VICTORIA Study (Vericiguat▼ in Patients with Heart Failure with Reduced Ejection Fraction)

Study Design & Main Results

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Reporting adverse events and quality complaints

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Verquvo® vericiguat

Date of preparation: July 2022
PP-VER-GB-0026

Armstrong PW *et al.* JACC Heart Fail 2018; 6(2): 96-1042

Background & Objectives[1,2]

- Mortality & morbidity very high in HFrEF patients who require hospitalisation/IV diuretics
- sGC-mediated production of cGMP essential for normal CV function
- In HF, reduced NO bioavailability results in relative sGC deficiency & reduction in cGMP
- Verquvo - oral, soluble, NO independent, direct sGC stimulator
- VICTORIA study designed to assess efficacy & tolerability in HFrEF patients
- Patients had undergone recent hospitalisation/received IV diuretics

HFrEF, heart failure with reduced ejection fraction; IV, intravenous; sGC, soluble guanylate synthase; cGMP, cyclic guanosine monophosphate; CV, cardiovascular; HF, heart failure; NO, nitric oxide

1. Armstrong PW *et al.* JACC Heart Fail 2018; 6(2): 96-1042; 2. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893

VICTORIA: Study Design[1,2]

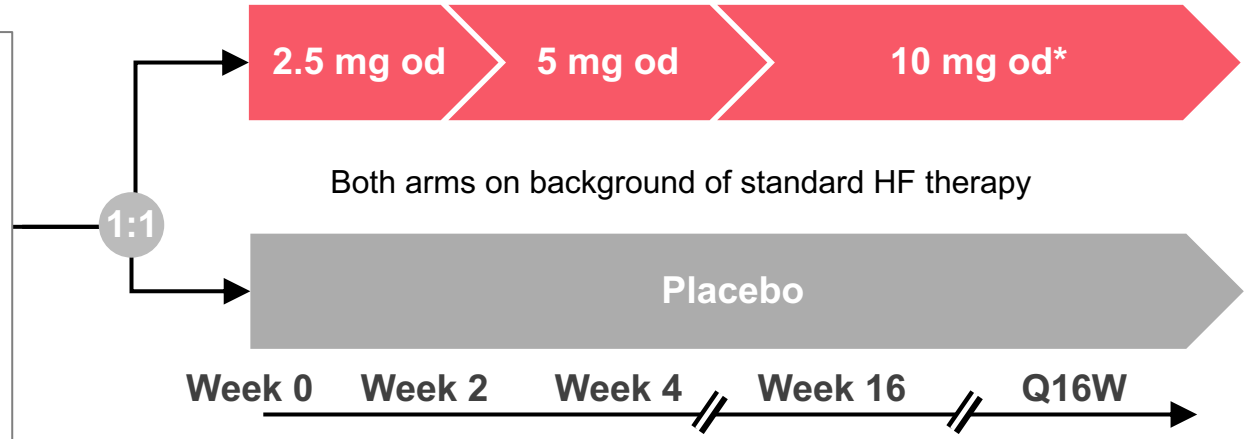
VICTORIA study: randomised, parallel-group, placebo-controlled, double-blind, event-driven, multicentre phase III trial

Key Inclusion criteria[1]

- HFrEF (LVEF <45%)
- NYHA Class II–IV
- BNP: ≥300 pg/ml SR; ≥500 pg/ml for patients in AF
- NT-proBNP: ≥1000 pg/ml SR; ≥1600 pg/ml for patients in AF
- Receiving guideline-directed medical therapy for HF
- eGFR: ≥15 ml/min/1.73 m^2 (15% cap: 15–30 ml/min/1.73 m^2)
- HFH within 6 months (20% cap: hospitalisation >3 months of randomisation) or outpatient IV diuretic treatment for HF within 3 months

Key Exclusion Criteria

- Clinically unstable / hypotensive / requiring inotropes
- Concurrent/anticipated use of long-acting nitrates; sGC stimulators; PDE-5 inhibitors



Secondary endpoints (up to approximately 3.5 years):

- Time to CV death
- Time to first HFH
- Time to first and subsequent HFHs
- Time to composite all-cause mortality or HFH
- Time to all-cause mortality

Primary endpoint: Time to first occurrence of the composite of CV death or HFH (up to approximately 3.5 years)

*If the 10 mg target dose was not reached, then up-titration was considered at subsequent study visits, based on protocol-specified criteria.

1. Adapted from Armstrong PW et al. *JACC Heart Fail.* 2018;6:96–104;
2. Adapted from Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

AF, atrial fibrillation; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HFH, hospitalisation for heart failure ; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; od, once daily; Q16W, every 16 weeks; SR, sinus rhythm;

Key Exclusion Criteria

- Clinically unstable
- Systolic blood pressure <100 mm Hg
- Concurrent or anticipated use of long-acting nitrates of sGC stimulator
- PDE5 inhibitors
- Receiving IV inotropes, an implantable LV assist device or awaiting heart transplantation
- Correctable, complex, or clinically active cardiac comorbidity
- Prior cardiac valve intervention <3 months or coronary revascularisation <60 days
- Unable to provide informed consent
- Females of reproductive age not using an acceptable form of contraception

Adapted from Armstrong PW et al. JACC Heart Fail. 2018;6:96–104;

IV, intra venous; LV, left ventricular, sGC, soluble guanylate synthase, PDE5,

VICTORIA: Pre-specified Exploratory & Subgroup Analyses[1,2]

Exploratory endpoints	Subgroup analyses
• Time to first HF event (composite of HFH or urgent HF visit) • Time to first CV hospitalisation • Total number of HFHs (first and recurrent) • Change in health-related QoL (KCCQ and EQ-5D) • Relationships among treatment effect, baseline biomarkers and genetic variation	• Age, gender and race • Geographical region • Index event (HFH 0–3 months, HFH 3–6 months, IV diuretic therapy [no hospitalisation] 0–3 months) • eGFR at randomisation (three categories of assessment: ≤30, >30 to ≤60, and >60 ml/min/1.73 m^2) • NYHA class at baseline • Baseline NT-proBNP by quartiles • Use of ARNi (sacubitril/valsartan) at baseline • Baseline EF (<35% vs ≥ 35%; <40% vs ≥ 40%)

EF, ejection fraction; EQ-5D, EuroQol 5-dimension questionnaire; HFH, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire hospitalization; QoL, quality of life

1. Adapted from Armstrong PW et al. JACC Heart Fail. 2018;6:96–104; 2. Adapted from Armstrong PW et al. N Engl J Med. 2020;382:1883–1893

Baseline Clinical Characteristics (1)

VICTORIA enrolled a large, international population of high-risk patients with symptomatic chronic HF (& LVEF <45%) who had a previous worsening HF event & who were receiving guideline-directed medical therapy.

- After approx. 12 months, 10 mg target dose achieved: Verquvo (89.2%); placebo (91.4%), n=5050

- Median follow-up for Primary endpoint (ITT): 10.8 months
- Adherence to trial drug was >80% in 93.8% of patients in Verquvo group & in 93.4% of patients in placebo group
- 14.5% of patients were on sacubitril/valsartan
- 59.7% of patients were on triple therapy
- 82.8% of patients hospitalised or received IV diuretic within 3 months prior to randomisation

Baseline characteristic	VICTORIA (N=5050)
Age, mean (SD), years	67.3 (12.2)
Female sex, n (%)	1208 (23.9)
Race, n (%)	
White	3239 (64.1)
Black	249 (4.9)
Asian	1132 (22.4)
Other	430 (8.5)
Geographical region, n (%)	
Eastern Europe	1694 (33.5)
Western Europe	889 (17.6)
Asia-Pacific	1183 (23.4)
Latin America	724 (14.3)
North America	560 (11.1)
Index event, n (%)	
HF hospitalisation within 3 months	3378 (66.9)
HF hospitalisation 3–6 months	871 (17.2)
IV diuretic for HF (without hospitalisation) within 3 months	801 (15.9)

Adapted from Armstrong PW et al. N Engl J Med. 2020;382:1883–1893

ITT, intention-to-treat; SD, standard deviation

Baseline Clinical Characteristics (2) [1,2]

