (66.9% had a HF hospitalization within 3 months, median NTproBNP 2816pg/mL, 85.7% LVEF <40%, NYHA class II 59%, NYHA class III 39.7%) who received vericiguat 10mg daily (versus placebo) x 10.8 months had:
  - A lower risk of CV death or first HF hospitalization (HR 0.9, 95% CI 0.82-0.98, p=0.02, **ARR 3%**, **NNT 34**; note: if using per 100 patient-years, the NNT was 24)
    - Primary composite endpoint driven by HF hospitalizations (HR 0.9, 95% CI 0.81-1, p=0.048, **ARR 2.2%**, **NNT 46**) as CV death was not statistically significant on its own, & the Kaplan-Meier curve for CV death did not consistently separate
  - A higher risk of anemia (7.6% vs 5.7%, **ARI 1.9%**, **NNH 53**; 1.6% vs 0.9% of the anemia cases were considered serious adverse events)
    - The risk of symptomatic hypotension & syncope was higher with vericiguat, but the difference was not statistically significant
- Only 60% of the participants were on HF triple therapy** (73.4% ACEi / ARB, 14.5% ARNI + 93.1% beta-blocker + 70.3% MRA), and ~90% were on 2 of the 3 HF medication classes
- At the time of print, vericiguat has not been approved by Health Canada or the FDA; cost & coverage is also unknown at this time
- Based on the available data to date... vericiguat will not replace first line agents (i.e. HF triple therapy) but may be considered as an add-on agent for patients with recently decompensated HF-rEF to reduce the risk of HF hospitalizations
- A direct comparison of vericiguat to other new HF therapies (e.g. **ENTRESTO**, dapagliflozin) is not available. Vericiguat has a novel mechanism of action and was studied in high-risk individuals. Vericiguat does not appear to impact electrolytes, renal function, symptomatic hypotension or syncope. However, post-marketing surveillance on the risk of anemia will be important.
- Patients, caregivers & healthcare providers will need to consider risk of HF hospitalizations, risk of adverse events (symptomatic hypotension, syncope, anemia), drug interactions (e.g. phosphodiesterase type 5 inhibitors for erectile dysfunction, long-acting nitroglycerin products), cost, coverage, & pill burden.

## BACKGROUND

- Vericiguat** is a novel oral soluble guanylate cyclase (sGC) *stimulator*
  - Soluble guanylate cyclase (sGC) is an enzyme that is activated by nitric oxide (NO). The activation initiates a signaling cascade which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP levels increase & protein kinase G (PKG) is activated, resulting in a decrease of intracellular free Ca<sup>++</sup> → vascular smooth muscle cell relaxation.
  - However, individuals with HF have reduced NO levels. Vericiguat, as a sGC stimulator, increases the enzymatic activity of sGC to generate cGMP independently of NO and enhances sGC sensitivity to endogenous NO
- Vericiguat is the 2<sup>nd</sup> drug in this class and follows riociguat **ADEMPAS**, which has been approved for treating pulmonary arterial hypertension
- SOCRATES-REDUCED** was a phase II dose-finding trial of vericiguat in HF-rEF. The primary endpoint, change in NTproBNP over 12 weeks, was not statistically significant compared to placebo. A secondary exploratory analysis suggested a dose-response relationship in which higher doses of vericiguat were associated with greater reductions in NTproBNP levels.<sup>2</sup>

## TRIAL BACKGROUND<sup>1,3,4</sup>

**DESIGN:** randomized, double-blind, placebo-controlled multi-national (42 countries, 616 sites) trial lead by the Canadian VIGOUR Centre. ITT analysis for efficacy endpoints; safety analyses included all patients who received a trial drug. Screening period (0-30 days) to assess adherence, no run-in phase. Enrollment September 2016 to December 2018. Funding: Merck & Bayer.

**INTERVENTION:** vericiguat 10mg po once daily versus placebo, in addition to guideline-based medical therapy

- **Initial dose:** 2.5mg po daily x 2 weeks
- **Titration:** increased to 5mg po daily x 2 weeks and then to target (10mg po daily); titration based on BP and clinical HF symptoms:
  - SBP ≥100mmHg: increase dose, or maintain dose if on 10mg po daily
  - SBP 90-99mmHg: maintain dose
  - SBP <90mmHg and asymptomatic: 5 or 10mg dose → decrease dose, 2.5mg dose → interrupt dose
  - SBP <90mmHg and symptomatic: interrupt dose

**INCLUSION:** NYHA class II-IV HF-rEF (LVEF <45% within the last 12 months), ≥18 years of age, elevated natriuretic peptide level within 30 days before randomization (sinus rhythm: BNP ≥300pg/mL or NTproBNP ≥1000pg/mL; atrial fibrillation: BNP ≥500pg/mL or NTproBNP ≥1600pg/mL), and **evidence of worsening heart failure** (HF hospitalization within 6 months of randomization, or IV diuretic therapy without hospitalization in the past 3 months)

