Vericiguat (available as VERQUVO™)
Pivotal Clinical Data Summary

Indications and Usage

VERQUVO™ is indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%.

WARNING: EMBRYO-FETAL TOXICITY

Females of reproductive potential: Exclude pregnancy before the start of treatment. To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment. Do not administer VERQUVO to a pregnant female because it may cause fetal harm.

Dosing and Administration

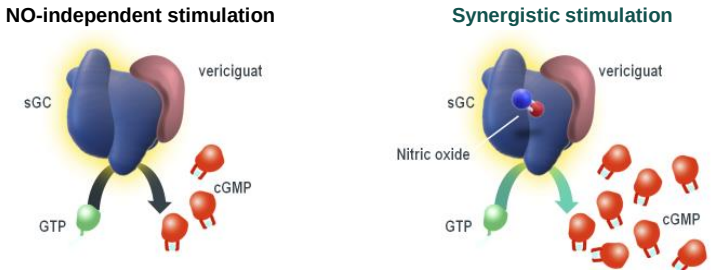
Recommended Dosage

The recommended starting dose of VERQUVO is 2.5 mg orally once daily with food.
Double the dose of VERQUVO approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient.
For patients who are unable to swallow whole tablets, VERQUVO may be crushed and mixed with water immediately before administration.

Pregnancy Testing in Females of Reproductive Potential

Obtain a pregnancy test in females of reproductive potential prior to initiating treatment with VERQUVO.

Suggested Mechanism of Action[1-3]



Vericiguat, a novel oral soluble guanylate cyclase (sGC) stimulator, directly generates cyclic guanosine monophosphate and restores the sensitivity of soluble guanylate cyclase to endogenous nitric oxide (NO).[1] Direct stimulation of native sGC by vericiguat can occur independently from endogenous NO, as well as synergistically with endogenous NO.[2,3]

VICTORIA Clinical Study Design[4,5]

VICTORIA: a Phase III, multinational, randomized, double-blind, placebo-controlled, event-driven trial that evaluated the efficacy and safety of vericiguat.

Intention-to-treat Population

5050 patients ≥18 years of age with chronic heart failure (NYHA class II, III, or IV) and reduced ejection fraction (<45%)[a]

Randomization (1:1)

- VERICIGUAT 10mg QD (titrated from 2.5mg, to 5mg, and to 10mg)[b] + guideline-based medical therapy (N=2,526)
- Placebo[b] + guideline-based medical therapy (N=2,524)

Primary Endpoint

Composite of CV death or first HF hospitalization

Secondary Endpoints

- Components of the primary endpoint:
  - CV death
  - HF hospitalization
- Composite of death from any cause or first hospitalization for heart failure

Study Limitations: Prespecified events were accrued earlier than expected, thereby leaving a relatively short exposure time and potentially limiting the assessment of a later effect. The median duration of follow-up was 10.8 months.

CV, cardiovascular; HF, heart failure; IV, intravenous; NO, nitric oxide. NYHA, New York Heart Association; QD, every day; sGC, soluble guanylate cyclase. VICTORIA, Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction.

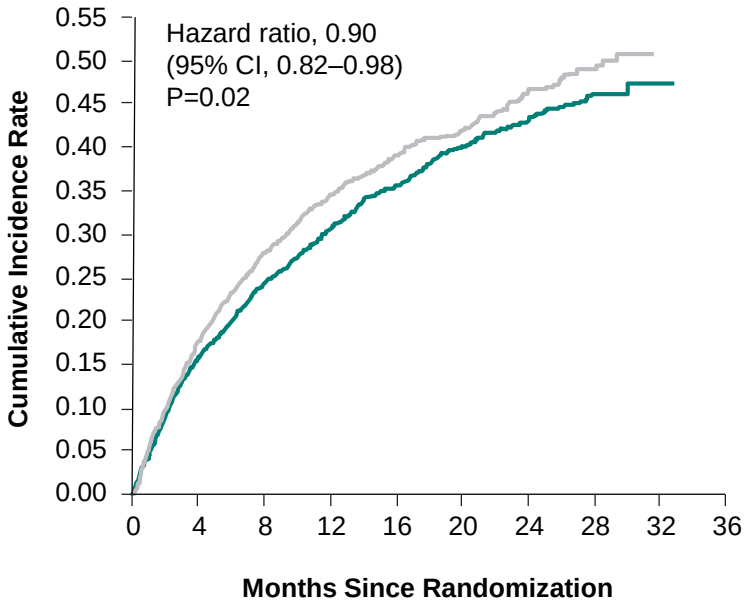
[a]Additional inclusion criteria included having elevated natriuretic peptides and evidence of worsening heart failure (prior HF hospitalization within 6 months or outpatient IV diuretic therapy for HF within 3 months prior to randomization).