Baseline characteristic	VICTORIA (N=5050)
EF at screening (%), mean (SD)	28.9 (8.3)
NYHA class at baseline, n (%)	
n	5046
II	2975 (59.0)
III	2003 (39.7)
IV	66 (1.3)
eGFR category at randomisation (ml/min/1.73 m^2), n (%)	
n	4959
≤30	506 (10.2)
>30 to ≤60	2118 (42.7)
>60	2335 (47.1)

Baseline characteristic	VICTORIA (N=5050)
NT-proBNP at randomisation (pg/ml)	
n	4805
Median (25th percentile, 75th percentile)	2816.0 (1556.0, 5314.0)
Triple therapy, n/N (%)	3009/5040 (59.7%)
ICD, n/N (%)	1399/5040 (27.8%)
Biventricular pacemaker, n/N (%)	739/5040 (14.7%)

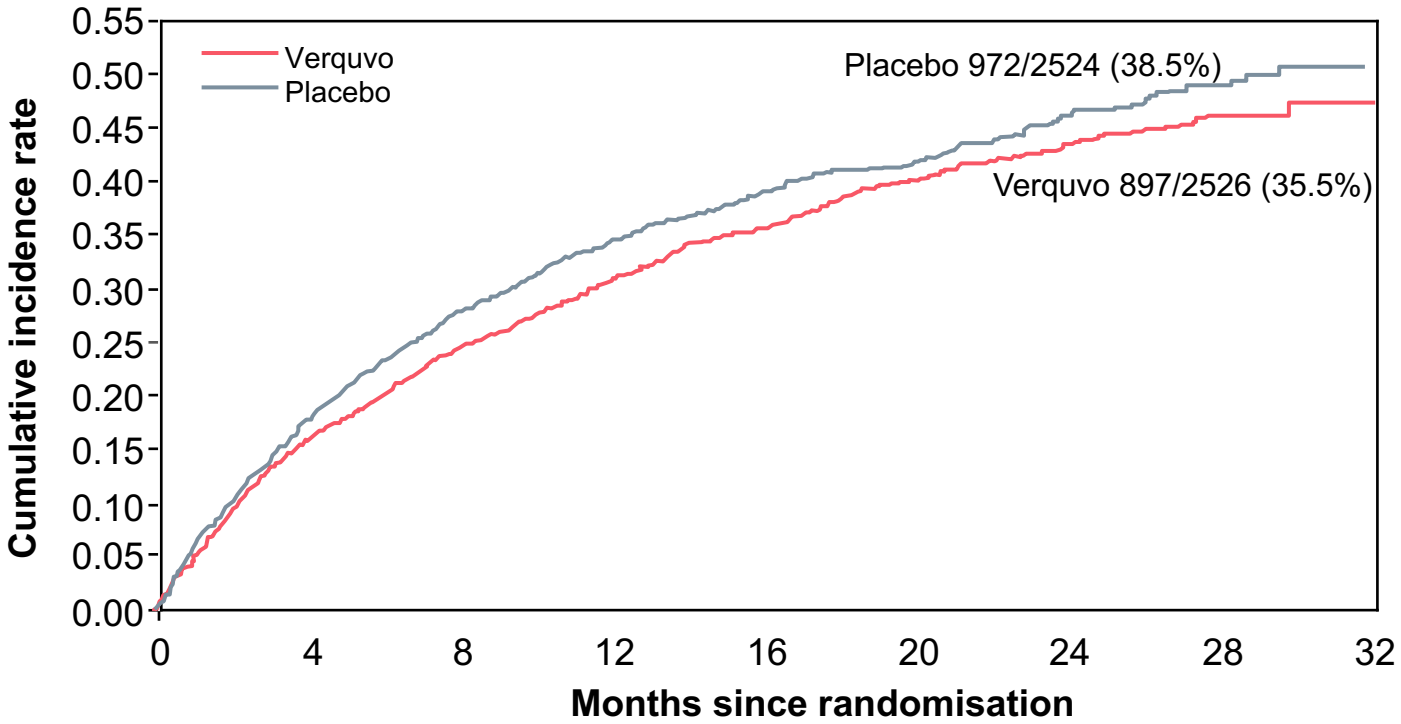
1. Adapted from Armstrong PW et al. N Engl J Med. 2020;382:1883–1893; 2. Adapted from Armstrong PW et al. N Engl J Med. 2020;382:1883–1893 Supplementary Appendix

ICD, implantable cardioverter defibrillator

Results: Efficacy

Results: Primary Composite Endpoint (Death from CV Causes or First HFH)*

Death from CV causes or first HFH



Number of subjects at risk									
Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

- Median follow-up for primary endpoint: 10.8 months
- Event rates for Verquvo and placebo per 100 patient-years were 33.6 and 37.8, respectively

HR=0.90 (95% CI 0.82–0.98); *p*=0.02
ARR=4.2 per year
Annual NNT=24‡

*Intention to treat (ITT) population, ‡Calculations: annual NNT = 100/4.2 = 24

Adapted from Armstrong PW et al. N Engl J Med. 2020;382:1883–1893

CV, cardiovascular; HFH, heart failure hospitalisation

Results: Primary Composite Endpoint & Components*

	Verquvo (n=2526)			Placebo (n=2524)			Treatment comparison	
	n	%	Events/100 patient-years*	n	%	Events/100 patient-years*	HR (95% CI)#	*p*-value‡
Primary composite outcome & components								
Death from CV Causes or First HFH	897	35.5	33.6	972	38.5	37.8	0.90 (0.82–0.98)	0.02
Death from CV Causes¶	206	8.2		225	8.9			
HFH	691	27.4		747	29.6			

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

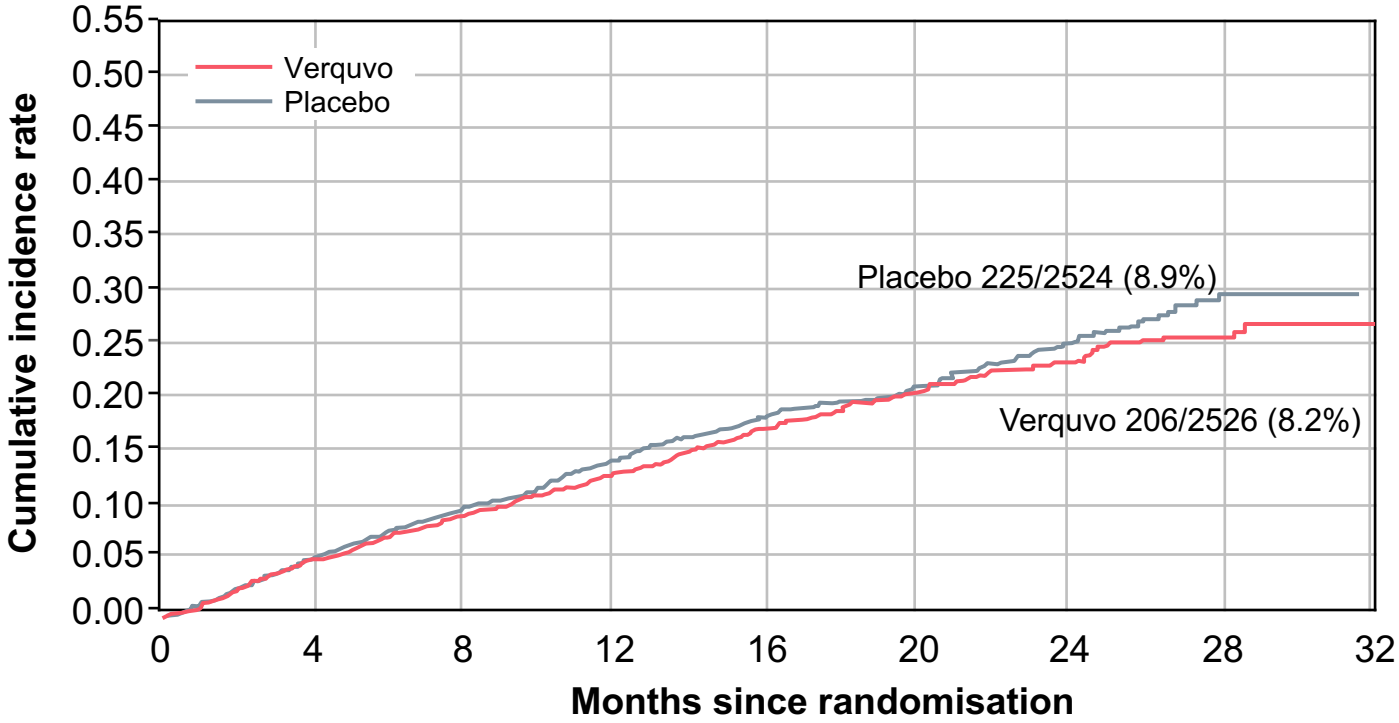
#HR (Verquvo versus placebo) and CI calculated from Cox proportional-hazards model controlling for stratification factors (defined by region and race); ‡Calculated from stratified log-rank test with stratification factors defined by region and race; ¶deaths included in the primary and secondary composite outcomes were not preceded by a hospitalisation for HF. Based on data up to the primary completion date (18 June 2019)