**EXCLUSION:** **SBP <100mmHg or symptomatic hypotension**; concurrent or anticipated use of **long-acting nitrates**, soluble guanylate cyclase stimulators (e.g. riociguat), or **phosphodiesterase type 5 inhibitors** (e.g. **VIAGRA**); awaiting heart transplant, IV inotropes or had / anticipated implantable LVAD; primary valvular heart disease requiring intervention or 3 months within intervention; hypertrophic obstructive cardiomyopathy, acute myocarditis, amyloidosis, sarcoidosis, Takotsubo cardiomyopathy, post-heart transplant cardiomyopathy, tachycardia-induced cardiomyopathy and/or uncontrolled tachyarrhythmia; ACS within 6 months; symptomatic carotid stenosis, TIA or stroke within 60 days; complex congenital heart disease; active endocarditis or constrictive pericarditis; **eGFR (MDRD) <15mL/min** (eGFR 15-30mL/min capped at 30% of population) or chronic dialysis; severe hepatic insufficiency; continuous home oxygen for severe pulmonary disease; interstitial lung disease.

**POPULATION** at baseline: ..... N=5050, 76.1% males

- **Age:** mean age 67.3 years (±12.2 years), **≥75 years** (12.2%, n=621)
- **Race / ethnicity:** 64.1% white, 22.4% Asian, 8.5% other, 4.9% black
- **Geographical region:** 33.5% Eastern Europe, 23.4% Asia-Pacific, 17.6% Western Europe, 14.3% Latin America, **11.1% North America**
- **Index event:** **66.9% HF hospitalization within 3 months**, 17.2% HF hospitalization in within 3-6 months, 15.9% IV diuretic therapy within 3 months

- **HF:** 85.7% LVEF <40%, NYHA class II 59%, NYHA class III 39.7%, NYHA class IV 1.3%, mean duration of HF 4.8 years (±5.4 years); drug therapy: 59.7% on HF triple therapy, ~90% on two HF medications, 73.4% ACEi / ARB, 14.5% ARNI, 93.1% beta-blocker, 70.3% MRA; 27.8% ICD, 14.7% CRT; median NTproBNP 2816pg/mL (IQR 1556-5314); mean EF 28.9% (±5.9)
- **Renal function:** ≤30mL/min 10.2%, 31-60mL/min 42.7%, >60mL/min 47.1%
- **Vitals:** mean BP 121.4 / 72.8mmHg (±15.7/11mmHg), mean HR 73bpm (±13bpm)
- **Comorbidities:** AF 44.9%, DM 46.9%, anemia 21.1% (mean Hgb 13.4g/dL ±1.9)

**RESULTS**<sup>1,4</sup>

Follow-up: Median 10.8 months

**TABLE 1: EFFICACY**

CLINICAL ENDPOINTS	VERICIGUAT 10MG N=2526	PLACEBO N=2524	HR (95% CI)	P VALUE	ARR/ARI	NNT / 0.9 YEARS	COMMENTS	
<b>PRIMARY ENDPOINTS</b>								
CV death or 1 <sup>st</sup> HF hospitalization	35.5% (n=897)	38.5% (n=972)	0.9 (0.82-0.98)	0.02	3%	34	- Mean dose: 9.2mg daily - At ~12 months 89.2% were on the target dose - 93.8% on vericiguat had >80% adherence - Subgroup analyses: consistent across groups except for age ≥75 years & NTproBNP (NTproBNP >5310pg/mL favoured placebo) - Kaplan-Meier curves for HF hospitalization separated at 3 months	
<b>SECONDARY ENDPOINTS</b>								
CV death	16.4% (n=414)	17.5% (n=441)	0.93 (0.81-1.06)	NS	-	-		
CV death not preceded by HF hospitalization	8.2% (n=206)	8.9% (n=225)	-	-	-	-		
HF hospitalization	27.4% (n=691)	29.6% (n=747)	0.9 (0.81-1)	0.048	2.2%	46		
Total HF hospitalizations	1223	1336	0.91 (0.84-0.99)	0.02				
All-cause mortality or 1st HF hospitalization	37.9% (n=957)	40.9% (n=1032)	0.9 (0.83-0.98)	0.02	3%	34		
All-cause mortality	20.3% (n=512)	21.2% (n=534)	0.95 (0.84-1.07)	NS	-	-		
All-cause mortality not preceded by HF hospitalization	10.5% (n=266)	11.3% (n=285)	-	-	-	-		

**TABLE 2: SAFETY**

CLINICAL ENDPOINTS	VERICIGUAT 10MG N=2519	PLACEBO N=2515	ARR / ARI	NNH / 0.9 YEARS	COMMENTS
Serious adverse event	32.8% (n=826)	34.8% (n=876)	-	-	- Change in Hgb (0-16 weeks): -0.38 ± 1.27g/dL vs -0.14 ± 1.3g/dL - 1.6% vs 0.9% of the anemia cases were considered serious adverse events
Symptomatic hypotension	9.1% (n=229)	7.9% (n=198)	-	NS	
Syncope	4% (n=101)	3.5% (n=87)	-	NS	
Anemia	7.6% (n=192)	5.7% (n=143)	ARI 1.9%	53	