[b]Patients received a starting dose of 2.5mg of vericiguat or placebo. Doses were increased to 5mg and ultimately to the target dose of 10 mg once daily in a blinded manner as guided by evaluation of blood pressure and clinical symptoms. Patients were evaluated at weeks 2 and 4, and every 4 months thereafter until the end of the trial.

Efficacy Results[4,a,b]

Vericiguat Placebo

Primary Composite Endpoint: CV Death or First HF Hospitalization[c]

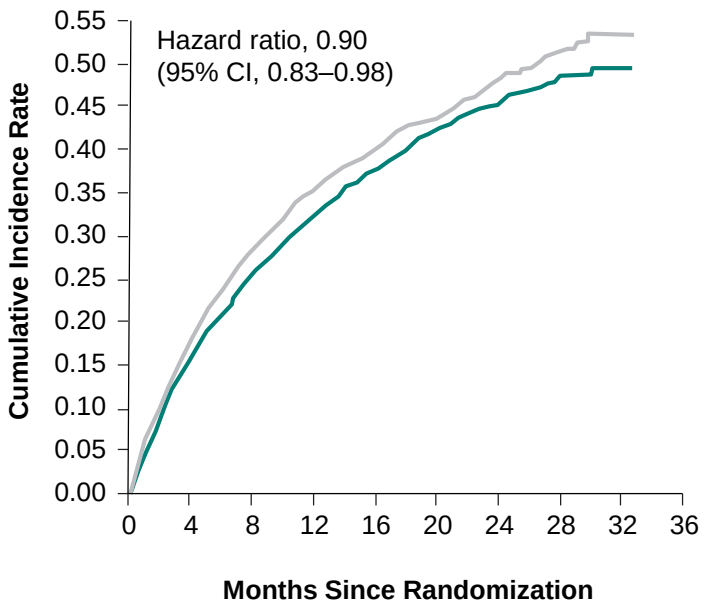


CV death or first HF hospitalization occurred in **35.5%** of patients in the vericiguat group and **38.5%** of patients in the placebo group

Annualized ARR: **4.2** events/100 patient-years

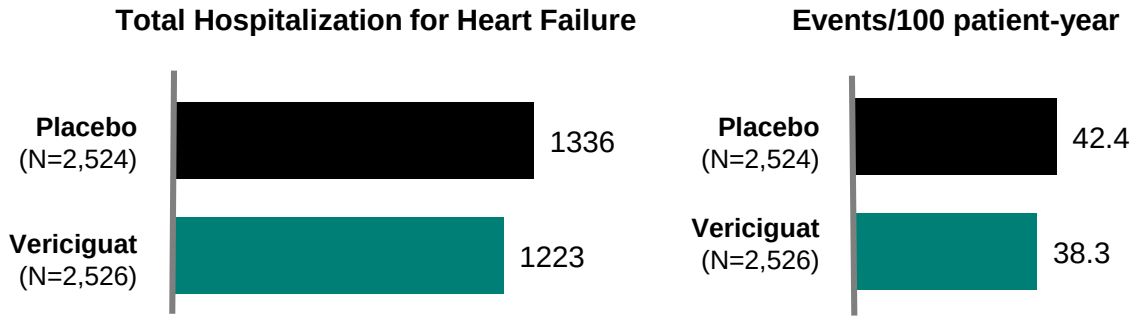
Annual NNT: **24** patients

Secondary Composite Endpoint: All-cause Death or First HF Hospitalization[c]