Adapted from Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

CV, cardiovascular; HFH, hospitalisation for heart failure

Results: Secondary Efficacy Endpoints (1)

Death from CV Causes



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

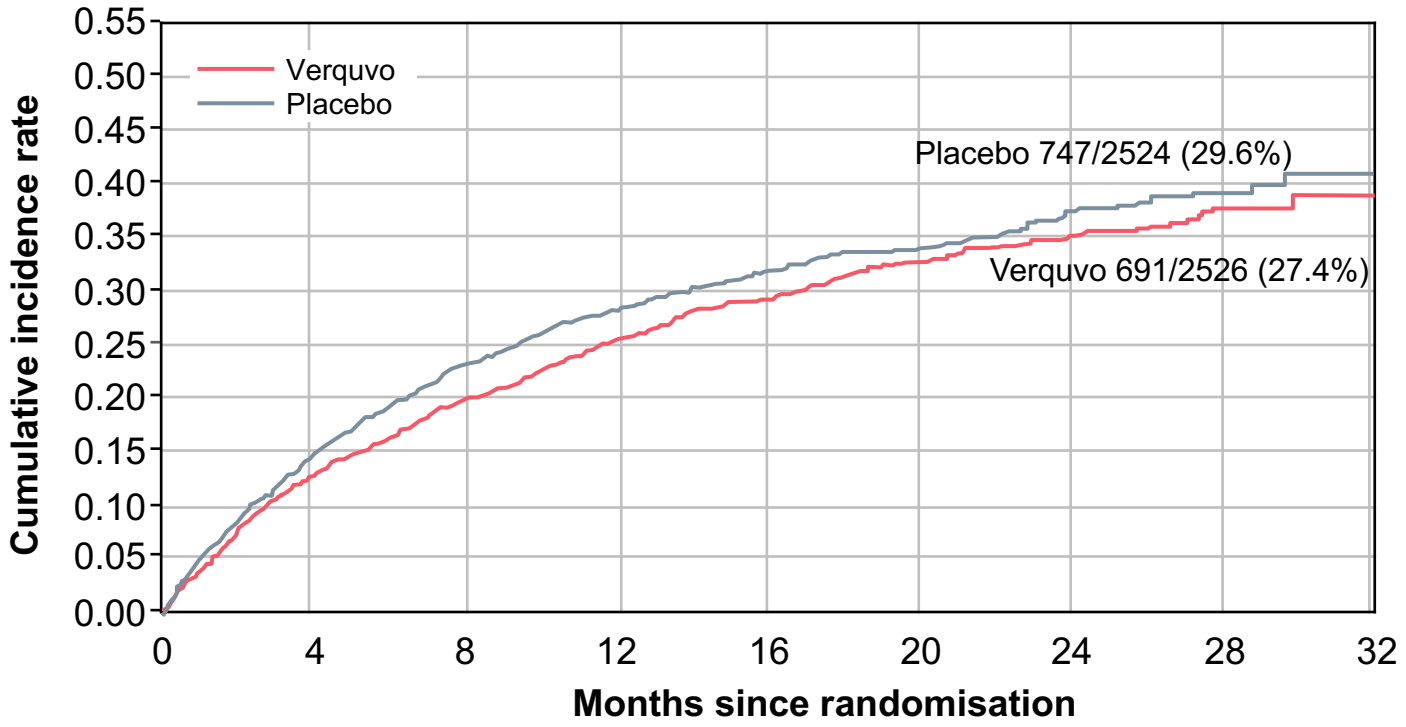
- Median treatment duration: 10.8 months[1]
- Annual event rates for Verquvo and placebo per 100 patient-years were 12.9 and 13.9, respectively

HR=0.93 (95% CI 0.81–1.06)

Adapted from Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

Results: Secondary Efficacy Endpoints (2)

HFH



Number of subjects at risk									
Vericiguat	2526	2098	1620	1153	825	577	348	125	1
Placebo	2524	2052	1554	1096	771	558	323	110	0

- Median treatment duration: 10.8 months
- Annual event rates for Verquvo and placebo per 100 patient-years were 25.9 and 29.1, respectively

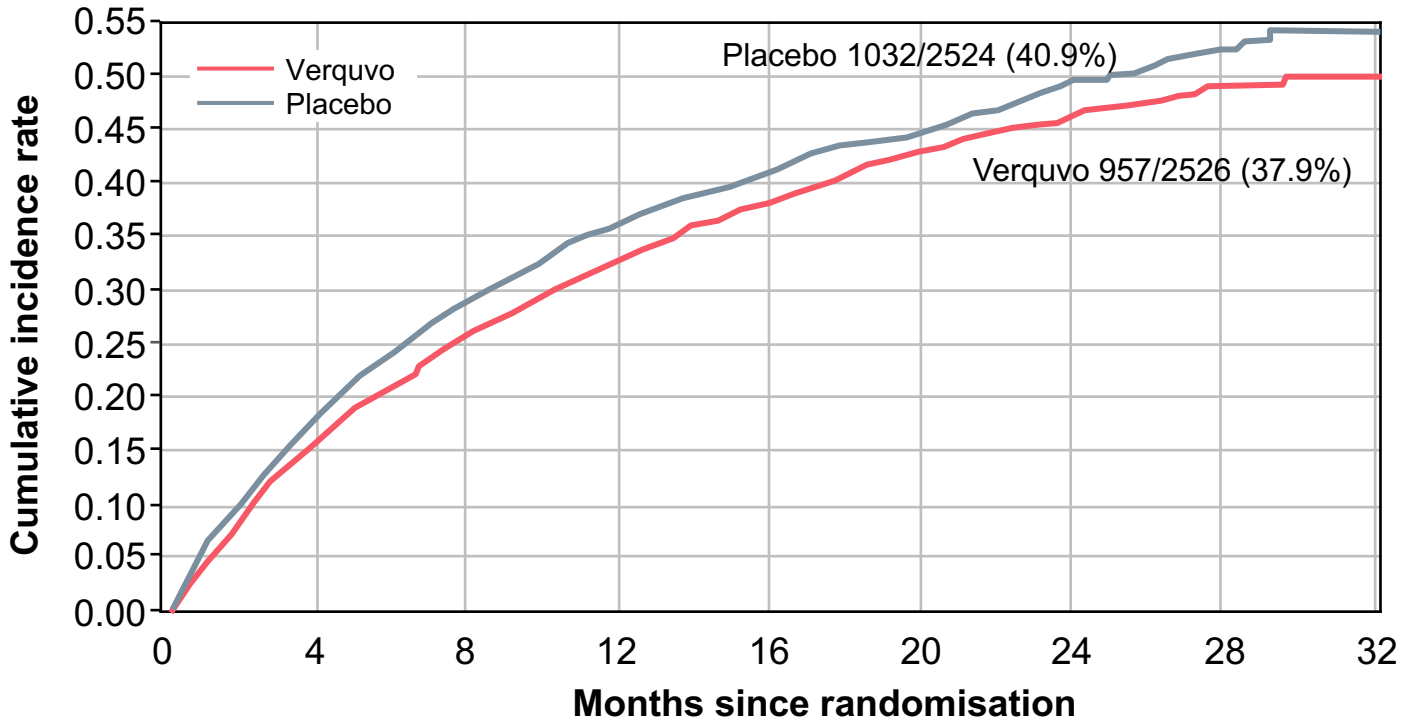
HR=0.90 (95% CI 0.81–1.00)