**STRENGTHS, LIMITATIONS, & UNCERTAINTIES**

**STRENGTHS:**

- Studied in a high-risk patient population (recently decompensated HF, median NTproBNP 2816pg/mL, NYHA class III ~40%)
- Blind adjudication of efficacy endpoints
- Only 0.5% lost to follow-up

**LIMITATIONS:**

- Only 11% of the study participants were from North America
- Only 15% were on an ARNI (i.e. **ENTRESTO**); prespecified subgroup analysis suggest similar results to overall cohort
- Only ~60% were on HF triple therapy
- The type of beta-blocker was not reported (i.e. was it a HF beta-blocker – bisoprolol, carvedilol, metoprolol)
- Doses were not reported for HF standard therapy (i.e. were target or maximally tolerated doses reached). The mean BP was 121.4 / 72.8mmHg (±15.7/11mmHg) suggesting there was room to optimize HF guideline-based medication doses. Mean HR was 73bpm (±13bpm) and 44.9% had AF.
- At the time of print, vericiguat is not available in Canada yet. Cost, coverage & brand name also unknown at this time.
- Testing of NT-pro-BNP may not be readily available to all prescribers (dependent on local lab)
- Short study duration of 10.8 months

**UNCERTAINTIES:**

- What is the benefit or harm when vericiguat is combined with an SGLT2-inhibitor? Only a small number of patients were on an SGLT2-inhibitor, & 46.9% had DM at baseline.
- As noted above, only 15% of the patients were on **ENTRESTO**. **ENTRESTO** augments particulate guanylate cyclase, and vericiguat targets soluble guanylate cyclase. Does treatment with both provide synergy for benefit & harm?
- Were any patients on ivabradine **LANCORA**?
- Would optimizing HF triple therapy, including target / maximally tolerated doses, result in less or even no benefit from vericiguat?
- What is the benefit / harm with therapy beyond 11 months? Original study design estimated 18 months for this event-driven trial; however, the event rate occurred faster than expected.
- What is the mechanism and clinical relevance of anemia with vericiguat? Patients with HF are at increased risk of anemia, and individuals with both conditions have an increased risk of HF symptoms, HF hospitalizations and mortality. Riociguat **ADEMPAS** has also been associated with an increased risk of anemia compared to placebo, however, it has been suggested this was due to hemodilution secondary to an increased intravascular volume due to the medication's vasodilating effect.<sup>5</sup>

**RxFILES RELATED LINKS**

- **Heart Failure Treatment:** <https://www-rxfiles-ca.cyber.usask.ca/RxFiles/uploads/documents/members/cht-Heart-Failure.pdf>
- **PARADIGM-HF Trial Summary:** <https://www-rxfiles-ca.cyber.usask.ca/RxFiles/uploads/documents/PARADIGM-HF-Trial-Sacubitril.pdf>
- **DAPA-HF Trial Summary:** <https://www-rxfiles-ca.cyber.usask.ca/RxFiles/uploads/documents/DAPA-HF-Dapagliflozin%20FORXIGA%20versus%20Placebo-with%20Heart%20Failure%20and%20Reduced%20EF.pdf>
- **SHIFT Trial Summary:** <https://www-rxfiles-ca.cyber.usask.ca/RxFiles/uploads/documents/SHIFT%20Trial%20Summary.pdf>

**ACEI**=angiotensin converting enzyme inhibitor **ACS**=acute coronary syndrome **AE**=adverse effect **AF**=atrial fibrillation **ARB**=angiotensin-receptor blocker **ARNI**=angiotensin receptor neprilysin inhibitor **ARI**=absolute risk increase **ARR**=absolute risk reduction **BP**=blood pressure **bpm**=beats per minute **Ca<sup>++</sup>**=calcium **cGMP**=cyclic guanosine monophosphate **CRT**=cardiac resynchronization therapy **CV**=cardiovascular **DM**=diabetes mellitus **EF**=ejection fraction **eGFR**=estimated glomerular filtration rate **GTP**=guanosine triphosphate **HF**=heart failure **HF-rEF**=heart failure with reduced ejection fraction **Hgb**=hemoglobin **HR**=heart rate **ICD**=implantable cardioverter-defibrillator **ITT**=intention to treat **IV**=intravenous **LVAD**=left ventricular assist devices **LVEF**=left ventricular ejection fraction **MDRD**=Modification of Diet in Renal Disease **MRA**=mineralocorticoid receptor antagonist **NO**=nitric oxide **NNH**=number needed to harm **NNT**=number needed to treat **NYHA**=New York Heart Association **NTproBNP**=N-terminal pro b-type natriuretic peptide **NS**=non-statistically significant **SBP**=systolic blood pressure **sGC**=soluble guanylate cyclase **SGLT2-inhibitor**=sodium-glucose transporter 2 inhibitor **TIA**=transient ischemic attack **PKG**=protein kinase G

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