All-cause death or first HF hospitalization occurred in **37.9%** of patients in the vericiguat group and **40.9%** of patients in the placebo group

Secondary Endpoint: Total Hospitalizations for Heart Failure[d]



Hazard ratio, 0.91 (95% CI: 0.84-0.99); P=0.02

ARR, absolute risk reduction; CI, Confidence interval; CV, Cardiovascular; HF, Heart failure; NNT, number needed to treat.

[a]Assuming a hazard ratio of 0.80 for the outcome of death from CV causes, a sample of 4872 patients, with an expected 782 events, was estimated to provide the trial with 80% power.
[b]The median follow-up duration was 10.8 months.
[c]Deaths included in the primary and secondary composite outcomes were not preceded by a hospitalization for heart failure.
[d]Patients could have been hospitalized more than once.

For US Health Systems Medical Affairs use with payors/population health decision makers in response to an unsolicited request.
Merck does not recommend the use of its products in any manner other than as described in the prescribing information.

Safety Results[4,a]

Patients With Adverse Events Within a System Organ Class (Incidence ≥2.0% in 1 or More Treatment Groups)

	Vericiguat (n=2,519) n (%)	Placebo (n=2,515) n (%)
With ≥1 AE	2027 (80.5)	2036 (81)
With ≥1 SAEs	826 (32.8)	876 (34.8)
Blood and lymphatic system disorders	53 (2.1)	29 (1.2)
Cardiac disorders **Cardiac failure**	203 (8.1) 80 (3.2)	269 (10.7) 110 (4.4)
Gastrointestinal disorders	100 (4.0)	92 (3.7)
Infections and infestations **Pneumonia**	269 (10.7) 101 (4.0)	270 (10.7) 112 (4.5)
Injury, poisoning and procedural complications	65 (2.6)	78 (3.1)
Metabolism and nutrition disorders	74 (2.9)	89 (3.5)
Nervous system disorders	82 (3.3)	83 (3.3)
Renal and urinary disorders **Acute kidney injury**	141 (5.6) 64 (2.5)	133 (5.3) 51 (2.0)
Respiratory, thoracic and mediastinal disorders	88 (3.5)	90 (3.6)
Vascular disorders	81 (3.2)	86 (3.4)

Patients With Adverse Events of Clinical Interest: Symptomatic Hypotension and Syncope

	Vericiguat (n=2,519) n (%)	Placebo (n=2,515) n (%)
Symptomatic hypotension	229 (9.1)	198 (7.9)
Syncope	101 (4.0)	87 (3.5)

AEs, Adverse events; SAEs, Serious adverse events
[a]Safety analyses included all patients who received a trial drug.

References

1. Armstrong PW, Lam CSP, Anstrom KJ, et al. Effect of Vericiguat vs Placebo on Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The VITALITY-HFpEF Randomized Clinical Trial. *JAMA.* 2020;324(15):1512-1521. doi:10.1001/jama.2020.15922 **2.** Follmann M, Griebenow N, Hahn MG, et al. The chemistry and biology of soluble guanylate cyclase stimulators and activators. *Angew Chem Int Ed Engl.* 2013;52(36):9442-9462. doi:10.1002/anie.201302588 **3.** Sandner P. From molecules to patients: exploring the therapeutic role of soluble guanylate cyclase stimulators. *Biol Chem*. 2018;399(7):679-690. doi:10.1515/hsz-2018-0155 **4.** Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2020;382(20):1883-1893. doi:10.1056/NEJMoa1915928 **5.** Armstrong PW, Roessig L, Patel MJ, et al. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator: The VICTORIA Trial. *JACC Heart Fail*. 2018;6(2):96-104. doi:10.1016/j.jchf.2017.08.013