Adapted from Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893;

HFH, heart failure hospitalisation

Results: Secondary Efficacy Endpoints (3)

Death from Any Cause or HFH



Number of subjects at risk									
Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

- Annual event rates for Verquvo and placebo per 100 patient-years were 35.9% and 40.1%, respectively

HR=0.90 (95% CI 0.83–0.98)
p=0.02

Adapted from Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

HFH, heart failure hospitalisation

Results: Secondary Efficacy Endpoints & Components (4)*

	Verquvo (n=2526)			Placebo (n=2524)			Treatment comparison	
	n	%	Events/100 patient-years*	n	%	Events/100 patient-years*	HR (95% CI)#	*p-value*‡
Secondary outcomes								
Death from CV Causes	414	16.4	12.9	441	17.5	13.9	0.93 (0.81–1.06)	N/A
HFH	691	27.4	25.9	747	29.6	29.1	0.90 (0.81–1.00)	N/A
Total HFH§	1,223	N/A	38.3	1,336	N/A	42.4	0.91 (0.84–0.99)	0.02
Secondary composite outcome & components								
Death from Any Cause or first HFH	957	37.9	35.9	1,032	40.9	40.1	0.90 (0.83–0.98)	0.02
HFH	691	27.4	25.9	747	29.6	29.1	0.90 (0.81–1.00)	N/A
Death from Any Cause¶	266	10.5	N/A	285	11.3	N/A	N/A	N/A
Death from Any Cause	512	20.3	16.0	534	21.2	16.9	0.95 (0.84–1.07)	0.38

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

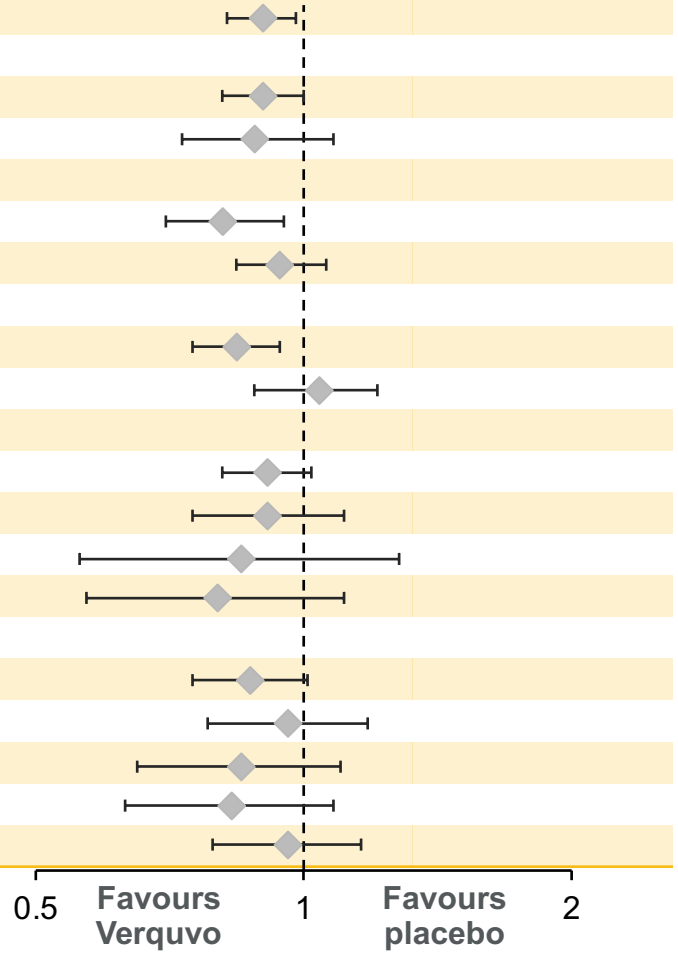
#HR (vericiguat over placebo) & CI calculated from Cox proportional-hazards model controlling for stratification factors (defined by region and race); ‡Calculated from stratified log-rank test with stratification factors defined by region and race; §patients could have been hospitalized more than once. ¶deaths included in the primary and secondary composite outcomes were not preceded by a hospitalisation for HF. Based on data up to the primary completion date (18 June 2019)

Adapted from Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

CV, cardiovascular; HFH, heart failure hospitalization ;NA, not available

Subgroup Analysis of Primary Composite Endpoint (CV death or First HFH) (1)

Characteristic	Number of events (Verquvo/placebo)	HR	95% CI
All Patients	897/972	0.90	(0.82–0.98)
Sex			
Male	704/762	0.90	(0.81–1.00)
Female	193/210	0.88	(0.73–1.08)
Age group (years)			
<65	290/348	0.81	(0.70–0.95)
≥65	607/624	0.94	(0.84–1.06)
Age group (years)			
<75	579/669	0.84	(0.75–0.94)
≥75	318/303	1.04	(0.88–1.21)
Race			
White	593/635	0.91	(0.81–1.02)
Asian	199/207	0.91	(0.75–1.11)
Black	41/50	0.85	(0.56–1.28)
Other	64/80	0.80	(0.57–1.11)
Geographical region			
Eastern Europe	310/345	0.87	(0.75–1.01)
Western Europe	173/178	0.96	(0.78–1.18)
North America	103/117	0.85	(0.65–1.10)
Latin and South America	100/116	0.83	(0.63–1.08)
Asia Pacific	211/216	0.96	(0.79–1.16)



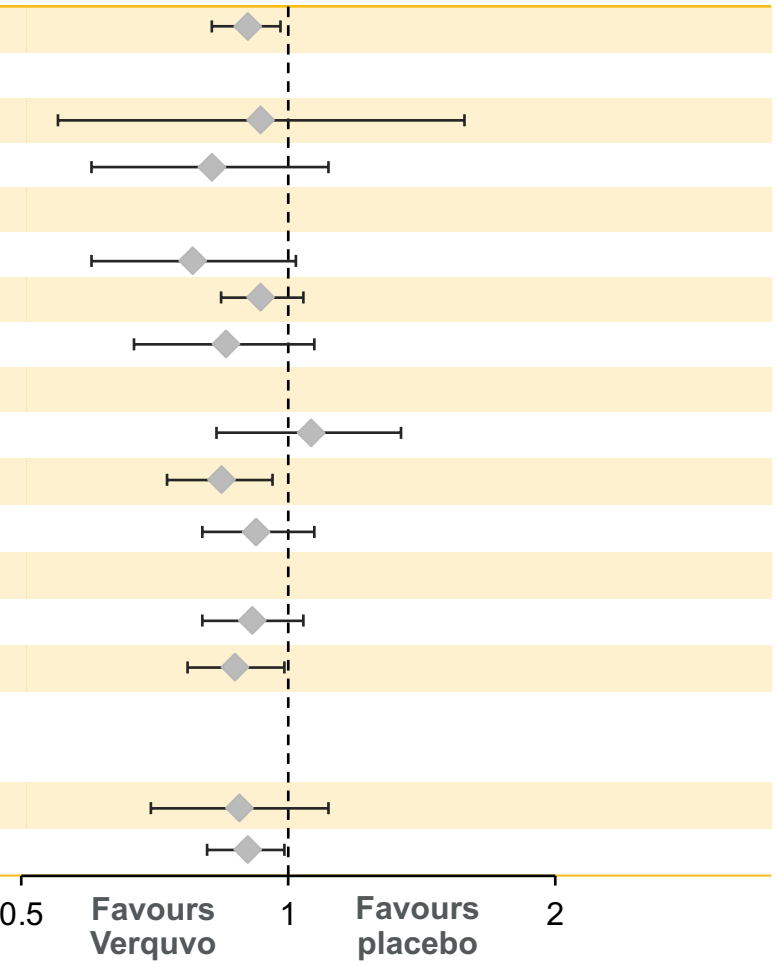
The effect of Verquvo on the primary outcome was consistent across most prespecified subgroups (including patients receiving sacubitril–valsartan), except in the subgroups defined according to age & NT-proBNP level

Adapted from Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

CV, cardiovascular; HFH, hospitalisation for heart failure

Subgroup Analysis of Primary Composite Endpoint (CV death or First HFH) (2)

Characteristic	Number of events (Verquvo/placebo)	HR	95% CI
All Patients	897/972	0.90	(0.82–0.98)
Race in North America			
Black	26/29	0.93	(0.55–1.58)
Non-black	77/88	0.82	(0.60–1.11)
Index event			
IV diuretic <3 months	96/120	0.78	(0.60–1.02)
Hospitalisation <3 months	660/701	0.93	(0.84–1.04)
Hospitalisation 3–6 months	141/151	0.85	(0.67–1.07)
eGFR at baseline (mL/min/1.73 m^2)			
≤30	143/128	1.06	(0.83–1.34)
>30 to ≤60	392/455	0.84	(0.73–0.96)
>60	346/372	0.92	(0.80–1.07)
NHYA class at baseline			
I/II	445/484	0.91	(0.80–1.04)
III/IV	451/487	0.87	(0.77–0.99)
Use of sacubitril/valsartan at baseline			
Yes	134/153	0.88	(0.70–1.11)
No	760/818	0.90	(0.81–0.99)



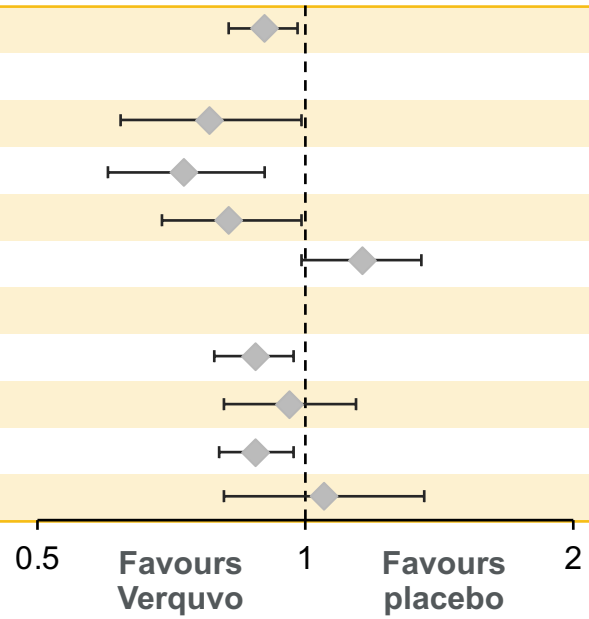
The effect of Verquvo on the primary outcome was consistent across most prespecified subgroups (including patients receiving sacubitril–valsartan), except in the subgroups defined according to age & NT-proBNP level

Adapted from Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

CV, cardiovascular; HFH, hospitalisation for heart failure; IV, intravenous; eGFR, estimated glomerular filtration rate; NYHA, New York heart Association

Subgroup Analysis of Primary Endpoint (CV death or First HFH) (3)

Characteristic	Number of events (Verquvo/placebo)	HR	95% CI
All Patients	897/972	0.90	(0.82–0.98)
NT-proBNP at baseline (pg/mL)			
Quartile 1 (≤1556)	128/161	0.78	(0.62–0.99)
Quartile 2 (1556–2816)	165/201	0.73	(0.60–0.90)
Quartile 3 (2816–5314)	213/257	0.82	(0.69–0.99)
Quartile 4 (>5314)	355/302	1.16	(0.99–1.35)
Ejection fraction at screening (%)			
<35	637/703	0.88	(0.79–0.97)
≥35	255/265	0.96	(0.81–1.14)
<40	773/851	0.88	(0.80–0.97)
≥40	119/117	1.05	(0.81–1.36)



The effect of Verquvo on the primary outcome was consistent across most prespecified subgroups (including patients receiving sacubitril–valsartan), except in the subgroups defined according to age & NT-proBNP level

Adapted from Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

CV, cardiovascular; HFH, hospitalisation for heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide

Results: Safety Profile

Results: Safety Profile (1)

	Verquvo		Placebo		Total	
	n	%	n	%	n	%
Subjects in population	2519		2515		5034	
With ≥1 AE	2027	80.5	2036	81.0	4063	80.7
With ≥1 SAE	826	32.8	876	34.8	1702	33.8

AE, adverse event; SAE, serious adverse event

Results: Safety Profile (2)

- Prespecified events of special interest: symptomatic hypotension & syncope

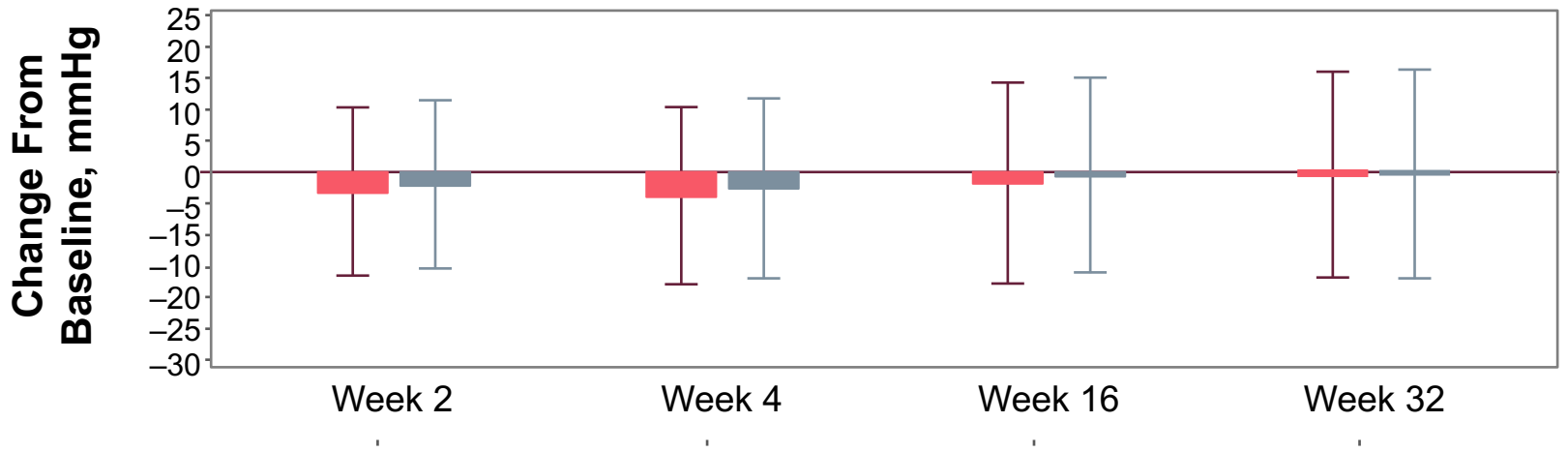
	Verquvo		Placebo		Difference in % vs placebo	
	N	%	n	%	Estimate (95% CI)*	*p*-value
Subjects in population	**2519**		**2515**			
Symptomatic hypotension	229	9.1	198	7.9	1.2 (–0.3 to 2.8)	0.12
Syncope	101	4.0	87	3.5	0.6 (–0.5 to 1.6)	0.30

*Based on Miettinen & Nurminen method. Note: Includes events/measurements from the day of first dose of study drug to 14 days after the last dose of study drug. Based on data up to the primary analysis cut-off date (18 Jun 2019)

CI, confidence interval

Mean Change in Systolic Blood Pressure from Baseline Over Time

Baseline SBP (mmHg)	N	Mean (SD)
Verquvo	2519	121.24 (15.67)
Placebo	2515	121.46 (15.76)



Number of subjects with SBP assessments at each time point

Verquvo	2516	2388	2147	1769
Placebo	2513	2388	2173	1774

Armstrong PW et al. N Engl J Med. 2020;382:1883–1893 Supplementary Appendix

SBP, systolic blood pressure; BP, blood pressure; SD standard deviation

Results: Safety Profile (3)

- There were similar incidence rates of organ class SAEs between the Verquvo & placebo arms, while small between-group imbalances were seen in renal, GI, blood disorder, & hypotensive AEs
- More anaemia developed with Verquvo (7.6%) vs. placebo (5.7%)

Subjects with serious adverse events within a system organ class (incidence ≥2% in one or more treatment groups) all subjects as treated

	Verquvo		Placebo		Total	
	n	%	n	%	n	%
Subjects in population	2519		2515		5034	
With one or more serious adverse events	826	32.8	876	34.8	1702	33.8
Blood and lymphatic system disorders	53	2.1	29	1.2	82	1.6
Cardiac disorders	203	8.1	269	10.7	472	9.4
Cardiac failure	80	3.2	110	4.4	190	3.8
Gastrointestinal disorders	100	4.0	92	3.7	192	3.8
Infections and infestations	269	10.7	270	10.7	539	10.7
Pneumonia	101	4.0	112	4.5	213	4.2
Injury, poisoning and procedural complications	65	2.6	78	3.1	143	2.8
Metabolism and nutrition disorders	74	2.9	89	3.5	163	3.2
Nervous system disorders	82	3.3	83	3.3	165	3.3
Renal and urinary disorders	141	5.6	133	5.3	274	5.4
Acute kidney injury	64	2.5	51	2.0	115	2.3
Respiratory, thoracic and mediastinal disorders	88	3.5	90	3.6	178	3.5
Vascular disorders	81	3.2	86	3.4	167	3.3

Adapted from Armstrong PW et al. N Engl J Med. 2020;382:1883–1893 Supplementary Appendix

GI, gastrointestinal

Analysis of NT-proBNP & Clinical Outcomes

Ezekowitz JA et al. *JACC.* 2020;8:931–939

NT-proBNP; N-terminal pro B-type natriuretic peptide

Background & Objectives

VICTORIA study:

- Verquvo added to SOC, significantly reduced risk of primary composite endpoint of CV death/HF hospitalisation vs. placebo (RRR 10%/ARR 4.2% p=0.02) in high-risk patients with HFrEF who had a recent HF hospitalisation/IV diuretic therapy[1] (Verquvo n=2526, placebo n=2524)[1]
- Potential heterogeneity of treatment effect was observed in the NT-proBNP analysis by quartile[1,2]
- NT-proBNP ≤5314 pg/ml (quartiles 1–3) at baseline indicates a trend for Verquvo treatment vs. placebo for composite primary endpoint[1]
- NT-proBNP >5314 pg/ml (quartile 4) at baseline indicates a trend for placebo vs. Verquvo for composite primary endpoint[1]

This sub-analysis explored the relationship of NT-proBNP across the spectrum of levels at randomisation with the treatment effect of Verquvo compared with placebo, in the VICTORIA trial[2]

SOC, standard of care; CV, cardiovascular; HF, heart failure;HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide

1. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 2. Ezekowitz JA et al. *JACC.* 2020;8:931–939.

Baseline Characteristics by NT-proBNP at Randomisation

	NT-proBNP at randomisation (pg/ml)		
Key characteristic	**≤4000 (n=3100)**	**>4000–8000 (n=1033)**	**>8000 (n=672)**
Median age, years (IQR)	67.0 (59.0–75.0)	70.0 (62.0–78.0)	70.0 (62.0–79.0)
Male, n (%)	2361 (76.2)	803 (77.7)	482 (71.7)
Index event, n (%)			
HFH ≤6 months	2534 (81.7)	913 (88.4)	589 (87.6)
IV diuretic for HF w/o hospitalisation <3 months	566 (18.3)	120 (11.6)	83 (12.4)
Median BMI, kg/m² (IQR)	27.6 (24.2–31.7)	25.9 (23.1–29.9)	25.4 (22.5–28.7)
Medical history			
AF, n (%)	1307 (42.2)	519 (50.2)	312 (46.4)
Diabetes mellitus, n (%)	1420 (45.8)	492 (47.6)	342 (50.9)
EF, median (25th–75th percentile)	30.0 (24.0–36.0)	27.0 (20.0–35.0)	26.0 (20.0–34.0)
NYHA Class II–III, n (%)	3073 (99.2)	1015 (98.3)	651 (96.9)
Standard of care therapy, n (%)			
ACEi/ARB	2358 (76.1)	747 (72.3)	435 (64.7)
Sacubitril/valsartan	460 (14.8)	129 (12.5)	95 (14.1)
Beta blocker	2904 (93.7)	957 (92.6)	610 (90.8)
MRA	2275 (73.4)	700 (67.8)	414 (61.6)
Triple therapy	1993 (64.3)	571 (55.3)	310 (46.1)
Median eGFR, ml/min/1.73 m² (IQR)	63.6 (47.1–82.7)	51.5 (36.8–71.1)	42.4 (30.4–61.2)
≤30, n (%)	176 (5.7)	141 (13.6)	161 (24.0)
>30–≤60, n (%)	1189 (38.4)	508 (49.2)	330 (49.1)
>60, n (%)	1707 (55.1)	378 (36.6)	179 (26.6)
Median MAGGIC risk score (IQR)	22 (18–27)	26 (21–30)	27 (23–32)

Higher baseline NT-proBNP levels tended to be associated with: older age; higher NYHA class; and lower BMI, EF and eGFR

245/5050 participants in the VICTORIA trial did not have evaluable NT-proBNP at randomisation and were excluded from this analysis.

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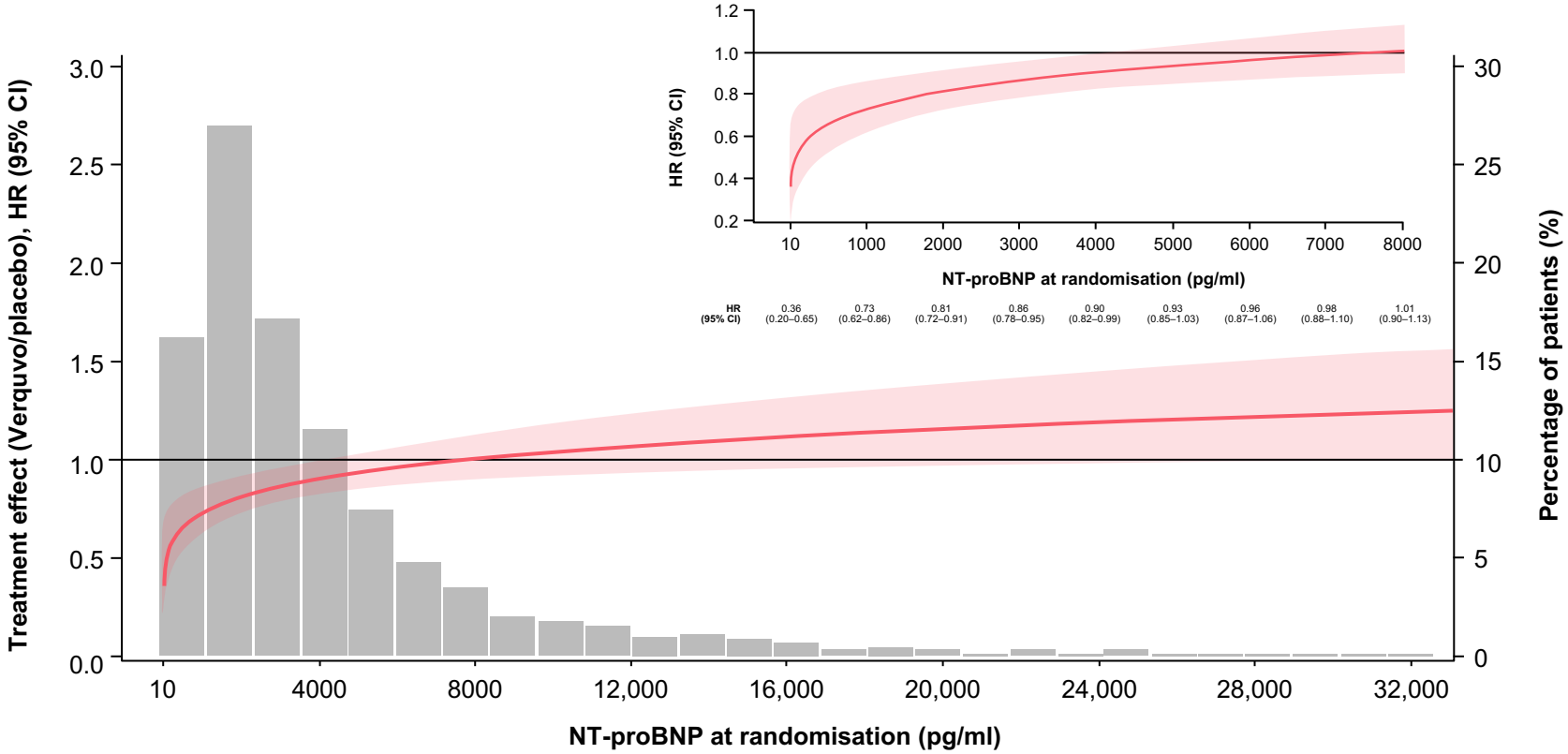
NT-proBNP, N-terminal pro B-type natriuretic peptide; IQR, inter quartile range; HFH, heart failure hospitalisation; IV, intravenous; BMI, body mass index; AF, atrial fibrillation; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticosteroid receptor antagonist; eGFR, estimated glomerular filtration rate; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure

Ezekowitz JA et al. *JACC.* 2020;8:931–939

Association of Treatment Effect with Primary Outcome by NT-proBNP at Randomisation



Range of the treatment effect of Verquvo compared with placebo for the primary composite endpoint for NT-proBNP at randomisation, adjusted for the MAGGIC risk score

Treatment effect of Verquvo vs. placebo on the primary composite endpoint (adjusted for the MAGGIC risk score):

- HR = 0.85 (95% CI, 0.76-0.95) for patients with NT-proBNP ≤8000 pg/ml (86% of VICTORIA population)
- HR = 0.77 (95% CI, 0.68-0.88) for patients with NT-proBNP ≤4000 pg/ml (65% of VICTORIA population)

Ezekowitz JA et al. Suppl App. JACC. 2020; 8:931-939

NT-proBNP, N-terminal pro B-type natriuretic peptide; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure

Treatment Effect on Primary Composite Endpoint by Baseline NT-proBNP ≤4000, >4000, ≤8000 & >8000 pg/ml

Outcome	NT-proBNP at randomisation (pg/ml)							
	≤4000 (n=3100)				>4000 (n=1705)			
	P events/ 100 PY	V events/ 100 PY	ARR	Treatment effect (V vs P)* Adjusted# HR (95% CI)	P events/ 100 PY	V events/ 100 PY	ARR	Treatment effect (V vs P)* Adjusted# HR (95% CI)
CV death/HFH	28.4	21.6	6.8	0.77 (0.68–0.88)	61.4	64.7	-3.3	1.05 (0.92–1.20)
CV death	5.2	3.9	1.3	0.75 (0.60–0.94)	16.9	18.5	-1.6	1.10 (0.92–1.31)
HFH	23.2	17.7	5.5	0.78 (0.67–0.90)	44.6	46.2	-1.6	1.05 (0.90–1.22)
	≤8000 (n=4133)				>8000 (n=672)			
	P events/ 100 PY	V events/ 100 PY	ARR	Treatment effect (V vs P)* Adjusted# HR (95% CI)	P events/ 100 PY	V events/ 100 PY	ARR	Treatment effect (V vs P)* Adjusted# HR (95% CI)
CV death/HFH	33.7	28.3	5.4	0.85 (0.76–0.95)	74.5	87.2	-12.7	1.16 (0.94–1.41)
CV death	6.9	6.1	0.8	0.84 (0.71–0.99)	22.9	26.5	-3.6	1.32 (1.01–1.71)
HFH	26.8	22.2	4.6	0.84 (0.75–0.95)	51.6	60.7	-9.1	1.17 (0.92–1.48)

Treatment effect of Verquvo on the primary outcome was greatest with NT-proBNP levels ≤8000 pg/ml at randomisation & was further amplified if NT-proBNP levels were ≤4000 pg/ml

*All study treatment interactions were statistically significant ($p<0.05$); #adjusted for the modified MAGGIC score.

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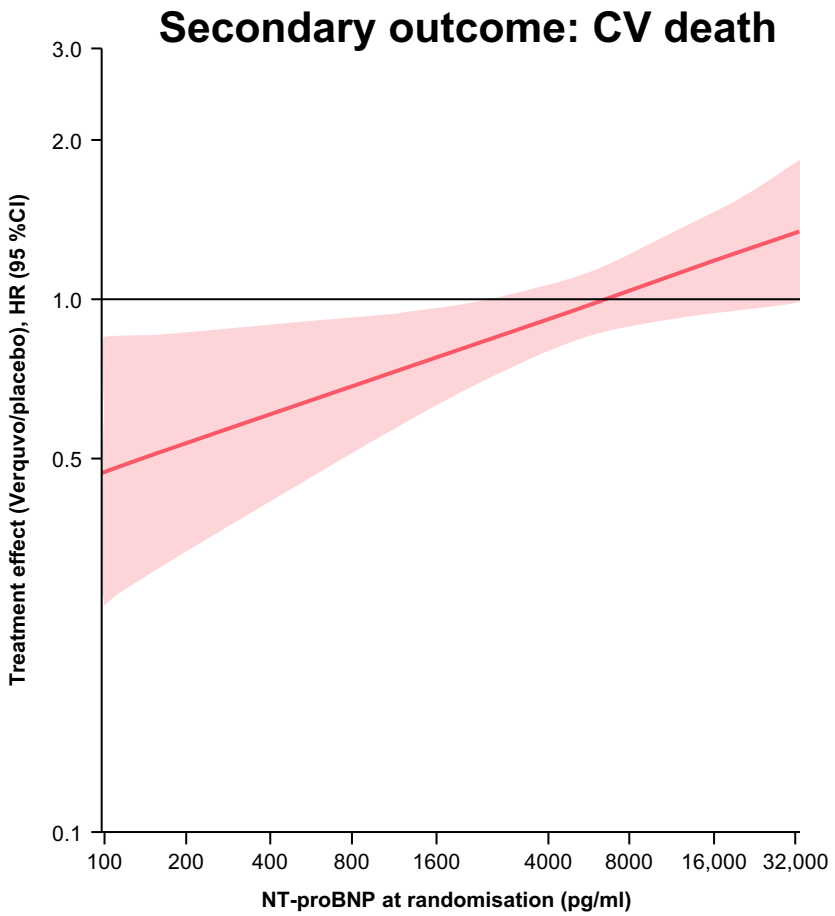
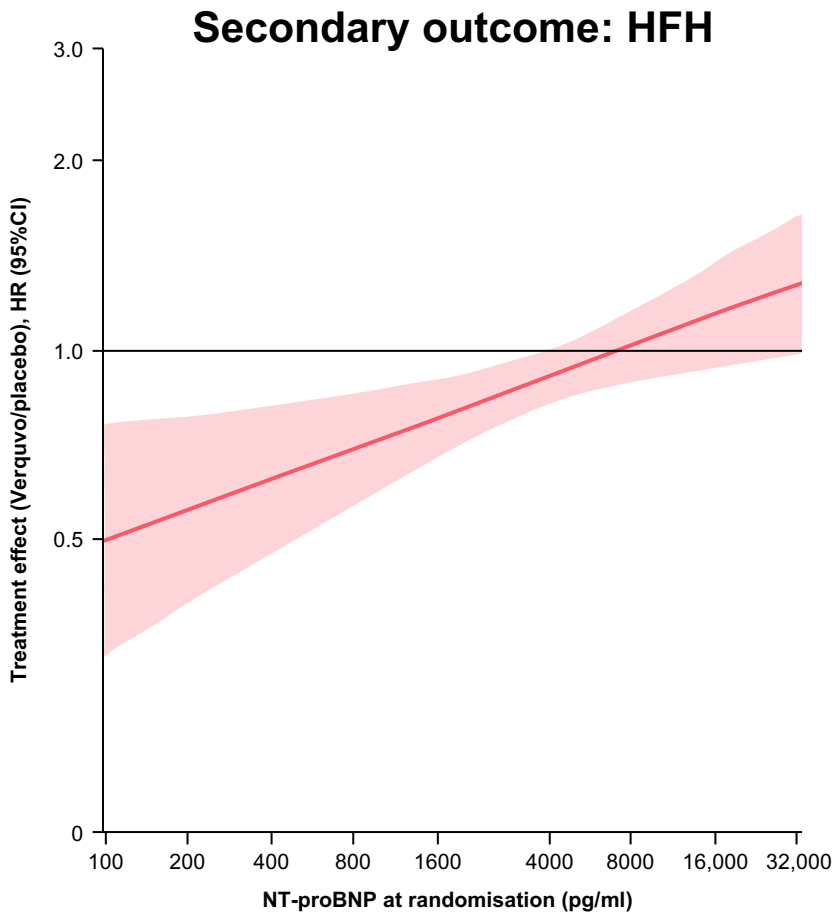
Adapted from Ezekowitz JA et al. *JACC.* 2020;8:931–939

P, placebo; PY, patient-years; V, Verquvo.

Association of Treatment Effect with CV death & HFH by NTproBNP Level at Randomisation





For patients with NT-proBNP ≤8000 pg/ml (n=4133), the treatment effect of Verquvo extended to both CV death and HFH

Adjusted for MAGGIC risk score and presented using log scale

Adapted from Ezekowitz JA et al. *JACC.* 2020;8:931–939 (Supplementary Appendix)

Association of Log-Transformed NT-proBNP with Primary Efficacy Endpoint & Components

	Unadjusted HR (95% CI) per NT-proBNP doubling (pg/ml)*	*p*[#]	*p*-interaction[‡]	Adjusted HR (95% CI) per NT-proBNP doubling (pg/ml)[§]	*p*[#]	*p*-interaction[‡]
CV death/HFH						
All patients	1.43 (1.38–1.47)	<0.0001	0.001	1.36 (1.31–1.41)	<0.0001	0.002
Placebo	1.35 (1.29–1.41)			1.29 (1.23–1.35)		
Verquvo	1.51 (1.43–1.58)			1.43 (1.36–1.51)		
CV death						
All patients	1.62 (1.54–1.70)	<0.0001	0.012	1.50 (1.43–1.58)	<0.0001	0.015
Placebo	1.52 (1.42–1.63)			1.41 (1.31–1.52)		
Verquvo	1.72 (1.61–1.84)			1.60 (1.49–1.71)		
HFH						
All patients	1.35 (1.30–1.41)	<0.0001	0.003	1.29 (1.24–1.34)	<0.0001	0.005
Placebo	1.28 (1.21–1.35)			1.22 (1.15–1.29)		
Verquvo	1.43 (1.36–1.51)			1.36 (1.29–1.44)		

There was an excess hazard of clinical outcomes per doubling of NT-proBNP with & without adjustment for the MAGGIC risk score. Relationship was more pronounced in patients assigned to Verquvo vs. placebo

*Unadjusted estimates in 4805 patients; [#]HR (95% CI) and *p*-value for log-transformed NT-proBNP as a main effect only in the model; [‡]HR (95% CI) and *p*-value for the interaction of log-transformed NT-proBNP at randomisation with assigned study treatment; [§]estimates adjusted for the MAGGIC risk score in 4734 patients.

Ezekowitz JA et al. *JACC.* 2020;8:931–939.

Limitations

- In this NT-proBNP continuous variable analysis, 245 patients were missing NT-proBNP levels at randomisation; however, no marked differences in these patients vs. overall cohort & therefore any impact on results is unlikely

- As with all secondary analyses, the possibility of unmeasured confounders despite adjustment with MAGGIC cannot be excluded

Ezekowitz JA et al. *JACC.* 2020;8:931–939.

Conclusions

- Treatment effect of Verquvo vs. placebo on primary composite endpoint observed in patients with NT-proBNP levels <8000 pg/ml at randomisation
- Treatment effect further amplified if NT-proBNP levels <4000 pg/ml

Ezekowitz JA et al. *JACC.* 2020;8:931–939.

Verquvo® (vericiguat) 2.5, 5, 10 mg film-coated tablets
Prescribing Information

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 2.5 mg / 5 mg / 10 mg vericiguat tablet. **Indication:** Verquvo is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilised after a recent decompensation event requiring IV therapy. **Posology & method of administration:** Vericiguat is administered in conjunction with other heart failure therapies. Before starting vericiguat, optimise volume status & diuretic therapy to stabilise patients after the decompensation event, particularly those with very high NT-proBNP levels. ***Adults:*** *Dose titration:* recommended starting dose is 2.5 mg once daily. Double the dose approx. every 2 weeks to reach target maintenance dose of 10 mg once daily, as tolerated by patient. If patient has tolerability issues, temporary down-titration or discontinuation is recommended. Do not initiate treatment in patients with SBP <100 mmHg. If dose is missed, it should be taken as soon as patient remembers on same day of missed dose. Patients should not take 2 doses on the same day. ***Elderly:*** no dose adjustment ***Renal impairment:*** no dose adjustment in patients with eGFR ≥15 mL/min/1.73 m^2 (without dialysis). Treatment not recommended in patients with eGFR <15 mL/min/1.73 m^2 at treatment initiation or on dialysis. ***Hepatic impairment:*** no dose adjustment for mild/moderate hepatic impairment; treatment not recommended in patients with severe hepatic impairment. ***Paediatrics:*** Safety & efficacy have not been established. No clinical data available. Undesirable effects were observed on growing bone in non-clinical studies. **Contra-indications:** Hypersensitivity to the active substance or to any of the excipients; concomitant use of other soluble guanylate cyclase (sGC) stimulators, such as riociguat. **Warnings & precautions (W&P):** Vericiguat may cause symptomatic hypotension. Patients with SBP less than 100 mmHg or symptomatic hypotension at treatment initiation were not studied. The potential for symptomatic hypotension should be considered in patients with hypovolaemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, history of hypotension, or concomitant treatment with antihypertensives or organic nitrates. If patients experience tolerability issues (symptomatic hypotension or SBP less than 90 mmHg), temporary down-titration or discontinuation of vericiguat is recommended. Concomitant use of vericiguat & PDE5 inhibitors, such as sildenafil, has not been studied in patients with heart failure & is therefore not recommended due to the potential increased risk for symptomatic hypotension. This medicinal product contains lactose. **Interactions:** see Contraindications, W&P section and SmPC for full details. **Pregnancy & breast feeding:** No data on use of vericiguat in pregnant women. Animal studies have shown reproductive toxicity in presence of maternal toxicity. As a precautionary measure, vericiguat should not be used during pregnancy & in women of childbearing potential not using contraception. No information regarding presence of vericiguat in human milk, the effects on breasfed infant or milk production. Vericiguat is present in the milk of lactating rats. Risk to a breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or discontinue/abstain from vericiguat therapy, taking into account the benefit of breast-feeding for the child & the benefit of therapy for the woman. **Effects on ability to drive & use machines:** Vericiguat has minor influence on the ability to drive or use machines. When driving vehicles or operating machines it should be taken into account that dizziness may occur occasionally. **Undesirable effects:** *Very common:* hypotension; *Common:* anaemia, dizziness, headache, nausea, dyspepsia, vomiting, gastro-oesophageal reflux disease. **Overdose:** Overdose of vericiguat may lead to hypotension. If necessary, treat symptoms. Vericiguat is unlikely to be removed by haemodialysis due to high protein binding. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** *2.5mg* - 14 tablets: £45.78. *5mg* – 14 tablets: £45.78. *10mg* - 28 tablets: £91.56. **MA Number(s):** *Great Britain* – PLGB 00010/0748 (2.5 mg), 00010/0749 (5 mg), 00010/0750 (10 mg); *Northern Ireland* - EU/1/21/1561/001–011 (2.5 mg), EU/1/21/1561/012–022 (5 mg), EU/1/21/1561/023–033 (10 mg). **Further information available from:** Bayer plc, 400 South Oak Way, Reading, RG2 6AD, U.K. Telephone: 0118 206 3000.
Date of preparation: July 2021

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in Google Play or Apple App Store. Adverse events should also be reported to Bayer plc. Tel.: 0118 206 3500, Fax.: 0118 206 3703, Email: pvuk@bayer.com